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RESEARCH ARTICLE

AN EFFICIENT SYNTHESIS OF 2-CINNAMOYL-BENZO [G] INDAZOLES USING PEG-400 AS GREEN REACTION SOLVENT

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ABSTRACT

A Simple and an efficient procedure for the synthesis of 2-cinnamoyl-benzo[g] indazoles are reported. A new series of 2-cinnamoyl- benzo[g] indazole derivatives were synthesized by the treatment of appropriate of 2-(Substitued arylidene)-1-tetralones with cinnamoyl hydrazide using catalytic amount of acetic acid in polyethylene glycol-400 as reaction solvent under mild reaction condition. The newly synthesized compounds were characterized by the spectral analysis. The advantage of this method is simple and efficient work up, shorter reaction time and use of inexpensive catalyst is reported.

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INTRODUCTION

The chemistry of heterocyclic compound is the most interesting for its theoretical implication the diversity of its synthetic products and the physiological and industrial significance. The versatile applications of nitrogen-sulphur heterocyclic compounds were received considererable attention in recent years due to their wide physiological activity. Amongst various heterocyclic compounds, nitrogen-containing heterocycles are widely found as a core framework in the library of heterocycles molecules. Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids (Srivastava, 2012 and Pai G, 2016). Indazoles derivatives display a wide-ranging variety of biological activities. Mainly because of their occurrence in drugs, there has been a sustained interest, in the past few years, for the discovery of new and efficient methods to prepare variously substituted 1*H*- and 2*H*-indazoles. The indazole nucleus is a pharmaceutically important structure that constitutes the key subunit in many drugs with a broad range of pharmacological activities. The 1,3,5-substituted indazoles have been studied as receptor antagonists of the peptideo-leukotrienes (Srinivasan, 2008).

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Most of the derivatives of Indazole are recognized to have effective pharmacological activity, for instance, anti-inflammatory, anti-tumor or HIV protease inhibition (Matassa, 1990 and James, 1996) and inhibition of protein kinase C-B/AKt inhibitors (Vicente, 2005). In actual fact, compounds with Indazole frame are notorious for their variety of biological activities (Bakr, 2014) such as high binding affinity for estrogen receptor (Woods, 2006), antifungal and antibacterial activity (Meri, 2005). On the other hand, cinnamic acid derivatives and especially those are combining the cinnamoyl moiety with hydroxyl groups, present strong free radical scavenging properties (Pontiki, 2014). Acids, esters, amides, hydrazides and related derivatives of cinnamic acid with such activities are reported in the literature for their health benefits (Sova, 2012 and Bernini, 2007). Keeping these biological observations of indazoles in mind along with social responsibilities and in continuation of our work on the synthesis of biologically active heterocyclic compounds [Dawane, 2010 and Konda, 2016], it was planned to synthesize some new series benzo[g] indazole heterocyclic compounds containing cinnamoyl moiety under mild condition.

MATERIALS AND METHODS

Melting points were determined by in an open capillary method and are uncorrected. The chemicals and solvents used for laboratory grade and were purified.

Purity of the compounds was checked on silica gel G TLC plates using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d_6) on Avance-300 MHz spectrometer using TMS as an internal standard. The mass were recorded on EI-Shimadzu-GC-MS spectrometer.

General procedure for the synthesis of 2-(Substitued arylidene)-1-tetralone (1a-f):An equimolar mixture of α-tetralone (1 mmol), and substituted aromatic aldehyde (1 mmol) was mixed in 20 mL polyethylene glycol-400 (PEG-400) taken in 100 mL conical flask. Then 2-3 mL of saturated solution of KOH (aprox 40%) was added into the flask. The solution becomes reddish brown color. The reaction mixture was stirred on magnetic stirrer for half an hour at room temperature. After completion of the reaction (monitored by TLC), then the contents of the flask were poured into 50 mL ice cold water. The corresponding solid was separated then filtered. The crude product was recrystallized from suitable solvent. The yield and M.P. of the product was noted. Similarly all the compounds were synthesized by the same procedure. The physical and analytical data of the compounds were mentioned in Table-1.

General procedure for the synthesis of 2-cinnamoyl-benzo[g] indazoles 3(a-f): An equimolar mixture of 2-(Substitued arylidene)-1-tetralone (**1a)** (1 mmol) and cinnamoyl hydrazide **2** (1 mmol) was mixed in 20 mL poly ethylene glycol-400 (PEG-400) taken in 50 mL round bottom flask. The catalytic amount of glacial acetic acid (2 ml) was added into the flask. The reaction mixture was stirred on magnetic stirrer at 50 °C for the time period shown in Table-2. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction contents was cooled to room temperature and poured into cold water. The solid was separated then filtered. The crude product **(3a)** was recrystallized from ethanol solvent. The yield and physical constant of the product was determined. Similarly, all the compounds were synthesized by the same procedure. The physical and analytical data of the compounds was mentioned in Table-2.

***(2E)-1- (3,3a,4,5-tetrahydro-3-(4-methoxyphenyl) benzo [g]indazol-2-yl)-3-phenylprop-2-en-1-one (3a)*:** IR (KBr, cm^{-1}): 1610, 1656, 2878, 3060; ^{1}H NMR (DMSO-d_6, δ ppm): 2.68-3.31 (m, 5H, CH_2-CH_2-CH), 3.52 (s, 3H, OCH_3), 4.61 (m, 1H), 6.65-7.95 (m, 15H, Ar-H+CH=CH); EIMS (*m/z*): 408 (M^+); Anal. Calcd. For $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86%. Found: C, 79.46; H, 5.84; N, 6.75%

(2E)-1-(3- (4-chlorophenyl)-3,3a,4,5-tetrahydrobenzo [g]indazol -2-yl)-3-phenylprop-2-en-1-one (3b): IR (KBr, cm^{-1}): 1615, 1650, 2910, 3045; ^{1}H NMR (DMSO-d_6, δ ppm): 2.72-3.26 (m, 5H, CH_2-CH_2-CH), 4.72 (m, 1H), 6.58-8.05 (m, 15H, Ar-H+CH=CH); EIMS (*m/z*): 412 (M^+), 414 (M+2); Anal. Calcd. For $C_{26}H_{21}N_2OCl$: C, 75.63; H, 5.13; N, 6.78%. Found: C, 75.56; H, 5.21; N, 6.71%

(2E)-1-(3, 3a,4,5-tetrahydro-3-(4-hydroxyphenyl) benzo [g]indazol-2-yl)-3-phenylprop-2-en-1-one (3c): IR (KBr, cm^{-1}): 1616, 1646, 2898, 3026; ^{1}H NMR (DMSO-d_6, δ ppm): 2.65-3.35 (m, 5H, CH_2-CH_2-CH), 4.68 (m, 1H), 6.61-8.11 (m, 15H, Ar-H+CH=CH), 10.62 (s, 1H, OH); EIMS (*m/z*): 394 (M^+); Anal. Calcd. For $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10%. Found: C, 79.11; H, 5.78; N, 6.89%

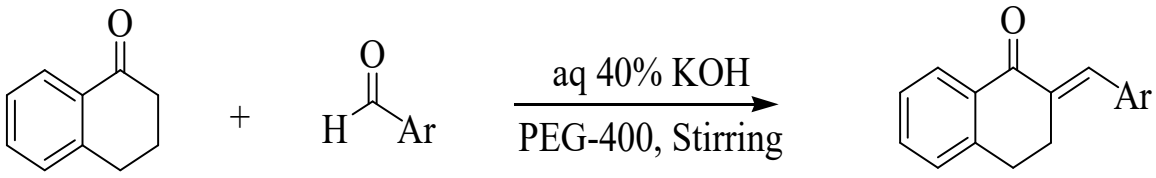
(2E)-1-(3,3a,4,5-tetrahydro-3-phenylbenzo[g]indazol-2-yl)-3-phenylprop-2-en-1-one (3d): IR (KBr, cm^{-1}): 1612, 1651, 2886, 3035; ^{1}H NMR (DMSO-d_6, δ ppm): 2.58-3.26 (m, 5H, CH_2-CH_2-CH), 4.62 (m, 1H), 6.55-7.92 (m, 16H, Ar-H+CH=CH); EIMS (*m/z*): 378 (M^+); Anal. Calcd. For $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40%. Found: C, 82.62; H, 5.74; N, 7.51%

***(2E)-1-(3,3a,4,5-tetrahydro-3-(4-hydroxy-3-methoxyphenyl) benzo[g]indazol-2-yl)-3-phenylprop-2-en-1-one (3e)*:** IR (KBr, cm^{-1}): 1615, 1648, 2885, 3051; ^{1}H NMR (DMSO-d_6, δ ppm): 2.62-3.32 (m, 5H, CH_2-CH_2-CH), 3.61 (s, 3H, OCH_3), 4.65 (m, 1H), 6.68-7.98 (m, 15H, Ar-H+CH=CH), 10.81 (s, 1H, OH); EIMS (*m/z*): 424 (M^+); Anal. Calcd. For $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60%. Found: C, 76.42; H, 5.78; N, 6.52%

***(2E)-1- (3,3a,4,5-tetrahydro-3-(thiophen-2-yl)benzo [g]indazol-2-yl)-3-phenylprop-2-en-1-one (3f)*:** IR (KBr, cm^{-1}): 1618, 1656, 2885, 3062; ^{1}H NMR (DMSO-d_6, δ ppm): 2.65-3.35 (m, 5H, CH_2-CH_2-CH), 5.11 (m, 1H), 6.61-8.26 (m, 15H, Ar-H+CH=CH); EIMS (*m/z*): 384 (M^+); Anal. Calcd. For $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29%. Found: C, 74.89; H, 5.32; N, 7.36%

RESULTS AND DISCUSSION

Solvents are widely used in organic synthesis and have been a cause of major concern due to their associated environmental hazards. The major disadvantages are their pyrophoric nature, volatility, and poor recovery. To address some of these issues, attempts have been made to develop solvent-free chemistry, which to some extent has been successful for a few transformations (Cave, 2001). However, in performing the majority of organic transformations, solvents play a critical role in making the reaction homogeneous and allowing molecular interactions to be more efficient. In recent years, polyethylene glycol (PEG-400) prompted reactions (Suryakiran, 2006; Dickerson, 2002; Kamal, 2005; Chen, 2005) have attracted the attention of organic chemists due to their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, ease of work-up, eco-friendly nature and economical cost. PEG is non-toxic, non-halogenated, inexpensive potentially recyclable and water soluble which facilitate its removal from reaction product. With our recent success on the development of new selective environmentally friendly methodologies using polyethylene glycol (PEG-400) (Konda, 2011; 2014) as a reaction solvent for the preparation of biologically active compounds, herein we report to attempt the synthesis of some new 2-cinnamoyl benzo[g] indazole derivatives by the cyclic condensation reaction of reaction of 2-(Substitued arylidene)-1-tetralones with cinnamoyl hydrazide using catalytic amount of acetic acid in PEG-400 as an efficient reaction solvent. The starting compounds 2-(Substitued arylidene)-1-tetralones 1(a-f) were prepared by the Claisen-Schmidt condensation method. The mixture of α-tetralone (1 mmol), and substituted aromatic aldehyde (1 mmol) was mixed in 20 mL polyethylene glycol-400 (PEG-400) taken in 100 mL conical flask. Then 2-3 mL of saturated solution of KOH (aprox 40%) was added into the flask. The solution becomes reddish brown color.



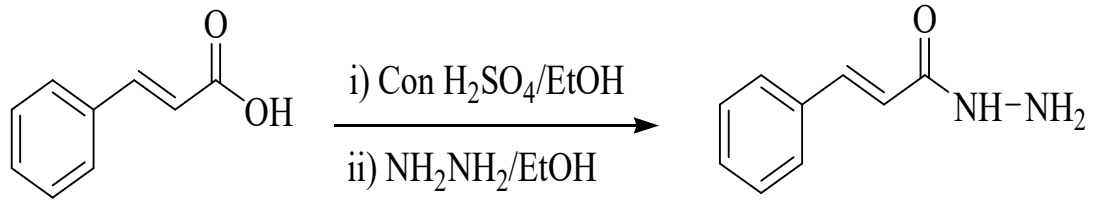
1-Tetralone Aromatic aldehydes **1(a-f)**

Scheme-1: Synthesis of 2-(Substitued arylidene)-1-tetralones using KOH in PEG-400

Table 1. The physical and analytical data of synthesized 1(a-f) derivatives

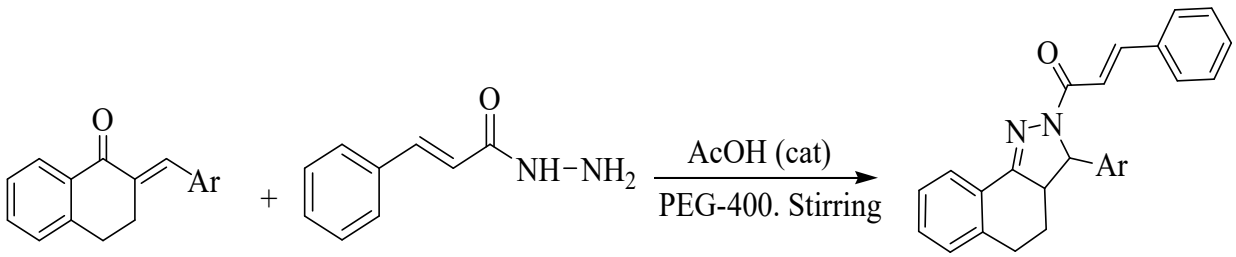
Entry	Substitution (Ar)	Molecular Formula	M.P. (°C)	Yield[a] (%)
1a	4-OMe-benzaldehyde	$C_{18}H_{16}O_2$	110	92
1b	4-Cl-benzaldehyde	$C_{17}H_{13}OCl$	132	92
1c	4-OH-benzaldehyde	$C_{17}H_{14}O_2$	124	90
1d	Benzaldehyde	$C_{17}H_{14}O$	98	88
1e	3-OMe-4-OH-benzaldehyde	$C_{18}H_{16}O_3$	128	90
1f	Thiophenaldehyde	$C_{15}H_{12}OS$	116	85

[a]Isolated Yields.



Cinnamic acid Cinnamoyl hydrazide **(2)**

Scheme 2. Synthesis of Cinnamoyl hydrazide



1(a-f) **(2)** **3(a-f)**

Scheme 3. Synthesis of 2-cinnamoyl benzo[g] indazole derivatives using AcOH in PEG-400

Table 2. The physical and analytical data of synthesized 2-cinnamoyl benzo[g] indazoles

Entry	Substitution (Ar)	Molecular Formula	Time[b] (hrs)	M.P. (°C)	Yield[a] (%)
3a	4-OMe-benzaldehyde	$C_{27}H_{24}N_2O_2$	1.5	152	90
3b	4-Cl-benzaldehyde	$C_{26}H_{21}N_2OCl$	1.5	164	92
3c	4-OH-benzaldehyde	$C_{26}H_{22}N_2O_2$	1.5	146	90
3d	Benzaldehyde	$C_{26}H_{22}N_2O$	3	138	78
3e	3-OMe-4-OH-benzaldehyde	$C_{27}H_{24}N_2O_3$	2.5	172	82
3f	Thiophenaldehyde	$C_{24}H_{20}N_2OS$	2.5	158	85

[a]Isolated Yields; [b]Reaction time in hours

The reaction mixture was stirred on magnetic stirrer for half an hour at room temperature. After completion of the reaction (monitored by TLC), then the contents of the flask were poured into 50 mL ice cold water. The corresponding solid was separated then filtered. The crude product was recrystallized from suitable solvent (Scheme-1, Table-1). The reagent cinnamoyl hydrazide was prepared by the classical esterification method. The synthesis of cinnamoyl hydrazide was carried out from the esterification of cinnamic acid with ethanol in conc.H_2SO_4 followed by the treatment with hydrazine hydrate under reflux condition for 2 hours to yielded corresponding cinnamoyl hydrazide (Scheme-2).

This formed cinnamoyl hydrazide was used as intermediate for the synthesis of 2-cinnamoyl benzo[g] indazole derivatives. In the beginning, 2-(4-Chlorophenyl)-arylidene-1-tetralone (1a) and cinnamoyl hydrazide (2) reagent/intermediate was mixed in 20 mL poly ethylene glycol-400 (PEG-400) taken in 50 mL round bottom flask. The catalytic amount of glacial acetic acid (2 ml) was added into the flask. The reaction mixture was stirred on magnetic stirrer at 50 °C for the period of 1.5 hr as shown in Table-2. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction contents was cooled to room temperature and poured into cold water. The corresponding solid product was formed then filtered. The yield of the product was 90%. The crude product (3a) was recrystallized from ethanol solvent. The yield and physical constant of the product was determined. Similarly, all other compounds were synthesized by the same procedure (Scheme-3). The physical and analytical data of the synthesized compounds were mentioned in Table-2.

Initially, we carried out the above reaction in different solvents such as ethanol, acetic acid, DMF and polyethylene glycol-400. The reaction time and yield of the product was not significant. The only PEG-400 solvent showed satisfactorily shorter reaction time than reported method (Thadhaney, 2009). Further, we turned our attention towards to obtain good to excellent yields of the products and smother reaction. The catalytic amount of acetic acid was used in combination with PEG-400; the reaction was completed very smoothly in high yield. Encouraged by the results, we focused our attention to variety of 2-(Substitued arylidene)-1-tetralones. In all cases, the reaction proceeded efficiently in high yields under mild reaction temperature using catalytic amount of acetic acid in PEG-400 as an alternative reaction solvent. Structures of all newly synthesized 2-cinnamoyl benzo[g] indazole derivatives were confirmed by the spectroscopic methods.

The IR spectra of the products showed a presence of characteristic stretching frequency between 1610-1620 cm^{-1} referring to C=N double band. The IR spectrum of the products were also showed 1645-1660 cm^{-1} stretching frequency revealed to C=O of cinnamoyl moiety. The absorption bands associated with other functionalities appeared in the expected regions. The ^1H NMR spectra 2-cinnamoyl benzo[g] indazole showed multiplet pattern in the region δ 2.51-3.35 region corresponding to the -CH_2-CH_2-CH protons. The double bonded protons of the cinnamyol moiety are merged in the aromatic region and observed at excepted regions. Phenolic proton appeared as a singlet near δ 10.55-11 ppm while other aromatic and aliphatic protons were observed at excepted regions. The mass spectra of the synthesized 2-cinnamoyl benzo[g] indazole derivatives were showed molecular ion peak corresponding to their molecular formula.

Conclusion

In summary, we have developed a simple and efficient system towards the synthesis of some new 2-cinnamoyl-benzo[g] indazole derivatives. The reaction of2-(substitued arylidene)-1-tetralones with cinnamoyl hydrazide using catalytic amount of glacial acetic acid in polyethylene glycol (PEG-400) as an efficient and as green reaction solvent at mild reaction condition is described. The advantages of the present protocol are the simple and easy work up procedure, high yields of products and shorter reaction time is reported. The avoidance of expensive catalyst and PEG-400 is used as alternative green reaction solvent is the main advantage of this methodology.

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