



A facile method for the preparation of carbodiimides from thioureas and (Boc)₂O

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ABSTRACT

A concise method for the preparation of carbodiimides from thioureas using di-*tert*-butyl dicarbonate [(Boc)₂O] as the dehydrosulfurizative reagent has been developed. Using DMAP as the catalyst, a variety of symmetric and asymmetric 1,3-diaryl thioureas were converted into the corresponding carbodiimides efficiently in a short time.

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Introduction

Carbodiimides are a class of especial heterocumulene compounds bearing N=C=N skeletons. They have played a decisive role in synthetic organic chemistry. Their particularly significant uses are as condensing agents in the synthesis of esters, amides, lactams, peptides, and nucleotide.¹ Owing to the especial structure of carbodiimides, they have shown a broad application as synthetic intermediates in the synthesis of diverse guanidines,² amidines,³ and heterocycles⁴ etc. through nucleophilic addition, cycloaddition, or cascade reactions.¹ Steric hindered carbodiimides are also one of the most important precursors used for the preparation of various *N*-donor ligands and metal complexes.⁵ A lot of methods have been developed for their preparation.⁶ Dehydrosulfurization of thioureas and dehydration of ureas represent the two most widely used strategies.¹ In the case of dehydrosulfurization of thioureas, mercuric oxide (HgO) and sulphonyl chloride have remained as the most frequently used reagent so far (Scheme 1).⁷ However, the high toxicity of HgO restricts its large-scale use. The sulphonyl chloride has the disadvantage of leading to sulfonothioic acid byproducts. Oxidation or thioureas with molecular iodine or hypervalent iodine is another commonly used approach.⁸ But, element sulphur or aryl iodide is generated as the byproducts. In addition to these, the cross-coupling of isocyanides with amines,⁹ dehydrogenative desulfurization of thioureas using hydrosilane,¹⁰ di-2-pyridyl thionocarbonate (DPT),¹¹ dibromotriphenylphos-

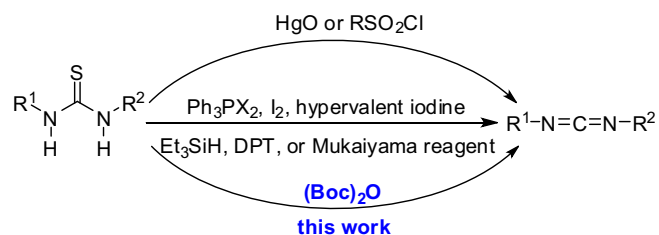
phorane,¹² or Mukaiyama reagent¹³ have also been reported (Scheme 1). Drawbacks of these methods are the use of expensive reagents, transition metals, or the formation of phosphorous and 2-hydroxypyridine byproducts. Furthermore, most of these methods needed tedious work-up procedure. These inspire us to develop a more concise and cleanly method to access them. Recently, using bis(trichloromethyl)carbonate (BTC) or di-*tert*-butyl dicarbonate [(Boc)₂O] as the desulfurylating reagent for the preparation of isothiocyanates from dithiocarbamates attracts our attention.¹⁴ In their procedures, only HCl, S=C=O, and tertiary butanol are generated as the byproducts, which can be easily removed. We wondered whether the BTC and (Boc)₂O can react with thioureas through a similar process to afford carbodiimides. If it is feasible, it will be the greenest approach to synthesize carbodiimides. The reaction of thioureas with BTC has been reported to form 3-aryl-4-(arylimino)-1,3-thiazetidin-2-ones through a double nucleophilic substitutions.¹⁵ Only sterically hindered thioureas provided carbodiimides. Herein, we reported the base-catalyzed reaction of thioureas with (Boc)₂O for the synthesis of carbodiimides.

Results and discussion

To validate the feasibility of a base catalyzed-desulfurization of thioureas, 1,3-bis(4-methylphenyl)thiourea (**1a**) was chosen as the model substrate to react with (Boc)₂O. In a preliminary experiment, **1a** was reacted with 1.1 equiv of (Boc)₂O in the presence of 0.2 equiv of 4-dimethylaminopyridine (DMAP) in acetonitrile at room temperature. Delightfully, the reaction proceeded quickly and was completed within half an hour. The main product carbodi-

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Scheme 1. Preparation of carbodiimides from thioureas.

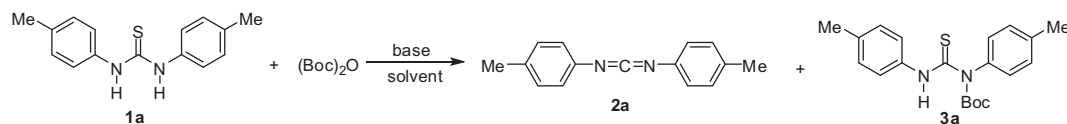
imide **2a** was obtained in 60% yield accompanied by 25% yield of *N*-Boc substituted thiourea **3a** as the byproduct (Table 1, entry 1). In order to improve the selectivity, more reaction conditions were screened (Table 1). At first, the solvent effect was evaluated with DMAP as the base catalyst (Table 1, entry 1–6). Among all the tested solvents (CH₃CN, EtOH, THF, EtOAc, CHCl₃, DMF), the generation of **3a** was inevitable. No reaction occurred in ethanol due to the very poor solubility of thiourea. The THF gave a comparable yield of **2a** with that of CH₃CN. When CHCl₃ was used as the solvent, the selectivity was reversed and the *N*-substituted thiourea **3a** became the main product. When the reaction was carried out in EtOAc, the *N*-substituted thiourea **3a** could be suppressed effectively (5%) and **2a** was obtained in 84% yield (Table 1 entry 4). DMF was also a good solvent, albeit giving a slightly lower yield. Either improving or decreasing the temperature had no significant influence on the reaction. (Table 1, entries 7 and 8). Reducing the amount of DMAP to 0.05 or 0.1 equiv resulted in a noticeable decrease of the yield of **2a** (Table 1, entries 9 and 10). We noticed that the **2a** has a poor solubility in ethyl acetate. When 0.2 equiv of DMAP was used, the dispersed suspension mixture turned into homogeneous phase within 5 min, whereas, the thiourea **2a** was in a suspension state all the time when using either 0.05 or 0.1 equiv of DMAP as the base. This would be the main reason for the tremendous contrast in the yield of **2a** (Table 1, entries 4, 9, and 10). Base screening revealed that only DMAP was the effective

base catalyst in this transformation and other commonly used base such as Et₃N, pyridine, DBU, K₂CO₃ did not show catalytic activity (Table 1, entries 11–14). The DABCO gave a poor result with the remainder of many unreacted starting materials (Table 1 entry 15). Finally, the optimal reaction conditions were established by employing DMAP (0.2 equiv) as the base and EtOAc as the solvent.

With the optimal conditions in hand, the versatility of this methodology was examined and the results were shown in Table 2. For the diaryl substituted thioureas, strong electronic effect of the substituent groups on the phenyl ring was observed. All the symmetrical thioureas with electron-donating groups (**1a–f**) afforded the corresponding carbodiimides (**2a–f**) in moderate to good yields while the symmetric aromatic thioureas with even slight electron-withdrawing group (**1g**) gave a trace amount of product (**2g**). When the reaction temperature was increased to 70 °C, **2g** could be produced in 41% yield. In the case of asymmetric thioureas, acceptable yields of carbodiimides (**2h–m**) could be obtained when no strong electron-withdrawing group located on each of the phenyl ring. In the case of substrates **1l** and **1m**, in which a weak electron-withdrawing group connected on one of the phenyl ring, only moderate yield of **2l** (50%) and **2m** (59%) was achieved. Increasing the temperature to 70 °C improved the yield to 68% and 70%, respectively. When one of the phenyl rings linked with a moderate electron-withdrawing group such as ester group (**1n**), only trace of carbodiimide was achieved even reacting at 70 °C. When one of the aryl groups was replaced by an alkyl group, regrettably, no desired product was achieved (Scheme 2). For example, the reaction of **1q** with (Boc)₂O delivered the regioselective *N*-Boc substituted thiourea **3q**. The dibutyl substituted thiourea **1r** gave the same result as **1q**.

To assess the practicality of this protocol, a large-scale experiment was carried out by performing the reaction of 10 mmol of **1b** with 1.1 equiv of (Boc)₂O in 40 mL ethylacetate in the presence of 0.2 equiv of DMAP (Scheme 3). To our disappointment, the reaction efficiency was far away from the small amount operation. The selectivity decreased notably and the **2b** was obtained in 40% yield accompanied by 33% yield of **3b**. We found when the reaction tem-

Table 1
Screening of the conditions.^a



Entry	Base catalyst	Temperature (°C)	Solvent	1a :(Boc) ₂ O:base	Time (h)	Yield (%) of 2a	Yield (%) of 3a
1	DMAP	rt	CH ₃ CN	1:1.1:0.2	0.5	60	25
2	DMAP	rt	EtOH	1:1.1:0.2	4	0	0
3	DMAP	rt	THF	1:1.1:0.2	0.5	65	15
4	DMAP	rt	EtOAc	1:1.1:0.2	0.5	84	5
5	DMAP	rt	CHCl ₃	1:1.1:0.2	0.5	28	58
6	DMAP	rt	DMF	1:1.1:0.2	1	77	7
7	DMAP	0	EtOAc	1:1.1:0.2	1	82	5
8	DMAP	50	EtOAc	1:1.1:0.2	0.5	78	9
9	DMAP	rt	EtOAc	1:1.1:0.1	4	15	12
10	DMAP	rt	EtOAc	1:1.1:0.05	4	10	11
11	K ₂ CO ₃	rt	CH ₃ CN	1:1.1:0.2	2	trace	trace
12	Et ₃ N	rt	EtOAc	1:1.1:0.2	5	0	0
13	Pyridine	rt	EtOAc	1:1.1:0.2	5	0	0
14	DBU	rt	EtOAc	1:1.1:0.2	5	0	0
15	DABCO	rt	EtOAc	1:1.1:0.2	5	11	13

^a Unless notified, the reactions were carried out (**1a**, 0.5 mmol) in 2 mL of solvent.

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