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Ultrasonic-assisted synthesis of carbodiimides from N,N'-disubstituted thioureas and ureas

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Abstract A facile and efficient sonochemical method for the preparation of carbodiimides from their corresponding thioureas or ureas was described. Using Ph_3P-I_2 combination in the presence of triethylamine, various diaryl, aryl–alkyl, as well as dialkyl substituted substrates could be converted into carbodiimides in good-to-excellent yields within short reaction times under mild conditions with simple experimental setup.

Graphical abstract





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Introduction

Carbodiimides are an important class of reagents which exhibit several useful applications in organic synthesis [1]. While N,N'-dicyclohexylcarbodiimide (DCC) and N,N'-diisopropylcarbodiimide (DIC) are well-known dehydrative coupling agents in peptide chemistry, a number of the titled compounds have shown a widespread use as key intermediates in the synthesis of nucleotides, glycol-conjugates, substituted guanidines, as well as various heterocycles [1–4].

Owing to the synthetic advantages of carbodiimides, several methods have been developed for their preparation. Some examples included thermolysis-decarboxylation of isocyanates [5], dehydration of ureas [6–11], dehydrosul-furization of thioureas [8, 12–17], rearrangements of amidoximes [18, 19], as well as metal-catalyzed direct condensation of an amine with an isonitrile [20, 21]. Nevertheless, there are still some limitations associated with some of the existing methods including the use of expensive or highly toxic reagents, long reaction times, harsh reaction conditions, and/or limited substrate scope. Therefore, the development of efficient protocols toward wider range of carbodiimides using low cost, easy to handle, and innocuous reagents under mild conditions is highly desirable.

Phosphine reagents have been proven to be highly powerful for various organic transformations [22]. Particularly, triphenylphosphine (Ph₃P) has been used along with carbon tetrachloride [8, 23, 24], carbon tetrabromide [25– 27], diethyl azodicarboxylate [16], or bromine [7, 28, 29] in the synthesis of carbodiimides from N,N'-disubstituted ureas or thioureas. In several cases, triphenylphosphine dibromide has been used directly in the dehydration of a number of functionalized ureas [7, 30–36]. However, the

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reagent has to be freshly prepared and extra-dry conditions are required to achieve good conversion. To the best of our knowledge, the combination of Ph₃P with iodine which is more easy to handle has never been reported with either thiourea or urea precursors.

In the recent years, ultrasound has been increasingly applied as an effective process intensification tool for organic synthesis [37–42]. It is well known that ultrasonic energy can lead to the formation and collapse of small bubbles of gaseous substances as the ultrasonic wave is passing through the liquid media. This cavitation effect gives rise to the rate and yield enhancement in certain reactions. Compared to the conventional stirring technique, reactions under ultrasonic irradiation have often been proceeded with shorten times, improved yields, and selectivity. Thus, the use of ultrasound provides a simple yet efficient approach for promoting the traditional reactions, especially when force reaction conditions are required.

In continuation of our study involving the Ph_3P-I_2 reagent system [43–46], herein we wish to report a facile and effective sonochemical method for the synthesis of carbodiimides from thioureas and ureas using the Ph_3P-I_2 system.

Results and discussion

We start our investigation in the ultrasonic-assisted dehydrosulfurization of N,N'-diphenylthiourea. Ph₃P was used in combination with various halogenated additives in the presence of triethylamine. Typically, the reaction was carried out by a brief sonication of a mixture of Ph_3P (1.2 equiv) and the additive (1.2 equiv) in dichloromethane before adding a solution of the starting thiourea (1.0 equiv) and Et_3N (2.5 equiv) in dichloromethane. The reaction was further sonicated for 5 min, followed by isolation of the carbodiimide product.

According to Table 1, the Ph_3P-I_2 combination was the most effective system leading to 1,3-diphenylcarbodiimide in high yield (entry 5). The influence of base on the reaction efficiency was then evaluated using the mixed Ph_3P-I_2 system (entries 6–8). Apparently, changing the base from triethylamine to other bases including *N*,*N*-dimethylaminopyridine (DMAP), pyridine or imidazole led to lower yields of the product. In these reactions, the remaining thiourea indicated incompletion of the reaction under the applied conditions.

To further confirm the benefit of the ultrasound, the reaction mediated by the Ph_3P-I_2/Et_3N system was carried out under conventional stirring. Comparing with the sonochemical method (entry 5), the reaction under stirring (entry 9) required significantly longer time to produce the corresponding product in a slightly lower yield.

With the optimized reaction conditions in hand (Table 1, entry 5), the scope and the limitations of the developed protocol were further investigated using a range of N,N'-disubstituted thioureas 1 as well as ureas 2 bearing aromatic or aliphatic appendages.

Based on the results shown in Table 2, the reaction proceeded smoothly with both diaryl and aryl–alkyl (thio)ureas to afford the desired carbodiimides **3** in good-

Table 1 Dehydrosulfurization of N,N'-diphenylthiourea using different mixed reagent systems



Entry	Mixed reagent	Base	Conditions	Yield/%	
1	Ph ₃ P/CCl ₄	Et ₃ N	Sonication 5 min	70	
2	Ph ₃ P/NBS	Et ₃ N	Sonication 5 min	51	
3	Ph ₃ P/NCS	Et ₃ N	Sonication 5 min	48	
4	Ph ₃ P/Br ₂	Et ₃ N	Sonication 5 min	Complex mixture	
5	Ph ₃ P/I ₂	Et ₃ N	Sonication 5 min	95	
6	Ph ₃ P/I ₂	DMAP	Sonication 5 min	74	
7	Ph ₃ P/I ₂	Pyridine	Sonication 5 min	52	
8	Ph ₃ P/I ₂	Imidazole	Sonication 5 min	43	
9	Ph ₃ P/I ₂	Et ₃ N	Stirring 60 min	90	

Reaction conditions: 0.0872 g triphenylphosphine (0.33 mmol), halogenated additive (0.33 mmol), 0.0639 g N,N'-diphenylthiourea (0.275 mmol), and base (0.69 mmol) in 2 cm³ CH₂Cl₂ at room temperature; *NBS N*-bromosuccinimide, *NCS N*-chlorosuccinimide

Table 2 Ultrasound-assisted synthesis of carbodiimides 3 from 1,3-disubstituted thioureas 1 or ureas 2

$$R^{1} \underset{H}{\overset{N}{\longrightarrow}} R^{2} \underset{H}{\overset{PPh_{3}, l_{2}}{\overset{PPh_{3}, l_{2}}{\overset{PPh_{3}, l_{2}}{\overset{PPh_{3}, l_{2}}{\overset{PPh_{3}, l_{2}}}}} \\ 1 (X = S) \\ 2 (X = O) \\ R^{2}$$

Entry	1 or 2	R^1	R ²	Time/ min	Yield of 3/% [References]
1	1a	C ₆ H ₅	C ₆ H ₅	5	3 a, 95 [15]
2	1b	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	5	3b , 89 [15]
3	1c	C ₆ H ₅	PhCH ₂	10	3c , 90 [47]
4	1d	C ₆ H ₅	C ₆ H ₁₁	10	3d , 88 [15]
5	1e	C ₆ H ₅	butyl	10	3e , 89 [47]
6	1f	C ₆ H ₅	isopropyl	15	3f , 85 [48]
7	1g	C ₆ H ₅	<i>tert</i> -butyl	15	3g , 86 [49]
8	1h	$4-CH_3C_6H_4$	C ₆ H ₁₁	10	3h , 87 [50]
9	1i	$4-ClC_6H_4$	C ₆ H ₁₁	10	3i , 90 [50]
10	1j	$4-FC_6H_4$	C ₆ H ₁₁	10	3j , 92 [5 1]
11	1k	$4-NO_2C_6H_4$	C ₆ H ₁₁	5	3k , 95 [15]
12	11	C ₆ H ₁₁	C ₆ H ₁₁	60	31 , 81 [15]
13	2a	C ₆ H ₅	C ₆ H ₅	5	3a , 92 [15]
14	2b	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	10	3b , 85 [15]
15	2h	$4-CH_3C_6H_4$	C ₆ H ₁₁	10	3h , 83 [50]
16	2m	$4-NO_2C_6H_4$	<i>tert</i> -butyl	10	3m , 86 [49]
17	21	C ₆ H ₁₁	C ₆ H ₁₁	60	31 , 78 [15]

A mixture of 0.0844 g iodine (0.33 mmol) and 0.0872 g triphenylphosphine (0.33 mmol) in 2.0 cm³ CH₂Cl₂ was added a solution of thiourea or urea (0.275 mmol) and 0.0701 g triethylamine (0.69 mmol) in 2 cm³ CH₂Cl₂, followed by sonication for a specified time

to-excellent yields. Under ultrasonic irradiation, the presence of electron-donating (e.g., $-CH_3$) or electronwithdrawing substituents (e.g., -CI, -F, and $-NO_2$) on the aryl moiety of the substrates did not significantly affect the yields or the rate of the reaction. The respective carbodiimides were obtained in good yields within comparable times (entries 8–13). However, slightly longer times were required when increasing the bulkiness of the alkyl substituents (entries 6, 7) or when changing the substrate to those containing 1,3-dialkyl groups (entries 12 and 17).

It is important to note that the conversion of 1,3-dialkyl substituted thioureas or ureas into the respective carbodiimides is generally much more difficult than the bis-aryl or arylalkyl substrates. As summarized in Table 3, all the reported reactions toward the synthesis of N,N'-dicyclohexylcarbodiimide (**31**) were rather sluggish requiring harsh conditions or long reaction times. A related system using iodine alone in the dehydrosulfurization of 1,3-dicyclohexylthiourea (entry 7) gave no conversion [14]. In comparison with other reported procedures, our method (entry 8) provided rapid access to carbodiimide **31** in satisfactory yield using simple and low-cost reagents.

In a control experiment where the reaction of the thiourea **11** was carried out under conventional stirring method, only 56 % yield of the product was obtained after 16 h. Evidently, the reaction was efficiently promoted by ultrasound irradiation leading to a significant decrease in the reaction times from 16 to 1 h with higher yield.

Conclusion

In summary, we have developed a simple and effective sonochemical method for the preparation of carbodiimides from their corresponding 1,3-disubstituted thioureas and ureas. Unlike other existing phosphine-mediated methods which only work well toward N,N'-diaryl or N-alkyl, N'-aryl carbodiimides and required extra-dry conditions, our protocol enables rapid synthesis of a wide range of carbodiimides including the N,N'-dialkyl derivatives using

Table 3 Comparison of the reported methods for the synthesis of N,N'-dicyclohexylcarbodiimide (31) under different conditions



Entry	Conditions	Х	Time/h	Yield/% [References] 95 [17]
1	(EtO) ₃ SiH, iron catalyst, THF, 60 °C	S	24	
2	N-Methyl-2-pyridinecarbamoyl chloride, DMAP, Et ₃ N, THF	S	7	84 [19]
3	p-(HO(Ph)IOS(=O) ₂)C ₆ H ₄ Me, Et ₃ N, AcOEt, 0 °C	S	8	67 [15]
4	Phosphorous pentoxide, pyridine, reflux	0	2.25	76 [10]
5	o-Iodoxybenzoic acid, Et ₃ N, CH ₂ Cl ₂ , 0 °C-RT	0	2	45 [47]
6	4-BrC ₆ H ₄ SO ₂ Cl, K ₂ CO ₃ , BnN(CH ₃) ₃ Cl, CHCl ₃ , reflux	0	NA	50 [6]
7	I ₂ , Et ₃ N, AcOEt, 0 °C	S	NA	0 [14]
8	Ph ₃ P, I ₂ , Et ₃ N, CH ₂ Cl ₂ , sonication, RT	S,O	1	78, 81 [this work]

low-cost and easy to handle reagents with simple experimental setup.

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Experimental

All compounds were used as received from the suppliers. Ultrasonic bath equipped with thermostat with operating at 37 kHz [Elmasonic S 30(H), Germany] was used for all ultrasonic-assisted synthesis. The reaction was monitored by thin-layer chromatography carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (245 nm). Column chromatography was performed over silica gel 60 (70–230 mesh, MERCK, Germany). Melting points were determined using SANYO, Gallenkamp apparatus at a heating rate of 10 °C/min. NMR measurements were conducted on a Bruker AVANCETM (400 MHz for ¹H NMR) using chloroform-*d* (CDCl₃) as the solvent and tetramethylsilane (TMS) as an internal standard.

General procedure for the synthesis of carbodiimide

To a solution of 0.0844 g iodine (0.33 mmol) and 0.0872 g triphenylphosphine (0.33 mmol) in 2 cm³ CH₂. Cl₂ was added a solution of thiourea or urea (0.275 mmol) and 0.0701 g triethylamine (0.69 mmol) in 2 cm³ CH₂Cl₂ under sonication. The reaction mixture was further sonicated until completion of the reaction as indicated by TLC. The crude mixture was concentrated under reduced pressure then purified by column chromatography using hexane to give the carbodiimide (see supporting information for characterization data of all products).

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