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A new and convenient in-situ method of generating phenyl isocyanates from anilines using oxalyl chloride

Lynette M. Oh,* P. Grant Spoors and Richard M. Goodman

Synthetic Chemistry, Chemical Development, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA

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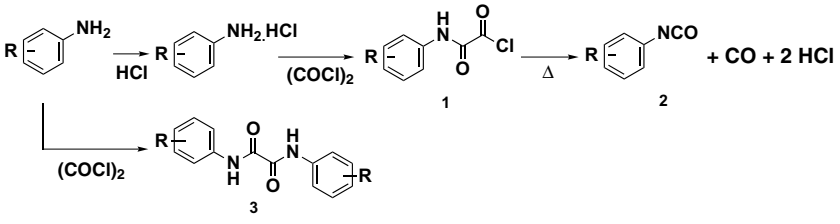
Abstract—A new and convenient method of generating phenyl isocyanates from anilines using oxalyl chloride is described. Acylation of a variety of substituted aniline hydrochlorides with oxalyl chloride affords the intermediate oxamic chlorides, which smoothly undergo thermal decomposition to the corresponding isocyanates.

Isocyanates are useful compounds capable of participating in a variety of reactions including nucleophilic addition reactions with alcohols and amines to produce carbamates and ureas; cycloaddition reactions to generate heterocycles; and polymerization reactions to produce commodities such as polyurethanes.[1] The high yields and lack of by-products associated with isocyanate chemistry have led to their widespread application in the pharmaceutical, agrochemical and polymer industries. Typically, aliphatic and aromatic isocyanates are generated from amines reacting with phosgene[2] or phosgene equivalents, such as diphosgene (trichloromethyl chloroformate)[3] or triphosgene [bis(trichloromethyl) carbonate],[4] or via thermal dissociation of carbamic acid derivatives using chloroformates,[5] diphenylcarbonate[6] or N,N′-carbonyldiimidazole.[7] Aryl isocyanates can also be generated from non-amine precursors via the rearrangements of acyl azides (Curtius rearrangement)[8] and hydroxamic acids (Lossen rearrangement).[9]

The reactions of oxalyl chloride with primary amides[10] and sulfonamides,[11] and subsequent decomposition to form acyl isocyanates and sulfonyl isocyanates, respectively, are well known. However, there are only scant examples in the literature applying this protocol to amines to generate isocyanates, and none towards substituted anilines, substrates in which we had interest. In those examples, only aminobenzo-1,4-quinones[12] and electron-poor heterocylic aromatic substrates such as perchloro-pyrimidines, pyrazines, pyridines and triazines[13] were converted to their respective isocyanates. Herein, we report the use of oxalyl chloride as a general and convenient alternative to phosgene in the generation of substituted phenyl isocyanates from various anilines (Scheme 1).



Scheme 1.

Keywords: Phenyl isocyanates; Anilines; Oxalyl chloride.
* Corresponding author. Tel.: +1-6102705492; fax: +1-6102704829; e-mail: lynette.m.oh@gsk.com

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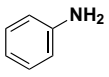
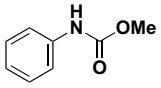
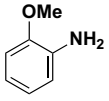
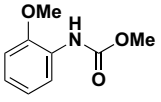
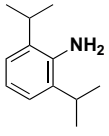
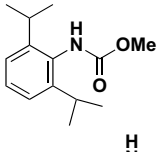
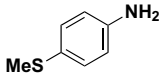
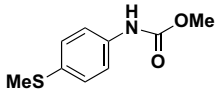
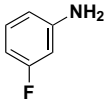
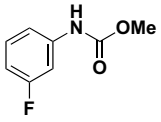
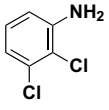
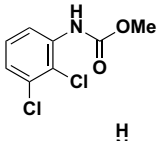
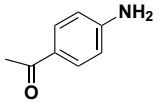
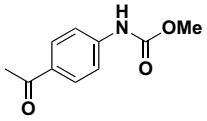
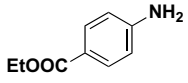
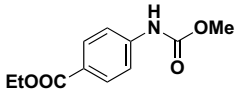
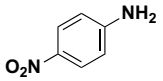
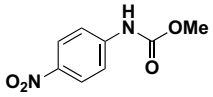
Initially, oxalyl chloride (1.0–2.0 equiv) was added to a solution of the aniline in dichlorobenzene; depending on the nucleophilicity of the aniline though, significant amounts of the byproduct bisoxamide of general structure **3** were formed. Suppression of bisoxamide **3** was not observed even when a large excess of oxalyl chloride (>10 equiv) was used, either in dichlorobenzene or neat. However, we discovered that by simply employing the hydrochloride salt of the aniline (from commercial sources or by generation before use), the aniline's nucleophilicity was sufficiently attenuated to provide the desired oxamic chloride **1** in good yield.[14] Several solvents were screened (THF, dioxane and ethyl acetate) for the acylation step with oxalyl chloride and ethyl acetate was determined to be optimal in terms of minimizing bisoxamide generation. Once the aniline hydrochloride substrate was fully consumed, the intermediate oxamic chloride **1** was heated to 130 °C in a nonreactive solvent such as chlorobenzene or dichlorobenzene to effect a smooth thermal decomposition to the corresponding isocyanate **2** in 2–3 h. For the purpose of analysis, carbamates were generated by adding methanol to the reactions (Table 1). It is interesting to note that the analogous reactions of substituted aniline hydrochlorides with phosgene are very slow and low-yielding, and require catalysts such as tetramethylurea, tetramethylphenylguanidine or N,N-dimethylformamide in order to generate good yields of the isocyanates.[15]

Example of a typical procedure: Under a nitrogen atmosphere, ethyl aminobenzoate (5.0 g, 30.3 mmoles) was slurried in ethyl acetate (150 mL) at 0 °C. 4 N Hydrochloric acid in dioxane (9.8 mL, 39.3 mmoles, 1.3 equiv) was added and the resulting thick slurry was stirred for approximately 30 min. Oxalyl chloride (3.4 mL, 39.3 mmoles, 1.3 equiv) was then added dropwise at 5–10 °C. After the oxamic chloride was formed and consumption of ethyl aminobenzoate was judged complete (via HPLC),[16] 50 mL of dichlorobenzene was added. The reaction temperature was brought to 130 °C,

Table 1. In-situ formation of phenyl isocyanates with oxalyl chloride

Entry	Substrate	Dissociation temperature (°C)	Time (h)	Product[a]	Solution yield (isolated yield)%
1		130	2		85
2		140	2		81[17]
3		130	3		72[17]
4		130	2		98 (90)
5		130	2		79
6		130	2		74
7		140	2		71 (67)
8		130	3		91 (86)
9		140	2		98 (90)

[a] For the purposes of calculating the solution yields (via HPLC) of the in-situ generated phenyl isocyanates, the corresponding methyl carbamate derivatives were formed.

during which time ethyl acetate and excess oxalyl chloride were distilled off. At approximately 130 °C, the thermal decomposition to the isocyanate occurred, accompanied by vigorous gas evolution, and was complete within 3 h. After the reaction mixture was cooled to 20–30 °C, excess methanol (approximately 10–15 volumes with respect to aniline substrate) was added and the methyl carbamate formed instantly. With formation of the methyl carbamate complete, the mixture was filtered to remove the highly crystalline bisoxamide. Alternatively, the crystalline bisoxamide may be filtered off under an inert atmosphere prior to performing the thermal decomposition to the isocyanate. Yields were determined by solution weight percent (via HPLC) using the methyl carbamates formed from the corresponding commercially available isocyanates as a standard (prepared in a 50:50 methanol/acetonitrile diluent). In this case, the 4-[(methoxycarbonyl)amino] ethyl benzoate was also isolated by concentration of the filtrate followed by crystallization from dichlorobenzene/hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, $J = 9.2$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H), 6.73 (br s, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 1.32 (t, $J = 8.4$ Hz, 3H).

As illustrated in Table 1, a variety of functional groups are tolerated under the reaction conditions, such as methyl thioethers, esters and ketones (entries 4, 7 and 8). Sterically hindered isocyanates are of great interest as the electrophilic components in urea and carbamate syntheses because the corresponding anilines are poor nucleophiles. We were pleased to find that 2,6-diisopropyl-aniline (entry 3) was converted to its isocyanate under these conditions in 72% yield. Additionally, both electron-rich and electron-poor oxamic chlorides appear to dissociate smoothly to afford the corresponding isocyanates.

In conclusion, we have described a new and convenient method of generating substituted phenyl isocyanates in high yields from their corresponding aniline hydrochloride salts using oxalyl chloride.

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16. HPLC samples were diluted with 50:50 methanol/acetonitrile to form the oxamic methyl ester, whose presence was confirmed by LCMS.
17. To facilitate the carbamate formation of electron-rich isocyanates (entries 2 and 3, 5.0 g scale), the reactions were cooled down to 20 °C and 65 mL of MeOH and sodium methoxide (0.5 mL; 25% wt % solution in methanol) were added.