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RESEARCH ARTICLE

ENVIRONMENTALLY BENIGN AND FACILE ONE-POT SYNTHESIS OF CYANAMIDES MEDIATED BY PHASE TRANSFER REAGENT ETHYLTRIPHENYLPHOSPHONIUM TRIBROMIDE

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ABSTRACT

A mild and improved procedure is reported for the synthesis of cyanamides from the corresponding dithiocarbamic acid salts *via* a desulfurization strategy using phase transfer reagent ethyltriphenylphosphonium tribromide (ETPPTB) and sodium bicarbonate in water / ethyl acetate biphasic medium. This method is highly appealing because of its one-pot process, convenient operation, environmental friendly, mild reaction conditions and broad substrate scope.

INTRODUCTION

Phase transfer catalysis has attracted great interest in recent times as an effective synthetic tool by which liquid-liquid or liquid-solid phase-separated reactions are accelerated (Dehmlow and Dehmlow, 1997). Onium salts (phosphonium, ammonium and sulfonium salts), crown ethers and cryptands, and solvents and co-solvents have been widely used as PTCs in manufacturing specialty chemicals resulting in extensive reviews both on chemistry and engineering viewpoints (He *et al.*, 2008). On the other hand, the applications of alkyl and aryl cyanamides in present day chemistry are now well documented. Due to their unique structure and reactivity, they have attracted considerable attention in organic synthesis (Sandler and Karo, 1972) as well as in the fields of inorganic and material sciences (Miyasaka *et al.*, 2001). They are important precursors in the synthesis of *N*-alkyl and *N*-aryl imides (Stephens *et al.*, 1992) and also find widespread applications as protecting groups in the synthesis of secondary and tertiary amines containing heterocycles due to the easy removal of the cyano group (Donetti *et al.*, 1969). They are useful intermediates in the synthesis of *N*-mono and *N*-di-substituted-2-aminothiazoles (Brown *et al.*, 1982) and *N*-substituted hydantoins which have important pharmaceutical activities as anti-tumour (Gilman *et al.*, 1990), antiarrhythmic (Matsukura *et al.*, 1992), anticonvulsants (Novelli *et al.*, 1954), herbicides and a vasodilator medication called minoxidil (McCall *et al.*, 1975) known for its ability to reduce hair loss and promote hair regrowth.

Due to the wide applications of cyanamides, several methods for their synthesis has been developed over the years out of which, the general and classical method of synthesis involves the reaction of cyanogen chloride / bromide with amines or with imide salts (Von *et al.*, 1900). However this method involves the use of potassium / sodium cyanide and bromine for the preparation of cyanogen halide (which is again highly toxic), making the protocol environmentally unacceptable.

Various other methods for preparation of cyanamide includes different synthetic strategies such as cyanation of amines using CN^+ equivalents as synthons, (Davis *et al.*, 1983) coupling reactions involving Pd isocyanides, allyl carbonates and trimethylsilyl azide, (Shin *et al.*, 2001) sodium bis (trimethylsilyl)amide as deoxygenating or desulfurizing agents (Wong *et al.*, 2006) and Tiemann rearrangement of amidoximes (Bakunov *et al.*, 2000) reaction of hypervalent iodine (V) species with *N.N'*- disubstituted glycylamide [17] and hypervalent iodine reagent diacetoxyiodobenzene (DIB) as thiophilic / desulfurizing agent (Ghosh *et al.*, 2009). These procedures, however, seem to have severe environmental concern as they involve direct or indirect use of toxic and corrosive reagents, expensive reagents and catalysts, strong

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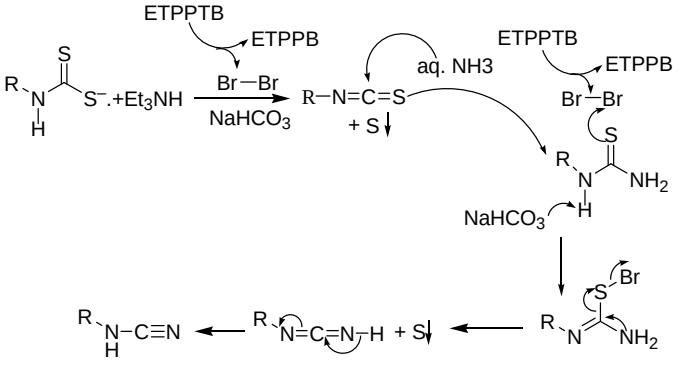
alkaline conditions, high reaction temperatures and tedious purification procedures. The synthesis of this important class of compounds has been an area of interest for our group for quite sometime and in this context we recently developed a method involving molecular iodine as an efficient thiophilic / desulfurizing agent for the preparation of these compounds from dithiocarbamate salts (Nath *et al*., 2009). This protocol, however high yielding and facile, has some drawbacks from a Green Chemistry concept due to the use of toxic base (Et_3N). In addition, difficulty of molecular iodine to readily dissolve in the organic reaction medium ethylacetate gave us grounds to further modify the reported methodology. In continuation of our efforts in the synthesis of cyanamides, we thought it would be worthwhile to further investigate an alternative methodology for its synthesis from alkyl/ aryl dithiocarbamate salts that would be more agreeable with the Green chemistry aspects. In line with this, we were keen to develop a protocol which would proceed efficiently without the use of any toxic chemicals and would not generate any toxic byproducts.

RESULTS AND DISCUSSION

In the present protocol, the use of toxic triethylamine was replaced with a safe, water soluble inorganic base sodium bicarbonate and the thiophilic / desulfurizing agent of choice was ethyltriphenylphosphonium tribromide (ETPPTB) which our group has reported for the first time (Jamir *et al*., 2011). Further, in order to provide suitable mediums for both organic dithiocarbamate salt and ETPPTB and also for inorganic sodiumbicarbonate, a cheap and biphasic water and ethyl acetate solvent system was employed. It may be noted herein that ETPPTB bearing the triphenylphosphine moiety is a well known phase transfer agent, analogous to its percursor ethyltriphenylphosphonium bromide (ETPPB) (He *et al.*, 2008). This very nature of ETPPTB makes it superior over the use of iodine as the phase tranfer property makes it readily available for reaction in both the aqueous as well as organic phases of the present protocol.

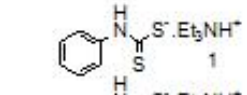
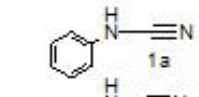
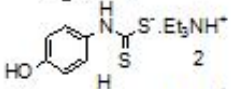
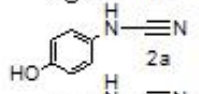
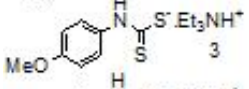
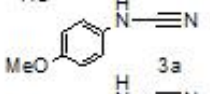
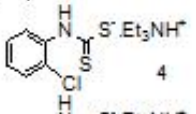
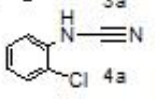
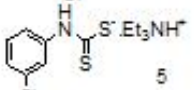
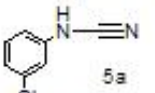
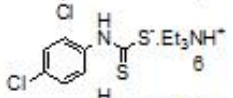
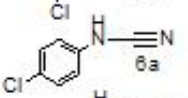
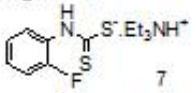
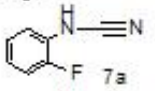
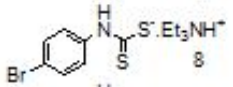
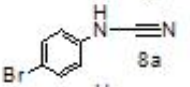
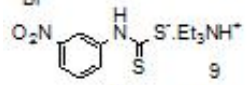
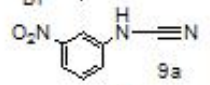
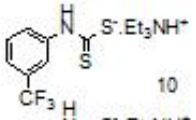
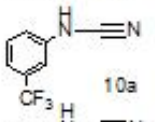
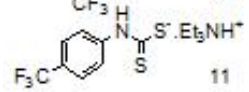
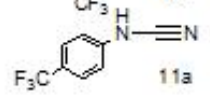


Scheme 1. Plausible mechanism for the formation of cyanamide

The present methodology involves the preparation of isothiocyanate from alkyl / aryl dithicarbamate salt by desulfurization with ETPPTB in the presence of $NaHCO_3$ as the base in a water / ethylacetate biphasic solvent medium. The *in-situ* generated isothiocyanate is treated with aqueous NH_3 to afford alkyl / aryl thioamides which is further oxidised to cyanamide with ETPPTB in the presence of $NaHCO_3$. After isolation and characterization of each of the intermediates, the following mechanism has been proposed for the synthesis. Isolation of the precipitated elemental sulfur further supports the mechanism proposed.

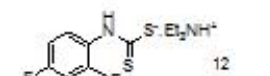
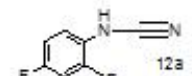
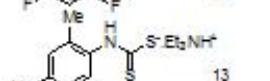
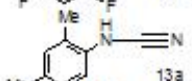
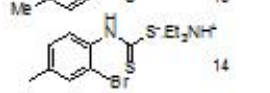
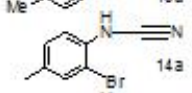
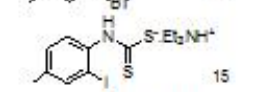
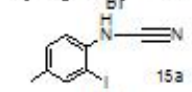
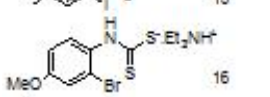
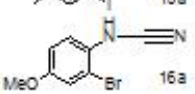
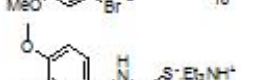
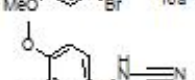
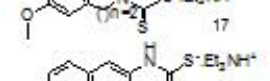
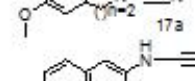
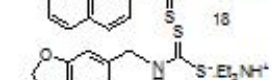
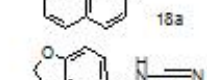
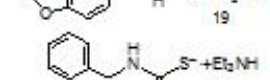
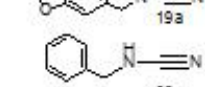
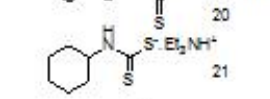
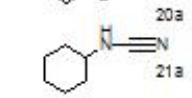
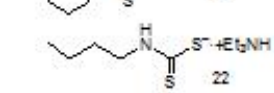
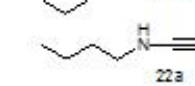
Following the present protocol, a wide variety of alkyl / aryl cyanamides were successfully synthesized in good to excellent yields. Table 1 and Table 2 summarises the range of dithiocarbamate salts that could be succesfully reacted to form the corresponding cyanamides. Aromatic substrates containing strongly activating (2 and 3) as well as weakly deactivating groups (4 - 8) reacts efficiently to give cyanamides (2a - 8a) in good yields. This methodology is equally successful for substrates containing strongly deactivating (9 – 11) substituents which afforded the corresponding cyanamides (9a – 11a) in excellent yields. Through this strategy, we were able to obtain excellent yields of arylcyanamides (12a – 17a) having various di- and tri- substitutions. Fused substrates such as (18) also gave the corresponding cyanamide (18a) in good yields. Dithiocarbamates of benzylic amines (19 - 20) and aliphatic amines (21 - 22) readily gave their corresponding cyanamides in good yields.

Table 1. Preparation of cyanamides from dithiocarbamates using ETPPTB[a]

Substrate	Product[b]	Yield (%)[c]
 1	 1a	93%
 2	 2a	83%
 3	 3a	91%
 4	 4a	80%
 5	 5a	83%
 6	 6a	82%
 7	 7a	79%
 8	 8a	85%
 9	 9a	80%
 10	 10a	84%
 11	 11a	84%

a Reactions were monitored by TLC. b Confirmed by IR, 1H NMR and 13C NMR. c Isolated yield.

Table 2. Preparation of cyanamides from dithiocarbamates using ETPPTB[a]

Substrate	Product[b]	Yield (%)[c]
 12	 12a	84%
 13	 13a	84%
 14	 14a	84%
 15	 15a	78%
 16	 16a	78%
 17	 17a	70%
 18	 18a	80%
 19	 19a	76%
 20	 20a	82%
 21	 21a	71%
 22	 22a	71%

Conclusion

In conclusion, we have developed a general, environmentally benign and effecient method for the preparation of cyanamides from their corresponding dithiocarbamic acid salts. Although literature enumerates a number of procedures for the preparation of cyanamides, the simplicity, environmental acceptability, and cost effectiveness of this one pot strategy makes it a practical alternative.

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