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Communication

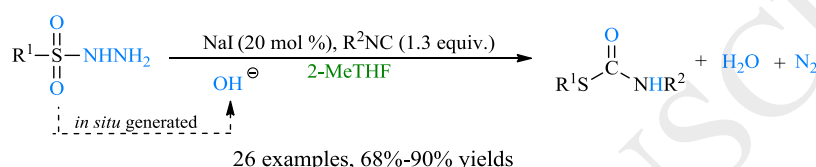
Clean preparation of *S*-thiocarbamates with in situ generated hydroxide in 2-methyltetrahydrofuranWen-Hu Bao^{a,‡}, Zheng Wang^{a,‡}, Xiao Tang^a, Yun-Fu Zhang^a, Jia-Xi Tan^{a,c}, Qin Zhu^b, Zhong Cao^b, Ying-Wu Lin^d, Wei-Min He^{a,*}^a Department of Chemistry, Human University of Science and Engineering, Yongzhou 425100, China^b Hunan Provincial Key Laboratory of Materials Protection for Electric Power and Transportation, Changsha University of Science and Technology, Changsha, 410114, China^c School of Chemistry and Chemical Engineering, Human University of Science and Technology, Xiangtan 411201, China^d School of Chemistry and Chemical Engineering, University of South China, Hengyang 421001, China

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Graphical abstract



A simple and clean protocol for the synthesis of various alkyl and (hetero)aryl *S*-thiocarbamates was established. The usage of *in situ* generated hydroxide as both an oxygen source and hydrogen source as well as biomass-derived 2-methyltetrahydrofuran as a green reaction medium, the avoidance of phosphorus-containing reductant, and the generation of harmless water and nitrogen as the side-products have given the present method atom-economy and environmental friendliness.

Abstract

A simple and clean protocol for the synthesis of various alkyl and (hetero)aryl *S*-thiocarbamates was established. The usage of *in situ* generated hydroxide as both an oxygen source and hydrogen source as well as biomass-derived 2-methyltetrahydrofuran as a green reaction medium, the avoidance of phosphorus-containing reductant, and the generation of harmless water and nitrogen as the side-products have given the present method atom-economy and environmental friendliness.

Keywords:

Green chemistry

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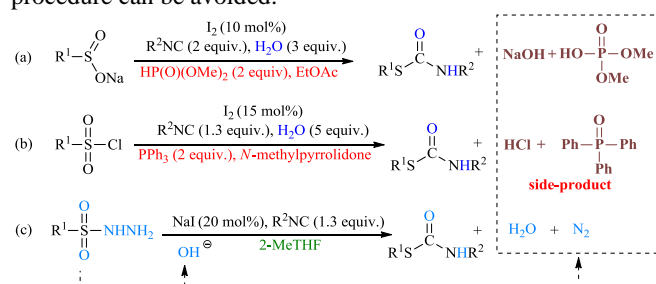
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Green chemistry aims at the employment of renewable environment-benign materials as well as minimizing the generation of chemical waste, and it is of particular significance to develop sustainable synthetic protocols for that purpose. For most chemical synthesis, a large amount of petroleum solvents are required to facilitate the reaction process, which not only consumes many non-renewable fossil resources but also results in serious environmental issue. Therefore, a lot of effort has been paid to substitute conventional hazardous organic solvents with eco-friendly ones to conserve non-renewable fossil fuels [1]. Typical examples include biomass-derived solvents [2], ionic liquid [3], and water [4], which are either abundant in nature or not limited by petroleum resources. Of the developed biomass-derived solvents, 2-methyltetrahydrofuran (2-MeTHF) is a rising star which has drawn increasing attention, because it can be obtained from biomass feedstocks as a safe and innocuous solvent, allowing an exposure in human up to 6.2 mg per day, and it is down gradable when subjected to environmental factors like ambient air or sunlight. Therefore, being as a suitable green solvent, it is in line with the 3rd (less hazardous chemical synthesis), 5th (safer solvents and auxiliaries), 7th (use of renewable

feedstocks) and the 10th (design for degradation) principles of green chemistry, and during the past years a lot of synthetic reactions have been executed by using 2-MeTHF as the reaction medium [5].

Sulfur-containing compounds have received considerable attention from organic and medicinal chemists due to their versatility in organic synthetic procedures and their valuable biological activities [6]. Among them, the *S*-thiocarbamates is an essential ingredient in many pharmaceuticals and agrochemicals, and they have also been employed as important building block in organic synthesis [7]. During the past few decades, numerous efforts have been made to prepare such motifs. However, most synthetic protocols have one or more disadvantages, such as the usage of highly harmful chemical reactants (monoxide, phosgene, isocyanates and thiols), harsh reaction conditions and narrow scopes [8]. Recently, Wei and coworkers pioneered the molecular iodine-catalyzed synthesis of thiocarbamates through multicomponent reaction [9] of aryl sodium sulfinates, isonitriles and water in the presence of dimethyl phosphite (2 equiv.) as the reductant in ethyl acetate (EtOAc) [10]. Very recently, our group developed the I₂-catalyzed synthesis of thiocarbamates with sulfonyl chlorides using triphenylphosphine (PPh₃, 2 equiv.) as the reductant in *N*-methylpyrrolidone (NMP) [11]. However, these methods employed a lot of petroleum based volatile organic chemicals as the reaction medium. Moreover, they still require a large amount of toxic phosphorus-containing compounds as the reductants, thus plenty of harmful chemical waste is inevitably produced and the tedious organic solvent exaction is inevitable.

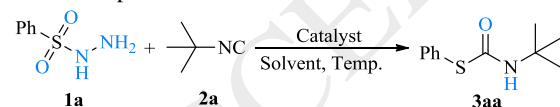
As a part of our research program in green chemistry [12], herein, we wish to report a simple and eco-friendly protocol for the clean preparation of *S*-thiocarbamates using 2-MeTHF as the solvent (Scheme 1c). The remarkable achievements of our developed catalytic reaction are: (1) neither petroleum-solvent nor harmful phosphorus-containing reductant is required; (2) *in situ* generated hydroxide instead of external water serves as the reductant; (3) water and nitrogen are generated as clean side-products, thus the tedious extraction procedure can be avoided.



Scheme 1. Synthesis of *S*-thiocarbamates.

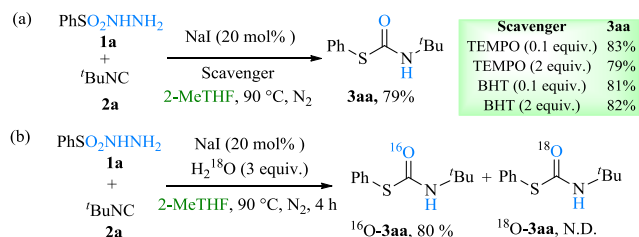
Benzenesulfonylhydrazine (**1a**) with *tert*-butylisocyanide (**2a**) was chosen as a model reaction for the condition optimization. By employing 10 mol% KI as a catalyst under an air atmosphere at 90 °C, a 64% NMR yield of *S*-phenyl *tert*-butylcarbamothioate (**3aa**) was obtained after 4 h when 2-MeTHF was applied as a reaction medium (Table 1, entry 1). To increase the reaction efficiency, various other catalysts (entries 2-7) were investigated and the results showed that NaI was a superior catalyst affording a 69% yield (entry 2). The exploration on the suitable loading of NaI (entries 8-10) revealed that 20 mol% NaI (entry 8) was an optimal amount for this transformation. No further improvement was observed when other solvents, such as THF, DMF, EtOAc, 1,4-dioxane, DMSO, *N*-Methyl pyrrolidone (NMP) and water (entries 11-17) was used instead of 2-MeTHF. No improvement in the reaction efficiency was observed when surfactant (10 wt% sodium dodecyl sulfate) was employed (entry 18). Reaction temperature assessment (entries 19 and 20) showed that 90 °C was an appropriate reaction temperature for the reaction. Changing the air atmosphere to nitrogen atmosphere elevated the reaction efficiency and the desired **3aa** was generated in an 85% NMR yield (entry 21). Performing the reaction under oxygen atmosphere did not provide improved yield of the desired product (entry 22). Control experiment revealed that the NaI catalyst was essential for the novel eco-friendly thiocarbamation reaction (entries 23).

Table 1. Optimization of reaction conditions.^a



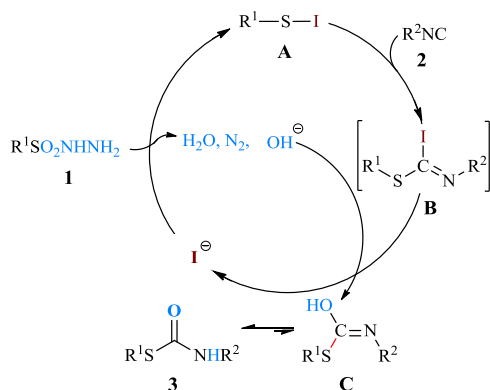
Entry	Cata. (mol%)	Solvent	Temp. (°C)	Yield (%) ^b
1	KI (10)	2-MeTHF	90	64
2	NaI (10)	2-MeTHF	90	69
3	NH ₄ I (10)	2-MeTHF	90	32
4	TBAI (10)	2-MeTHF	90	46
5	HI (10)	2-MeTHF	90	56
6	NIS (10)	2-MeTHF	90	47
7	I ₂ (10)	2-MeTHF	90	43
8	NaI (20)	2-MeTHF	90	74
9	NaI (30)	2-MeTHF	90	74
10	NaI (5)	2-MeTHF	90	50
11	NaI (20)	THF	90	58
12	NaI (20)	DMF	90	51
13	NaI (20)	EtOAc	90	37
14	NaI (20)	1,4-Dioxane	90	52
15	NaI (20)	DMSO	--	trace
16	NaI (20)	NMP	90	trace
17	NaI (20)	H ₂ O	90	28

in an ionic pathway. Performing the reaction with three equiv. of H_2^{18}O , no ^{18}O -**3aa** was observed by GC-MS, suggesting that the oxygen atom of carbamothioate did not originate from water (Scheme 4b).



Scheme 4. Control experiments.

Based on the aforementioned experimental results and the related studies [10,11], a proposed reaction pathway was illustrated in Scheme 5. First, sulfonyl hydrazide **1** with catalytic amount of iodide resulted in the formation of intermediate R-S-I (**A**) with the release of N_2 , H_2O and hydroxide (OH^-) [13]. Subsequently, the reaction of isonitrile **2** with intermediate **A** generated the intermediate **B**, which was attacked by OH^- to produce carbonimidothioate intermediate **C** and regenerated the iodide ion to complete the catalytic cycle. Finally, the intermediate **C** upon tautomerization (*i.e.*, migration of proton) formed the target product **3**.



Scheme 5. Plausible reaction mechanism.

In conclusion, a simple and clean protocol for the synthesis of *S*-thiocarbamates has been established. The usage of *in situ* generated hydroxide both as an oxygen source and hydrogen source as well as 2-methyltetrahydrofuran as a green reaction medium, and the avoidance of phosphorus-containing reductant have made the present method atom-economic and environmentally friendly. A series of alkyl and (hetero)aryl *S*-thiocarbamates were prepared in good to excellent yields. In the viewpoint of green and sustainable chemistry, this current protocol is very attractive compared with the previous reports, owing to the avoidance of non-renewable petroleum-based solvents, clean water and nitrogen as the side-products, easy operation and simple work-up (without extraction). This research could open the possibilities in the future application of biomass resource and provide new approach for the utilization of side-product instead of external additives.

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