o-Iodoxybenzoic Acid Mediated Oxidative Desulfurization of 1,3-Disubstituted Thioureas to Carbodiimides

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Abstract: An efficient and mild oxidative desulfurization procedure using *o*-iodoxybenzoic acid has been developed for the synthesis of carbodiimides starting from easily synthesizable 1,3-disubstituted thioureas.

Key words: *o*-iodoxybenzoic acid, oxidation, desulfurization, thiourea, carbodiimide

Dicyclohexylcarbodiimide (DCC) is used in automated stepwise synthesis of polypeptides to activate the carboxyl group, for example, in the Merrifield method for the synthesis of the polypeptide ribonuclease A, consisting of 124 amino acids.[1] Oligonucleotides are also synthesized using carbodiimides in automated condensation steps.[2] Carbodiimides have been extensively used in organic synthesis as auxiliary reagents in reactions such as Moffatt oxidation of primary alcohols to aldehydes using DCC/DMSO combination, conversion of alcohols or phenols into hydrocarbons via hydrogenation of acylisoureas derived from the corresponding carbodiimide adducts, and dehydration of aldoximes to nitriles and others.[3] Carbodiimides have also found use as key synthetic intermediates in agricultural chemicals[4] and pharmacologically active compounds viz. substituted indoles, quinolidines, and isoquinolines displaying strong cytostatic antitumor activity.[5] Aromatic carbodiimides have huge industrial applications such as stabilizers for polyester-based polyurethanes.[6]

Methods available for synthesis of carbodiimides can be broadly classified into three categories:

(i) Thermolysis–decarboxylation of isocyanates.[7] Generally, these reactions are carried out at high temperature in the presence of metal catalyst and silicon-based reagents.[7b] However, this approach suffers from drawbacks including low yields, use of toxic transition metals such as palladium and nickel, toxic waste generation and formation of dimers or polymers.[7c]

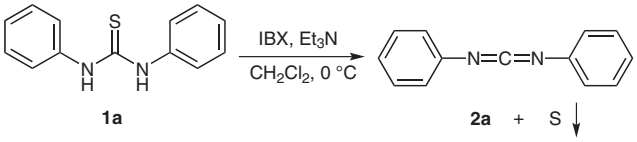
(ii) Dehydration of ureas.[8] Dehydration is effected using phosgene and alkyl/arylsulfonyl reagents in combination with bases. Although the process generally results in good yields, the major concern is formation of highly reactive side products such as *N*,*N*-dimethylcarbamoyl chloride, excessive use of triethylamine[8a] as base and possibility of product instability during isolation after aqueous workup.

(iii) Desulfurization of thioureas.[9,10] This represents the most general method of synthesis. Desulfurization is effected by reagents such as methanesulfonyl chloride,[9b] sulfur dioxide and thionyl chloride,[9g] phosgene,[9j] mercuric oxide[9k,l] and, very recently, molecular iodine.[10] Drawbacks of these methods are use of noxious and toxic reagents and removal of phosphorous byproducts formed during Mitsunobu reaction.[9g,h] The molecular-iodine-based method is mild and efficient but suffers from the limitation of not being applicable for the synthesis of bis-dialkylcarbodiimides.

The rich chemistry exhibited by hypervalent organoiodine(V) reagents such as *o*-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP) is attributed to the central iodine atom having strong electrophilic character coupled with the leaving ability of the phenyliodino group. The soft electrophilic iodine center can be attacked by a wide range of nucleophiles including oxygen, nitrogen, and sulfur nucleophiles. Many transformations have been reported in the literature with sulfur nucleophiles[11] including ring expansion of dithianes,[11d] sulfoxidation,[11f] and thioacetal cleavage.[11g] Our group is extensively working on hypervalent iodine(V) reagents,[12] and has recently reported oxidative dimerization of thioamides to 1,2,4-thiadiazoles with removal of sulfur.[12b]

Desulfurization of 1,3-disubstituted thiourea with the hypervalent organoiodine(III) reagent, diacetoxyiodobenzene (DIB) to form N-acylated ureas via carbodiimide intermediates has been reported.[13] Based on this, we hypothesized that, in the absence of reactive nucleophiles such as acetate ion under mild reaction conditions, it should be possible to isolate the carbodiimide intermediate and we succeeded.

When 1,3-diphenylthiourea (**1a**) was added portionwise to a cooled solution of IBX and triethylamine in CH_2Cl_2, thiourea was rapidly converted into carbodiimide **2a** in high yield with precipitation of sulfur (Scheme 1).



Scheme 1 Reaction of 1,3-diphenylthiourea with IBX

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The reaction conditions were optimized with respect to solvent, temperature, and molar ratio. Reaction occurred in different aprotic solvents such as DMF, EtOAc, MeCN, $CHCl_3$, CH_2Cl_2, THF, and toluene with yields in the range of 60–90% while a higher yield was observed in CH_2Cl_2. At room temperature a number of side products was observed (by TLC). For complete reaction a molar ratio of 1:1:2 for substrate/IBX/triethylamine was found to be satisfactory.

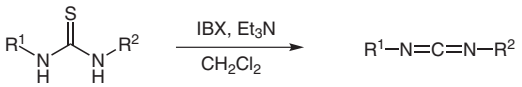
To establish the generality of the reaction, a variety of 1,3-disubstituted thioureas was subjected to the optimized conditions, and the results are summarized in Table 1. In general, reactions were very fast and yields were comparable irrespective of the nature of substitution on the aromatic rings (entries 2–6). Reaction also proceeded smoothly with sterically hindered 1,3-disubstituted thioureas (entries 2 and 10).

In the case of 1,3-dicyclohexylthiourea reaction was very slow at 0 °C but proceeded smoothly at room temperature for two hours to give **2h** in 45% yield with recovery of starting material and without formation of byproducts (entry 8). The reaction was equally efficient with unsymmetrical thioureas (entries 9–14). The rate of hydration of carbodiimides is well documented in the literature and has been shown to be relatively slow[14] and so the rapid reaction, mild conditions, and nonaqueous workup during isolation of the carbodiimides meant that this was not a problem in the present method.

A plausible mechanism for the formation of carbodiimides is presented in Scheme 2. Precipitation of sulfur during the reaction supports the postulated mechanism. Recovery of the generated trivalent iodine reagent **A** for recycling after re-oxidation to IBX by Oxone® was also possible.

In summary, an efficient method based on oxidative desulfurization of 1,3-disubstituted thioureas using IBX has been developed for the synthesis of carbodiimides. The mild reaction conditions, ease of isolation, and suitability for a wide range of substrates makes this approach superior to other syntheses. IBX oxidations are selective and tolerate a wide range of functional groups; therefore the present method could be easily extended to carbodiimide-

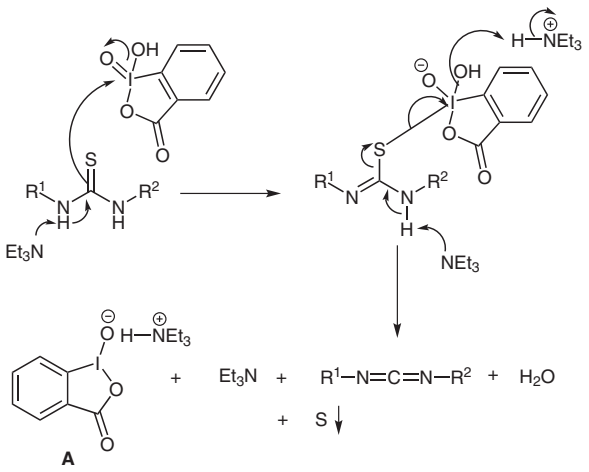
Table 1 Preparation of Carbodiimides from 1,3-Disubstituted Thioureas[a]



1 **2**

Entry	Substrate **1**			Time (min)	Product **2**	Yield (%)
Symmetrical ($R^1 = R^2$)						
1	**1a**	Ph		10	**2a**[15]	90
2	**1b**	2-$OMeC_6H_4$		10	**2b**	88
3	**1c**	3-MeC_6H_4		10	**2c**	90
4	**1d**	4-$OMeC_6H_4$		10	**2d**	92
5	**1e**	4-ClC_6H_4		10	**2e**	88
6	**1f**	4-BrC_6H_4		10	**2f**	88
7	**1g**	Bn		10	**2g**	86
8	**1h**	*c*-Hex		120	**2h**	45[b]
Unsymmetrical ($R^1 \neq R^2$)						
		R^1	**R^2**			
9	**1i**	Ph	4-MeC_6H_4	10	**2i**	88
10	**1j**	Ph	2-ClC_6H_4	10	**2j**	86
11	**1k**	Ph	Bn	10	**2k**	90
12	**1l**	Ph	$C_6H_4CH(Me)$	10	**2l**	88
13	**1m**	Ph	*n*-Bu	10	**2m**	88
14	**1n**	Ph	*c*-Hex	10	**2n**	85

[a] Reaction conditions: Thiourea (1 equiv), IBX (1 equiv), Et_3N (2 equiv) in CH_2Cl_2 at 0 °C.
[b] Reaction carried out at r.t.



Scheme 2 Plausible mechanism for the formation of carbodiimides from 1,3-disubstituted thioureas

mediated reactions, and investigations in this direction are in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **Typical Procedure**
Preparation of 1,3-Diphenyl Carbodiimide 2a
To a stirred solution of IBX (0.6 g, 2.19 mmol) and Et_3N (0.6 mL, 4.38 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added 1,3-diphenylthiourea (0.5 g, 2.19 mmol) portionwise over a period of 5 min. After completion of reaction, as indicated by TLC, reaction mixture was concentrated under vacuum, and the residue was extracted with hexane (2 × 15 mL). Pure product was isolated after evaporation of the hexane extract followed by column chromatography (SiO_2, 60–120 mesh, eluent: hexane). Yield 0.38 g (90%), oily liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (m, 6 H), 7.31 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124, 125.2, 129.2, 136.2, 138.4. IR (KBr): 2140, 2110 cm^{-1}. All synthesized compounds are known compounds. Characterization data are provided as Supporting Information.

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