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RESEARCH ARTICLE

1, 3-CYCLOHEXANEDIONE AND ITS DERIVATIVES AS PRECURSORS IN ORGANIC CHEMISTRY; SYNTHESIS AND REACTIONS

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ABSTRACT

The study reported in this review involved a detailed survey about the chemistry of 1,3-cyclohexandione and its derivatives, which considered versatile reagents for synthesis of different derivatives. Due to its active dicarbonyl groups and the methylene moiety at C2 possesses a high activity. The hydroxyl groups (enol form) react prior to the methylene at C2 with electrophilic reagents and that favorite synthesis of different heterocyclic products.

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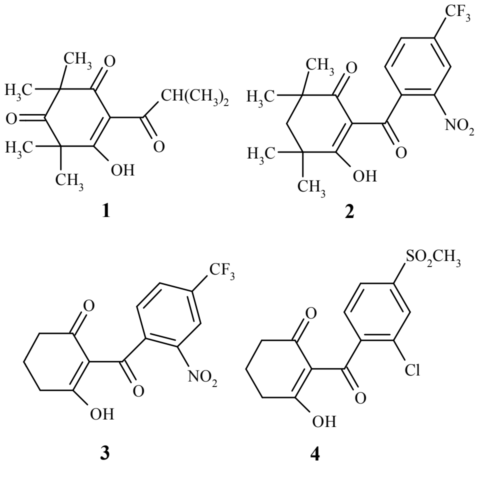
INTRODUCTION

Variety of different derivatives of 1,3-cyclohexanedione are used in various applications e.g. herbicides[1-5] plant growth promoters[1,6,7] antimalarials[8] and in different other uses.[9-15] The following study surveys the methods of preparation and reactions of 1,3-cyclohexanedione and its derivatives. 1,3-Cyclohexandione and its derivatives are used as start material for synthesis of the triketone herbicides which are used as inhibitors of 4-hydroxyphenyl-pyruvate dioxygenase (HPPD), key enzyme of the tyrosine transformation pathway, common for plants and animals. One of these herbicides, 2-[2-nitro-4-(trifuoromethyl) benzoyl]-1,3-cyclohexanedione (NTBC), is so selective and efficient that it can be applied as a medicine in a hereditary metabolic disease – tyrosinemia types 1-4 (Scheme 1).[16]



Scheme1. Different types of 1,3-cyclohexanedione derivatives used in medicinal proposes

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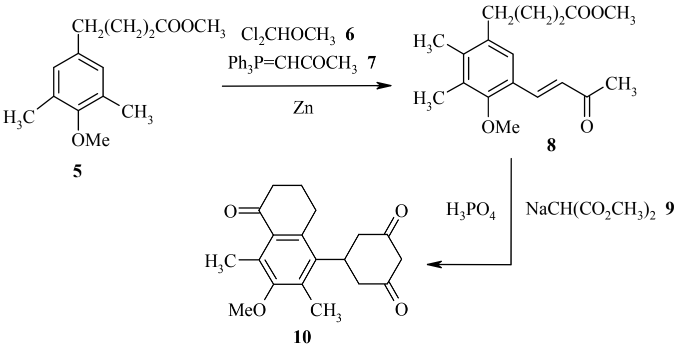
SYNTHESIS OF 1,3-CYCLOHEXANEDIONE AND ITS DERIVATIVES

From 3,5-dimethyl-4-methoxyphenyl-1-methylbutyrate

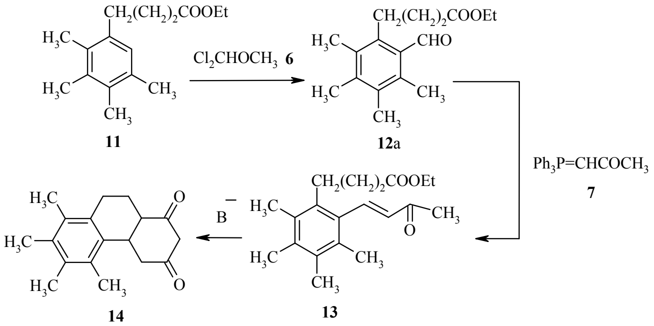
Cyclohexane-1,3-dione derivative 10 was obtained *via* sequence of reactions, thus acylation of 3,5-dimethyl-4-methoxyphenyl-1-methylbutyrate 5 followed by reduction with zinc metal and methylation formed the adduct 8. Condensation of 8 with dimethylmalonate anion 9 followed by cyclization by polphosphoric acid afforded the 1,3-cyclohexanedione derivative 10 (Scheme 2).[17]



Scheme 2. Synthesis of 1,3-cyclohexandione derivative from 3,5-dimethyl-4-methoxyphenyl-1-methylbutyrate

From 2,3,4,5-tetramethylphenyl-1-ethylbutyrate

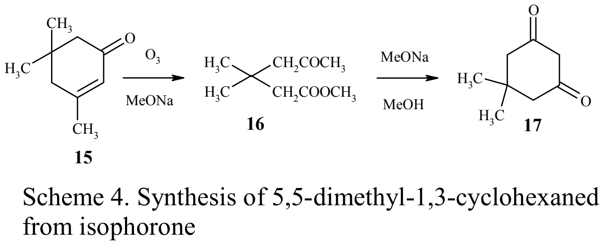
Fromylation of 2,3,4,5-tetramethylphenyl-1-ethylbutyrate 11 with dichloromethoxym- ethylene 6 gave the substituted benzaldehyde 12a. Condensation of 12a with acetone dervative 7 led to the formation of 13. Cyclization of 13 under base catalysis afforded the 1,3-cyclohexanedione derivative 14 (Scheme 3).[18]



Scheme 3. Synthesis of 1,3-cyclohexanedione derivative from 2,3,4,5-tetramethylphenyl-1-ethylbutyrate

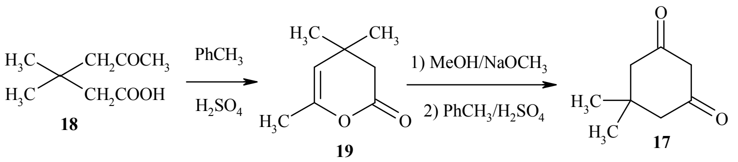
From isophorone

Treatment of isophorone 15 with 4% ozone at 0-2 °C resulted in ring opening and gave the ketoesters derivative 16. Recyclization of 16 in methanol/sodium methoxide mixture gave the 5,5-dimethyl-1,3-cyclohexanedione (dimedone) 17 (Scheme 4).[19]



Scheme 4. Synthesis of 5,5-dimethyl-1,3-cyclohexanedione from isophorone

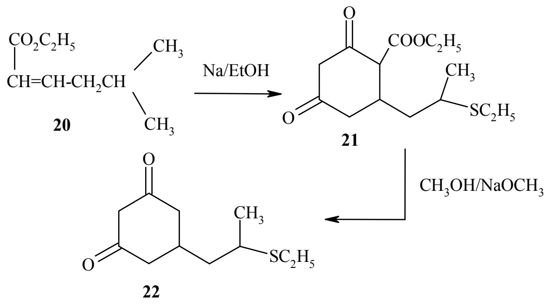
Consequently, treatment of 18 with toluene in the presence of sulfuric acid afforded the pyran derivative 19. Heating of the adduct 19 in a mixture of methanol/sodium methoxide followed by toluene/sulfuric acid mixture resulted in ring opening followed by recyclization and finally the 1,3-dione (dimedone) 17 is formed (Scheme 5).[20]



Scheme 5. Synthesis of dimedone

From 5-methyl-5-thioethyl-2-pentenoic acid methyl ester

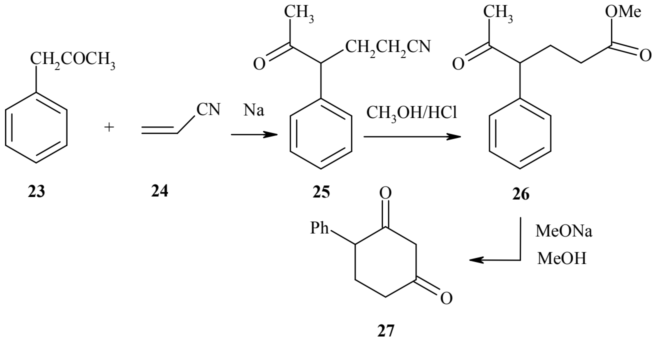
The 1,3-dione derivative 21 could be isolated under heating of 20 in ethanol and sodium metal. Refluxing of 21 in methanol/sodium methoxide mixture gave the 1,3-cyclohexanenedione derivative 22 (Scheme 6).[21]



Scheme 6. Synthesis of 1,3-cyclohexanedione derivative from 5-methyl-5-thioethyl-2-pentenoic acid methyl ester

From activated nitriles

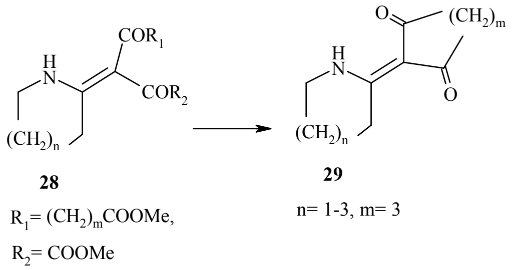
Treatment of phenylacetone 23 with acrylonitrile 24 in the presence of sodium metal was reported to proceed under Michael additions and formed the product 25. Acidification of 25 in methanol gave the ester 26. On heating 26 in methanolic sodium methoxide yielded the 6-phenyl-1,3-cyclohexanedione derivative 27 (Scheme 7).[22]



Scheme 7. Synthesis of 1,3-cyclohexanedione derivative from activated nitriles

From β-enaminoketodiesters

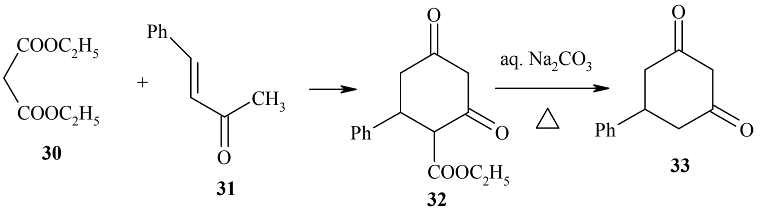
Decarboxylation of the β-enaminoketodiester 28 was achieved under heating at high temperature to form the cyclic diketone derivative 29 (Scheme 8).[23]



Scheme 8. Synthesis of 1,3-cyclohexandione derivative from B-enaminoketodiesters

From 1,3-diketones

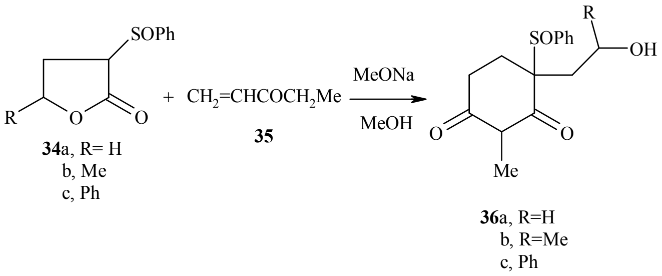
Cyclocondensation reaction of diethylmalonate 30 with chalcone 31 resulted in the formation of 1,3-cyclohexanedione derivative 32. Esters hydrolysis of 32 using aqueous sodium carbonate under heating afforded 5-phenyl-1,3-cyclohexanedione 33 (Scheme 9).[24]



Scheme 9. Synthesis of 5-phenyl-1,3-cyclohexanedione from diketones

From lactones

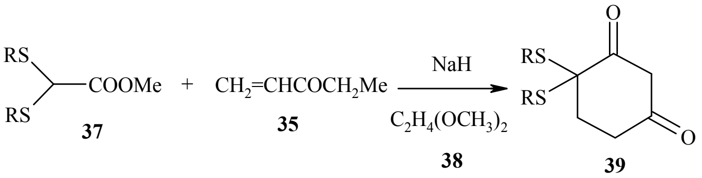
1,3-Cyclohexanedione derivatives 36 were obtained by treating the phenylsulfinyl lactones 34 with the unsaturated ketones 35 in methanolic sodium methoxide (Scheme 10) .[25]



Scheme 10. Synthesis of 1,3-cyclohexanedione derivatives from lactones

From thioacetals

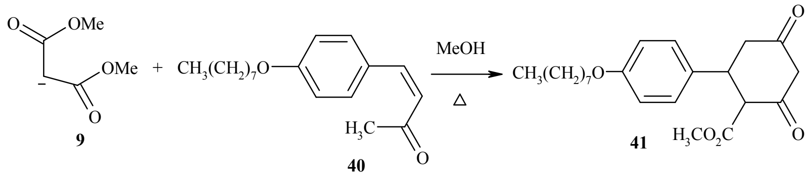
Michael-Claisen condensation reactions of the unsaturated ketones 35 and dimethoxy ethane 38 with the dithioacetals 37 resulted in the formation of 4,4-dithioalkyl-1,3-cyclohexanedione derivative 39 (Scheme 11).[26]



Scheme 11. Synthesis of 1,3-cyclohexanedione derivative from thioacetals

From substituted benzalacetones

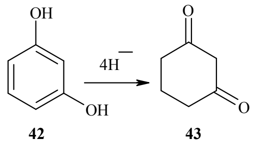
Michael addition of dimethylmalonate anion 9 to the substituted benzalacetone 40 at room temperature is considered a fruitful procedure for obtaining the cyclohexanedione derivative 41 (Scheme 12).[27]



Scheme 12. Synthesis of 1,3-cyclohexanedione derivative from substituted benzlacetone

From phenols

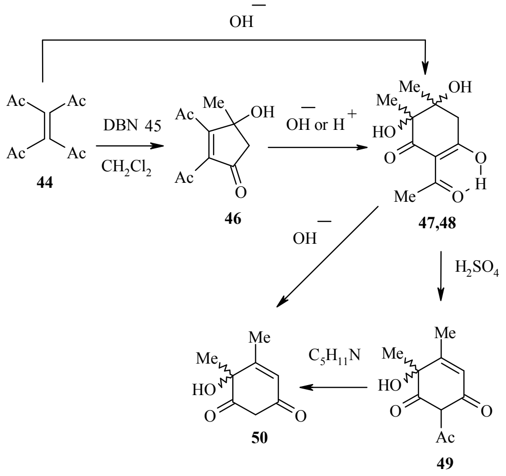
Reduction of the resorcinol 42 with a hydrogen donor in the presence of a catalyst yielded the corresponding 1,3-cyclohexanedione 43 (Scheme 13).[28]



Scheme 13. Synthesis of 1,3-cyclohexanedione

From Tetraacetylethylene

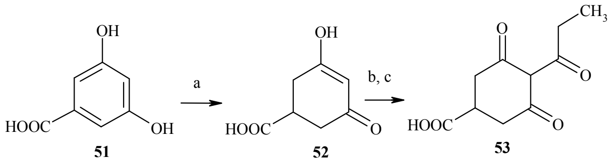
Treatment of Tetraacetylethylene (TAE) 44 in CH_2Cl_2 as solvent with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) 45 or sodium acetate, formed a high yield of cyclopentenone 46 and a small amount of a dimmer. The adduct 46 was separated by column chromatography. Treatment of 46 with aqueous sodium hydroxide and acidification, afforded epimeric 2-acetyl-4,5-dihydroxy-4,5-dimethylcyclohexane-1,3-diones 47 and 48. Heating of 47 and 48 with acids under mild conditions gave the cyclohexene-1,3-dione 49, which reacted with base at room temperature to give compound 50. The adduct 50 could also be obtained from 47 and 48 under similar conditions but in low yields (Scheme 14).[29]



Scheme 14. Synthesis of 1,3-cyclohexanedione derivative from tetraacetylethylene

From 3,5-dihydroxybenzoic acid

Hydrogenation of 3,5-dihydroxybenzoic acid **51** using the method of van Tamelen and Hildahl[8] led to the formation of 3,5-dioxocyclohexanecarboxylic acid **52** which is used for the of synthesis of 2-acyl-5-carboxycyclohexane-l,3-diones **53** (Scheme 15).[30,31]

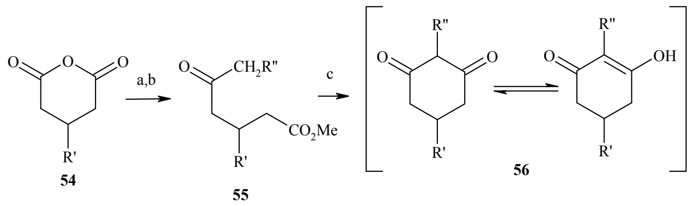


a:Raney Ni-H_2-NaOH; b: propionyl chloride- Et_3N, CH_2Cl_2; c: DMAP-CH_2Cl_2

Scheme 15. Synthesis of 1,3-cyclohexanedione derivative from 3,5-dihydroxybenzoic acid

From 4-alkylsubstituted glutaric anhydride

The symmetric 4-alkylsubstituted glutaric anhydride 54 was treated with dialkylcadmium and diazomethane to give the corresponding methyl esters 55 which when was treated with freshly prepared KO^{t}Bu furnished the adduct 56 (Scheme 16).[32-34]

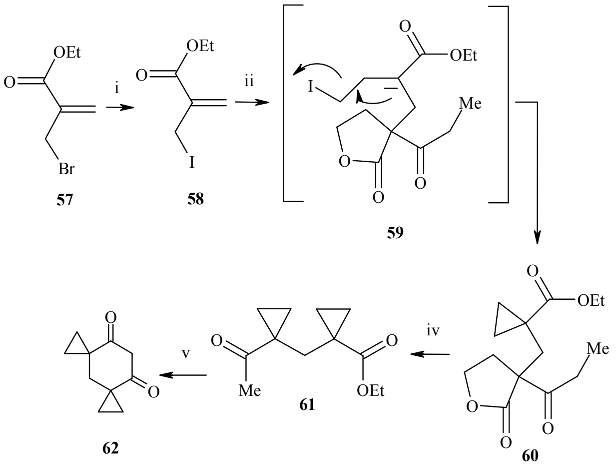


a) Cd(CH$_2$R'')$_2$ (78-99%); b) CH$_2$N$_2$ (quant.); c) KO^{t}Bu (73-98%)

Scheme 16. Synthesie of 1,3-cyclohexanedione derivative from 4-alkylsubstituted glutaric anhydride

From ethyl α-bromomethacrylate

Ethyl α-bromomethacrylate 57 was converted to the iodo adduct 58 which was treated with 2-acetyl-γ-butyrolactone to give the corresponding anionic intermediate 59. The intermediate 59 under reaction conditions cyclized to lactone 60. Lactone 60 converted under decarboxylative ring contraction conditions to give the intermediate 61 which was directly treated under Dieckmann conditions to give bis-spirocyclopropyl cyclohexane-1,3-dione 62 (Scheme 17).[35]

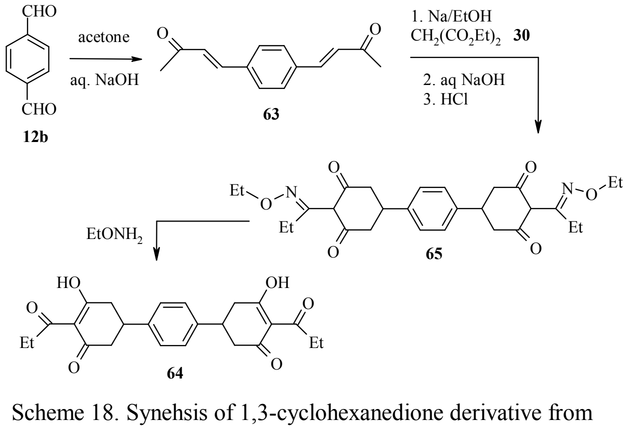


(i) Zn (1.0equiv), 1,2-dibromoethane (0.04equiv), trimethylchlorosilane (0.03equiv), diiodomethane (1.0equiv), THF, rt, 5h LiI (2.3equiv), CuI (1.2equiv), THF, rt, 16h, 80% (over two steps); (ii) 2-acetyl-γ-butyrolactone (1.0 equiv), NaH (1.1equiv), DMF, 0 °C to rt, 20h,77%; (iv) NaI (1.5equiv), NMP, microwaves, 240 °C, 2 x 10 min; (v) MeONa (1.5equiv), rt, 2h, 53%(over two steps).

Scheme 17. Synthesis of 1,3-cyclohexanedione from ethylα-bromomethacrylate

From aromatic aldeyhydes

A series of antiplasmodial activite compounds were synthesized by the treatment of the aromatic aldehyde 12b with aq. NaOH i n acetone to give 63. Subsequent treatment of 63 with diethylmalonate 30 furnished the adduct 64 which on treatment with EtONH$_2$ gave 1,3-cyclohexanedione oxime ethers 65 (Scheme 18).[36]

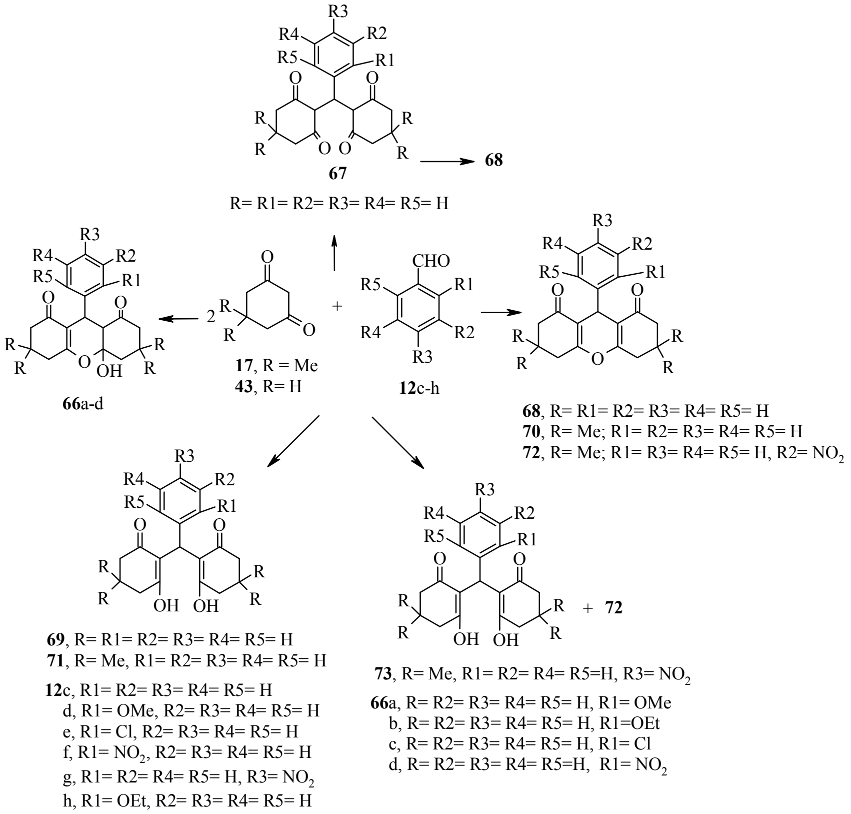


Scheme 18. Synehsis of 1,3-cyclohexanedione derivative from armoatic aldehydes

REACTIONS OF 1,3-CYCLOHEXANEDIONE AND ITS DERIVATIVES

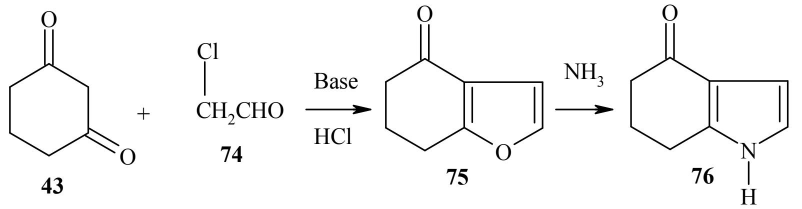
Reaction with aldehydes

Treatment of cyclohexane-1,3-dione 17 or 43 with aromatic aldehydes 12c-h afforded the adducts 66-73 (Scheme 19).[37-52]



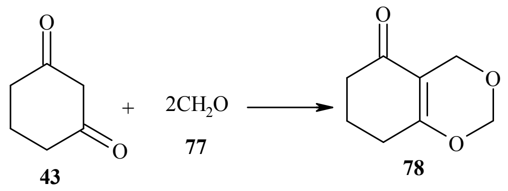
Scheme 19. Reaction of 1,3-cyclohexanedione or its derivatives with different aromatic aldehydes

While condensation of 43 with 2-chloroacetaldehyde 74 in the presence of a base (pyridine; triethylamine; $NaHCO_3$ or $Ba(OH)_2$) gave the tetrahydrobenzofuran 75. Heating the adduct 75 with amines gave 4-oxo-4,5,6,7-tetrahydroindoles 76 *via* ring opening and recyclization (Scheme 20).[53-56]



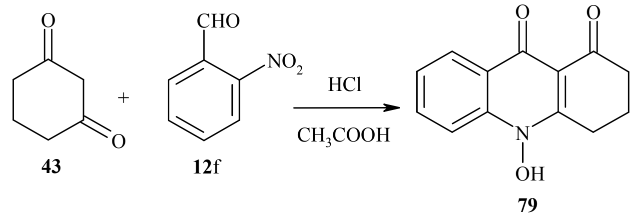
Scheme 20. Synthesis of 4-oxo-4,5,6,7-tetrahydroindole

Treating of 43 with formaldehyde 77 in the presence of BF_3/Et_2O gathered 78 (Scheme 21).[57]



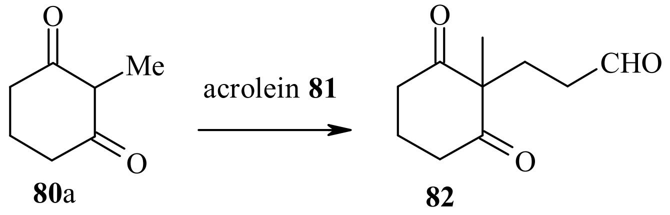
Scheme 21. Synthesis of 4,6,7,8-tetrahydrobenzo[1,3]dioxin-5-one from 1,3-cyclohexanedione and formaldehyde

1,3-Cyclohexanedione 43 was also condensed with 2-nitrobenzaldehyde 12f in a mixture of hydrochloric acid and acetic acid to give 10-hydroxy-2,3,4-trihydroacridine (10 *H*)-1,9-dione 79 (Scheme 22).[8]



Scheme 22. Synthesis of 10-hydroxy-2,3,4-trihydroacridine(10*H*)-1,9-dione from 1,3-cyclohexanedione and 2-nitrobenzaldehyde

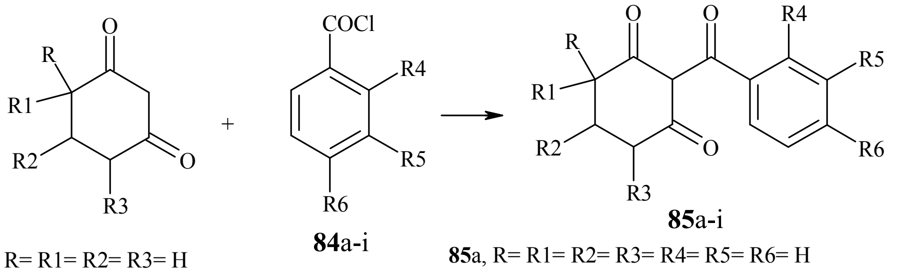
3-(2-Methyl-1,3-dioxocyclohexyl) propionaldehyde 82 was synthesized by the reaction of 2-methyl-1,3-cyclohexanedione 80a in tetrahydrofuran and acrolein 81 in distilled water by stirring (Scheme 23).[58]



Scheme 23. Synthesis of 3-(2-methyl-1,3-dioxocyclohexyl)propionaldehyde

Reaction with acetyling agents

Acylation of 1,3-cyclohexanedione 43 with benzoyl chloride derivatives 84a-g gives the adducts 85a-g. Also reaction of 1,3-cyclohexanedione 83a,b with benzoyl chloride derivatives 84h,i resulted in the formation of the dike tone derivatives 85h,i (Scheme 24).[1-3,6, 59-63]

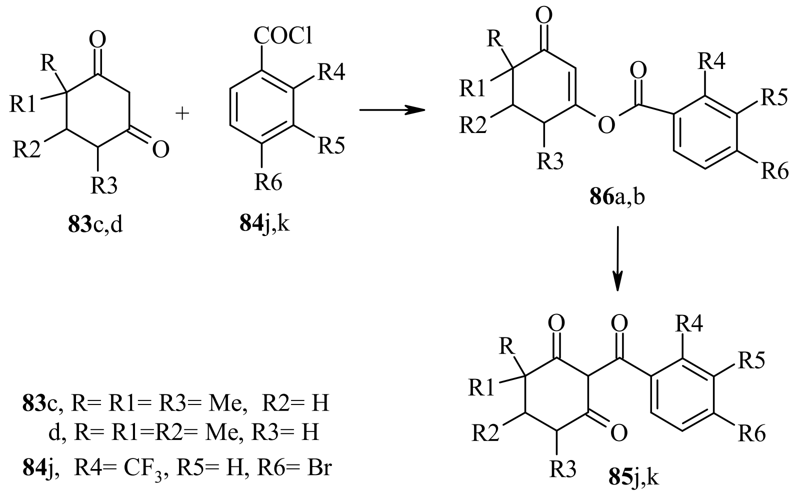


43, R= R1= R2= R3= H
83a,R= R1= R2= H, R3= 2-F-C_6H_4
b,R= R1=R3= H, R2= CH_3
84a, R4= R5= R6= H
b, R4= Cl, R5= H, R6= SO_2Me
c, R4= Br, R5= $O(CH_2)_2(OMe)_2$, R6= Br
d, R4= NO_2, R5= H, R6= Cl
e, R4= Cl, R5= H, R6= $OCHF_2$
f, R4= Cl, R5= CH=CHMe, R6= Cl
g, R4= Cl, R5= 3-mthoxyoxazolyl, R6= SO_2Me
h, R4= CF_3, R5= R6= H
i, R4= Cl, R5= OEt, R6= SO_2Et

85a, R= R1= R2= R3= R4= R5= R6= H
b, R= R1= R2= R3= R5= H, R4= Cl, R6= SO_2Me
c, R= R1= R2= R3= H, R4= Br, R5= $O(CH_2)_2(OMe)_2$, R6= Br
d, R= R1= R2= R3= R5= H, R4= NO_2, R6= Cl
e, R= R1= R2= R3= R5= H, R4= Cl, R6= $OCHF_2$
f, R= R1= R2= R3= H, R5= CH=CHMe, R4= R6= Cl
g, R= R1= R2= R3= H, R4= Cl, R5= 3-mthoxyoxazolyl, R6= SO_2Me
h, R= R1= R2= R5= R6= H, R3= 2-F-C_6H_4, R4= CF_3
i, R= R1= R3= H, R2= CH_3, R4= Cl, R5= OEt, R6= SO_2Et

Scheme 24.Acylation of 1,3-cyclohexanedione derivatives

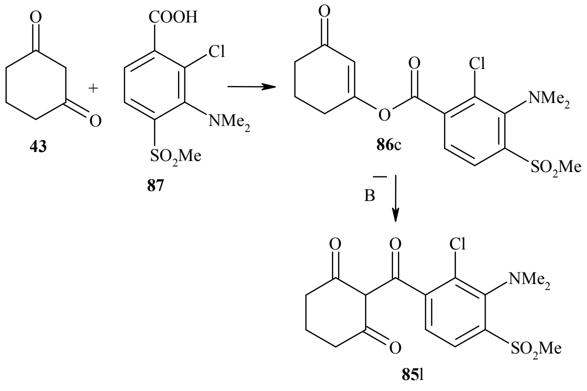
The reaction of 1,3-cyclohexanedione 83c,d with benzoyl chloride derivative 84j,k in different conditions resulted in the formation of 85j,k *via* 86a,b (Scheme 25).[64,65]



83c, R= R1= R3= Me, R2= H
d, R= R1=R2= Me, R3= H
84j, R4= CF_3, R5= H, R6= Br
k, R4= Cl, R5= OMe, R6= SO_2Me
85j, R= R1= R3=Me, R2= R5= H, R4= CF_3, R6= Br
k, R= R1= R2= Me, R3= H, R4= Cl, R5= OMe, R6= SO_2Me
86a, R= R1= R3=Me, R2= R5= H, R4= CF_3, R6= Br
b, R= R1= R2= Me, R3= H, R4= Cl, R5= OMe, R6= SO_2Me

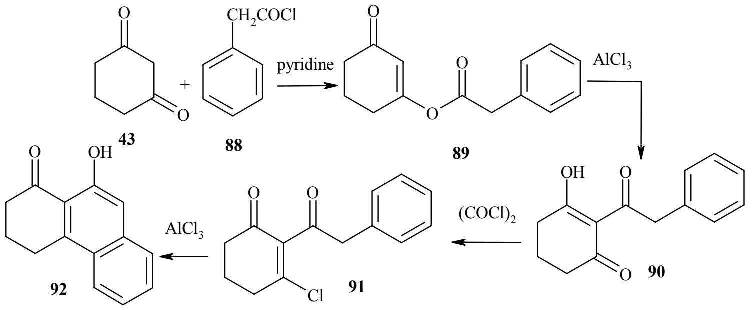
Scheme 25. Reaction of 1,3-cyclohexanedione derivatives with acylating agents

The reactivity of cyclohexane-1,3-dione 43 towards benzoic acid derivative 87 was reported and formed the intermediate 86c. Rearrangement of 86c in the presence of a base resulted in the formation of 85l (Scheme 26).[7,66,67]



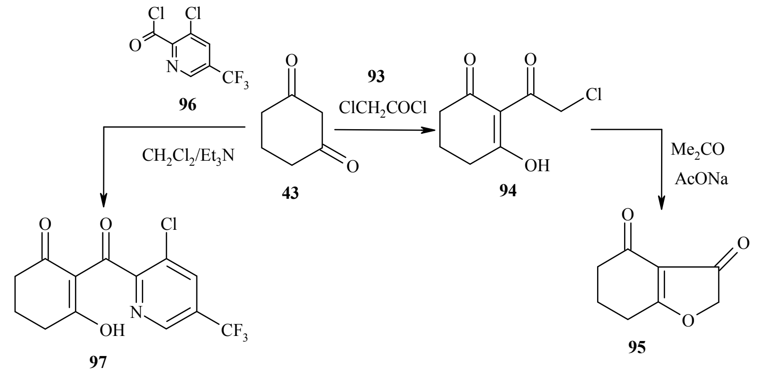
Scheme 26. Reaction of 1,3-cyclohexanedione with acylating agents

Using of acetyl chloride derivatives as acetyling agents for the 1,3-cyclohexanedione 43 were investigated, thus acylation of 43 with phenylacetyl chloride 88 in pyridine gave the cyclohexenone derivative 89. The adduct 89 under the influence of aluminium chloride furnished 2-phenylacetyl-1,3-cyclohexanedione 90. The reaction of 90 with oxalyl chloride led to the formation of chloroketo derivative 91. On treatment of 91 with aluminium chloride it gave 10-hydroxy-1,2,3,4-tetrahydrophenan- therene-1-one 92 (Scheme 27).[68]



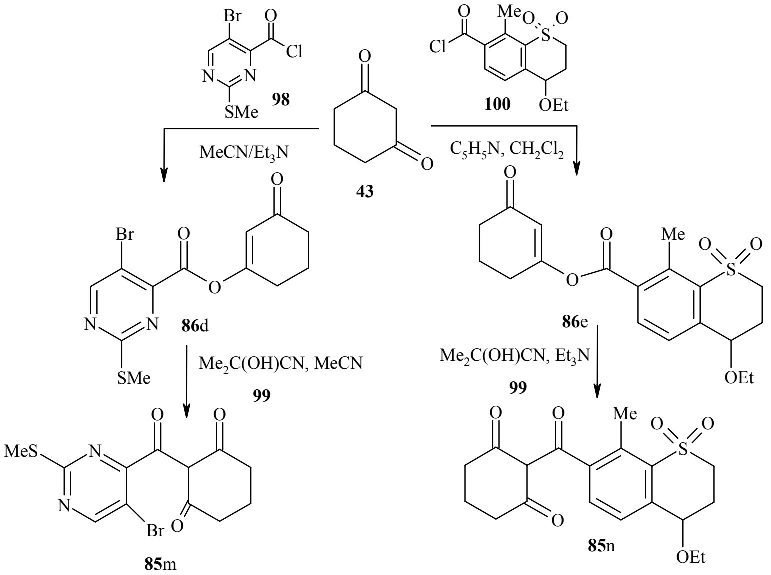
Scheme 27.Synthesis of phenantherene derivative

3,4-Dioxo2,3,4,5,6,7-hexahydrobenzo[*b*]furan 95 could be obtained from the reaction of 43 with chloroacetyl chloride 93 followed by treating of the product 94 with sodium acetate in acetone.[69] On the other hand, acylation of 43 with the acid chloride 96 at room temperature, produced the adduct 97 (Scheme 28).[70]



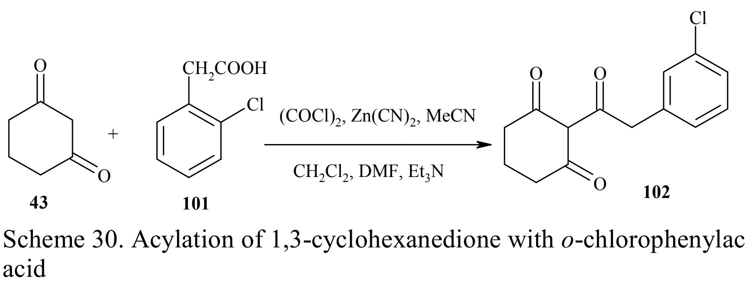
Scheme 28. Synthesis of 3,4-dioxo-2,3,4,5,6,7-hexahydrobenzo [*b*]furan and 2-(3-chloro-5-trifluoromethylpyridine-2-carbonyl) -3-hydroxycyclohex-2-enone

Acylation of 1,3-cyclohexanedione 43 with 5-bromo-2-(methylthio)pyrimidine-4-carbonyl chloride 98 gave 86d. Rearrangement of 86d in the presence of acetone cyanohydrine 99 gave the pyrimidine derivative 85m.[4] Also, on stirring 43 with 8-methy-4-ethoxy-1,1-dioxothiochroman-7-carbonyl chloride 100 in methylene chloride and pyridine gave the acylated product 86e. On stirring 86e with acetone cyanohydrine 99 and triethylamine in acetonitrile, the product 2-(8-methyl-4-ethoxy-1,1-dioxochroman-7-carbonyl)cyclohexane-2,3-dione 85n was yielded (Scheme 29).[9]



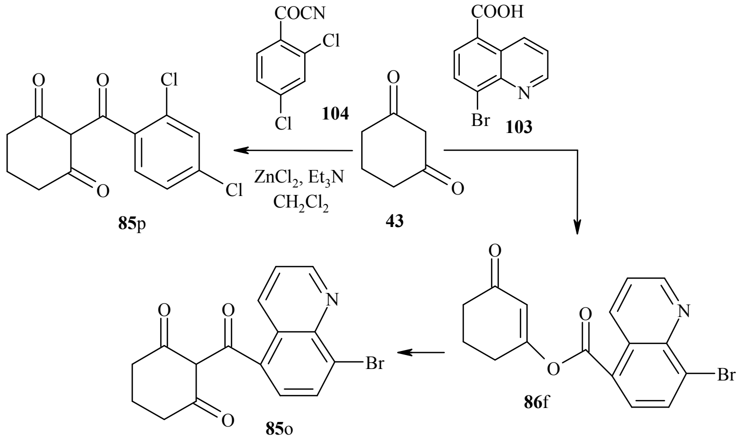
Scheme 29. Acylation of 1,3-cyclohexanedione afforded pyrimidine derivative **85**m and 2-(8-methyl-4-ethoxy-1,1-dioxochroman-7-carbonyl)cyclohexane-2,3-dione **85**n

On treating 1,3-cyclohexanedione 43 in methylene chloride and triethylamine with a mixture of *o*-chloro-phenylacetic cid 101, methylene chloride, dimeyhtlformamide, oxalyl chloride, zinc chloride and acetonitrile the product 102 was separated (Scheme 30).[71]



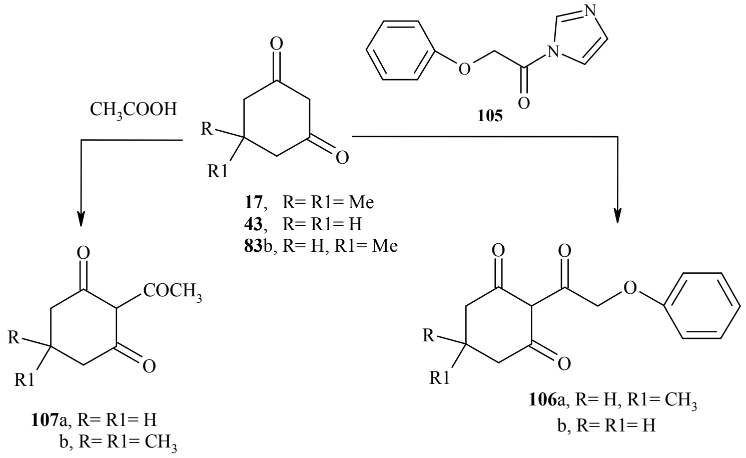
Scheme 30. Acylation of 1,3-cyclohexanedione with *o*-chlorophenylacetic acid

Treating of 1,3-cyclohexanedione 43 with 8-bromo-5-quinolinecarboxylic acid 103 gave the product 86f. Rearrangement of 86f the product 2-(8-bromo-5-quinolyl) carbonyl-1,3-cyclohexanedione 85o was obtained.[72] Cyclohexane-1,3-dione derivative 85p could also be isolated from the reaction of 43 with (2,4-dichlorophenyl) oxoacetonitrile 104 (Scheme 31).[5,73]



Scheme 31. Acylation of 1,3-cyclohexanedione with 8-bromo-5-quinolinecarboxylic acid and (2,4-dichlorophenyl)-oxoacetonitrile

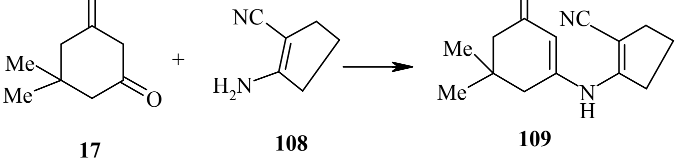
The reaction of 5,5-dimethyl-1,3-cyclohexanedione 17 or 5-methyl-1,3-cyclohexanedione 83b with benzyloxyacetamidazolide 105 favorite the formation of the product 106a,b.[74] Acyalation of 43 or its derivative 17 with acetic acid or propanoic acid in the presence of polyphosphoric acid gave the diketone 107a,b (Scheme 32).[75]



Scheme 32. Acylation of 1,3-cyclohexanedione or its derivatives

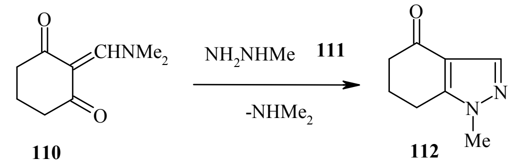
Reaction with amines

On reaction of 5,5-dimethyl-1,3-cyclohexanedione 17 with 1-amino-2-cyanocyclopentene 108 in the presence of ethylpolyphosphate at 55 ºC the adduct 109 was obtained (Scheme 33).[10]



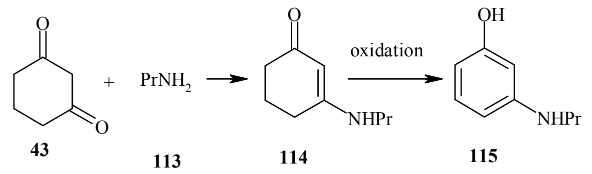
Scheme 33. Reaction of dimedone with 1-amino-2-cyanocyclopentene

While reaction of dimethylaminomethylene-1,3-cyclohexanedione 110 with methyl hydrazine 111 gave 1-methyl-1,5,6,7-tetrahydroindazol-4-one112 (Scheme 34).[76]



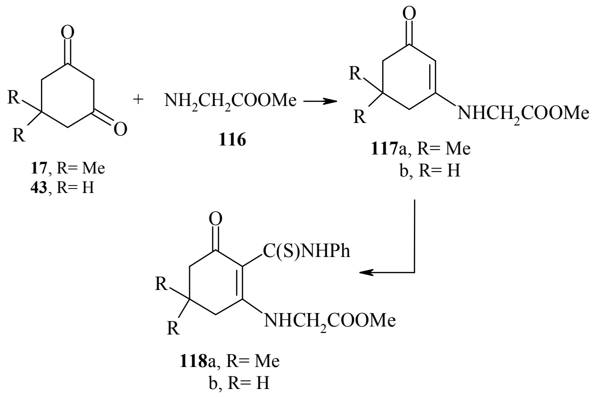
Scheme 34. Synthesis of 1-methy-1,5,6,7-tetrahydroindazol -4-one

Consequently, reaction of 43 with propylamine 113 gave the adduct 114. On oxidation of 114 with Hg(OAc) the adduct 115 was isolated (Scheme 35).[77]



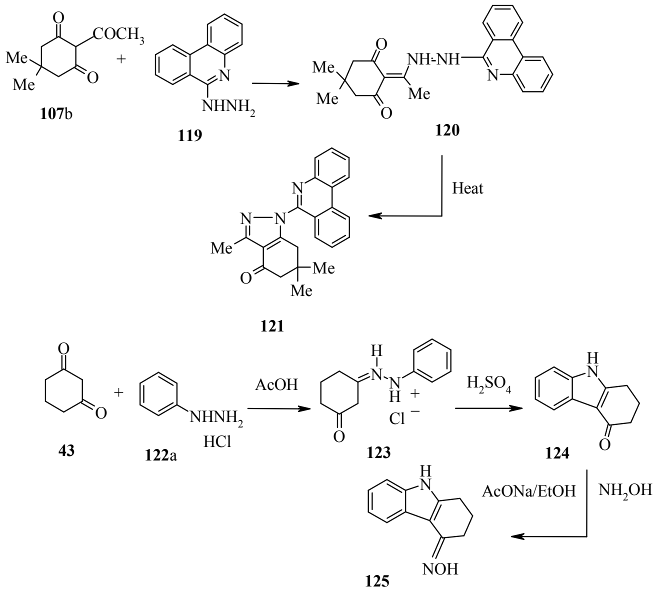
Scheme 35. Synthesis of 3-aminopropylphenol

Treatment of 17 or 43 with methyl glycinate 116 gave the enamines 117a,b. Treatment of 117a,b with phenylisothiocyanide gave phenylthiocarbamoyl derivatives 118a,b (Scheme 36).[78]



Scheme 36. Synthesis of phenythiocarbamoyl derivatives from 1,3-cylohexanedione or its derivatives and methyl glycinate

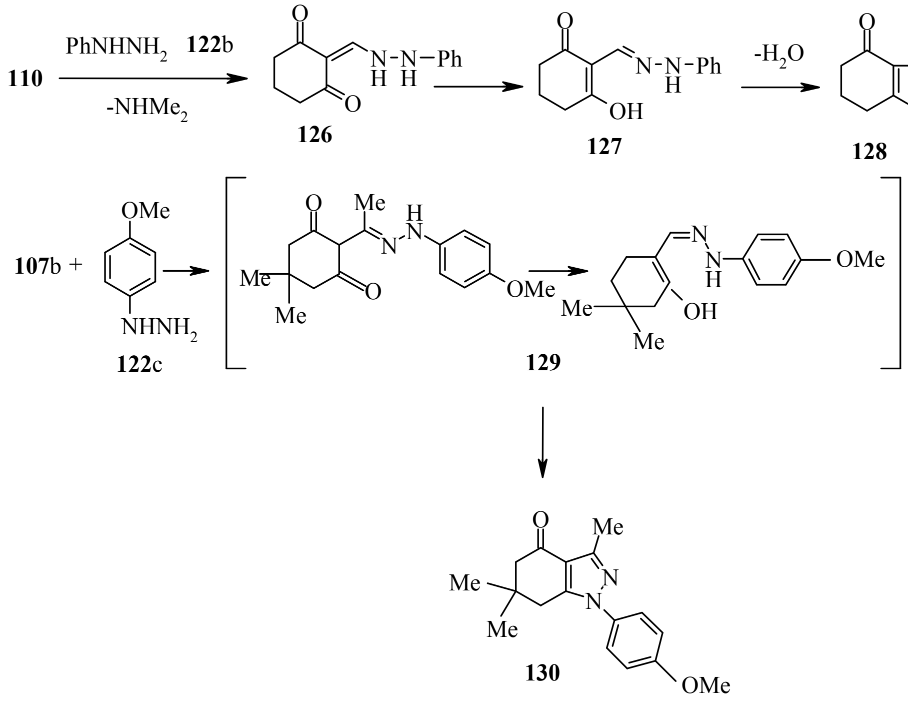
Condensation of 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione 107b with 6-hydrazinophenanthridine 119 gave enehydrazinoketones 120. On heating 120, the cyclization process gave tetrahydroindazoles 121.[79]



Scheme 37. Reaction of 1,3-cyclohexanedione or its derivatives with hydrazines

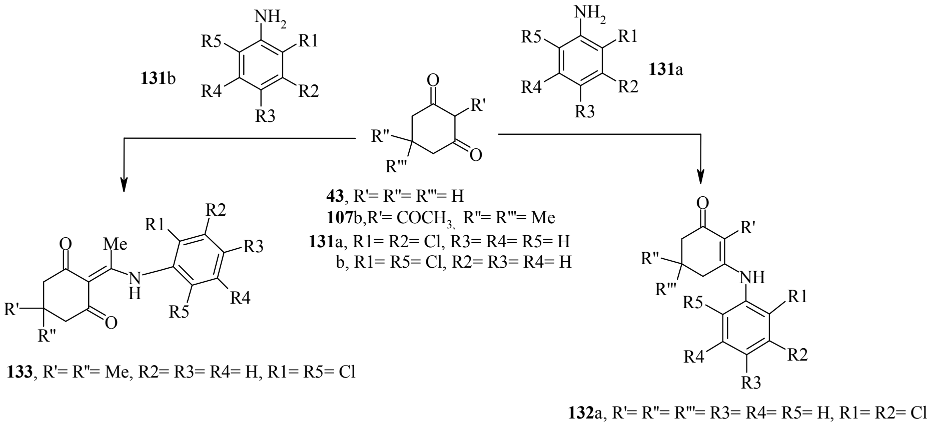
Furthermore, 1,3-cyclohexanedione 43 when reacted with phenylhydrazine hydrochloride 122a in aqueous acetic acid gave 3-phenylhydrazonocyclohexan-1-one 123. Treatment of 123 with sulfuric acid yielded 1,2,3,4-tetrahydocarbazol-4-one 124. Heating of the adduct 124 with hydroxylamine hydrochloride in ethanol and water in the presence of sodium acetate trihydrate gave, 1,2,3,4-tetrahydro-carbazol-4-oneoxime 125 (Scheme 37).[80]

N-phenylpyrazole fused to cyclohexenone 128 could be obtained *via* the reaction of dimethylaminometh-ylene-1,3-cyclohexanedione 110 with phenylhydrazine 122b.[76] Also, reaction of 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione 107b with 4-methoxyphenylhydrazine 122c gave 1-(4-methoxyphenyl)-6,6-dimeth- yl-4-oxo-4,5,6,7-tetrahydroindazole 130 *via* 129 (Scheme 38).[81]



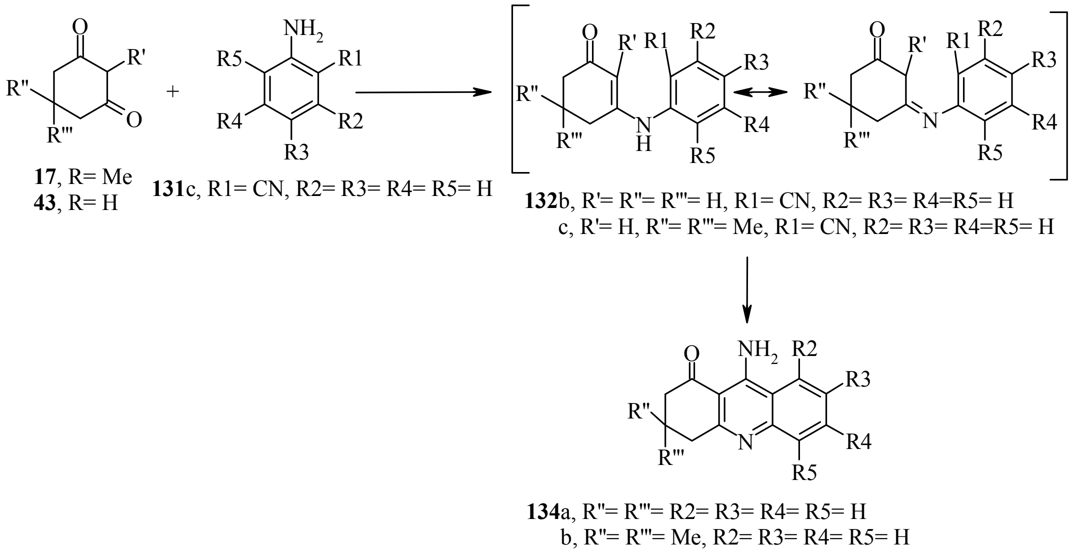
Scheme 38. Synthesis of indazole derivatives

The reaction of 43 with 2,3-dichloroaniline 131a in THF in acid medium produced 3-(2,3-dichloroanilin e)-2-cyclohexene-1-one 132.[11] Condensation of 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione 107b with 2,6-dichloroaniline 131b in the presence of *p*-toluenesulfonic acid gave 2-[1-(2,6-dichlorophenylamino) ethylidene]-5,5-dimethylcyclohexane-1,3-dione 133 (Scheme 39).[82]



Scheme 39. Synthesis of 3-(2,3-dichloroaniline)-2-cylohexene-1-one **132**a and 2-[1-(2,6-dichlorophenylamino)ethylidene]-5,5-dimethylcyclohexane-1,3-dione **133** from reaction of 1,3-cyclohexanedione or its derivatives with aromatic amines

Moreover reaction of 43 or its derivative 17 with 2-aminobenzonitrile 131c resulted in the formation of the intermediate 132b,c and finally the product 134a,b was formed (Scheme 40).[12,13]



17, R= Me
43, R= H

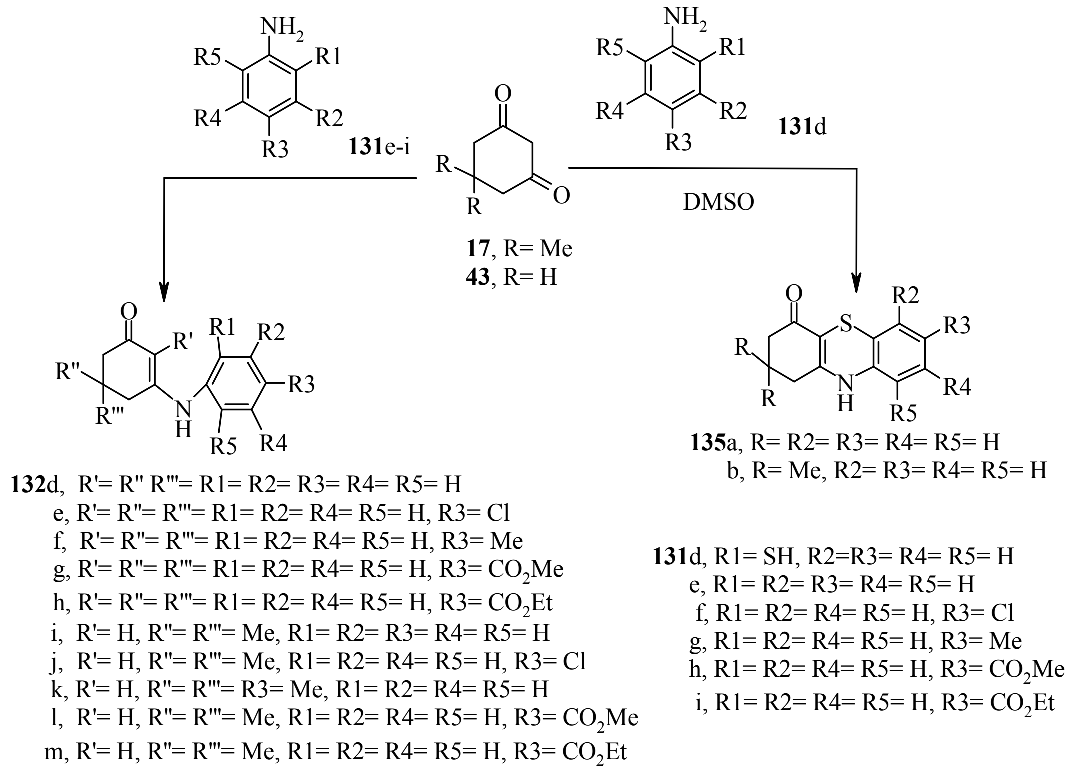
131c, R1= CN, R2= R3= R4= R5= H

132b, R'= R''= R'''= H, R1= CN, R2= R3= R4=R5= H
c, R'= H, R''= R'''= Me, R1= CN, R2= R3= R4=R5= H

134a, R''= R'''= R2= R3= R4= R5= H
b, R''= R'''= Me, R2= R3= R4= R5= H

Scheme 40.Synthesis of acridine derivatives

While the reaction of 43 or 17 with 2-aminobenzenethiol 131d gave 2,3-dihydro-2,2-dimethyl-1*H*-phenothiazin-4-(10*H*)ones 135a,b.[83-85] Similar to the prior, 43 or its 5,5-dimethyl derivative 17 when allowed to react with aromatic amines 131e-i the products 3-anilino-2-cyclohexen-1-one 132d-m were obtained with elimination of water (Scheme 41).[86]



131e-i

131d

DMSO

17, R= Me
43, R= H

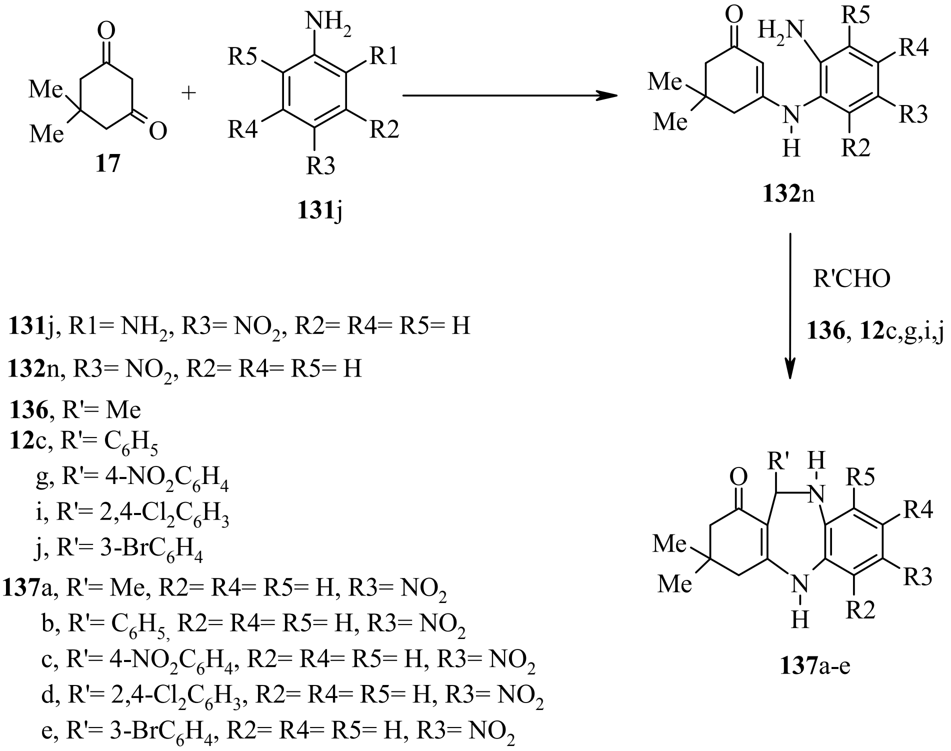
132d, R'= R'' R'''= R1= R2= R3= R4= R5= H
e, R'= R''= R'''= R1= R2= R4= R5= H, R3= Cl
f, R'= R''= R'''= R1= R2= R4= R5= H, R3= Me
g, R'= R''= R'''= R1= R2= R4= R5= H, R3= CO_2Me
h, R'= R''= R'''= R1= R2= R4= R5= H, R3= CO_2Et
i, R'= H, R''= R'''= Me, R1= R2= R3= R4= R5= H
j, R'= H, R''= R'''= Me, R1= R2= R4= R5= H, R3= Cl
k, R'= H, R''= R'''= R3= Me, R1= R2= R4= R5= H
l, R'= H, R''= R'''= Me, R1= R2= R4= R5= H, R3= CO_2Me
m, R'= H, R''= R'''= Me, R1= R2= R4= R5= H, R3= CO_2Et

135a, R= R2= R3= R4= R5= H
b, R= Me, R2= R3= R4= R5= H

131d, R1= SH, R2=R3= R4= R5= H
e, R1= R2= R3= R4= R5= H
f, R1= R2= R4= R5= H, R3= Cl
g, R1= R2= R4= R5= H, R3= Me
h, R1= R2= R4= R5= H, R3= CO_2Me
i, R1= R2= R4= R5= H, R3= CO_2Et

Scheme 41. Synthesis of 2,3-dihydro-2,2-dimethyl-1*H*-phenothiazin-4-(10*H*)ones **135**a,b and 3-anilino-2-cyclohexen-1-one **132**d-m

Reaction of the diketone 17 with 1,2-diamino-4-nitrobenzene 131j was found to pass through water elimination and the product 132n was isolated. On treating 132n with different aldehydes 136 and 12c,g,i,j the 1,4-diazepine derivatives 137a-e were obtained (Scheme 42).[87]



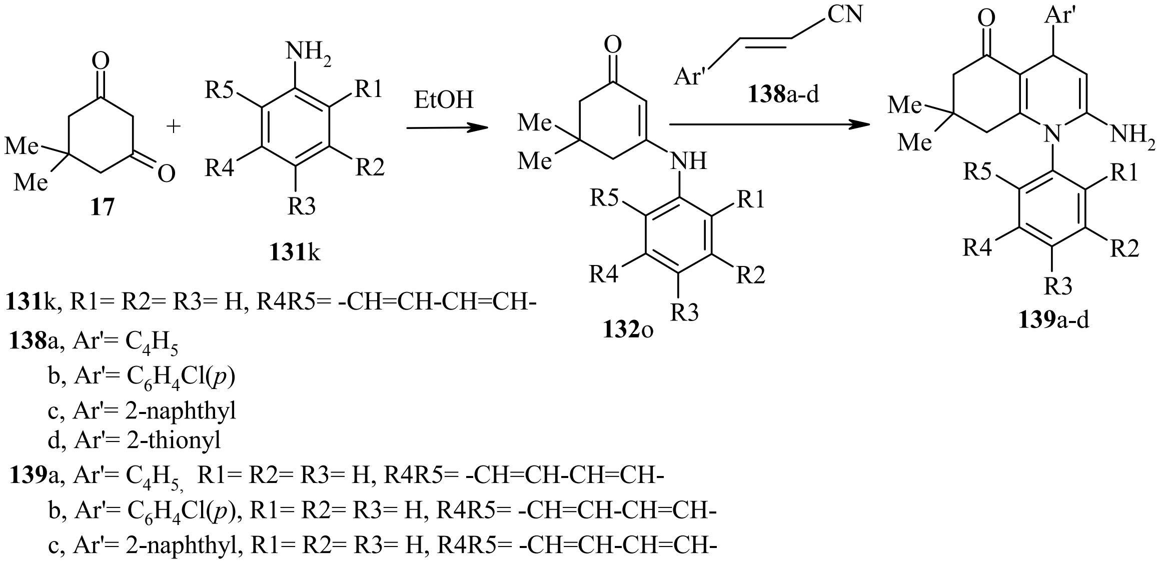
131j, R1= NH_2, R3= NO_2, R2= R4= R5= H

132n, R3= NO_2, R2= R4= R5= H

136, R'= Me
12c, R'= C_6H_5
g, R'= 4-$NO_2C_6H_4$
i, R'= 2,4-$Cl_2C_6H_3$
j, R'= 3-BrC_6H_4
137a, R'= Me, R2= R4= R5= H, R3= NO_2
b, R'= C_6H_5, R2= R4= R5= H, R3= NO_2
c, R'= 4-$NO_2C_6H_4$, R2= R4= R5= H, R3= NO_2
d, R'= 2,4-$Cl_2C_6H_3$, R2= R4= R5= H, R3= NO_2
e, R'= 3-BrC_6H_4, R2= R4= R5= H, R3= NO_2

Scheme 42. Synthesis of diazepine derivatives

Reaction of 5,5- dimethyl-1,3-cyclohexanedione 17 with 131k was carried out and the product 132o was collected. Also addition of cinnamonitrile 138a-d to 132o in ethanol and triethylamine in catalytic amount resulted in the formation of 2-amino-4-aryl-3-cyano (carboxamido)-*N*-(α-naphthyl)-7,7-dimethylhexahy- droquinoline 139a-d (Scheme 43).[88]

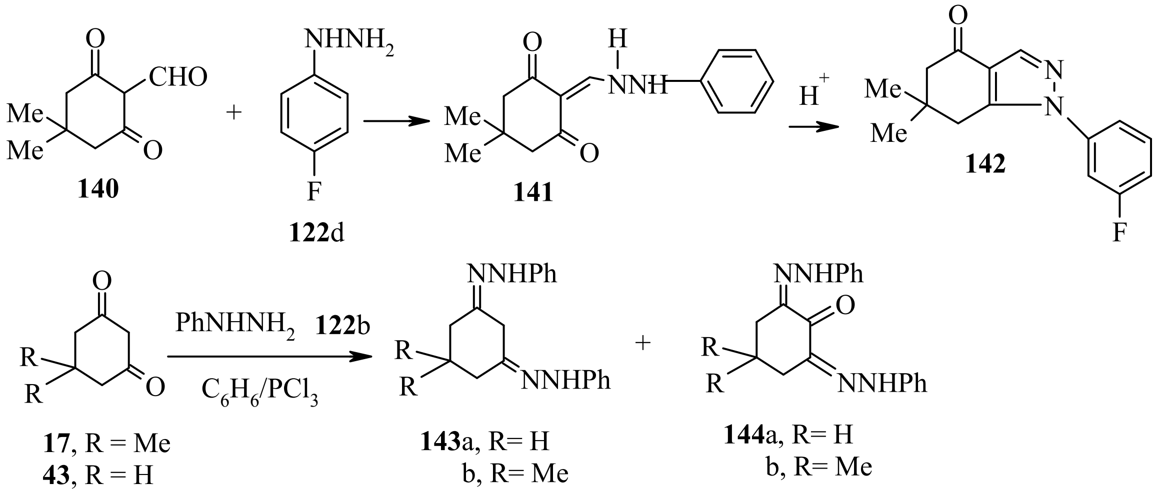


131k, R1= R2= R3= H, R4R5= -CH=CH-CH=CH-

138a, Ar'= C_4H_5
b, Ar'= C_6H_4Cl(*p*)
c, Ar'= 2-naphthyl
d, Ar'= 2-thionyl
139a, Ar'= C_4H_5, R1= R2= R3= H, R4R5= -CH=CH-CH=CH-
b, Ar'= C_6H_4Cl(*p*), R1= R2= R3= H, R4R5= -CH=CH-CH=CH-
c, Ar'= 2-naphthyl, R1= R2= R3= H, R4R5= -CH=CH-CH=CH-
d, Ar'= 2-thionyl, R1= R2= R3= H, R4R5= -CH=CH-CH=CH-

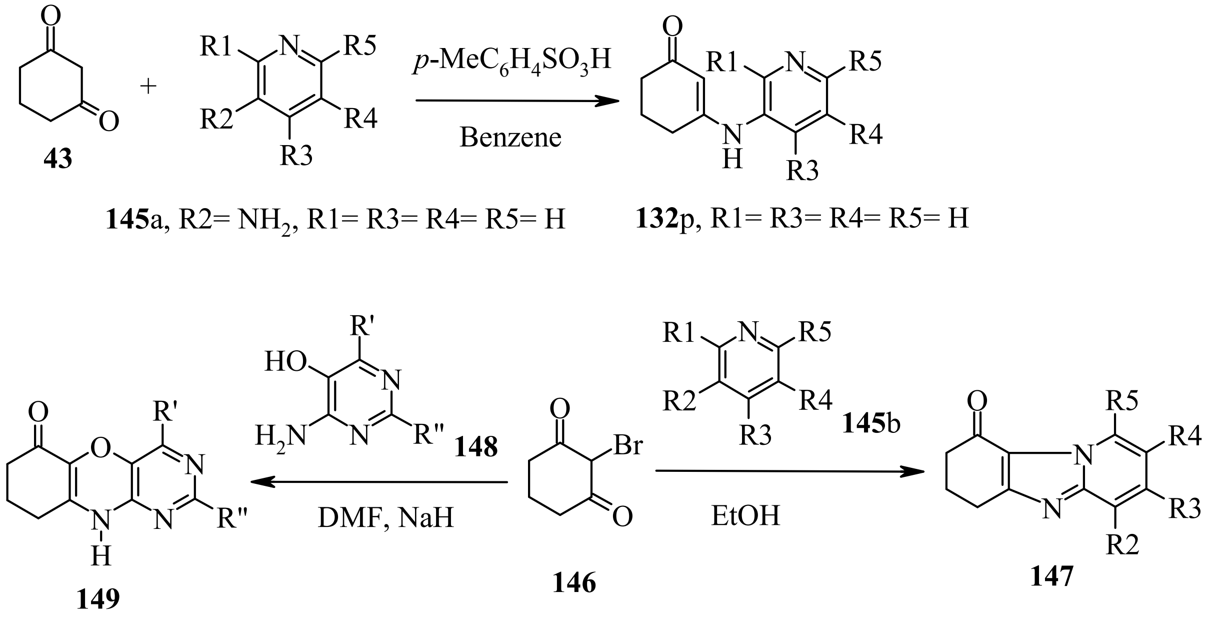
Scheme 43. Synthesis of 2-amino-4-aryl-3-cyano(carboxamido)-*N*-(1-naphthyl)-7,7-dimethylhexahydroquinoline

Condensation of 2-formyl-5,5-dimethyl-1,3-cyclohexanedione 140 with 4-fluorophenylhydrazine 122d gave 2-[(4-fluorophenylhydrazino)methyl]-5,5-dimethyl-3-cyclohexanedione 141. Treating of 41 with acid produced the substituted 6,6-dimethyl-4,5,6,7-tetrahydroindazole 142.[89] Treatment of cyclohexane-1,3-dione 43 or 5,5-dimethyl-1,3-cyclohexanedione 17 with two equivalents of phenylhydrazine 122b in dry benzene in the presence of two equivalents of phosphorous trichloride gave the corresponding bis-(phenylhydrazones) 143a,b and 2-oxo-bis (phenylhydrazones) 144a,b (Scheme 44).[90]



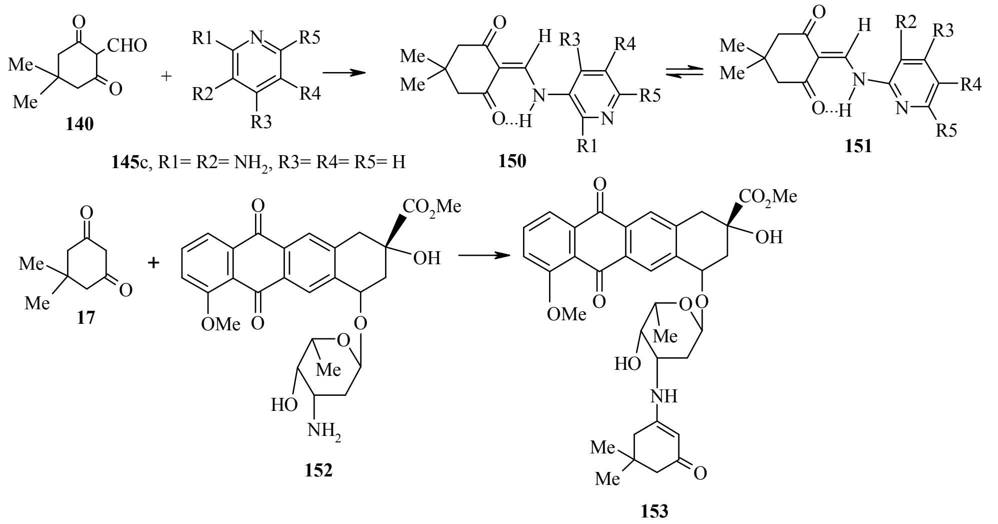
Scheme 44. Synthesis of 6,6-dimethyyl-4,5,6,7-tetrahydroindazole **142**, bis-(phenylhydrazones) **143**a,b and 2-oxo-bis-(phenylhydrazones) **144**a,b

Heating of 43 under reflux with 3-aminopyridine 145a in the presence of *p*-toluenesulfonic acid gave 3-(3-pyridylamino)-2-cyclohexen-1-one 132p.[14] While the reaction of 2-bromo-1,3-cyclohexaedione 146 with 2-aminopyridine 145b in ethanol produced 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one 147.[91] Moreover, 2-bromocyclohexane-1,3-dione 146 when reacted with 5- hydroxy-6-aminopyridine 148 in DMF in the presence of NaH gave 6,7,8,9-tetrahydro-10*H*-pyrimido-2-[5,4-*b*] [1,4] benzoxazine derivative 149 (Scheme 45).[92]



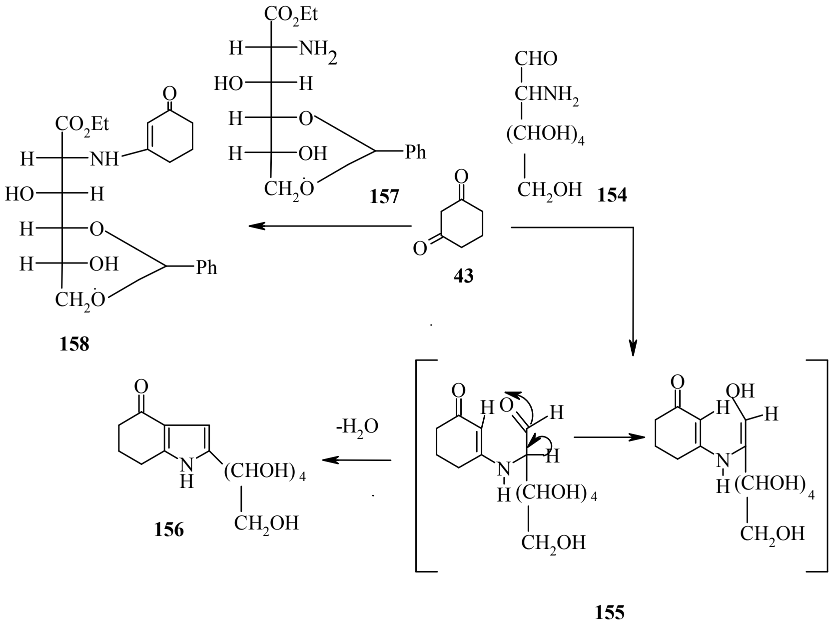
Scheme 45. Synthesis of 3-(3-pyridylamino)-2-cyclohexen-1-one **132**p, 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one **147** and 6,7,8,9-tetrahydro-10*H*-pyrimido-2-[5,4-*b*]benzoxazine derivative **149**

Furthermore, reaction of 2-formyl-5,5-dimethyl-1,3-cyclohexanedione 140 with 2,3-diaminopyridine 145c gave a mixture of 2-(2-amino-3-pyridylamino-methylene)-5,5-dimethyl-1,3-cyclohexanedione 150 and 2-(3-amino-2-pyridylaminomethylene)-5,5-cyclohexanedione 151.[93] Also, reaction of 5,5-dimethyl-1,3-cyclohexanedione 17 with daunorubicin 152 in DMF gave the adduct 153 (Scheme 46).[94]



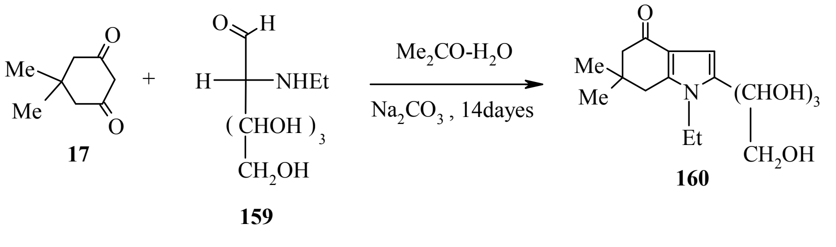
Scheme 46. Synthesis of 2-(2-amino-3-pyridylaminomethylene)-5,5-dimethyl-1,3-cyclohexanedione **150**, 2-(3-amino-2-pyridylaminomethylene)-5,5-cyclohexanedione **151** and 4-[4-(5,5-dimethyl-3-oxo-cyclohex-1-enylamino)-5-hydroxy-6-methyltetrahydropyran-2-yloxy]-2-hydroxy-7-methyl-6,11-dioxo-1,2,3,4,6,11-hexahydronaphthacene-2-carboxylic acid methyl ester **153**

Michael addition of 43 to 2-amino-2-deoxyheptoses 154 was investigated and gave indolones 156 *via* 155.[95,96] Ethyl-2-amino-4,6-*o*-benzylidene-2-deoxy-D-gluconate 157 when allowed to react with 43 isolated the derivative 158 (Scheme 47).[97]



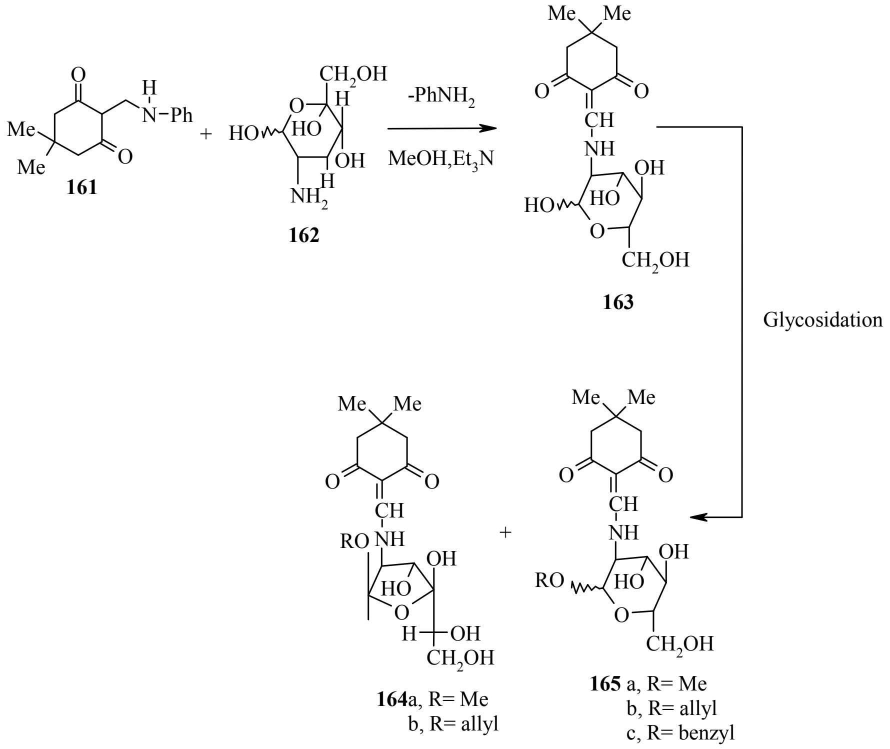
Scheme 47. Reaction of 1,3-cyclohexanedione with 2-amino-2-deoxyheptoses and ethy-2-amino-4,6-*o*-benzylidene-2-deoxy-D-gluconate

The product 2-(alditol-1-yl)-1-ethyl-4,5,6,7- tetrahydroindol-4-one 160 was simply synthesized from the reaction of 1,3-cyclohexanedione 43 or its 5,5-dimethyl derivative 17 with 2-deoxy-2-ethylamino-L-glucose 159 (Scheme 48).[98]



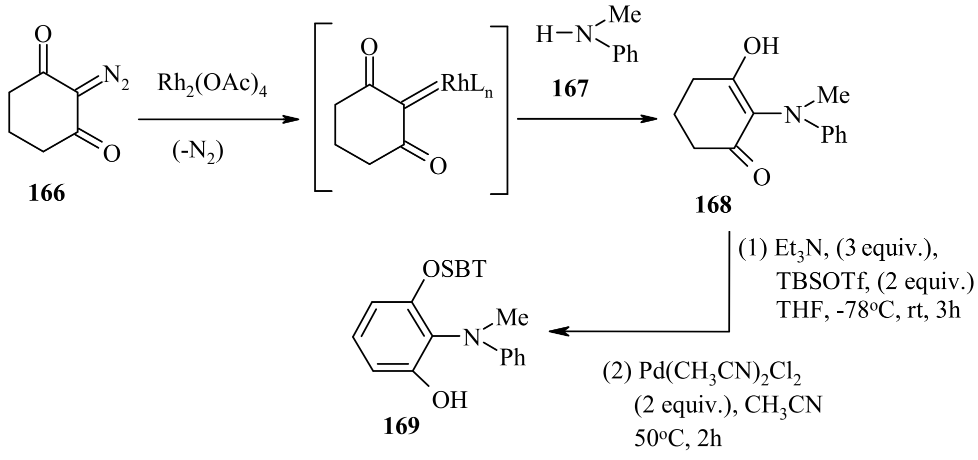
Scheme 48. Synthesis of 2-(alditol-1-yl)-1-ethyl-4,5,6,7-tetrahydroindol-4-one

Reaction of 5,5-dimehyl-2-phenylaminomethylene-1,3-cyclohexanedione 161 with 2-amino-2-deoxy-D-glucose hydrochloride 162 in methanol in the presence of triethylamine gave 2-deoxy 2-[(4,4-dimethyl-2,6-dioxocyclohexylidenemethyl)amino]-D-glucose 163. It was believed that formation of the adduct 163 occurred *via* addition of 162 to the dione 161 and subsequent elimination of aniline molecule. Glycosidation of 163 with different alcohol e.g. methyl alcohol, allyl alcohol, and benzyl alcohol under Fischer conditions afforded mixtures of α,β-D-glucopyranosides 164 and α-D-glucofuranoside 165 (Scheme 49).[99]



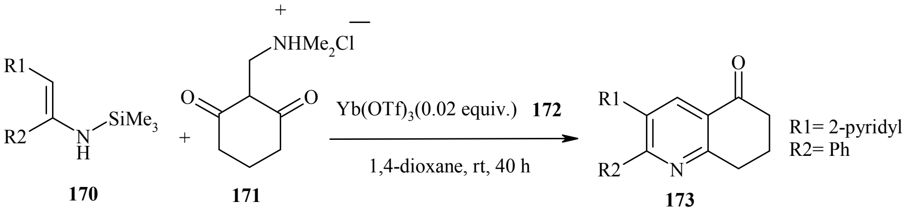
Scheme 49. Synthesis of α,β-D-glucopyranosides 164 and α-D-glucofuranoside 165

The reaction of 2-diazo-1,3-cyclohexanedione 166 with secondary amines such as *N*-methyl aniline 167 in the presence of $Rh_2(OAc)_4$ as a catalyst furnished 2-amino-3-hydroxy-2-cyclohexenone moiety 168 which may be aromatized *via* two steps and give 169 (Scheme 50).[100]



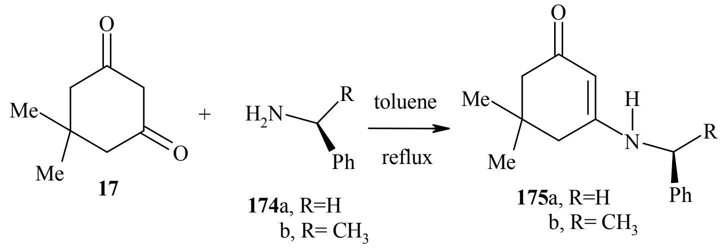
Scheme 50. Reaction of 2-diazo-1,3-cyclohexanedione with secondary amines

The in situ generated 2-methylene-1,3-cyclohexanedione 171 reacts with *N*-silylenamine 170 in the presence of a catalytic amount of ytterbium triflate ($Yb(OTf)_3$) 172 which promotes the cyclization of 170 to produce the corresponding 2,3-disubstituted 7,8-dihydroquinolin-5-one 173 (Scheme 51).[101]



Scheme 51. Synthesis of 2,3-disubstituted -7,8-dihydroquinoline-5-one

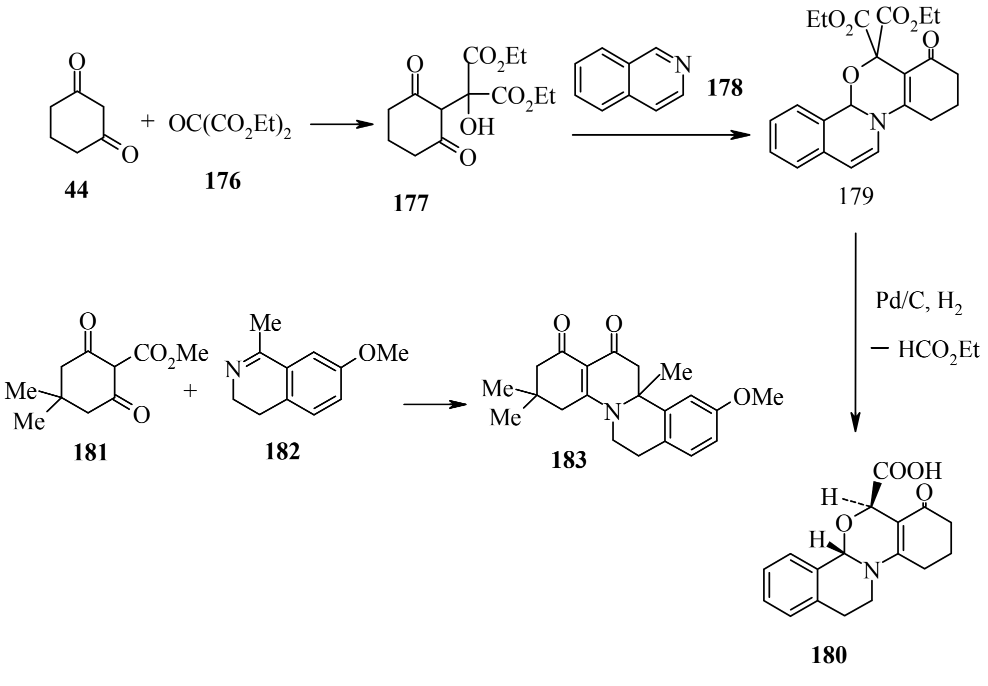
Condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione 17 with either benzylamine 174a or (*S*)-α-methylbenzylamine 174b in toluene at reflux conditions produced the β-enaminoketones 175a,b (Scheme 52).[102-104]



Scheme 52. Synthesis of β-enaminoketones

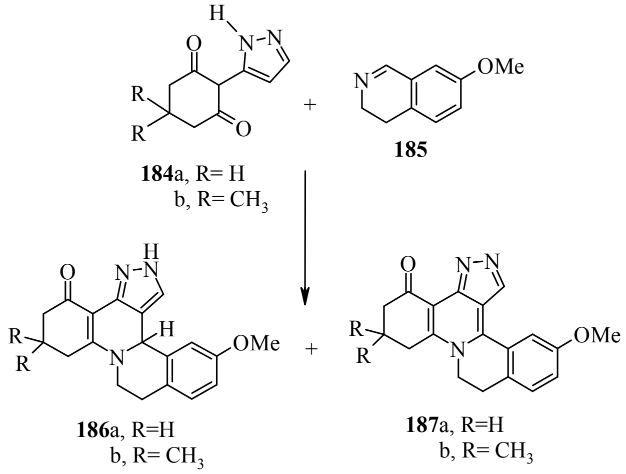
Reaction with isoquinoline and quinoline

Addition of 43 to $OC(CO_2Et)_2$ 176 gave 1,3-cyclohexeneyldiethylmalonatedione 177 which on treating with isoquinoline 178 afforded oxazagonane derivative 179. Reduction of 179 over Pd/C resulted in decarboxylation and the adduct 180 was obtained.[105] On reaction of 1,3-cyclohexanedione derivative 181 with 3,4-dihydroisoquinoline 182 yielded 8-aza-D-homo gonatetraenediones 183 (Scheme 53).[106]



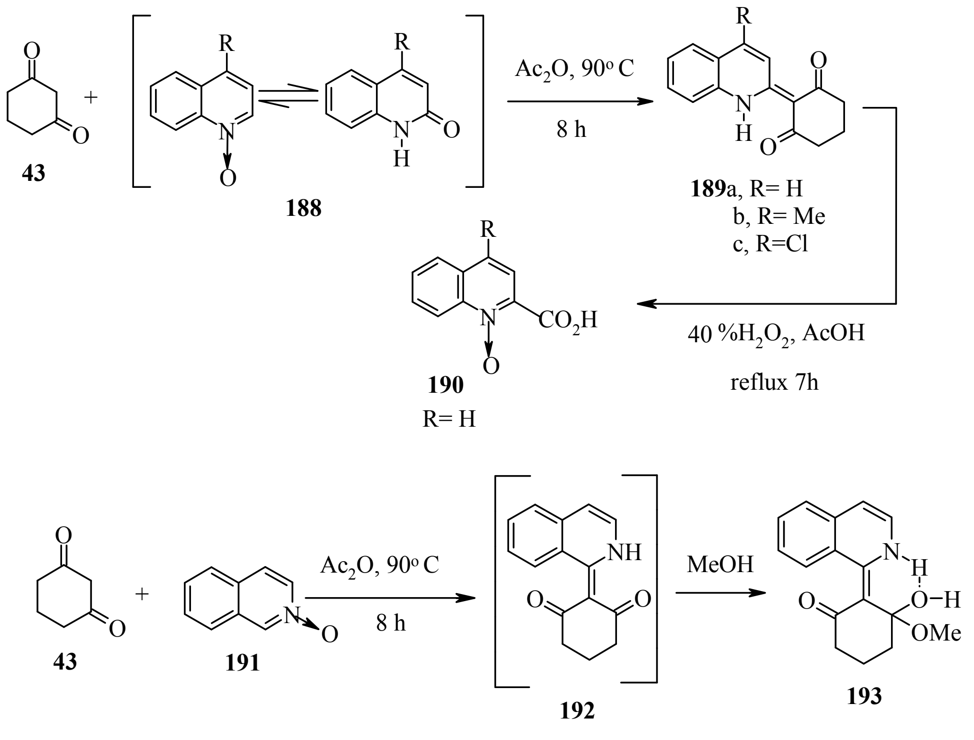
Scheme 53. Reaction of 1,3-cyclohexanedione or its derivative with isoquinoline or its derivative

Addition of pyrazolyl-1,3-cyclohexanediones 184a,b to the hydroisoquinoline derivatives 185 gave a mixture of adducts 186a,b and 187a,b (Scheme 54).[107,108]



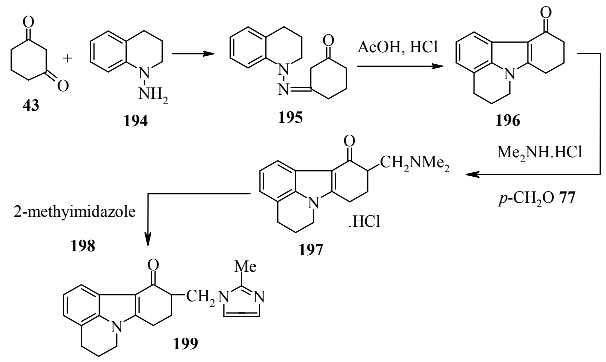
Scheme 54. Reaction of 1,3-cyclohexanedione derivative with isoquinoline derivative

Furthermore, 1,3-cyclohexanedione 43 reacted with quinoline-*N*-oxide 188 in Ac_2O or in DMF containing a catalytic amount of acetic anhydride to afford 2-(2-quinolyl) cyclohexane-1,3-dione 189a-c. Oxidation of 189a-c with H_2O_2 gave the product 190. The reaction of 43 with isoquinoline-*N*-oxide 191 gave 2-(isoquinolyl) cyclohexane-1,3-dione 192, which on triturating with methanol gave 193 (Scheme 55).[109]



Scheme 55. Reaction of 1,3-cyclohexanedione with quinoline-*N*-oxide and isoquinoline-*N*-oxide

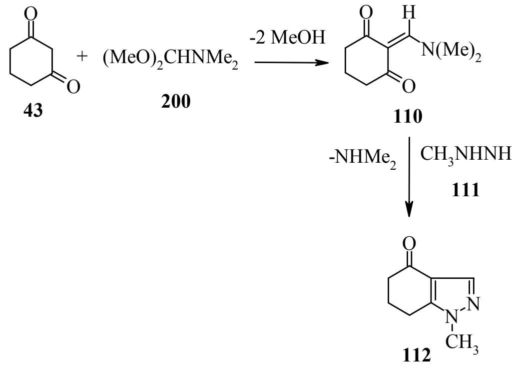
Reaction of 1,3-cyclohexanedione 43 with 1-amino-1,2,3,4-tetrahydroquinoline 194 in ethanol gave the adduct 195. Heating of 195 in acetic acid and hydrochloric acid mixture gave the fused carbazole 196. Further heating of 196 in the presence of paraformaldehyde 77 and dimethylamine hydrochloride yielded 197. Treatment of 197 with 2-methylimidazole 198 resulted in the formation of 199 (Scheme 56).[110]



Scheme 56. Synthesis of 10-(2-methylimidazol-1-ylmethyl)-5,6,9,10-tetrahydro-4*H*,8*H*-pyrido[3,2,1-jk]carbazol-11-one

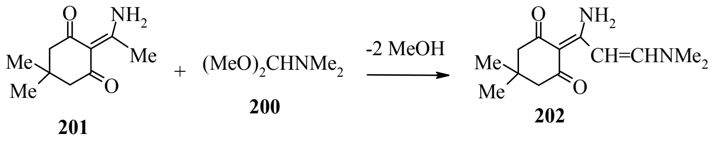
Reaction with amides

Fused *N*-methylpyrazoline to cyclohexene 112 can be obtained *via* reaction of 43 with 200 to give 110. Treatment of 110 with methylhydrazine 111 yielded the required product 112 (Scheme 57).[111]



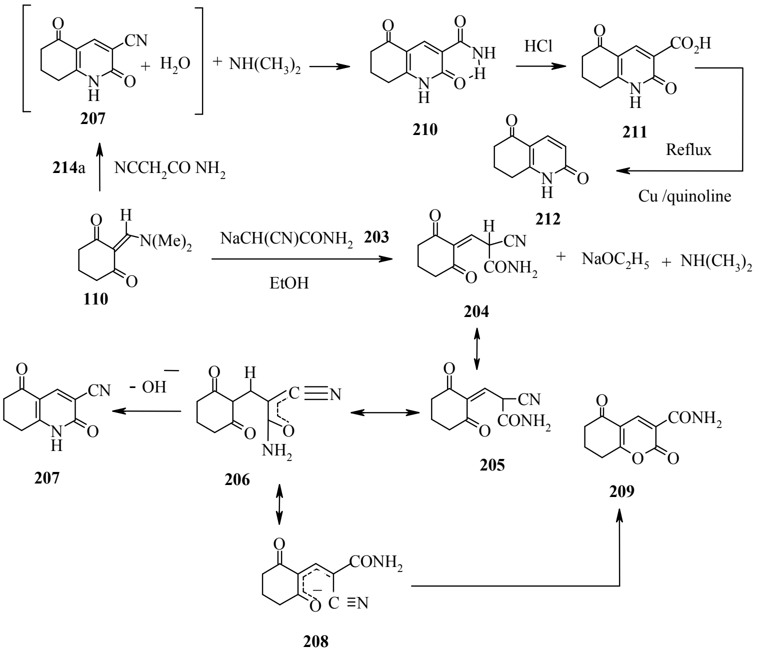
Scheme 57. Synthesis of 1-methyl-1,5,6,7-tetrahydroindazol-4-one **112**

Also, reaction of 1,3-cyclohexanedione derivative 201 with *N*,*N*-dimethylformamide dimethylacetal 200 gave 2-(1-amino-3-dimethylaminoallylidene)-5,5-dimethylcyclohexane-1,3-dione 202 (Scheme 58).[112]



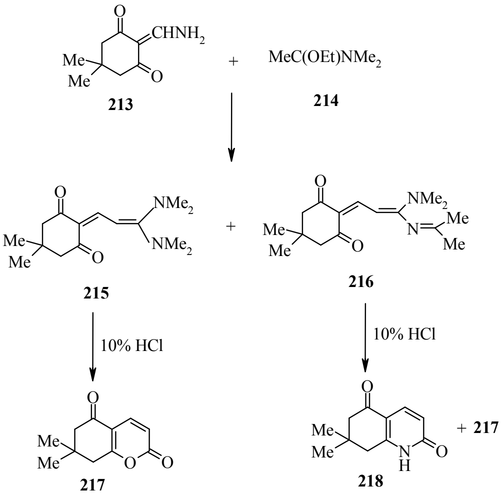
Scheme 58. Synthesis of 2-(1-amino-3-dimethylaminoallylidene)-5,5-dimethylcyclohexane-1,3-dione

Reaction dimethylaminomethylene-1,3-cyclohexanedione 110 with sodium cyanoacetamide 203 gave a mixture of 1,2,5,6,7,8-hexahydro-2,5-dioxo-3-quinolinecarbonitrile 207 and 5,6,7,8-tetrahydro-2,5-dioxo-2*H*-benzopyran-3-carboxamide 209, while the reaction of 110 with cyanoacetamide 214a in refluxing anhydrous ethanol gave 1,2,5,6,7,8-hexahydro-2,5-dioxo-3-quinolinecarboxamide 210. Hydrolysis of 210 with hydrochloric acid gave the corresponding acid 211, which on decarboxylation by refluxing in quinoline containing a catalytic amount of copper powder gave 7,8-dihyro-2,5-(1*H*,6*H*) quinolinedione 212 (Scheme 59).[113]



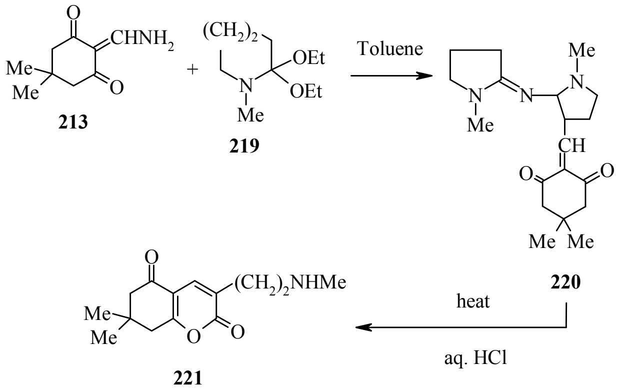
Scheme 59. Reaction of 1,3-cyclohexanedione derivative with amides

Reaction of 2-(aminomethylene)-5,5-dimethylcyclohexane-1,3-dione 213 with *N*,*N*-dimethylacetamide-diethylacetal 214 gave 2-aminobutadienyl -5,5-dimethylcyclohexane-1,3-dione 215 and 216. Cyclization of 215 under the effect of 10% hydrochloric acid gave dihydrobenzopyran-2,5-dione 217, while in the case of 216 the products 217 and dihydroquinolinedione 218 were obtained (Scheme 60).[114]



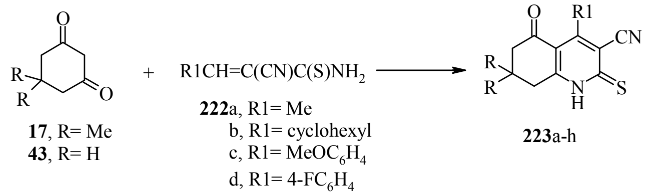
Scheme 60. Synthesis of benzopyran derivative **217** and quinoline derivative **218**

Boiling of 2-(aminomethylene)-5,5-dimethylcyclohexane-1,3-dione 213 with amide acetals 219 in toluene isolated the *N*-methylpyrrolopiperidine derivative 220. Subsequent heating of 220 in dilute hydrochloric acid led to formation of the coumarin derivative 221 (Scheme 61).[115]



Scheme 61. Reaction of 1,3-cyclohexanedione derivative with amide acetals

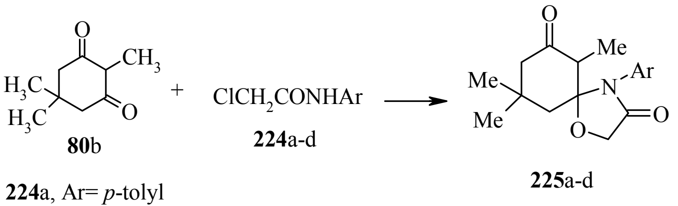
Addition of 43 or its 5,5-dimethyl derivative 17 to the alkylidenecyaothioamides 222a,b was fruitful and gave 5-oxo-5,6,7,8-tetrahydroquinoline derivative 223a-d (Scheme 62).[116,117]



223a, R= H, R1= Me
b, R= H, R1= cyclohexyl
c, R= R1= Me
d, R= Me, R1= cyclohexyl
e, R= H, R1= 4-MeOC$_6$H$_4$
f, R= H, 4-FC$_6$H$_4$
g, R= Me, R1= 4-MeOC$_6$H$_4$
h, R= Me, R1= 4-FC$_6$H$_4$

Scheme 62. Synthesis of quinolinne derivative

Reaction of 1,3-cyclohexanedione derivative 80b with α-chloro-*N*-arylacetamides 224 gave 4-arylspiro [4,5]oxazolidinones 225 (Scheme 63).[118]

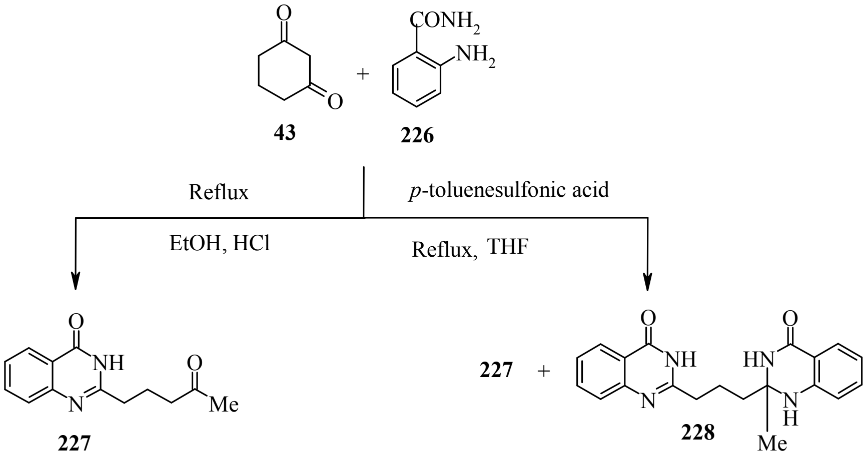


224a, Ar= *p*-tolyl
b, Ar= *p*-anisyl
c, Ar= *p*-chlorophenyl
d, Ar= *o*-tolyl
e, Ar= *o*-chlorophenyl
f, Ar= benzyl

225a, Ar= *p*-tolyl
b, Ar= *p*-anisyl
c, Ar= *p*-chlorophenyl
d, Ar= *o*-tolyl
e, Ar= *o*-chlorophenyl
f, Ar= benzyl

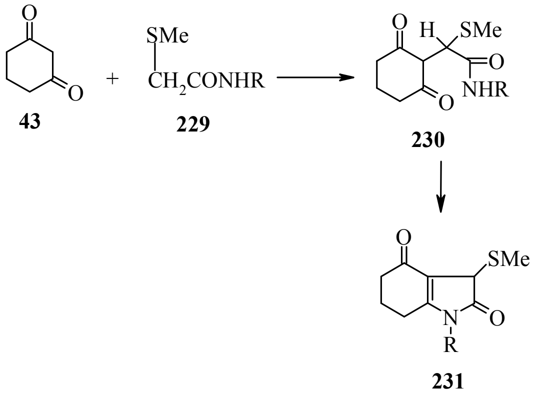
Scheme 63. Synthesis of 4-arylspiro[4,5]oxazolidinones

Condensation of 1,3-cyclohexanedione 43 with anthranilimide 226 in the presence of *p*-toluene sulfonic acid at the reflux temperature of THF afforded compounds 2-(4-oxo-pentyl)-3*H*-quinazolin-4-one 227 and 2-[3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-propyl]-3*H*-quinazolin-4-one 228. However, refluxing of 43 with 226 in ethanolic hydrogen chloride provided compound 227 only (Scheme 64).[119]



Scheme 64. Reaction of 1,3-cyclohexanedione with amide derivative

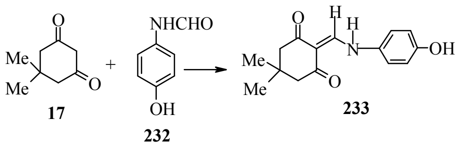
Addition reaction of 43 to α-methylsulfinylacetamides 229 favorite formation of *N*-(3-oxo-1-cyclohexe-ne-1-yl)-α-(methylsulfinyl)acetamides 230, on heating 230 with *p*-toluenesulfonic acid in methylene chloride the adduct, 3-methylthio-1*H*-indole-2,4-dione 231a,b could be isolated (Scheme 65).[120]



231a, R= 3,4-$(MeO)_2CH_2CH_2$
b, R= 3,4-$(MeO)_2(CH_2)_2CH_2$

Scheme 65. Synthesis of indole derivatives

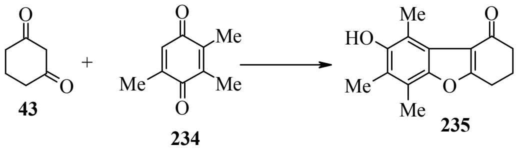
Furthermore condensation reaction of 17 with *N*-(4-hydroxyphenyl) formamide 232 was studied in acidic medium and the resultant product 2-[(4-hydroxyphenylamino) methylene]-5,5-dimethylclohexane-1,3-dione 233 was given (Scheme 66).[15]



scheme 66. Synthesis of 2-[4-(hydroxyphenylamino)methylene]-5,5-dimethylcyclohexane-1,3-dione

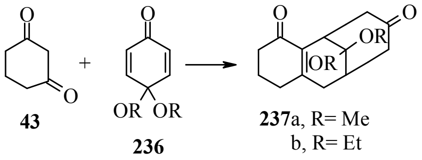
Reaction with quinines

Michael addition of 1,3-cyclohexanedione 43 with 2,3,5-trimethyl-1,4-benzoquinone 234 was also studied in the presence of sodium methoxide and gave 8-hydroxy-6,7,9-trimethyl-3,4-dihydro-2*H*-dibenzofuran-1-one 235 (Scheme 67).[121]



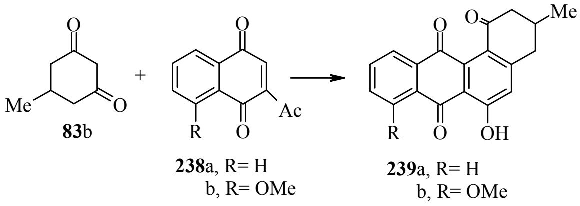
Scheme 67. Reaction of 1,3-cyclohexaneione with 1,4-benzoquinone

The addition of 1,3-cyclohexanedione 43 to quinone monoacetal 236 was also studied to give polycyclic endo products 237a,b (Scheme 68).[122]



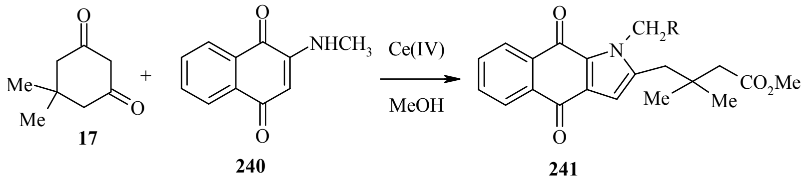
Scheme 68. Reaction of 1,3-cyclohexanedione with quinone derivatives

Similarly, benzanthracenetriones 239a,b were prepared by reaction of 5-methyl-1,3-cyclohexanedione 83b with 2-acetyl 1,4-naphthoquinone 238a,b and cyclization with base (Scheme 69).[123]



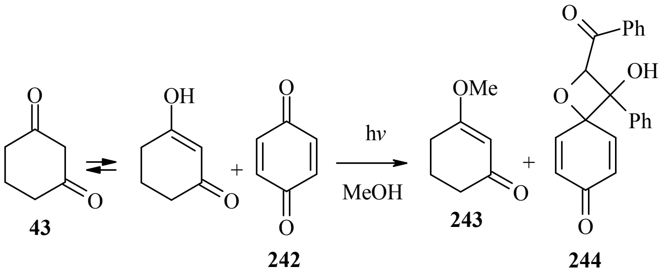
Scheme 69. Reaction of 1,3-cyclohexanedione derivative with 1,4-naphthoquinone derivatives

The reaction of 5,5-dimethyl-1,3-cyclohexanedione 17 with 2-(methylamino)-1,4-naphthoquinone 240 and cerium(IV) sulfate in methanol at room temperature gave 3,3-dimethyl-4-(1-alkyl-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indol-2-yl)-butyric acid methyl ester 241 (Scheme 70).[124]



Scheme 70. Reaction of dimedone with 1,4-naphthoquinone derivative

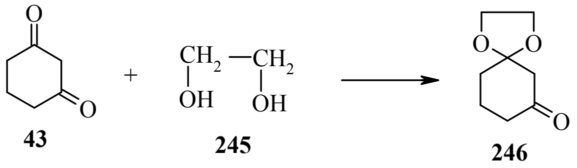
Irradiation of cyclic 1,3-cyclohexanedione 43 and *p*-benzoquinone 242 in methanol gave rise to 3-meth-oxycyclohex-2-en-1-one 243 as a major product. On the other hand, the expected product 2-benzoyl-3-hydroxy-3-phenyl-1-oxa-spiro[3.5]nona-5,8-dien-7-one 244 as 1:1 photo adduct, was isolated in only 2% yield (Scheme 71).[125]



Scheme 71. Synthesis of 3-methoxycyclohex-2-en-1-one and 2-benzoyl-3-hydroxy-3-phenyl-1-oxa-spiro[3.5]nona-5,8-dien-7-one

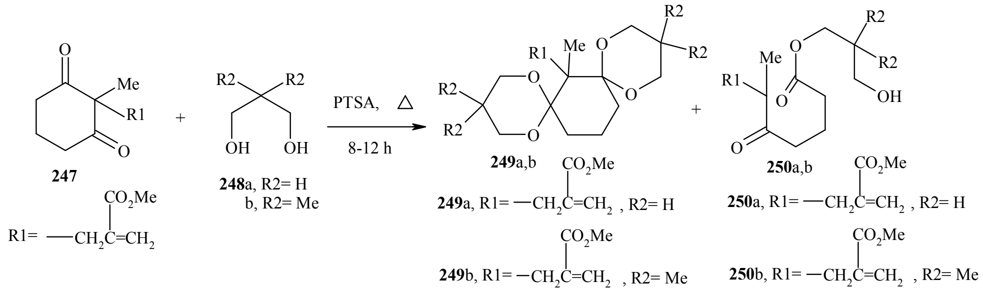
Reaction with alcohols and thioalcohols

Addition elimination reaction of 1,3-cyclohexanedione 43 with ethylene glycol 245 was reported to give 246 (Scheme 72) .[126]



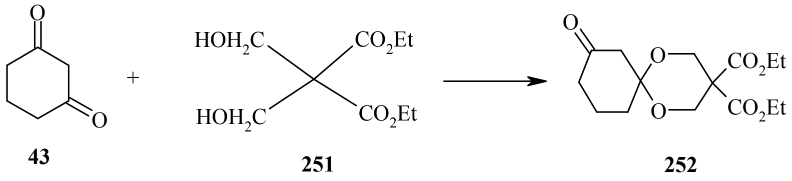
Scheme 72. Synthesis of 1,4-dioxaspiro[4.5]deca-7-one

Similar to the prior reaction, two moles of 247 when treated with the diols 248a,b in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrat (PTSA), the diketal 249a,b and the ring cleavage 250a,b were obtained (Scheme 73).[127]



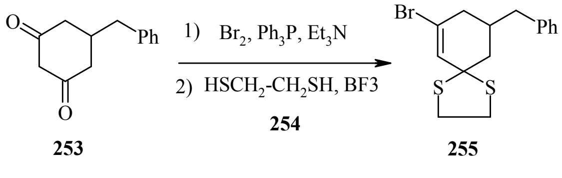
Scheme 73. Synthesis of spiro adduct and ethers from reaction of 1,3-cyclohexanedione derivatives and alcohol derivatives

While the reaction of 1,3-cyclohexanedione 43 with diols type 251 gave 8-oxo-1,5-dioxa-spiro[5.5]undecane-3,3-dicarboxylic acid diethyl ester 252 (Scheme 74).[128]



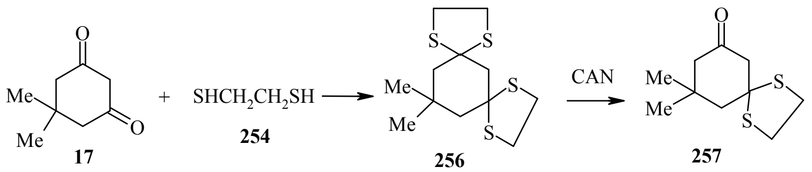
Scheme 74. Synthesis of spiro dduct *via* reacion of 1,3-cyclohexanedione with glycols

Addition of 1,3-cyclohexanedione derivative 253 to the dithiols 254 in the presence of bromine, triphenylphosphine and triethylamine was achieved and 9-benzyl-7-bromo-1,4-dithiaspiro[4.5]dec-6-ene 255 was obtained (Scheme 75).[129]



Scheme 75. Synthesis of dithiole by reaction of 1,3-cyclohexanedione derivative and thioalcohols

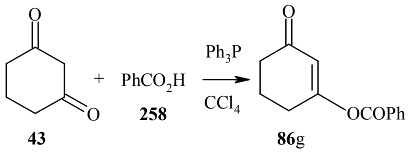
In similar to the above reaction, treatment of 17 with ethanedithiol 254 using Dean-Stark conditions, the product bis-dithiolane 256 was isolated. The selective hydrolysis of 256 to ketodithiolane 257 is employed in ceric ammonium nitrate under optimal conditions (Scheme 76).[130]



Scheme 76. Reaction of dimedone with thioalcohols

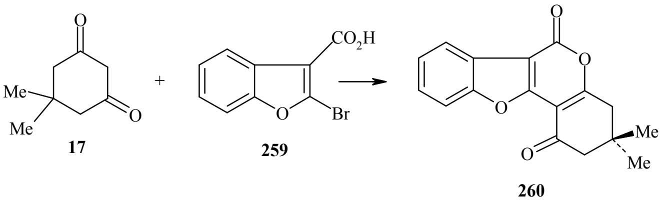
Reaction with carboxylic acids

The dione 43 on subjection to reaction with benzoic acid 258 in the presence of triphenylphosphine and carbon tetrachloride, the *cis*-form 86g was obtained (Scheme 77). [131]



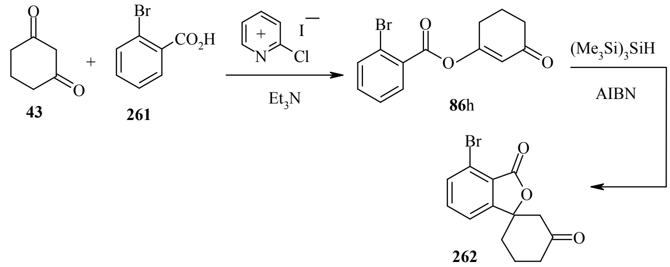
Scheme 77. Synthesis of 3-benzoyloxycyclohex-2-en-1-one

When the dione 17 was allowed to react with 2-bromo-3-benzo-furancarboxylic acid 259 in the presence of copperI bromide and subsequent lactonization it gave 6*H*-benzofuro[3,2-*c*][1] benzopyran-6-one 260 (Scheme 78).[132]



Scheme 78. Synthesis of 3,3-dimethyl-3,4-dihydro-2*H*-benzo[4,5]furo [3,2-*c*]chromene-1,6-dione **260**

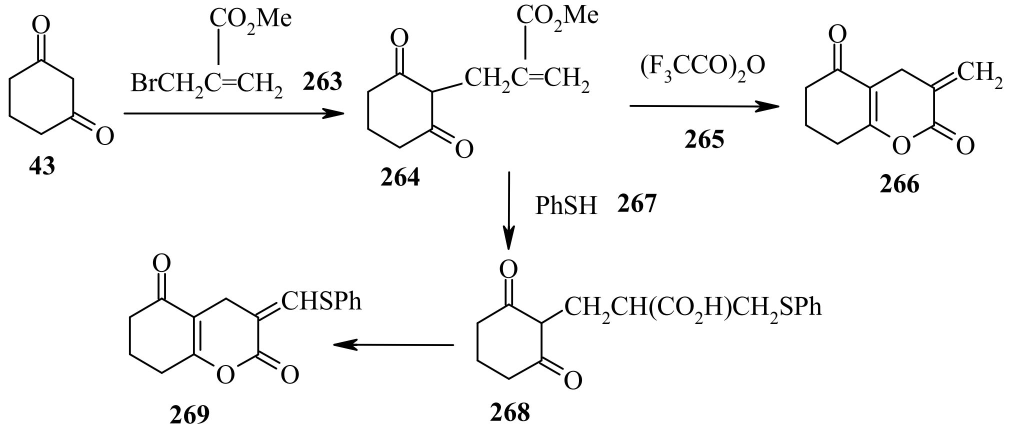
Reaction of 43 with 2-bromobenzoic 261 acid gave 86h. On heating 86h in benzene in the presence of $(CH_3Si)_3SiH$ and 2,2'-azobis(2-methylpropionitrile) (AIBN) separated the keto spiro γ –lactones 262 (Scheme 79).[133]



Scheme 79. Synthesis of keto spiro γ –lactones from 1,3-cyclohexanedione and 2-bromobenzoic acid

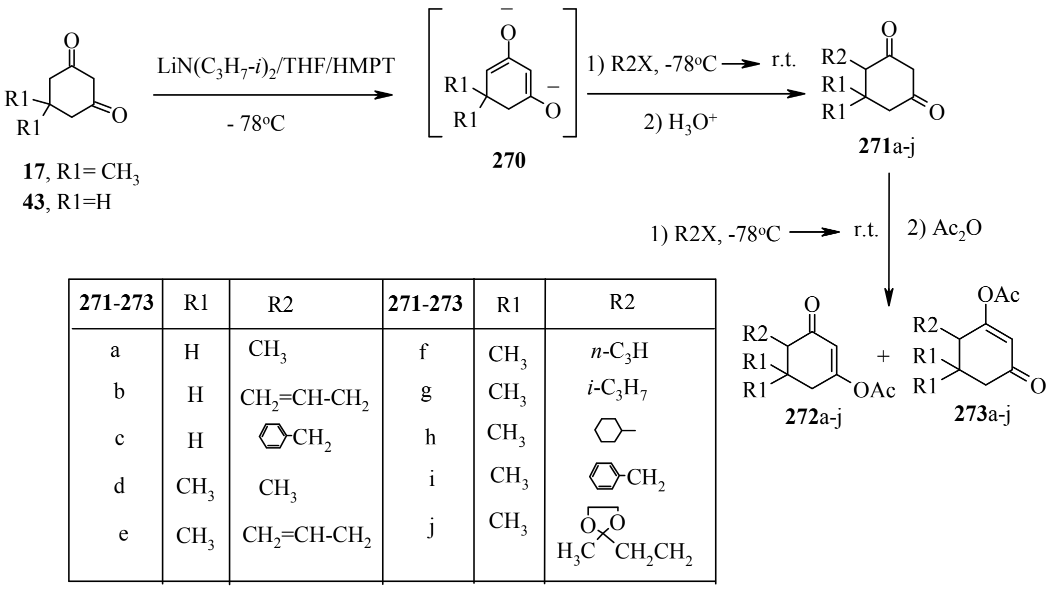
Reaction with alkylating agents

Alkylation of 1,3-cyclohexanedione 43 with bromomethylpropenoate 263 was found to behave through addition behavior and gave the product 264. On heating 264 with trifluoroacetic anhydride 265, the product 266 was achieved. Treating of 264 with thiophenol 267 resulted in the formation of 269 *via* 268 (Scheme 80).[134]



Scheme 80. Synthesis of benzopyran derivatives **266** and **269**

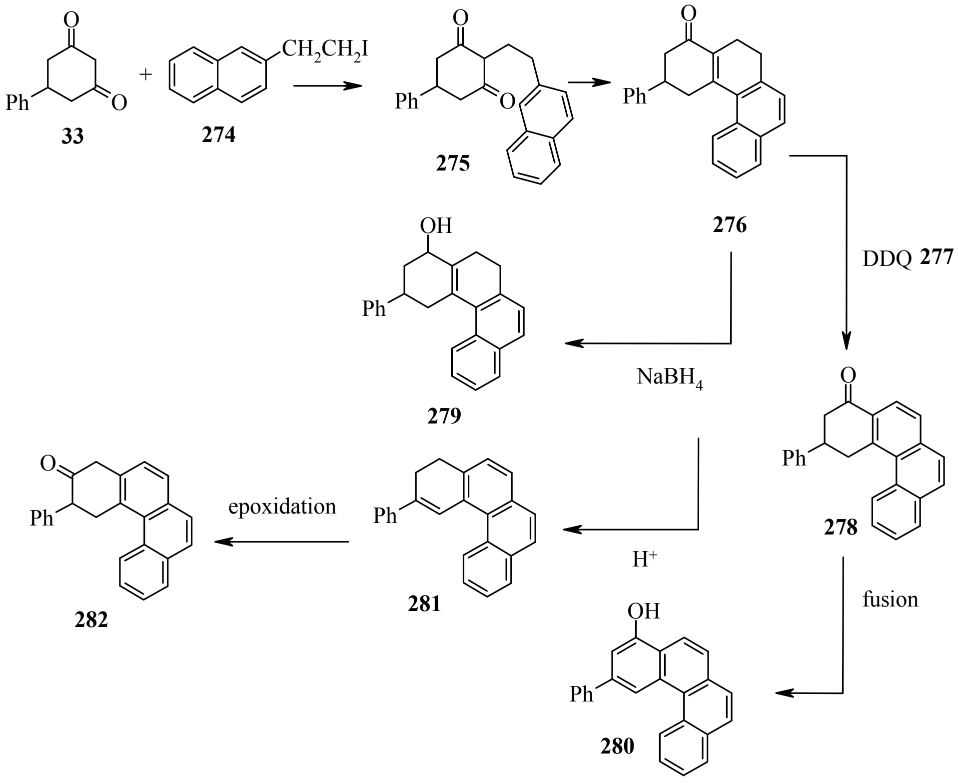
The addition of 1,3-cyclohexanedione 43 or its 5,5-dimethyl derivative 17 with 2 equivalents of lithium diisopropylamide at –78 °C in the presence of three equivalents of hexamethylphosphoric triamide was achieved and the intermediate 270 was obtained . Reaction of various alkylhalides under the above conditions followed by warming to room temperature and work–up afforded the required alkylated derivatives 271-273 respectively (Scheme 81).[135]



271-273	R1	R2	271-273	R1	R2
a	H	CH$_3$	f	CH$_3$	n-C$_3$H
b	H	CH$_2$=CH-CH$_2$	g	CH$_3$	i-C$_3$H$_7$
c	H	⌬-CH$_2$	h	CH$_3$	⬡-
d	CH$_3$	CH$_3$	i	CH$_3$	⌬-CH$_2$
e	CH$_3$	CH$_2$=CH-CH$_2$	j	CH$_3$	O O H$_3$C CH$_2$CH$_2$

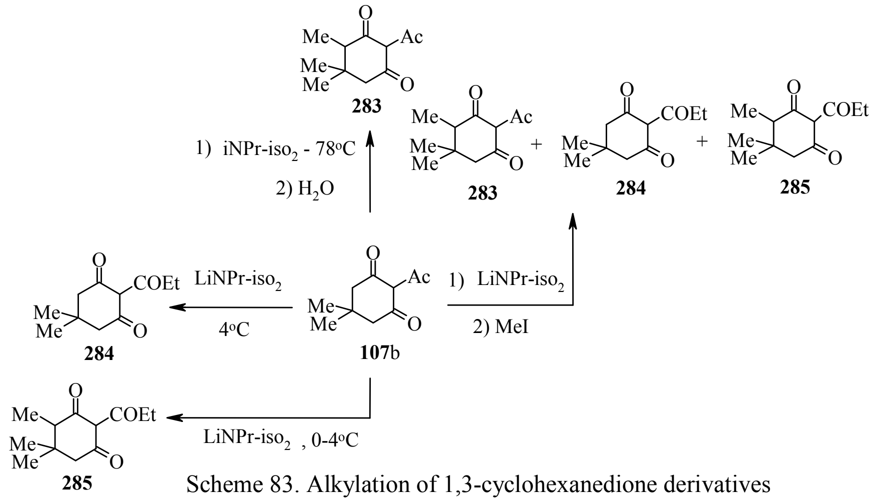
Scheme 81. Synthesis of different alkylated adducts by reaction of 1,3-cyclohexanedione or dimedone with alkylating agents

Also, alkylation of 5-phenyl-1,3-cyclohexanedione 33 with 2-(2-naphthyl)-5-ethyliodide 274 was reported to give 2-(2-naphthalen-2-ylethyl)-5-phenylcyclohexane-1,3-dione 275. Cyclization of 275 to the phenathrene derivative 276 was easily carried out. Dehydrogenation of 276 using DDQ 277 resulted in the formation of phenathrene derivative 278. Reduction of 276 using NaBH$_4$ gave the corresponding phenathrenol 279. Similarly, heating of 278 under fusion condition gave 280. Consequence reduction of 278 yielded the phenanthrene derivative 281. Epoxidation and acidification of 281 gave the semisteroidal structure 282 (Scheme 82).[136]



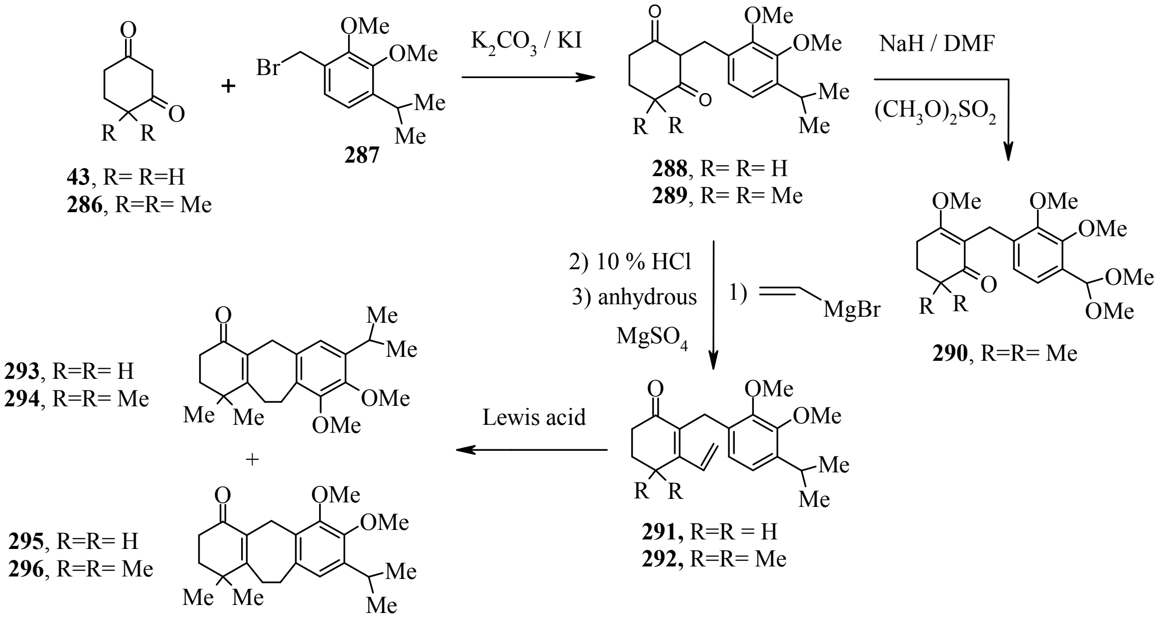
Scheme 82. Synthesis of phenathrene derivatives

Treatment of 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione 107b with MeI in the presence of LiNPr-iso$_2$ afforded the adducts 283-285, but when 107b was treated with LiNPr-iso$_2$ at 4 ºC it gave the adduct 284 only. Deprotonation of 117b with LiNPr-iso$_2$ at –78 ºC for 1h followed by H_2O afforded 283 only. The adduct 285 was obtained also as a single product by treating 107b with LiNPr – iso$_2$ at 0-4ºC (Scheme 83).[137]



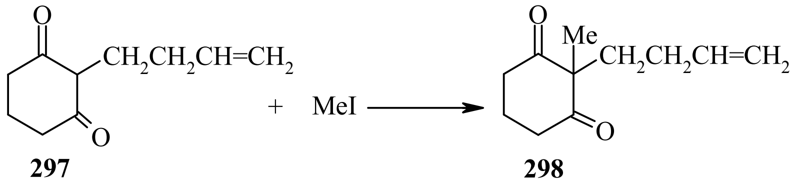
Scheme 83. Alkylation of 1,3-cyclohexanedione derivatives

Reaction of 1,3-cyclohexanedione 43 or its derivative 4,4-dimethylcyclohexane-1,3-dione 286 with 1-bromomethyl-4-isopropyl-2,3-dimethoxybenzene 287 gave 2-(4-isopropyl-2,3-dimethoxybenzyl)-cycloh-exane-1,3-dione 288 and 2-(4-isopropyl-2,3-dimethoxybenzyl)-4,4-dimethylcyclohexane-1,3-dione 289. Reaction of 289 with dimethylsulfate in DMF in the presence of sodium hydride gave 6,6-dimethyl-2-(2,3-dimethoxy-4-isoprpylphenylmethyl)-3-methoxycyclohexenone 290. Treatment of 288 or 289 with vinylmagnesium bromide and $CeCl_3$ in ether, the adducts 2-(4-isopropyl-2,3-dimethoxybenzyl)-3-vinyl-cyclohex-2-enone 291 and 2-(4-isopropyl-2,3-dimethoxybenzyl)-4,4-dimethyl-3-vinyl-cyclohex-2-enone 292. By the effect of Lewis acid the adduct 291 under went cyclization and gave the adducts 7-isopropyl-8,9-dimethoxy-1,2,3,5,10,11-hexahydrodibenzo[*a*,*d*]cyclohepten-4-one 293 and 8-isopropyl-6,7-dimetho-xy-1,2,3,5,10,11-hexahydrodibenzo[*a*,*d*]cyclohepten-4-one 295 also under the same conditions the adduct 292 converted to 7-isopropyl-8,9-dimethoxy-1,1-dimethyl-1,2,3,5,10,11-hexahydrodibenzo [*a*,*d*] cyclo-hepten-4-one 294 and 8-isopropyl-6,7-dimethoxy-1,1-dimethyl-1,2,3,5,10,11-hexahydrdibenzo[*a*,*d*] cyc-lohepten-4-one 296 (Scheme 84).[138]



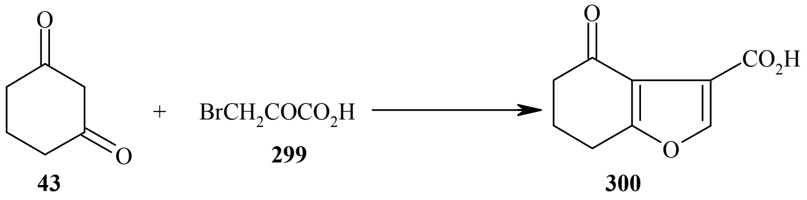
Scheme 84. Alkylation of 1,3-cyclohexanedione or its derivatives

Alkylation of 2-(3'-butenyl)-1,3-cyclohexanedione 297 in K_2CO_3 and methyl iodide was reported to give 2-(3'-butenyl)-2-methyl-1,3-cyclohexanedione 298 (Scheme 85).[139]



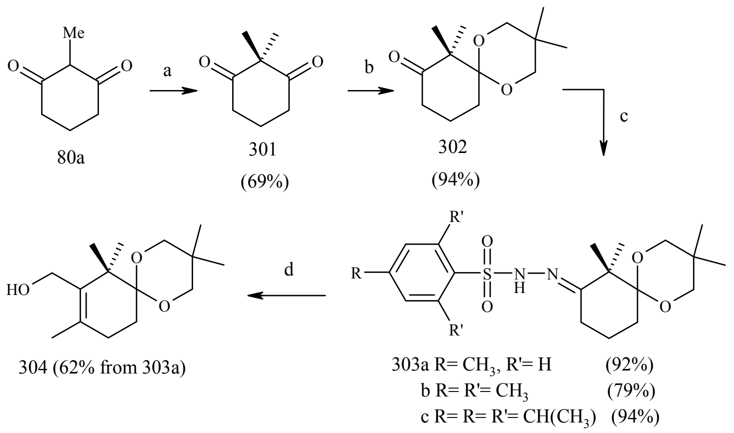
Scheme 85. Synthesis of 2-(3'-butenyl)-2-methyl-1,3-cyclohexanedione

Furthermore, when 43 underwent cyclocondensation reaction with 3-bromo pyruvic acid esters 299 yielded cyclohexenonefuran derivative 300 (Scheme 86).[140-144]



Scheme 86. Reaction of 1,3-cyclohexanedione with bromopyrovic acid

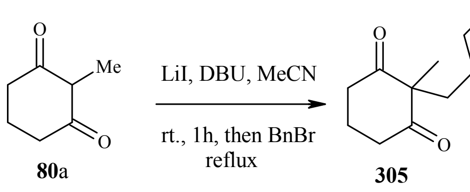
Methylation of 2-methyl-1,3-cyclohexanedione 80a was carried out with K_2CO_3/ CH_3I in acetone to give 2,2-dimethyl-1,3-cyclohexanedione 301. Treatment of 301 with $Me_2C(CH_2OH)_2$, *p*-TsOHXH$_2$O in refluxing CH_2Cl_2 furnished the ketone 302 which on treating with hydrazide gave 303a-c. On treatment of 303a-c with *n*-butyl lithium, CH_3I, *p*-formaldehyde in THF gave the adduct 304 (Scheme 87).[145,146]



(a) K$_2$CO$_3$/CH$_3$I, acetone, reflux, 8 h; (b) CH$_2$Cl$_2$, MeC(CH$_2$OH), p-TsOHxH$_2$O, CH$_2$Cl$_2$, reflux 7 h
(c) EtOH, (THF in 303b),hydrazine, + 0°C, 16 min. then rt. 6 h; (d) THF, - 50°C, *n*-BuLi, 30 min., CH$_3$I, 30 min., *n*-BuLi, from - 50°C to rt., 25 mn., paraformaldehyde, 30 min.

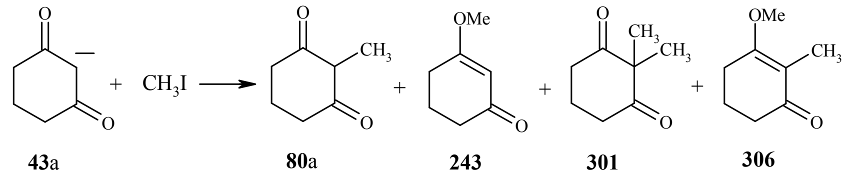
Scheme 87. Alkylation of 2-methyi-1,3-cyclohexanedione and fornation of spiro adducts

C-alkylation of 2-methyl-1,3-cyclohexanedione 80a with benzyl bromide furnished 2-benzyl-2-methylcyclohexane-1,3-dione 305 (Scheme 88).[147]



Scheme 88. Synthesis of 2-benzyl-2-methyl-1,3-cyclohexanedione

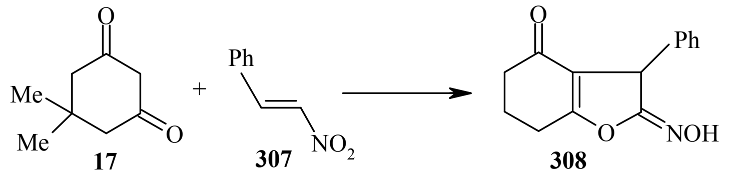
Anion of 1,3-cyclohexanedione 43a was methylated with iodomethane in aprotic solvents and afforded the adducts 80a, 243, 301 and 306 (Scheme 89).[148]



Scheme 89. Alkylation of 1,3-cyclohexanedione anion and formation of different alkylated adducts

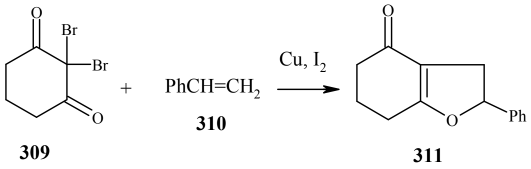
Reaction with unsaturated compounds

Cycloaddition reaction of 17 to 1-phenyl-2-nitroethylene 307 and subsequent cyclization gave oxabicycl- ononenones 308 (Scheme 90).[149]



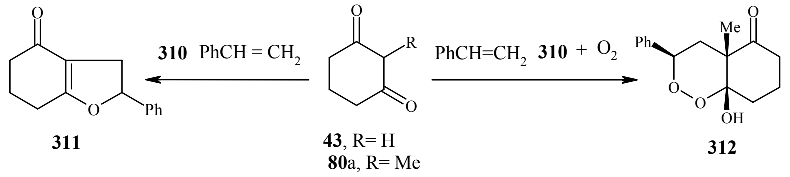
Scheme 90. Formation of benzofuran derivative

Reaction of 2,2-dibromo-1,3-cyclohexanediones 309 with Cu powder and olefins such as 310 yielded furan derivatives 311 (Scheme 91).[150]



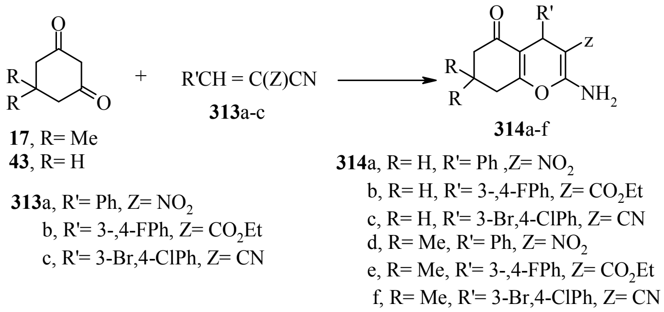
Scheme 91. Reaction of 1,3-cyclohexanedione derivative with ethylene derivative

On the other hand, 1,3-cyclohexanediones 43 when reacted with phenylethylene 310 could isolate benzofuran derivative 311, while 2-methyl-1,3-cyclohexanedione 80a when reacted with phenylethylene 310 under oxygen could separate a cyclic peroxide 312 (Scheme 92).[1451,152]



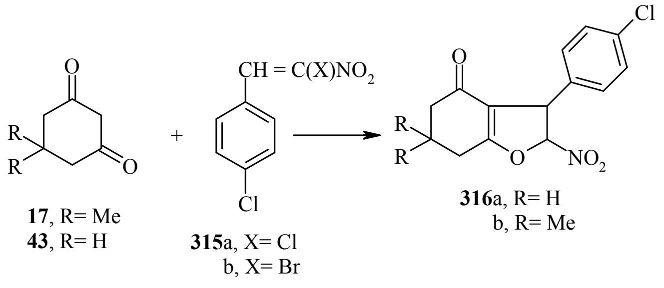
Scheme 92. Synthesis of different adducts from the reaction of 1,3-cyclohexanedione or its derivaives with ethylene derivatives

Cycloaddition reaction of 1,3-cyclohexanedione 43 or its derivative 17 was also underwent reaction with 1-substituted-2-arylacrylonitriles 313a-d to give chromene derivatives 314a-f (Scheme 93).[153,154]



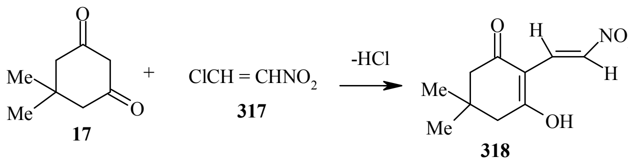
Scheme 93. Synthesis of coumarin derivatives from 1,3-cyclohexanedione or dimedone with ethylene derivatives

Moreover reaction of 1,3-cyclohexanedione 43 or its derivative 17 with 315a,b is reported to path through Michael addition and cyclization to give the adduct 316a,b (Scheme 94).[155,156]



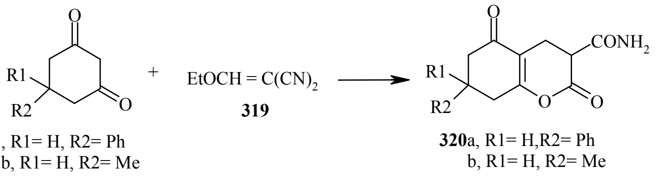
Scheme 94. Reaction of 1,3-cyclohexanedione or dimedone with unsaturated compounds and formation of benzopyran derivatives

The addition of 17 to 1-chloro-2-nitroethene 317 gave 2-(2-nitroethylene)-3- hydroxy-5,5-dimethylcy-clohexe-2-enone 318 (Scheme 95).[157]



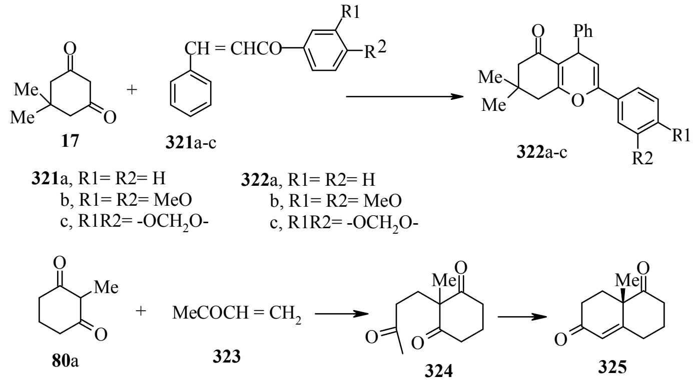
Scheme 95. Synthesis of cyclohexenone derivatives

1,3-Cyclohexanediones 33 or 83b when reacted with 1,1-dicyano-2-ethoxyethylene 319 the benzopyran 320a,b was afforded (Scheme 96).[158]



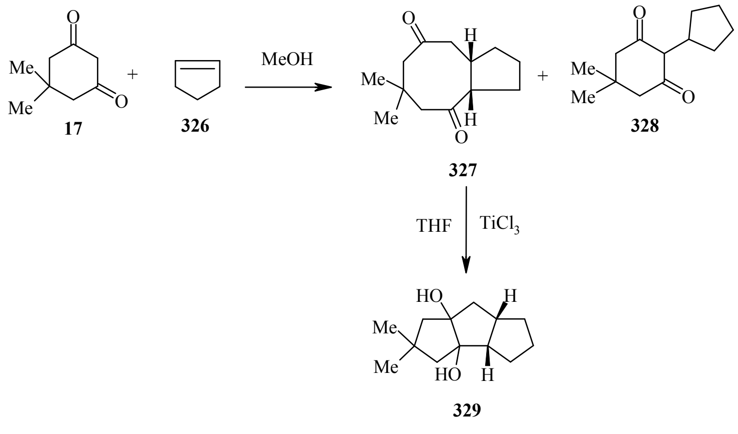
Scheme 96. Synthesis of coumarin deriative *via* reaction of 1,3-cyclohexanedione derivatives and unsaturated compounds

Condensation of 17 with 1-benzoyl-2-phenylethene 321a-d was found fruitful and gave 2,4-diaryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyrans 322a-d.[159] 2-Methyl-1,3-cyclohexanedione 80a reacted with 1-acetyl-ethene 323 and afforded the trione 324, which underwent asymmetric ring closure in the presence of L-proline in Me_2SO to give 8*a*-methyl-3,4,8,8*a*-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione 325 (Scheme 97).[160]



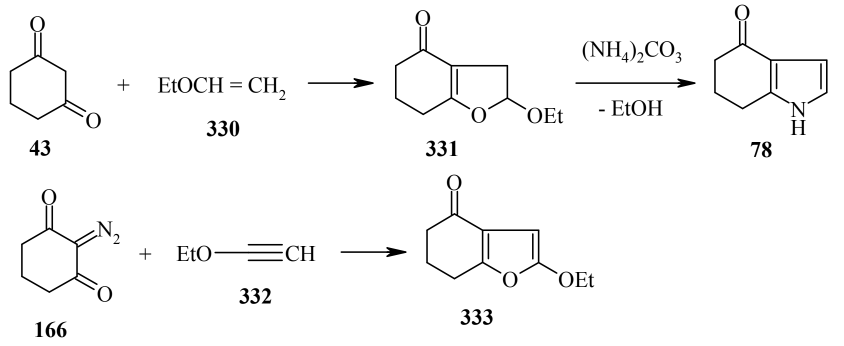
Scheme 97. Synthesis of coumarin and naphthalene derivatives

Photochemical addition of 17 with cyclopentene 326 in methanol supported the formation of cyclooctanedione 327 and 328. Treatment of 327 with $TiCl_3$ and potassium in THF gave 2,2-dimethyl-octahydrocyclopenta[*a*]pentalene-3*a*,7*a*-diol 329 (Scheme 98).[161]



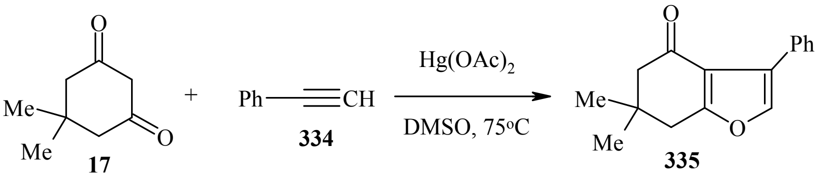
Scheme 98. Synthesis of cyclooctanedione, 1,3-cyclohexanedione derivative and 2,2-dimethyloctahydrocyclopenta[*a*]pentalene-3a,7a-diol

Electrooxidative coupling of 43 with ethoxyethylene 330 in EtOH (Pt electrodes) gave the fused system cyclohexanonhydrofuran derivative 331, while on treating 331 with $(NH_4)_2CO_3$ and MeOH in a sealed tube at 150 ºC for 14 h, eliminated the ethoxy moiety and furnished formation of cyclohexenone pyrrole 76.[162] Diazocyclohexanediones 166 undergo dipolar cycloadditions with substituted acetylene 332 to provide 2-substituted tetrahydrobenzofuran-4-ones 333 (Scheme 99).[163]



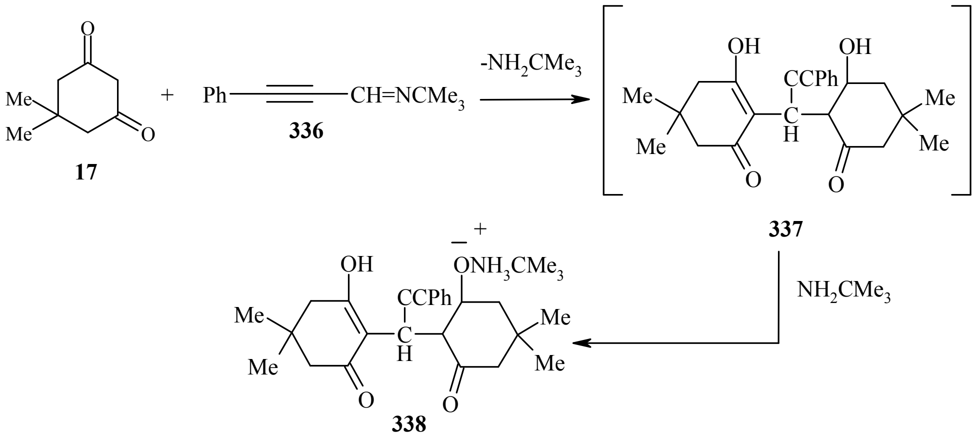
Scheme 99. Synthesis indole derivative and benzofuran derivative

Consequently, cyclization of 17 with phenylacetylene 334 in the presence of $Hg(OAc)_2$ in DMSO at 75 ºC afforded tetrahydrobenzofuran 335 (Scheme 100).[164]



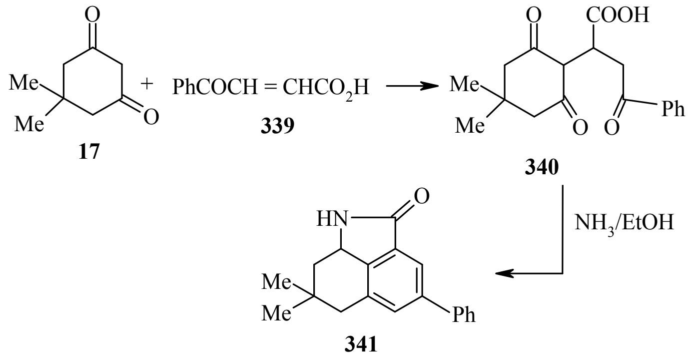
Scheme 100. Reaction of dimedone withacetylene derivatves

While the reaction of 17 with substituted phenylacetylene 336 gave ammonium enol salt 338 *via* 3-hydroxy-2-[1-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohexyl)-3-phenylprop-2-ynyl]-5,5-dimethylcyclohex-2-enone 337 (Scheme 101).[165]



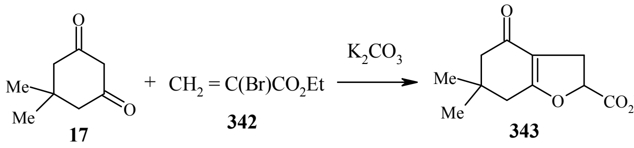
Scheme 101. Reaction of dimedone with acetylene derivatives

Moreover, treatment of 5,5-dimethyl-1,3-cyclohexanedione 17 with benzoylpropenoic acid 339 gave the adduct 340. The reaction of 340 with NH_3/EtOH resulted in cyclization process and the product pyrrolo[4,3,2-*d*,*e*]quinoline derivative 341 was reported (Scheme 102).[166]



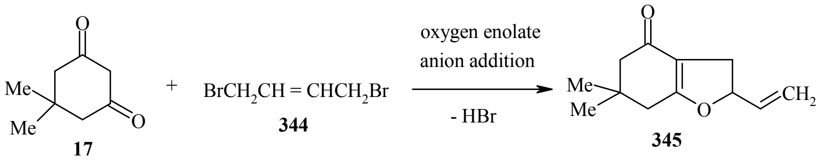
Scheme 102. Reaction of dimedone with ethylene derivative

On treating compound 17 with 2-bromoethylpropenoate 342 in the presence of K_2CO_3 the corresponding dihydrobenzofuran 343 was obtained (Scheme 103).[167,168]



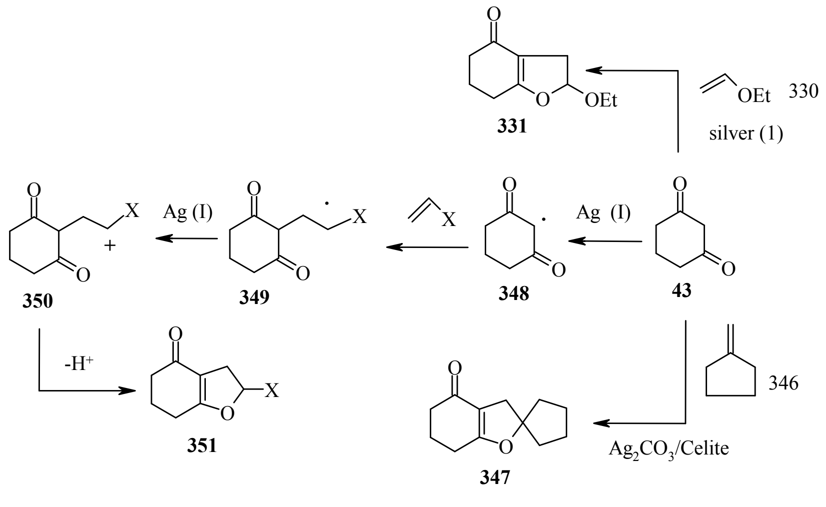
Scheme 103. Synthesis of benzofuran derivative from dimedone and ethylene derivative

The reaction of 17 with (*E*)-1,4-dibromo-2-butene 344 in the presence of sodium hydride produced 6,6-dimethyl-2-vinyl-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one 345 in an anion addition/elimination reaction (Scheme 104).[169]



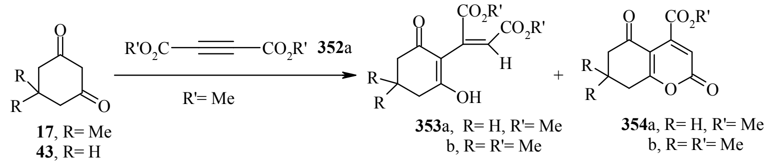
Scheme 104. Synthesis of 6,6-dimethyl-2-vinyl-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one

Treatment of 1,3-cyclohexanedione 43 with ethyl vinyl ether 330 in the presence of silver (I) oxide and silver (I) carbonate provided dihydrobenzofuran 331. The dione 43 reacted with methylenecyclopentane 346 and produced 347. The compound 43 was oxidized by silver (I) to generate the α-oxoalkyl radical 348. The radical 348 when was treated with olefin it furnished the enolate 349, which then underwent oxidation by silver (I) to a carbonium ion 350 which cyclized to form dihyrofuran 351 (Scheme 105).[170]



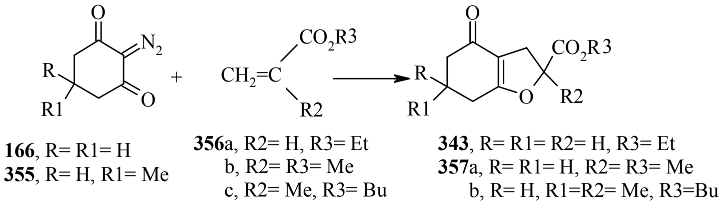
Scheme 105. Synthesis of benzofuran derivatives

Michael reaction of 43 or 17 with dimethyl acetylenedicarboxylate 352a in the presence of sodium methoxide or KF-Al_2O_3 gave a mixtures of adducts 353 and 354 (Scheme 106).[171]



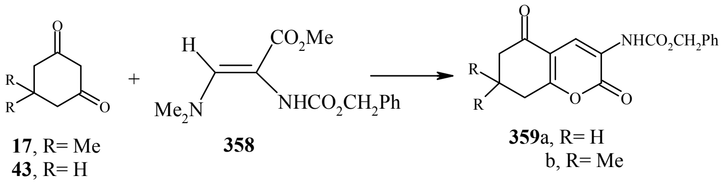
Scheme 106. Synthesis of cyclohexene derivatives and coumarin derivatives *via* reaction of 1,3-cyclohexanedione or dimedone with acetylene derivatives

The diazo-1,3-cyclohexanedione 166 or its derivative 355 when reacted with α,β-unsaturated esters 356a-c by rhodium catalyzed cycloaddition reaction gave 343 and 357a,b (Scheme 107).[172]



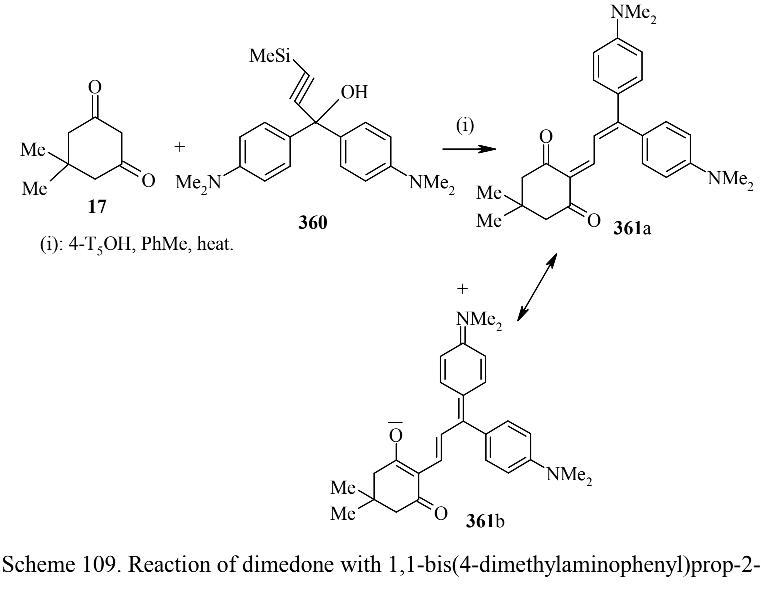
Scheme 107. Synthesis of benzofuran derivatives

Furthermore, 1,3-cyclohexanedione 43 or its 5,5-dimethyl derivative 17 when reacted with methyl-2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate 358 could provide the products 3-(benzyloxyc-arbonyl)amino-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one 359a and 3-(benzyl-oxycarbonyl) amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one 359b (Scheme 108).[173]



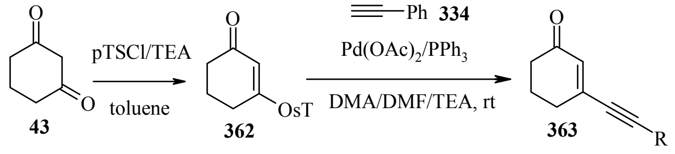
Scheme 108. Synthesis of benzopyran derivatives

The addition of a catalytic quantity of 4-toluenesulfonic acid monohydrate to a stirred solution of a 1,1-bis(4-dimethylaminophenyl)prop-2-yn-1-ol 360 and 5,5- dimethyl-1,3-cyclohexanedione 17 in anhydrous toluene resulted in the immediate development of an intense maroon colour (Scheme 109).[174-176]



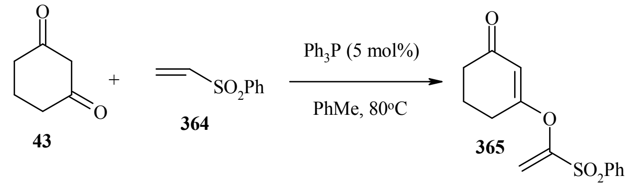
Scheme 109. Reaction of dimedone with 1,1-bis(4-dimethylaminophenyl)prop-2-yn-1-ol

By using Heck reaction conditions the tosylate 362 was prepared by reacting 1,3-cyclohexanedione 43 with *p*-toluenesulfonly chloride in the presence of triethylamine The solvent was replaced with DMA/ DMF/ TEA and the intermediate 362 was coupled with phenyl acetylene 334 to form 3-(phenylethynyl)-2-cyclohexen-1-one 363 in the presence of palladium acetate and triphenyl phosphine (Scheme 110).[177]



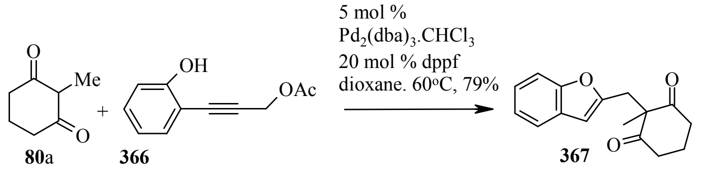
Scheme 110. Synthesis of cyclohexenone derivative

Heating a mixture of 1,3-cyclohexanedione 43 and phenylsulfonyl-1,2-propadiene 364 in toluene in the presence of a catalytic amount of Ph_3P gave 3-(1-benzenesulfonyl-vinyloxy)-cyclohex-2-enone 365 (Scheme 111).[178, 179]



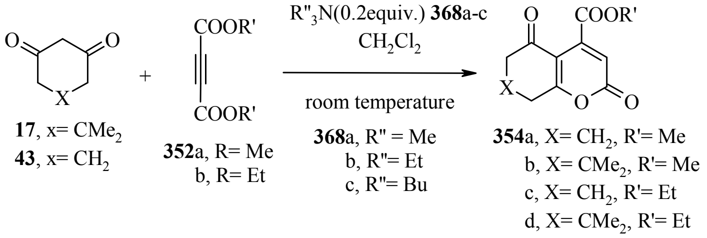
Scheme 111. Synthesis of cyclohexanone derivatives

The reaction of methyl-1,3-cycohexanedione 80a with 1-(2-hydroxyphenyl)-3-methoxycarbonyloxy-1-propyne 366 yielded the substituted benzofurans 367 (Scheme 112).[180]



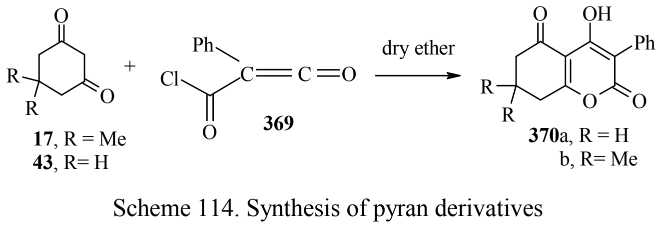
Scheme 112. Synthesis of benzofuran derivatives

The reaction of dialkyl acetylenedicarboxylates 352a,b with six-membered cyclic 1,3-diketones such as 1,3-cyclohexanedione 43 or 5,5-dimethyl-1,3-cyclohexanedione 17 in the presence of a catalytic amount of trimethylamine, triethylamine or tributylamine 368a-c in CH_2Cl_2 led to formation of alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates 354a-d in good yields (Scheme 113).[181]



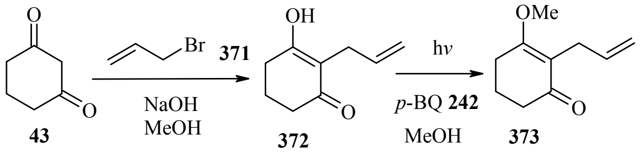
Scheme 113. Synthesis of coumarin derivatives

1,3-Cyclohexanediones 43 or 17 was treated with (chlorocarbonyl)phenyl ketene 369 in dry ether to give 2-pyran derivatives 370a,b (Scheme 114).[182]



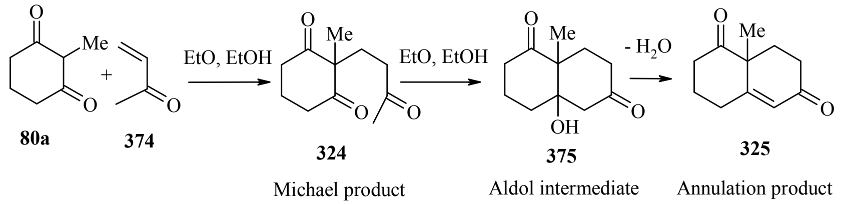
Scheme 114. Synthesis of pyran derivatives

Allyl derivatives 372 and 373 were synthesized from allyl bromide 371 and 1,3-cyclohexanedione 43 using sodium hydroxide in methanol. In this case, the final product isolated was not 1,3-diketone but the enolic tautomer 372 of the diketone. Irradiation of 372 and *p*-benzoquinone 242 gave the same type of methoxy enone 373 (Scheme 115).[125]



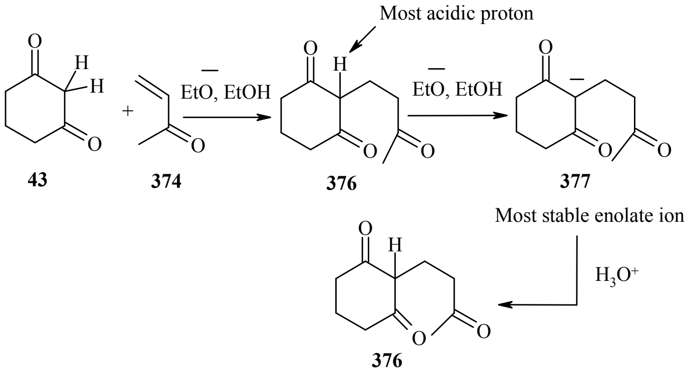
Scheme 115. Synthesis of cyclohexenone derivatives

The Robinson annulation reaction took place when dione 80a was treated with unsaturated ketone 374 to yield 2-methyl-2-(3-oxo-butyl)-cyclohexane-1,3-dione 324, 4*a*-hydroxy-8*a*-methyl-hexahydronaphtha-lene-1,6-dione 375 and 8*a*-methyl-3,4,8,8*a*-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione 325 respectively (Scheme 116).[183]



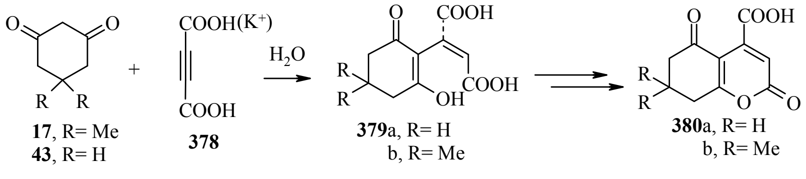
Scheme 116. Synthesis of naphthalene derivatives

On the other hand the reaction of the dione 43 with but-3-en-2-one 374 and the adducts 376 and 377 were achieved because the only difference between 2-methyl-1,3-cyclohexanedione 80a and 1,3-cyclohexanedione 43 occurs at the carbon between the two carbonyl groups. 2-Methyl-1,3-cyclohexanedione 80a has a methyl group where 1,3-cyclohexanedione 43 has two hydrogen atoms. The lack of a methyl group in 1,3-cyclohexanedione 43 allows the formation of a fourth possible enolate ion 377. This fourth enolate ion 377 is much more stable than the other three enolate ions, so it predominates (Scheme 117).[183]



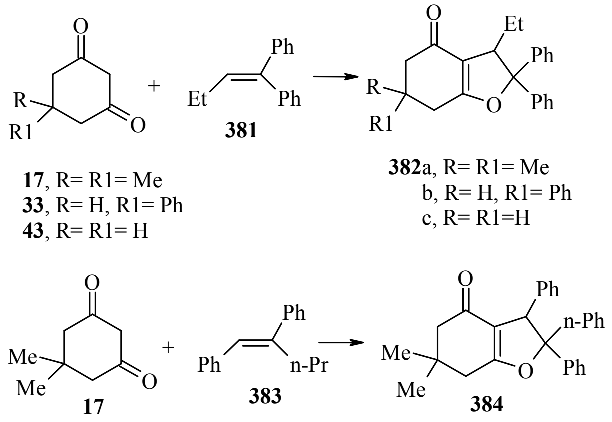
Scheme 117. Synthesis of 2-(3-oxo-butyl)-cycloheane-1,3-dione

The reaction of 1,3-diketones 43 or 17 with acetylenedicarboxylic acid salt 378 in water led to the formation of the acid 379a,b which cyclized to 380a,b (Scheme 118).[184]



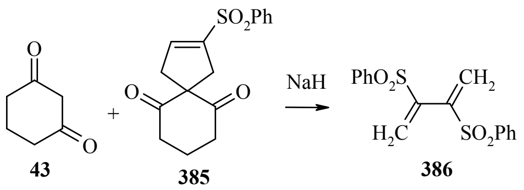
Scheme 118. Reaction of 1,3-cyclohexanedione or dimedone with acetylenedicarboxylic acid salt

Dimedone 17; 1,3-cyclohexanedione 43 and 5-phenyl-1,3-cyclohexanedione 33 when were treated with 1,1-diphenyl-1-butene 381 afforded tetrahydrobenzofurans 382a-c. Treatment of 17 with 1,2-diphenyl-1-pentene 383 resulted in the formation of tetrahydrobenzofuran 384 in lower yields (Scheme 119).[185]



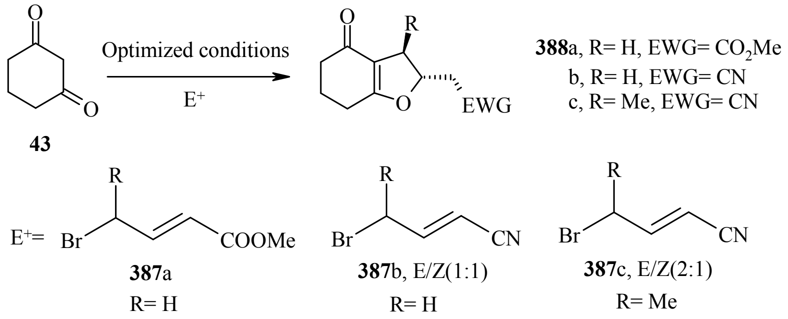
Scheme 119. Synthesis of benzofuran derivatives

Treatment of cyclohexane-1,3-dione 43 with dione 385 in the presence of NaH (THF) gave rise to spirocyclopentene 386 (Scheme 120).[186]



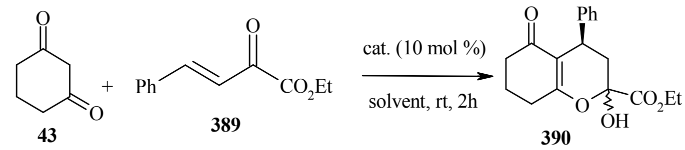
Scheme 120. Reaction of 1,3-cyclohexanedione with spiro adducts

C-alkylation of 1,3-cyclohexanedione 43 by 4-bromocrotonate 387a-c followed by oxa-Michael cyclization to furnish 388a-c (Scheme 121).[187]



Scheme 121. Reaction of 1,3-cyclohexanedione with unsaturated esters

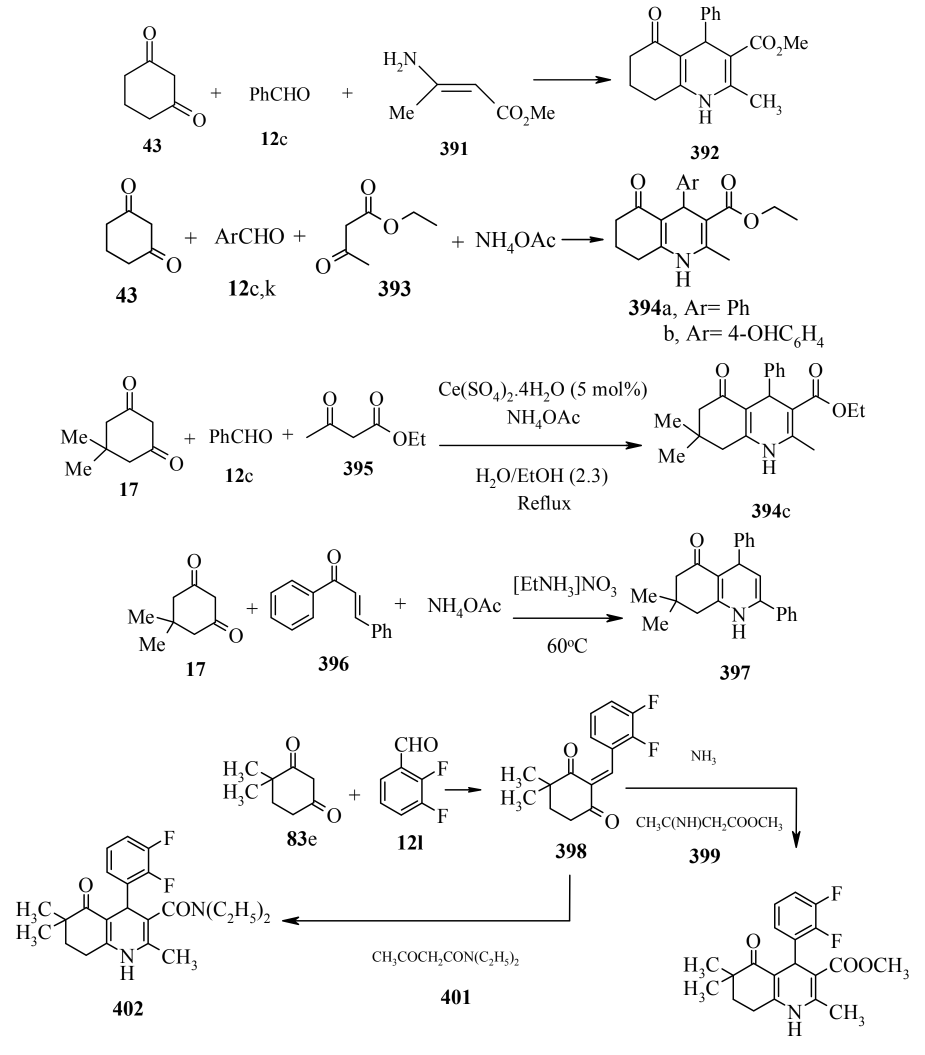
Reaction between 1,3-cyclohexanedione 43 and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate 389 in the presence of bifunctional catalysts at room temperature in protic solvents such as toluene; dichloromethane; acetonitrile or THF furnished benzopyran derivative 390 (Scheme 122).[188]



Scheme 122. Formation of benzopyran derivatives

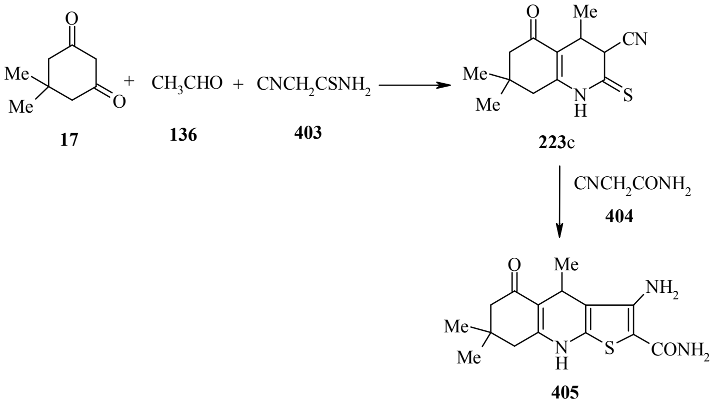
Multicomponent reactions

A series of hydroquioline derivatives were synthesized by mixing 1,3-cyclohexanedione or its derivatives with different compounds through a one-pot reaction mixture under different conditions (Scheme 123).[189-197]



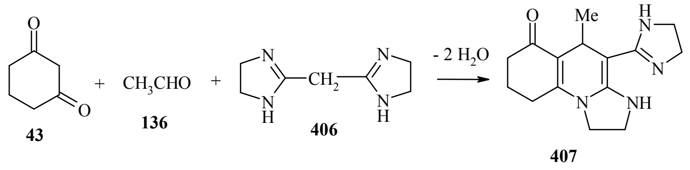
Scheme 123. Synthesis of hydroquinoline derivatives

Condensation of acetaldehyde 136 with 5,5-dimethyl-1,3-cyclohexanedione 17 and cyanothiacetamide 403 gave the adduct 223c. Treating of 223c with cyanoacetamide 404 is reported to give 3-amino -4,7,7- trimethyl-5-oxo-4,5,6,7,8,9-hexahydrothieno[2,3-*b*]quinoline-2-carboxylic acid amide 405 (Scheme 124).[198]



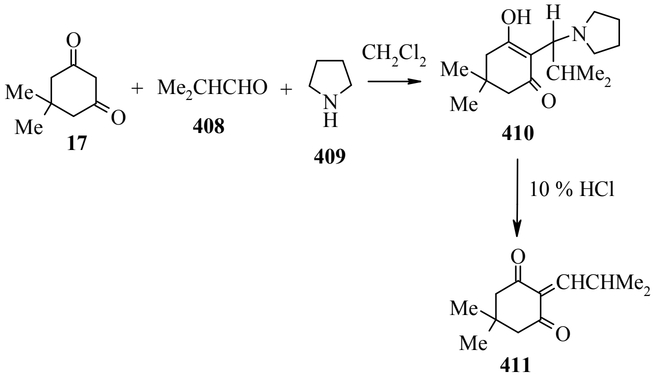
Scheme 124. Synthesis of thienoquinoline

Consequently, the condensation of 1,3-cyclohexanedione 43 with acetaldehyde 136 in the presence of 2,2'-methylenediimidazolin 406 gave the adduct 4-(4,5-dihydro-1*H*-imidazol-2-yl)-5-methyl-2,3,5,7,8,9-hexahydro-1*H*-imidazo[1,2-*a*]quinolin-6-one 407 (Scheme 125).[199]



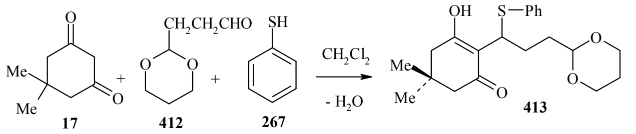
Scheme 125. Reaction of 1,3-cyclohexanedione with acetaldehyde and 2,2'-methylenediimidazolin

Similarly, condensation of dimedone 17 with isobutraldehyde 408 and pyrrole 409 in methylene chloride gave 3-hydroxy-5,5-dimethyl-2-(2-methyl-1-pyrrolidin-1-yl-propyl)-cyclohex-2-enone 410. Hydrolysis of 410 with 10 % hydrochloric acid gave isopropylidine derivative 411 (Scheme 126).[200]



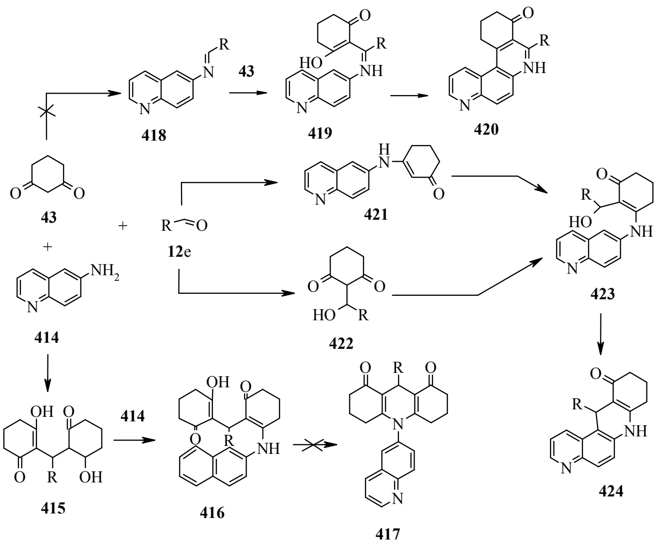
Scheme 126. Synthesis of isopropylidene derivative

Condensation of dimedone 17 with a mixture of 2-(2-formylethyl-1,3-dioxane) 412 and thiophenol 267 in dichloromethane in the presence of silica gel gave the adduct 2-(3-[1,3]dioxan-2-yl-1-phenylsulfanyl-propyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone 413 (Scheme 127).[201]



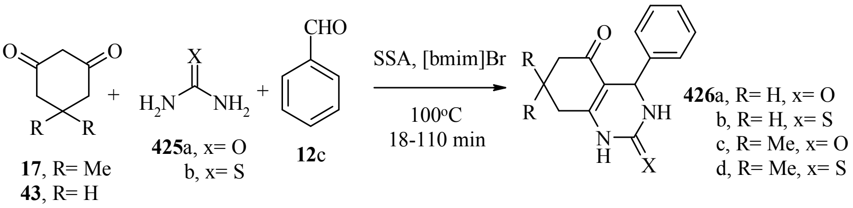
Scheme 127. Reaction of dimedone with 2-(2-formylethyl-1,3-dioxane) and thiophenol

A solution of 1,3-cyclohexanedione 43, quinolylamine 414 and appropriate aldehydes 12e in 1-butanol was heated under reflux for 3-4 hours to give 12- aryl (heteyl, cyclohexenyl)-8,9,10,12-tetrahydro-7*H*-benzo[*b*][4,7]phenanthrolin-11-ones 424 (Scheme 128).[202]



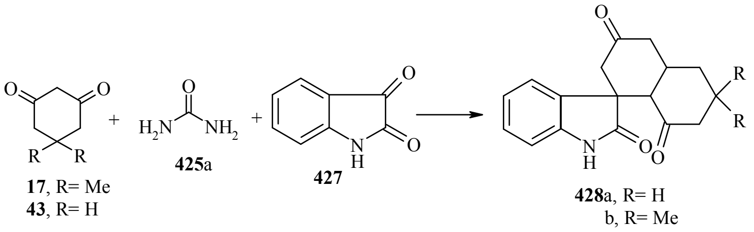
Scheme 128. Reaction of 1,3-cyclohexanedione with quinolylamine and aldehydes

The dihydropyrimidines (DHPMs) could be obtained from ureas, aldehydes and 1,3-dicarbonyls 43 or 17. It was reported that quinazolin-2,5-dione derivatives 426a-d may be achieved *via* the reaction between dimedone 17 or 1,3-cyclohexanedione 43, benzaldehyde 12c and urea or thiourea 425a,b using a combination of [bmim]Br and silica sulfuric acid (SSA) as a solid acid catalyst (Scheme 129).[203-205, 206]



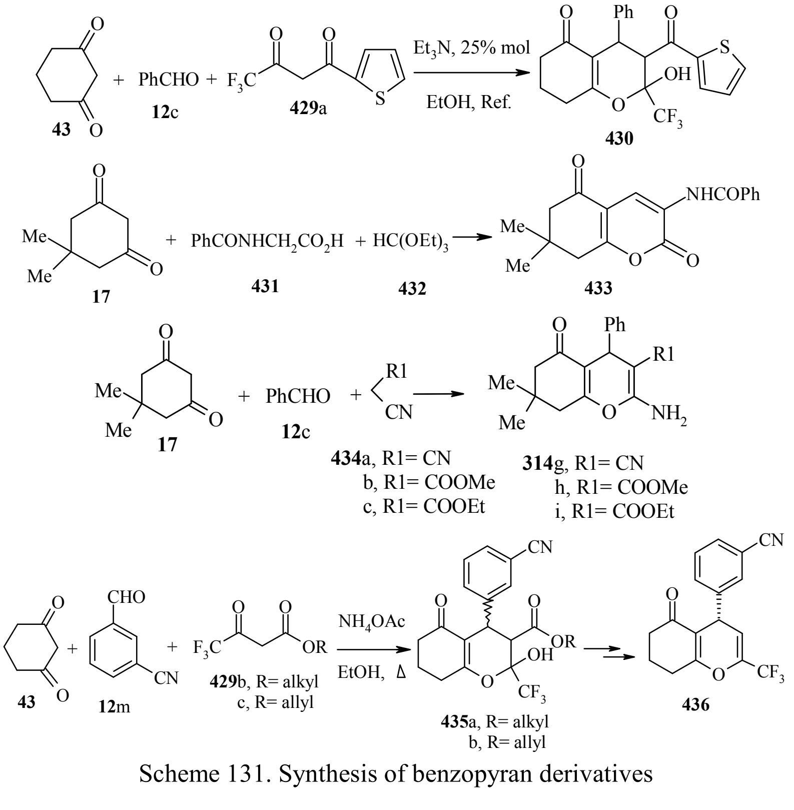
Scheme 129. Reaction of 1,3-cyclohexanedione or dimedone with aldehydes and urea or thiourea

Some new spiro[oxindolequinazoline/pyrimidine]ones 428a,b were synthesized *via* a novel three-component Biginelli-like reaction between isatin 427, cyclic or acyclic 1,3-dicarbonyl compounds, and urea 425a in a one-pot reaction (Scheme 130).[207]



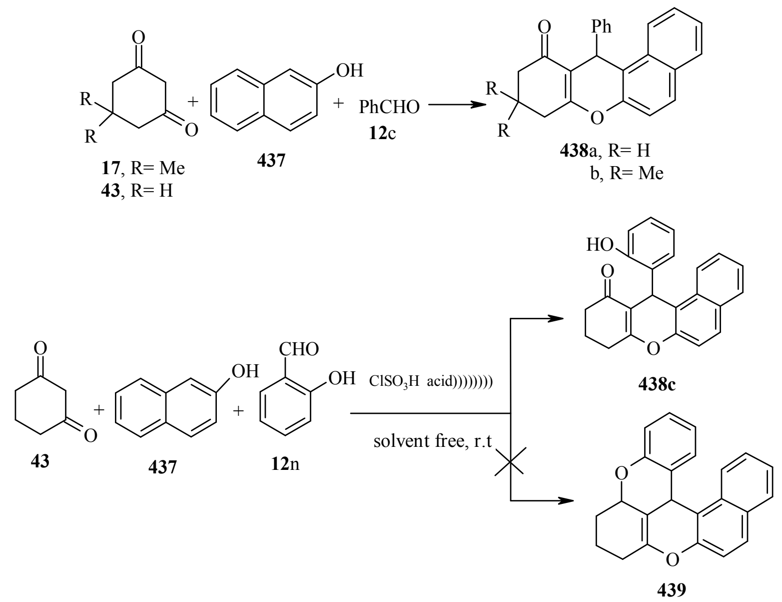
Scheme 130. Reaction of 1,3-cyclohexanedione or dimedone with isatin and urea

Several trials were achieved *via* a one-pot reaction mixture of 1,3-cyclohexanedione or its derivatives and different compounds using different catalysts (Scheme 131).[43,208-215, 216]



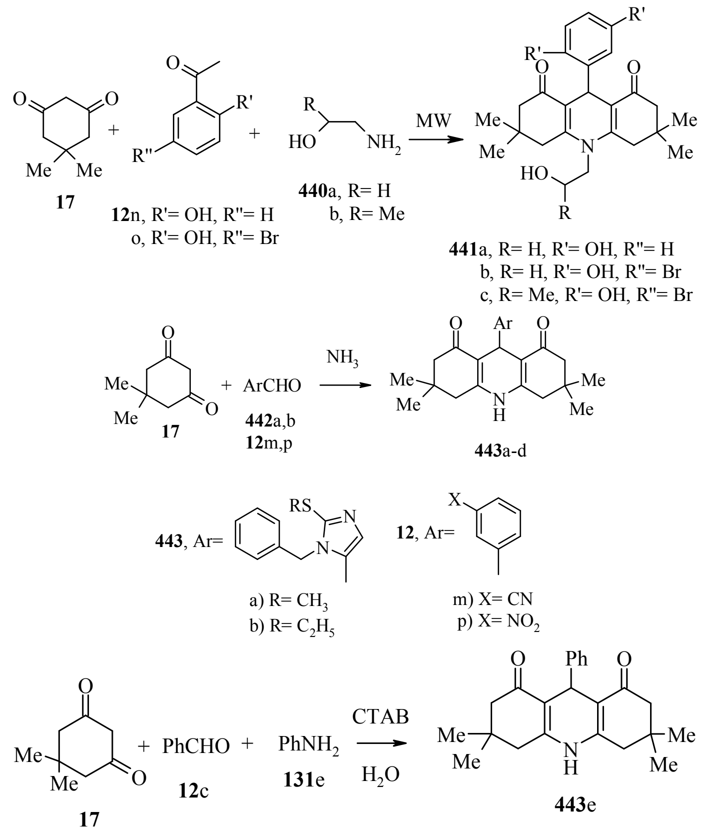
Scheme 131. Synthesis of benzopyran derivatives

Xanthene derivatives can be obtained by a one-pot reaction mixture of 1,3-cyclohexanedione or its derivatives, aromatic aldehydes and β-naphthol (Scheme 132).[217,218]

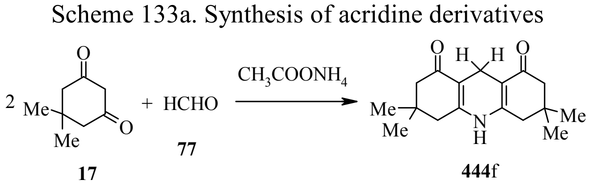


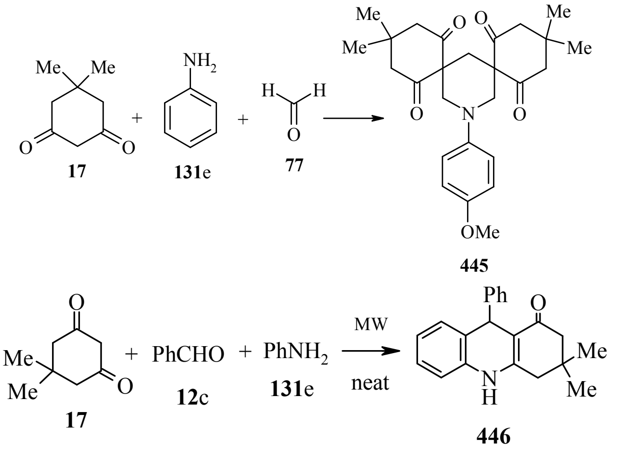
Scheme 132. Reaction of 1,3-cycclohexanedione with aldehydes and naphthols

Acridene derivatives by mixing 1,3-cyclohexanedione or its derivatives with different compounds (Scheme 133a,b). [191,219-223,227]



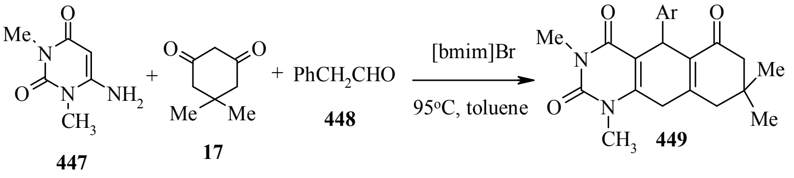
Scheme 133a. Synthesis of acridine derivatives





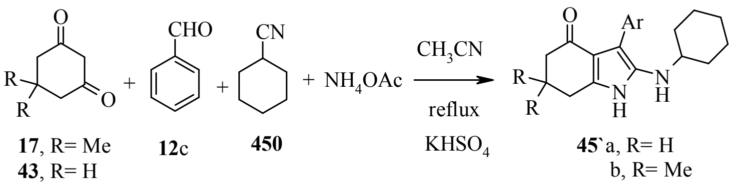
Scheme 133b. Synthesis of acridine derivatives

The reaction between dimedone 17, 6-aminopyrimidine-2,4-dione 447 and various aromatic aldehydes in [bmim]Br led to isolation of the corresponding pyrimido-[4,5-*b*]quinolines 449 easily (Scheme 134).[205,224]



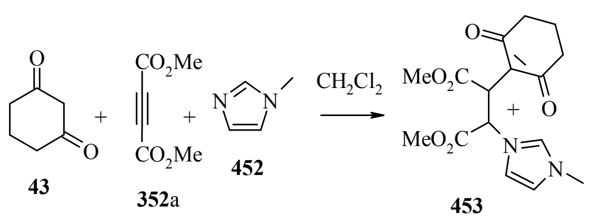
Scheme 134. Synthesis of pyrimidoquinoline derivatives

A simple and efficient synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones 451a,b was achieved *via* a one-pot multicomponent reaction of cyclohexyl isocyanide 450, aldehyde 12c, 1,3-cyclohexanediones 43 or 17 and ammonium acetate in the presence of a catalytic amount of $KHSO_4$ in acetonitrile (Scheme 135).[225]



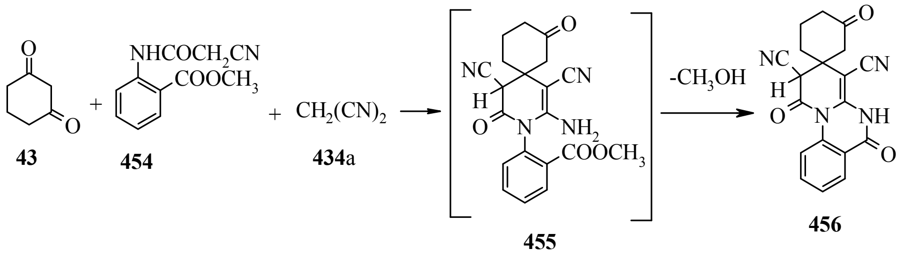
Scheme 135. Formation of indole derivatives *via* reaction of 1,3-cyclohexanedione or its derivatives, aromatic aldehydes and cyanocyclohexane

The three component reaction of *N*-methylimidazole 452, dimethylacetylenedicarboxylate 352a with cyclic 1,3-cyclohexanedione 43 in methylene dichloride proceeded smoothly at room temperature to give the expected 1,4-zwitterionic salts 453 (Scheme 136).[226]



Scheme 136. Formation of 1,4-zwitterionic salt

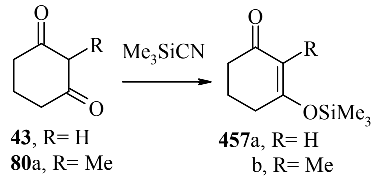
The one-pot cyclocondensation reaction of 1,3-cyclohexanedione 43, cyanoacetanilide 454, and malononitrile 434a in an equivalent ratio (1:1:1molar ratio) in refluxing ethanolic piperidine solution afforded pyrido[1,2-*a*]quinazoline derivative 456 (Scheme 137).[227,228]



Scheme 137. Synthesis of pyridoquinazoline derivatives

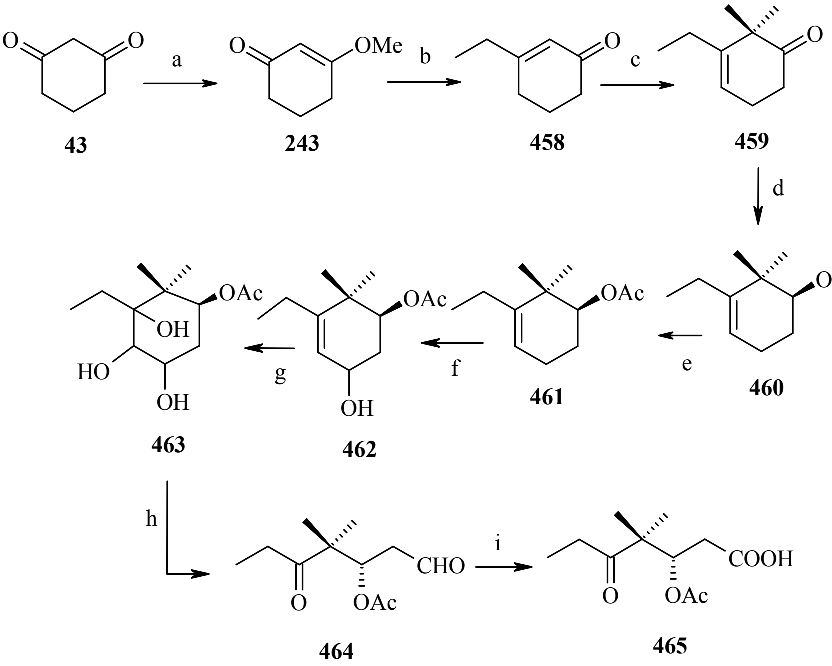
Miscellaneous

The reaction of 2-methyl-1,3-cyclohexanedione 43 or 80a with Me_3SiCN in $CDCl_3$ solution produced the corresponding trimethylsilyl enol ethers 457a,b (Scheme 138).[229]



Scheme 138. Synthesis of trimethylsilyl ether

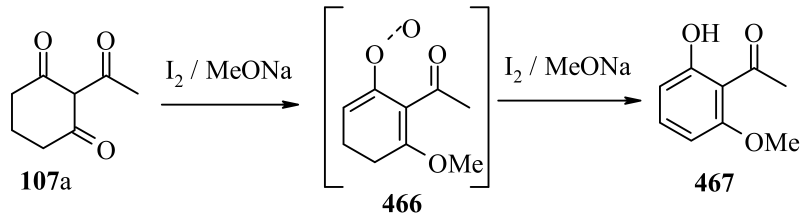
A mixture of cyclohexane-1,3-dione 43, *p*-toluene sulfonic acid, methanol and trimethylorthoformate was heated under reflux in benzene to give 3-methoxy-2-cyclohexenone 243 which was treated with ethylmagnesium bromide followed by acidification and gave the enone 458. Alkylation of the ethyl cyclohexenone 458 using potassium *tert*-butoxide and methyl iodide in THF yielded 459, which was reduced with oxazaborolidine (Corey'sreagent)[230] to furnish the chiral alcohol 460. On acetylation the alcohol 460 gave 461 which on treatment with SeO_2 furnished the allylic hydroxyl compound 462. Dihydroxylation of 462 with osmium tetroxide then afforded the triol 463. Aldehyde 464 was obtained by sodium periodate cleavage of triol 463, which was further oxidized to give the required fragment 465 (Scheme 139).[231]



(a) $CH(OCH_3)_3$, MeOH, PTSA (cat.) benzene, reflux, 80 min, 92%; (b) EtMgBr, THF, H+,0°C, 2 h, 86%; (c) (i) ^{t}BuOK, MeI, THF, -78°C, 5 h, 80%; (d) (*S*)-diphenylprolinol, BH_3, DMS, THF, 45°C, 17h, 81%; (e) Py., Ac_2O, CH_2Cl_2, rt, 11 h, 90%; (f) SeO_2, TBHP, CH_2Cl_2, rt, 5 h, 60%; (g) OsO_4, NMO, acetone/H_2O (8:2), rt, 16 h, 86%; (h) $NaIO_4$, SiO_2, CH_2Cl_2/H_2O (9:1), rt, 4 h, 77%; (i) NaH_2PO_4, ^{t}BuOH, rt, 4 h, 76%.

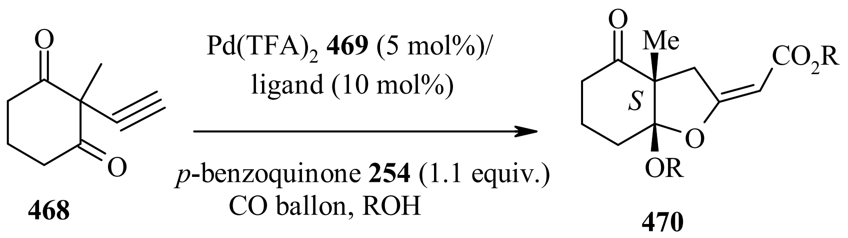
Scheme 139. 3-acetoxy-4,4-dimethyl-5-oxo-heptanoic acid

2-Acetylcyclohexane-1,3-dione 107a was oxidized in methanol in the presence of iodine under reflux conditions and gave 1-(2-hydroxy-6-methoxyphenyl)-ethanone 467 *via* 466 (Scheme 140).[232]



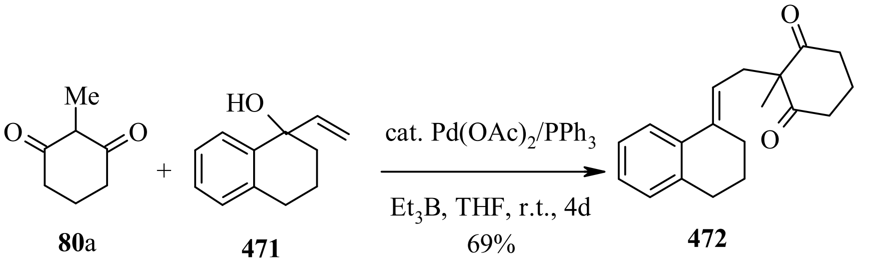
Scheme 140. Synthesis of 1-(2-hydroxy-6-methoxyphenyl)-ethanone

Cyclization of 2-methyl-2-propargylcyclohexane-1,3-dione 468 in the presence of $Pd(CF_3CO_2)_2$ 469, ligand and *p*-benzoquinone 242 in methanol at -30 °C under a carbon monoxide atmosphere (balloon) afforded *cis*- 470 as a single diastereomer (Scheme 141).[233]



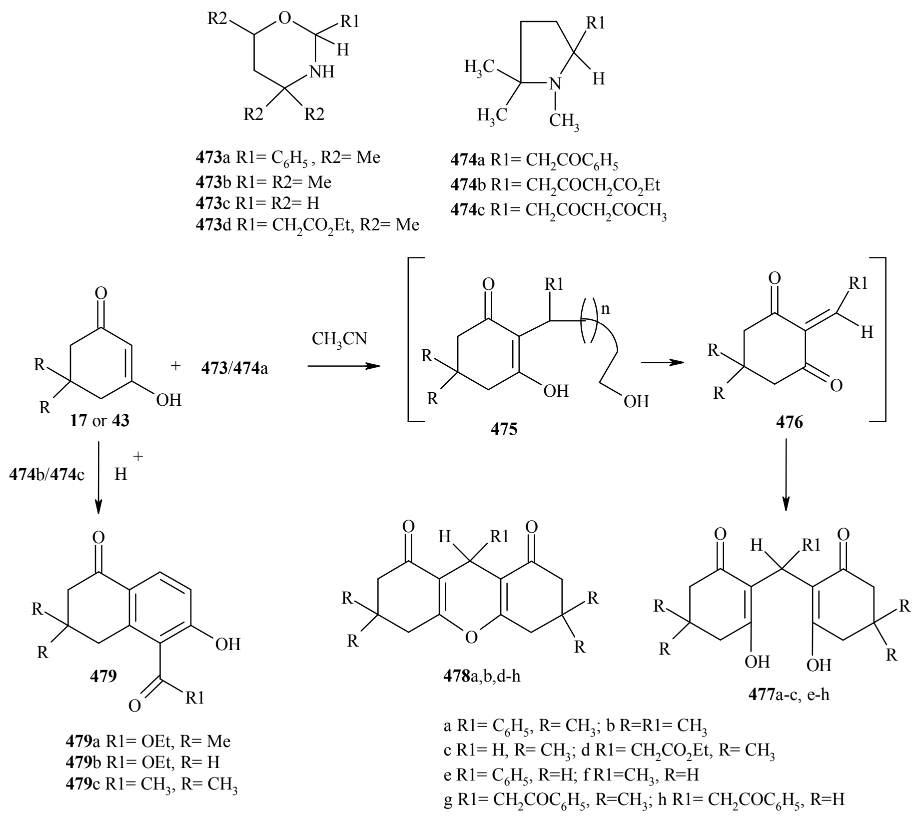
Scheme 141. Cyclization of 1,3-cyclohexanedione derivatives

Palladium catalyzed the reaction of 2-methyl-1,3-cyclohexanedione 80a with tetralone derivative 471 in the presence of Et_3B in THF proceeded smoothly at room temperature to give 2-[2-(3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methylcyclohexane-1,3-dione 472 (Scheme 142).[234,235]



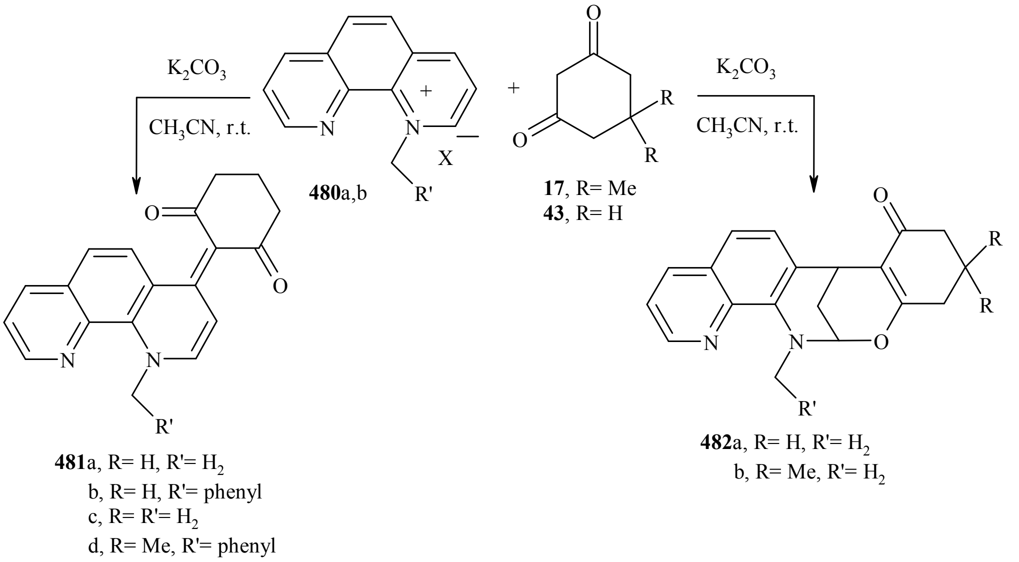
Scheme 142. Reaction of 1,3-cyclohexanedione derivative with tetralone derivative

5,5-Dimethyl-l,3-cyciohexanedione (dimedone) 17 reacted with 2-phenyloxazinane 473a in refluxing acetonitrile and acetic acid furnished 2,2'-(phenylmethylene)-bis [5,5-dimethyl-l-hydroxycyclohex-l-en-3-one] 477a. When the reaction is carried out in refluxing acetic acid, 1,8-dioxo-3,3,6,6-tetrame-thyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroxanthene 478a is formed. 2-substituted oxazinanes reacted with dimedone 17 and provide 477 and/or 478. However, in the reaction of 473c with dimedone 17 only 477e is formed and 478e was not isolated. Reaction of 473d with dimedone 17 in refluxing acetonitrile and trifluoroacetic acid resulted in the formation of 478d. When 474a reacted with dimedone 17 in refluxing acetonitrile and acetic acid furnished the corresponding 478g without the isolation of 477g. 1,3-Cyclohexanedione 43 reacted with 1,3-oxazinanes 473a,b and provided the corresponding 477 in refluxing CH_3CN and CH_3COOH and 478 in refluxing acetic acid. Reaction of 1,3-cyclohexanedione 43 with 474a yielded 478h.[236] 474b Reacted with dimedone 17 and 1,3-cyclohexanedione 43 in acetonitrile and acetic acid and furnished different products such as α-tetralones 479a and 479b respectively and 474c gave 479c with dimedone 17 (Scheme 143).[237]



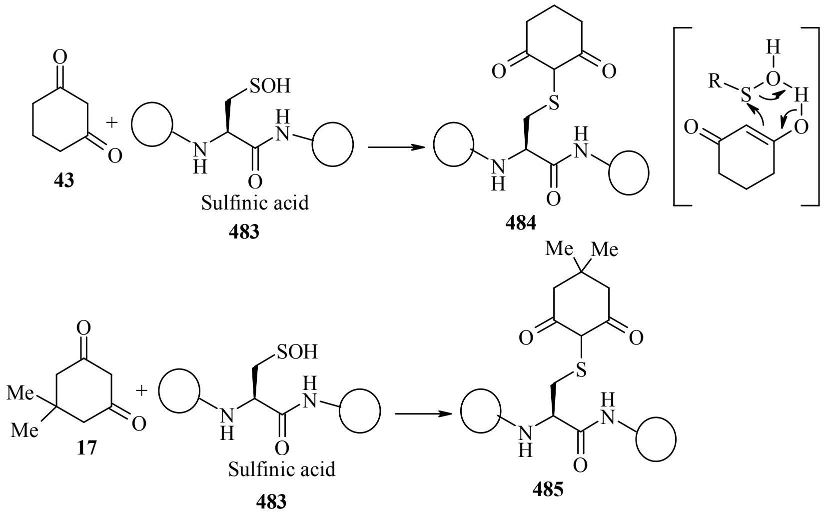
Scheme 143. Reaction of 1,3-cyclohexanedione or its derivatives with oxinane derivatives and pyrrolidine derivatives

The reaction of *N*-methylphenanthrolinium iodide 480a with either 1,3-cyclohexanedione 43 or dimedone 17 resulted in the formation of 1,4-disubstituted-1,10-phenanthroline derivatives 481a-d and 1,3-oxazabicyclic compounds 482a,b (Scheme 144).[238,239]



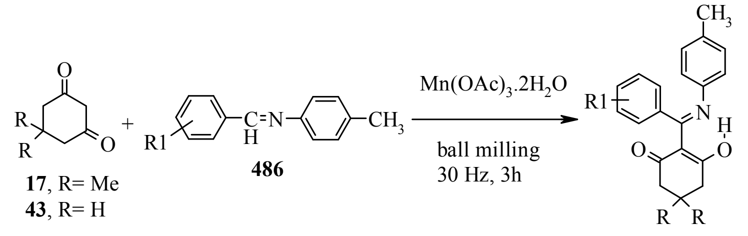
Scheme 144. Reaction of 1,3-cyclohexanedione or dimedone with N-methylphenanthrolinium iodide

Condensation reaction of sulfenic acid 483 with 1,3-diketones such as 1,3-cyclohexanedione 43 or its derivative 17 under physiological conditions gives the corresponding thioether derivatives 484 and 485 (Scheme 145).[240, 241]



Scheme 146. Synthesis of thioether derivatives from 1,3-cyclohexanedione or dimedone with sulfenic acid

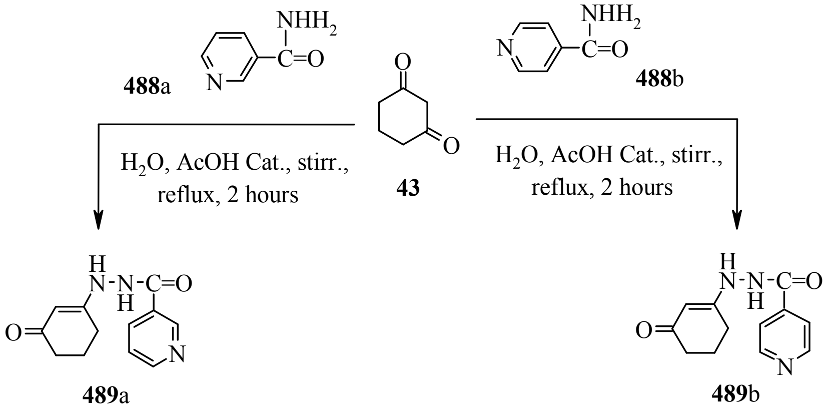
The reaction of 1,3-cyclohexanedione 43 or 5,5-dimethyl-1,3-cyclohexanedione 17 with in situ generated imines proceeded under solid-state conditions in the presence of manganese(III) acetate-mediated radical and the adducts 487a,b were obtained (Scheme 147).[242]



487a, R= H, R1= 4-NO_2
b, R= Me, R1= 4-NO_2

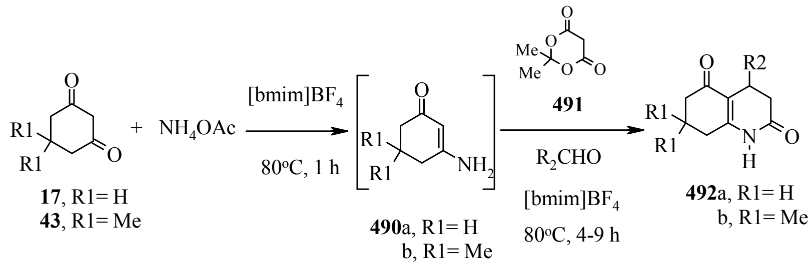
Scheme 147. Synthesis of cyclohexenone derivatives

Condensation of nicotinic, isonicotinic acid hydrazides 488a,b with 1,3-cyclohexanedione 43, in water, using acetic acid as catalyst, afforded enaminone derivatives 489a,b (Scheme 148).[243]



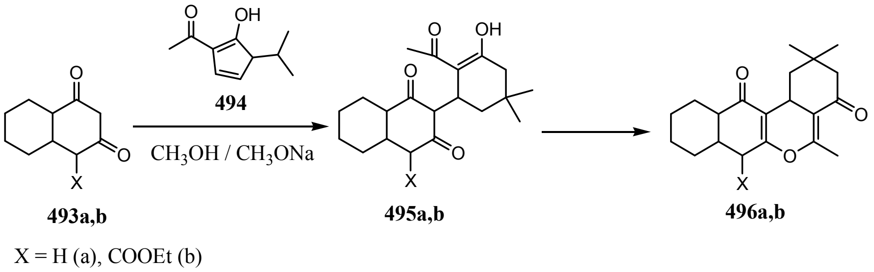
Scheme 148. Synthesis of enaminones derivatives

Hantzsch reaction involving 1,3-dicarbonyl compounds, aldehydes and primary amines, led to the formation dihydropyridines (DHPs). In 2006, Fan *et al.* reported the sequential synthesis of DHPs through a four-component reaction in ionic solvents.[205,244]



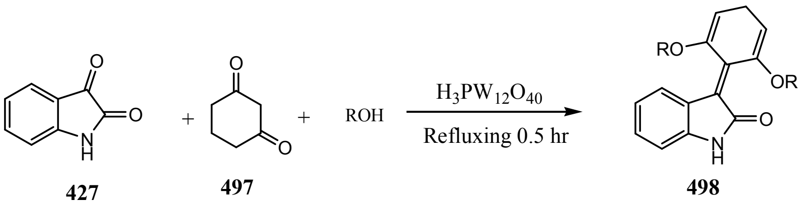
Scheme 149. Synthesis of quinoline derivatives

Decalin-1,3-dions 493a, b reacts with 2-Acetyl-5, 5-dimethyl-2-cyclohexen-l-one 494 via Michael additionto form tricyclic compounds 495a, b. Dehydration of the adduct gives tetracyclic compounds 496a, b.[245]



Scheme 150. Synthesis of tetracycles skeleton 496a,b

Condensation of 1,3-cyclohexanedione isatin 427 and alcohol 497 afforeded and 3-(cyclohexa-2,5-dienylidene)-2-indolinone 498.[246]



Scheme 151. Synthesis of 3-(cyclohexa-2,5-dienylidene)-2-indolinone

Conclusion

1,3-Cyclohexanedione or its derivatives are very important in different fields and they are considered as a key synthons for several organic compounds. It is found that the 2-acyl-1,3-cyclohexanediones are plant growth retardants. It is believed that spirocyclopropyl cyclohexane-1,3-dione is to be incorporated into potent HPPD inhibitors. A series of dimeric 1,3-cyclohexanedione oxime ethers have significant antip-lasmodial activity. 1,3-cyclohexanedione or its derivative dimedone can be used in synthesis of very important series of xanthenes which have anti-inflammatory effects, antibactericide activities in agriculture, new clinical agents in treatment of cancer and have antiviral activities. Xanthenes which prepared from 1,3-cyclohexanedione or its derivative dimedone are also used as a key-units for synthesis of several nature products. In addition to the multi uses of 1,3-cyclohexanedione or its derivatives they also can be used for preparation of pyran derivatives which have biological and pharmacological properties, such as anticoagulant, diuretic, anticancer, spasmolytic and antianaphylactin. These advantageous of 1,3-cyclohexanedione or its derivatives encourage us to make a survey on the methods of synthesis of these important compounds and the substances resulted from their reactions with different reagents.

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