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Synthesis of novel dithiocarbamates and xanthates using dialkyl azodicarboxylates: S–N bond formation

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ABSTRACT

A one–pot three–component route for the synthesis of a novel category of dithiocarbamates or xanthates is developed by a reaction of in-situ generated dithiocarbamic acids or xanthates with dialkyl azodicarboxylates under mild and catalyst-free conditions. The reaction is characterized by a wide scope, high efficiency and straightforward isolation protocol. The synthetic utility of the dithiocarbamates and xanthates was demonstrated on the preparation of symmetrical and unsymmetrical thioureas, isothiocyanates, and thiocarbamates.

1. Introduction

Heteroatom-heteroatom bond formation is a versatile tool for the synthesis of various reagents, bioactive molecules, and functional materials. Among various heteroatom–heteroatom bonds, the nitrogen–sulfur bond (N–S) is present in many bioactive compounds including sulfenamides,[1] sulfinamides,[2] sulfonamides,[3] sulfenyl and sulfonylhydrazines,[4] sulfonyl azides[5] and heterocycles.[6] For example, Captan is a commercially important sulfenamide with fungicidal effect. Recently, transition metal–catalyzed aerobic oxidation[7] and hypervalent iodine(III)–mediated oxidative cyclization reactions[8] have been used for the formation of compounds with S–N bonds. However, in view of cost and environmental concerns of transition metal usage, the development of novel eco–friendly protocols is still highly desirable for the formation of S–N bonds.

Dithiocarbamates are interesting category of functional groups with diverse applications in agriculture,[9] medicinal chemistry,[10] synthetic organic chemistry,[11] analytical chemistry,[12] coordination chemistry[13] and material science.[14] Traditional methods for the synthesis of dithiocarbamates, xanthates, thiocarbamates, isothiocyanates and thioureas consist of using highly toxic thiophosgene or related thiocarbonyl group transfers agents.[15] Recently, a novel method for the transformation of primary amines to isothiocyanates using $Me_4N^+(CF_3S)^-$ was reported.[16] Although the formation of (di) thiocarbamates and thioureas from amines and CS_2 is intensively investigated the available methods usually suffer from drawbacks such as need of extra reagents, multi-step procedures, and elevated temperatures.[17] Synthesis of dithiocarbamates via a one–pot three–component reaction of an amine, CS_2 and an electrophile is a well-documented strategy. Dithiocarbamic acids, derived from an amine and CS_2, are good mono– and bis–nucleophiles toward various electrophiles including alkyl halides,[18] epoxides,[19] alkenes,[20] aldehydes,[21] alcohols,[22] etc.[23] for construction of C–S bonds. In addition to dithiocarbamates, xanthates have recently found wide applications as radical precursors in synthetic organic chemistry for the C–C and C–S bond formation.[24] However, to the best of our knowledge, a direct N–S bond formation via the reaction of dithiocarbamic acid or xanthates with dialkyl azodicarbozylates has not been reported.[25] Furthermore, a general, simple, and efficient protocol for the synthesis of diverse functional groups including

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dithiocarbamates, xanthates, isothiocyanates, thioureas, and thiocarbamates is still in demand.

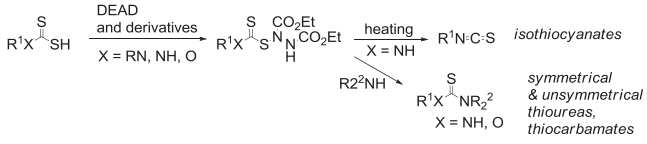
2. Results and discussion

In line with our research on the development of mild and eco–friendly protocols toward novel dithiocarbamates,[19–21] we herein present a one–pot three–component approach for the synthesis of a novel category of dithiocarbamates and xanthates by the reaction of in situ generated dithiocarbamic acids or xanthates with dialkyl azodicarboxylates and their synthetic application in the preparation of isothiocyanates, symmetrical and unsymmetrical thioureas, and thiocarbamates (Scheme 1).

Reaction of dithiocarbamic acids with dialkyl azodicarboxylates was optimized using butylamine, CS_2, and DEAD (**1a**). Initially, we observed that the reaction of butyl amine (1 equiv.) with CS_2 (1.5 equiv.) in water for 10 min, followed by the addition of DEAD (1 equiv.) and stirring for 30 min at room temperature afforded a mixture containing a new dithiocarbamoyl hydrazine 2a, 1,3-dibutylthiourea and butyl isothiocyanate. Performing the same reaction in THF in an ice bath with slow heating to ambient temperature gave a similar result. However, decreasing the reaction temperature to −40 °C and stirring for 5 min, afforded the product **2a** in 85% isolated yield. By providing the dithiocarbamic acid in different vessel and adding the prepared dithiocarbamic acid to **1a** at −40 °C, similar result was obtained. The order of addition of starting materials is important; addition of butylamine to a mixture of DEAD and CS_2 afforded 1,3-dibutylthiourea in 90% isolated yield with 10% of **2a**. In summary, regarding to the benefit of multi-component reactions, stirring butylamine (1 equiv.) and CS_2 (1.5 equiv.) in THF at −40 °C for 10 min, followed by a slow addition of DEAD (1.05 equiv.) at the same temperature, until the yellow color of the reaction mixture is established was considered as optimal reaction conditions.

In order to explore the scope of the reaction under optimized reaction conditions, various commercially available primary and secondary amines were examined. As shown in Table 1, all tested aliphatic primary and secondary amines reacted with carbon disulfide followed by addition of DEAD or DIAD to afford novel dithiocarbamoyl hydrazines **2** in high yields. In the case of secondary amines, the work–up procedure was very easy without the need of column chromatography; solvent removal and trituration with petroleum ether afforded pure products. Importantly, the process is amenable to scale–up as demonstrated on a reaction with allylamine on 50 mmol scale. Products **2** are stable and they were fully characterized by spectroscopic methods. Crystal structure of **2m** (Fig. 1) (CCDC no. 1581343; for details of the crystal structure data and refinement of **2m** see the Supporting Information) further confirmed the expected configuration and showed planar geometry of the dithiocarbamoyl moiety and all three nitrogen atoms. The N–S bond length is 1.675 Å and C–N–N–C torsion angle is 92.5°.

A proposed mechanism for synthesis of compounds **2a-w** is shown in Scheme 2. The reaction of an amine with carbon disulfide gives dithiocarbamic acid **A** as intermediate which then adds to DEAD to provide product **2** after hydrogen transfer.



Scheme 1. Reactions of dithiocarbamates and xanthates with azodicarboxylates and their synthetic applications.

Aromatic amines are not suitable substrates for this reaction. To overcome this drawback, the corresponding triethylammonium dithiocarbamate salt **3** was prepared by the reaction of aniline, CS_2 and triethylamine in diethyl ether. The generated salt was treated with DEAD under optimized reaction conditions. Although, the corresponding diethyl 1-[(phenylcarbamothioyl)sulfanyl]hydrazine-1,2-dicarboxylate was obtained at low temperatures, the product was not stable during purification and it decomposed at room temperature to the corresponding phenyl isothiocyanate. This instability compare to the products of primary aliphatic amines may be due to the conjugation of isothiocyanate group with phenyl ring. Similar behavior was observed for *p*-anisidine and *p*-chloroaniline. This finding prompted us to develop a direct route for the synthesis of phenyl isothiocyanate. For this purpose, dithiocarbamate salt **3** and DEAD was mixed at −40 °C in THF in the presence of acetic acid and stirred with slow heating to 35 °C for 2 h. This way, phenyl isothiocyanate **4** was obtained in 80% isolated yield (Scheme 3).

Synthetic utility of dithiocarbamoyl hydrazines **2** was demonstrated on **2c** (Scheme 4). Heating **2c** to 120 °C under solvent–free conditions afforded allyl isothiocyanate (**5**) in a high yield. According to literature, synthesis of isothiocyanates from amines and CS_2 needs a desulfurylation reagent and a base. For this reason, recently various reagents such as cyanuric chloride (TCT)/K_2CO_3,[26] diethyl chlorophosphate/NaOH,[27] phosphonium-and uranium-based coupling reagents together with *N*,*N*-diisopropylethylamine or triethylamine,[28] di-*tert*-butyl dicarbonate (Boc_2O)/DMAP or DABCO,[29] TsCl/Et_3N,[30] $FeCl_3$/DABCO,[31] triphosgene/Et_3N[32] and 1,1'-(ethane-1,2-diyl) dipyridinium bistribromide/Et_3N[33] have been developed for this transformation. Most of these methods suffer from the cost of the desulfurylation reagent, using a base, and the extra step for formation of the dithiocarbamic acid salts. The present method represents an alternative procedure for the synthesis of isothiocyanates from amines and CS_2 by using safe dialkylazodicarboxylates as desulfurylation reagent without need to a base, only by simple heating of the intermediate.

Reactions of **2c** with aniline, butylamine, and diethylamine afforded unsymmetrical thioureas **6**–**8**, respectively. The reactions took place at ambient temperature with the exception of weakly nucleophilic aniline, which required heating. A symmetrical thiourea **9** was formed by the reaction of **2c** with allylamine. The same product is obtained by a one–pot two–step route starting from allyl amine, carbon disulfide and DEAD, followed by addition of another equivalent of allylamine (Scheme 4). No reaction was occurred between 1-butanol and compound **2** at room temperature for overnight or at 70 °C for 16 h. The side–products of all these reactions are diethyl hydrazine-1,2-dicarboxylate and elemental sulfur. Compounds **2** derived from secondary amines were not suitable for the synthesis of thioureas. These reactions proceed via isothiocyanates or by direct nucleophilic addition of nitrogen nucleophiles to the thiocarbonyl group of **2c**.

Among the procedures available for the synthesis of symmetrical and unsymmetrical thioureas, reaction of amines with thiophosgene or its less toxic derivatives and reaction of amines with isothiocyanates are well investigated in the literature.[34] However, these methods suffer from drawbacks and limitations related to harsh reaction conditions such as high reaction temperature, long reaction times, the use of a strong acid or base, and toxic reagents such as thiophosgene. The present method can be applied successfully for the synthesis of both symmetrical and unsymmetrical thioureas in a one-step or two-step route. In fact, dialkyl azodicarboxylate can be considered as activator for the synthesis of thioureas from amines and CS_2 by increasing the leaving character of the sulfur atom in the dithiocarbamic acid intermediate.