

Diethyl Chlorophosphate: A Mild and Versatile Reagent for the One-Pot Preparation of Isothiocyanates from Amines

Babak Kaboudin,* Ehsan Jafari

Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Gava Zang, Zanjan 45195-1159, Iran
 Fax +98(241)4214949; E-mail: kaboudin@iasbs.ac.ir

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Abstract: A simple, efficient, and new method has been developed for the synthesis of isothiocyanates from amines. The reaction of a variety of aromatic and aliphatic amines with carbon disulfide in the presence of diethyl chlorophosphate as an efficient reagent proceeded effectively to afford the corresponding isothiocyanates in moderate yields. This method is easy, rapid, and moderate-yielding for the synthesis of isothiocyanates from amines.

Key words: isothiocyanates, amines, diethyl chlorophosphate, phosphoroamidates

Isothiocyanates are valuable intermediates in organic synthesis.¹ The synthesis of isothiocyanates is an important objective in organic synthesis, since they have found use in the preparation of biologically active molecules and they are versatile intermediate in organic synthesis.² Isothiocyanates have also been used for the synthesis of various sulfur-containing heterocyclic compounds, for example, benzothiazines, thiohydantoin, thioquinazolones, thiopyrimidones, and thioamidazolones.³ Although there are many classical methods for the synthesis of isothiocyanates,^{4–7} these involve either long reaction times and expensive reagents or the use of very toxic reagents. Typically the procedure functions as an insertion reaction using thiocarbonyl reagents, for example, thiophosgene or dipyriddy thionocarbonate.⁸ Other electrophilic phosphorus reagents, such as triphenylphosphine dibromide, are used for the synthesis of isothiocyanates via iminophosphorane formation followed by reaction with carbon disulfide.⁹ However, these highly reactive reagents suffer from high toxicity and low selectivity and thus limit its general use. An alternative and efficient method for the synthesis of isothiocyanates proceeds by dithiocarbamate formation from the corresponding amine and carbon disulfide followed decomposition of the dithiocarbamate into an isothiocyanate.¹⁰ However, these reactions cannot be carried out in a one-step operation with the amine, carbon disulfide, and electrophilic desulfurizing reagent. The formation of a product from the amine and desulfurizing agent frequently accompanies the formation of the isothiocyanate. Recently, the chemoselective synthesis of isothiocyanates using phosphonium- and uranium-based coupling reagents together with *N,N*-diisopropylethylamine or triethylamine has

Table 1 Reaction of Aniline with Carbon Disulfide in the Presence of Diethyl Chlorophosphate under Various Conditions

$$\text{Ph-NH}_2 + \text{Cl-P(OEt)}_2 + \text{CS}_2 \longrightarrow \text{Ph-N=C=S}$$

1a 2a

Entry	Solvent ^b	Base	Time (h)	Yield ^a (%)
1	–	–	24	–
2	–	K ₂ CO ₃	24	–
3	–	K ₂ CO ₃ , NaOH	24	–
4	toluene	K ₂ CO ₃	24	–
5	toluene	K ₂ CO ₃ , NaOH	5	50
6	toluene	NaOH	5	50
7	CH ₂ Cl ₂	NaOH	24	–
8	MeCN	NaOH	24	–
9	dioxane	NaOH	24	<5

^a Isolated yield after column chromatography.

^b Reflux conditions.

been reported for the one-pot reaction of an amine, carbon disulfide, and a peptide coupling agent.¹¹ Although a variety of synthetic methods have been reported for the synthesis of isothiocyanates, a simple, one-pot, general method using easily starting materials is still lacking.

Diethyl chlorophosphate is a less reactive reagent hence the use of this reagent reduces the probability of side reactions.¹² In continuation of our interest in developing novel methodologies for organic transformations,¹³ herein we report an efficient, practical, environmentally benign, and good-yielding method for the three-component, one-pot synthesis of isothiocyanates from amines using diethyl chlorophosphate as an efficient reagent.

Initially, we carried out the three-component experiment with aniline, as a model compound, in the presence of diethyl chlorophosphate and carbon disulfide under a variety of conditions (Table 1).

In the absence of a base, aniline did not undergo the conversion reaction with a mixture of carbon disulfide and diethyl chlorophosphate (Table 1, entry 1). Recently potassium carbonate has been reported as an efficient basic catalyst for the addition of amines to electrophiles.¹⁴

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Table 2 Conversion of Amines into Isothiocyanates Using Carbon Disulfide in the Presence of Diethyl Chlorophosphate in Toluene

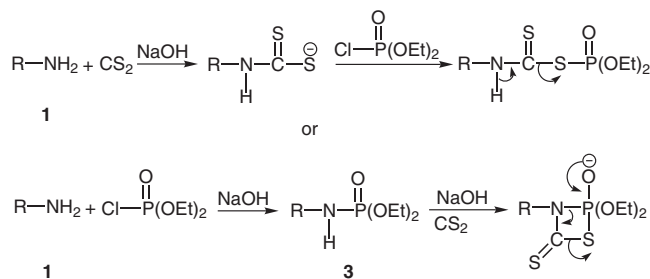
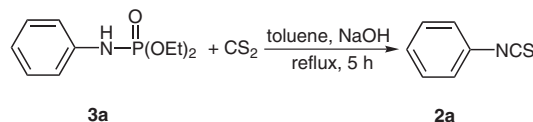
Entry	Amine	Product 2	Time ^a (h)	Yield ^b (%)	CAS Number
1		2a	5	50	103-72-0
2		2b	4	45	1985-12-2
3		2c	4	52	2284-20-0
4		2d	5	41	2131-61-5
5		2e	4	55	551-06-4
6		2f	3	47	622-78-6
7		2g	3	49	112-82-3
8		2h	3	48	4478-92-6

^a Conversions were monitored by TLC analysis.

^b Yields refers to the isolated pure products after column chromatography.

Therefore, we examined the reaction of aniline with a mixture of carbon disulfide and diethyl chlorophosphate in the presence of potassium carbonate as a basic catalyst under solvent-free conditions (Table 1, entry 2); no product was formed after 24 hours. The reaction was also unsuccessful in the presence of a mixture of potassium carbonate and sodium hydroxide as the base under solvent-free conditions after 24 hours. Using of a mixture of potassium carbonate and sodium hydroxide in toluene at reflux gave phenyl isothiocyanate (**2a**) in 50% yield after five hours. Aniline was converted into phenyl isothiocyanate (**2a**) in toluene at reflux in the presence of sodium hydroxide as base after five hours (Table 1, entry 6). The reaction was unsuccessful using other solvents such as dichloromethane and acetonitrile; only <5% of **2a** was detected using dioxane as solvent after 24 hours (Table 1, entry 9).

To study the scope and limitations of the reaction, various amines were subjected to treatment with carbon disulfide and diethyl chlorophosphate in refluxing toluene (Table 2). Aromatic amines reacted with carbon disulfide and diethyl chlorophosphate in refluxing toluene to afford the corresponding isothiocyanates **2a–d** in good yields. 1-Naphthylamine also reacted to give 1-naphthyl isothiocyanate (**2e**) in 55% yield. Aliphatic amines also reacted to give the corresponding isothiocyanates **2f–h** in 47–49% yield. The reactions were clean and no tar formation was observed.

**Scheme 1****Scheme 2**

It is suggested that dithiocarbamic acid salt may be generated in situ by treatment of an amine **1** with carbon disulfide in the presence of sodium hydroxide followed by reaction with diethyl chlorophosphate to produce isothiocyanates **2** via decomposition of dithiocarbamic acid salts (Scheme 1). An alternative path for this conversion is the formation phosphoramidate **3** followed by the reaction with carbon disulfide in the presence of sodium hydroxide to give the corresponding isothiocyanate **2** (Scheme 1). Interestingly, we found that diethyl phenylamidophosphate (**3a**) was converted into phenyl isothiocyanate (**2a**) in the presence carbon disulfide in toluene using sodium hydroxide as the base (reflux, 5 h, 45% yield, Scheme 2).

In summary, simple workup, fast reaction rates, mild reaction conditions, good yields, and relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of amines were converted into the corresponding isothiocyanates in one pot using this method.

All chemicals were commercial products and distilled or recrystallized before use. The IR spectra were determined using a FT-IR Bruker-Vector 22. NMR spectra were taken with a 250 MHz Bruker Avance with TMS as internal reference (¹H). Column chromatography used silica gel 100 (Merck No. 10184). Merck silica gel 60 F254 plates (No. 5744) were used for preparative TLC.

Amines **2a–h**; General Procedure

The amine (5 mmol) was added to a stirred mixture of diethyl chlorophosphate (5 mmol) and NaOH (0.4 g, 10 mmol) in toluene (10 mL) at reflux. CS₂ (10 mmol) was added to the mixture and the mixture was stirred for 3–5 h at reflux. The resultant soln was cooled to r.t. and then filtered. Evaporation under reduce pressure gave an oily mixture. This residue was extracted with hexane (2 × 50 mL) and the extract was filtered, washed with H₂O (2 × 50 mL), dried (MgSO₄), and filtered. The filtrate was concentrated in vacuo to give an oil that was passed through a silica gel plug (hexane). Evaporation of the solvent under reduced pressure gave the pure products in 41–55% yield. All products were identified by comparison with authentic samples (IR, NMR).

(*R*)-1-Phenylethyl Isothiocyanate (**2h**)

Colorless oil.

IR (neat): 2088 cm⁻¹ (N=C=S).

¹H NMR (250 MHz, CDCl₃): δ = 1.69 (d, *J* = 6.8 Hz, 3 H), 4.92 (q, *J* = 6.8 Hz, 1 H), 7.26–7.63 (m, 5 H).

¹³C NMR (62.9 MHz, CDCl₃): δ = 25.0, 57.0, 125.4, 128.2, 128.9, 140.1.

Diethyl Phenylamidophosphate (3a)

This compound was prepared using known methods.¹⁵

White solid; mp 95–96 °C [Lit.¹⁵ 96–97 °C].

¹H NMR (250 MHz, CDCl₃): δ = 1.30 (t, *J* = 7.0 Hz, 6 H), 3.95–4.30 (m, 4 H), 6.80–7.35 (m, 5 H + NH).

¹³C NMR (62.9 MHz, CDCl₃): δ = 16.1 (d, *J*_{PC} = 6.9 Hz), 62.6 (d, *J*_{PC} = 5.0 Hz), 117.2 (d, *J*_{PC} = 7.5 Hz), 121.3, 129.2, 139.8.

³¹P NMR (101.2 MHz, CDCl₃, H₃PO₄): δ = 2.88.

Phenyl Isothiocyanate (2a) from 3a

Diethyl phenylamidophosphate (**3a**, 5 mmol) was added to a stirred mixture of CS₂ (10 mmol) and NaOH (0.4 g, 10 mmol) in toluene (10 mL) at reflux. The mixture was stirred for 3–5 h at reflux. The resultant soln was cooled at r.t. and then filtered. Evaporation under reduced pressure gave an oily mixture. This residue was extracted with hexane (2 × 50 mL) and the extract was filtered, washed with H₂O (2 × 50 mL), dried (MgSO₄), and filtered. The filtrate was concentrated in vacuo to give an oil that was passed through a silica plug (hexane). Evaporation of the solvent under reduced pressure gave pure **2a** (45% yield).

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