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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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Keywords: carbodiimides di-tert-butyl dicarbonate (Boc)₂O thioureas

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 nucleophlic 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 wildly 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, dehydrogenative desulfurisation of thioureas using hydrosilane,¹⁰ di-2-pyridyl thionocarbonate (DPT),¹¹ dibromotriphenylphos phorane,¹² or Mukaiyama reagent¹³ have also been reported

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(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 nuclephilic 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.

Table 1 Screening of the Conditions^a

	Me S S	∠Me + (Boc) ₂ O <u>bas</u> solv	ent Me-√		Me —Me +		Me
	Н Н 1а			2a		H Boc 3a	
Entry	Base catalyst	Temperature (°C)	Solvent	1a:(Boc) ₂ O:base	Tme (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_2CO_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
^{<i>a</i>} Unless r	otified, the reactions we	re carried out (1a, 0.	5 mmol) in 2 r	nL of solvent.			

Results and discussion

To validate the feasibility of a base catalyzedthioureas, desulfrurization of 1,3-bis(4methylphenyl)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 carbodiimide 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 Et_3N , pyridine, DBU, K_2CO_3 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 11 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 alky 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**.

Table 2 DMAP-Catalyzed Reaction of Thioureas with (Boc)₂O for the Preparation of Carbodiimides^a

S

		1	eury acetate	2		
Entry	Substrate	\mathbb{R}^1	\mathbb{R}^2	Product	Time (h)	Yield(%
1	1a	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	2a	0.5	84
2	1b	C_6H_5	C_6H_5	2b	0.5	83
3	1c	4-OCH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	2c	0.5	71
4	1d	2-OCH ₃ C ₆ H ₄	2-OCH ₃ C ₆ H ₄	2d	0.5	80
5	1e	$2-CH_3C_6H_4$	$2-CH_3C_6H_4$	2e	0.5	75
6	1f	2,4-(CH ₃) ₂ C ₆ H ₃	2,4-(CH ₃) ₂ C ₆ H ₃	2f	0.5	62
7	1g		2-	0.5	trace	
		Ig	$4-CIC_6\Pi_4$	$4 - C_1 C_6 \Pi_4$	2g	0.5
8	1h	3,4-(OCH ₃) ₂ C ₆ H ₃	3,4-(OCH ₃) ₂ C ₆ H ₃	2h	0.5	70
9	1i	C_6H_5	$4-CH_3C_6H_4$	2i	0.5	80
10	1j	C_6H_5	$3-CH_3C_6H_4$	2j	0.5	73
11	1k	C ₆ H ₅	$4\text{-OCH}_3C_6H_4$	2k	0.5	79
10	11	C II		21	0.5	50
12	11	C_6H_5	$4-FC_6H_4$	21	15 min	68^b
13	1	CII			0.5	59
	Im	$C_6\Pi_5$	$4 - C_1 C_6 \Pi_4$	2m	15 min	70^b
14	1			0.5	trace	
	In	C_6H_5	$4-COUEtC_6H_4$	211	15 min	trace
15	10	C ₆ H ₅	3,4-(OCH ₃) ₂ C ₆ H ₃	20	0.5	81
16	1p	C ₆ H ₅	1-Naphthyl	2p	0.5	67

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 temperature was increase to 70 °C and the $(Boc)_2O$ was added dropwise to the mixture of **1a** and



condition A: $(Boc)_2O$ was added in one protion, stirred at rt. for 0.5 h conditon B: $(Boc)_2O$ was added dropwise within 3-5 min at 70 $^{\circ}C$ and then continued to stir for 15 min





Scheme 3 Large scale synthesis of 2b

DMAP in ethyl acetate the yield and selectivity could be improved obviously, affording 70% yield of 2b with the ratio of 2b/3b as 5.4/1.

All the known compounds were confirmed throuth comparison of their spectral data with those reported in the literature. The identification of new compounds was fully confirmed by their MS, ¹H NMR, and ¹³C NMR spectra (see Supporting Information).

A plausible mechanism for the formation of carbodiimides was illustrated in Scheme 4. Unlike the reaction of thiourea with alkyl halide produced exclusively the *S*-alkyl substituted product,¹⁶ the reaction of thioureas with $(Boc)_2O$ afforded *S*-Boc substituted intermediates **4** and *N*-Boc substituted thioureas **3**, respectively. The intrinsic reasons that influence the distribution of **3** and **4** was not very clear now. Decomposition of the intermediates **4** under basic condition delivered the carbodiimides **2** and released S=C=O and t-BuOH simultaneously. In large scale operation, the gaseous S=C=O could be absorbed with aqueous sodium hydroxide.



Scheme 4 Proposed mechanism

Conclusions

In summary, a concise method for the preparation of carbodiimides through the DMAP-catalyzed reaction of thioureas with $(Boc)_2O$ has been developed. The method shows several attractive merits such as rapid, mild conditions, simple work-up procedure, and low waste generation. Particularly, no more organic wastes are generated beside the S=C=O and t-BuOH, which can be easily removed from the reaction mixture. The shortcoming of the present method is that it only suitable for the synthesis diarylcarbodiimides.

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Supplementary Material

General synthetic procedures, characteristic data, and NMR spectra of the products can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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Highlight

1. A new method for the synthesis of carbodiimides from thioureas catalyzed by DMAP is developed.

ACCEPTER 2. Di-tert-butyl dicarbonate [(Boc)2O] is used as a new dehydrosulfurizative reagent.