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Curtius Rearrangement of Aromatic Carboxylic Acids to Access Protected Anilines and Aromatic Ureas

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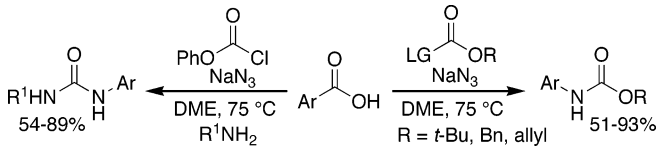
ABSTRACT



The reaction of a chloroformate or di-*tert*-butyl dicarbonate and sodium azide with an aromatic carboxylic acid produces the corresponding acyl azide, presumably through the formation of an azidoformate. The acyl azide undergoes a Curtius rearrangement to form an isocyanate derivative which is trapped either by an alkoxide or by an amine to form the aromatic carbamate or urea. The reaction conditions are compatible with a variety of functional groups and allow the synthesis of a number of aniline derivatives containing alkyl, halide, nitro, ketone, ether, and thioether substituents.

Polysubstituted aromatic anilines are an important class of compounds that display a variety of interesting properties. These are found as the active agent in a variety of areas, including pharmaceutical[1] and agrochemical[2] industries, as well as in materials science.[3] Although free anilines themselves are typically mutagenic and carcinogenic,[4] they serve as intermediates in the preparation of numerous aromatic carbon−nitrogen bond containing molecules. A number of methods to access anilines have been developed, including hydrogenation of nitro derivatives,[5] electrophilic nitration,[6] nucleophilic aromatic amination,[7] as well as palladium and copper-catalyzed amination.[8,9] Besides all these modern methods, Curtius rearrangement of acyl azides remains very popular, especially in the preparation of pharmacologically active compounds.[10] Diphenylphosphorazidate is the most widely used reagent, as it allows the direct transformation of carboxylic acids into carbamates.[11] However, the difficulty in purifying the desired product from the phosphorus residues remains a serious drawback associated with the use of this reagent.[12] Herein, we wish to disclose the use of di-*tert*-butyl dicarbonate or chloroformates and sodium azide as reagents for the preparation of aromatic carbamates directly from

(1) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347.

(2) (a) Harrison, W. *J. Biomol. Screen.* **1999**, *4*, 61−65. (b) Walter, M. W. *Nat. Prod. Rep.* **2002**, *19*, 278−291. (c) Lopez, O.; Fernandez-Bolanos, J. G.; Gil, M. V. *Green Chem.* **2005**, *7*, 431−442.

(3) (a) Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**, 1135−1136. (b) Honma, A.; Kanbara, T.; Hasegawa, K. *Mol. Cryst. Liq. Cryst.* **2000**, *345*, 449−454. (c) Thomas, K. R. J.; Lin, J. T.; Tao, Y. T.; Ko, C. W. *Adv. Mater.* **2000**, *12*, 1949−1951. (d) Thomas, K. R. J.; Lin, J. T.; Tsai, C. M.; Lin, H. C. *Tetrahedron* **2006**, *62*, 3517−3522.

(4) Benigni, R.; Giuliani, A.; Franke, R.; Gruska, A. *Chem. Rev.* **2000**, *100*, 3697−3714.

(5) (a) Rains, R. K.; Lambers, E. A.; Genetti, R. A. *Chem. Ind.* **1996**, *68*, 43−52. (b) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151. (c) Prasad, K.; Jiang, X. L.; Slade, J. S.; Clemens, J.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1769−1773.

(6) (a) Waller, F. J.; Ramprasad, D.; Barrett, A. G. M.; Braddock, D. C. *Chem. Ind.* **1998**, *75*, 289−305. (b) Laali, K. K.; Gettwert, V. J. *J. Org. Chem.* **2001**, *66*, 35−40. (c) Smith, K.; El-Hiti, G. A. *Curr. Org. Synth.* **2004**, *1*, 253−274.

(7) (a) Ibata, T.; Isogami, Y.; Toyoda, J. *Chem. Lett.* **1987**, 1187−1190. (b) Warawdekar, M. G.; Rajadhyaksha, R. A. *Zeolites* **1987**, *7*, 574−578. (c) Stern, M. K.; Cheng, B. K. *J. Org. Chem.* **1993**, *58*, 6883−6888. (d) Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **1996**, *61*, 2934−2935.

(8) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23−39 and references therein.

(9) Review: (a) Downing, R. S.; Kunkeler, P. J.; vanBekkum, H. *Catal. Today* **1997**, *37*, 121−136. Alternative method: (b) Neumann, H.; von Wangelin, A. J.; Klaus, S. N.; Strubing, D.; Gordes, D.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4503−4507.

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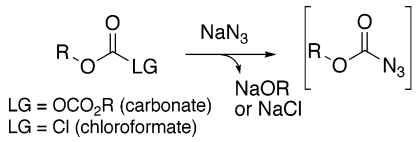
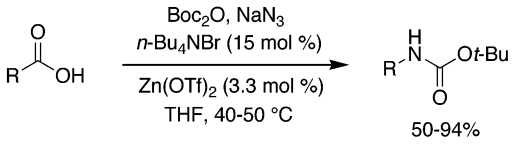
aromatic acids via a Curtius rearrangement, presumably through the formation of the corresponding azidoformate (eq 1). The use of a chloroformate containing a less nucleophilic



(1)

alkoxy moiety allowed the use of external nucleophiles, such as amines, thus leading to the formation of aromatic ureas.

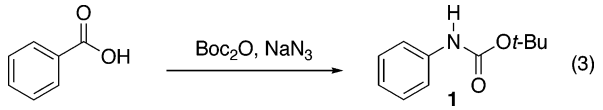
We have recently reported a mild and efficient one-pot Curtius rearrangement for the synthesis of aliphatic Boc-protected amines.[13] *Aliphatic* carboxylic acids were reacted with a mixture of di-*tert*-butyl dicarbonate and sodium azide to form an acyl azide intermediate, which underwent a Curtius rearrangement at 40−50 °C (eq 2).



(2)

The trapping of the isocyanate derivative in the presence of tetrabutylammonium bromide and zinc(II) triflate led to the desired *tert*-butyl carbamate in high yields. In sharp contrast, using similar reaction conditions, *aromatic* carboxylic acids led mainly to the formation of the corresponding *tert*-butyl ester, presumably via the displacement of an azide leaving group with *tert*-butoxide (Table 1, entry 1). We postulated that the Curtius rearrangement did not take place at 40 °C, as aromatic acyl azides are known to be more stable than their aliphatic counterparts. The reaction was thus heated at 75 °C to promote the rearrangement. Although carbamate **1** was produced under these reaction conditions, only 15% conversion was observed (entry 2). Neither the addition of pyridine nor the addition of 1-hydroxybenzotriazole (HOBT) increased the yield of carbamate **1** (entries 3 and 4). Indeed, the reaction proceeded to the same extent in the absence of catalyst (entry 5). Finally, solvent optimization led to high conversion when the reaction was run in 1,2-dimethoxyethane (DME) (entry 8). This observation suggested that the solubility of the various species and intermediates is crucial for the reaction to occur.[14]

Table 1. Curtius Rearrangement of Benzoic Acid: Optimization of the Reaction Conditions (Equation 3)[a]



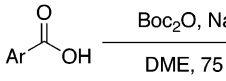
(3)

entry	reaction conditions	conversion (%)[b]
1	Bu_4NBr, $Zn(OTf)_2$/THF *c*	<5
2	Bu_4NBr, $Zn(OTf)_2$/THF	15
3	Bu_4NBr, pyridine,[d] $Zn(OTf)_2$/THF	10
4	Bu_4NBr, HOBT,[d] $Zn(OTf)_2$/THF	20
5	no additive or catalyst/THF	15
6	no additive or catalyst/toluene	15[e]
7	no additive or catalyst/MeCN	20[e]
8	**no additive or catalyst/DME**	**>95**[e]

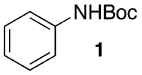
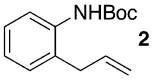
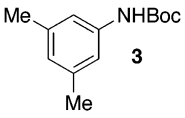
[a] Conditions: Boc_2O (1.1 equiv), NaN_3 (3.5 equiv), additive (15 mol %), catalyst (3.3 mol %), solvent, 16 h. [b] Conversion by GC-MS. [c] 40 °C. [d] Pyridine or HOBT (1.1 equiv). [e] NaN_3 (1.5 equiv).

The Boc-aniline **1** was isolated in 79% yield after 20 h of reaction (Table 2, entry 1). Other unfunctionalized anilines were isolated with similar yields (entries 2 and 3). However, functional groups such as methyl ether, thiomethyl ether,

Table 2. *tert*-Butylazidoformate in the Curtius Rearrangement of Benzoic Acids (Equation 4)[a]



(4)

entry	carbamate	yield (%)[b]
1	 **1**	79
2	 **2**	76
3	 **3**	74

[a] Conditions: Boc_2O (1.1 equiv), NaN_3 (1.5 equiv), 20 h. [b] Isolated yield.

(10) Selected examples: (a) Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. R. *Synthesis* **1994**, 846−850. (b) Proctor, G. R.; Harvey, A. L. *Curr. Med. Chem.* **2000**, *7*, 295−302. (c) Alonso-Alija, C.; Michels, M.; Peilstocker, K.; Schirok, H. *Tetrahedron Lett.* **2004**, *45*, 95−98. (d) Dombroski, M. A.; Letavic, M. A.; McClure, K. F.; Barberia, J. T.; Carty, T. J.; Cortina, S. R.; Csiki, C.; Dipesa, A. J.; Elliott, N. C.; Gabel, C. A.; Jordan, C. K.; Labasi, J. M.; Martin, W. H.; Peese, K. M.; Stock, I. A.; Svensson, L.; Sweeney, F. J.; Yu, C. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 919−923. (e) Gopalsamy, A.; Lim, K.; Ellingboe, J. W.; Mitsner, B.; Nikitenko, A.; Upeslacis, J.; Mansour, T. S.; Olson, M. W.; Bebernitz, G. A.; Grinberg, D.; Feld, B.; Moy, F. J.; O'Connell, J. *J. Med. Chem.* **2004**, *47*, 1893−1899. (f) Ple, P. A.; Green, T. P.; Hennequin, L. F.; Curwen, J.; Fennell, M.; Allen, J.; Lambert-van der Brempt, C.; Costello, G. *J. Med. Chem.* **2004**, *47*, 871−887. (g) Sit, S. Y.; Xie, K.; Jacutin-Porte, S.; Boy, K. M.; Seanz, J.; Taber, M. T.; Gulwadi, A. G.; Korpinen, C. D.; Burris, K. D.; Molski, T. F.; Ryan, E.; Xu, C.; Verdoorn, T.; Johnson, G.; Nichols, D. E.; Mailman, R. B. *Bioorg. Med. Chem.* **2004**, *12*, 715−734. (h) Takigawa, Y.; Ito, H.; Omodera, K.; Ito, M.; Taguchi, T. *Tetrahedron* **2004**, *60*, 1385−1392. (i) Dominguez, J. N.; Leon, C.; Rodrigues, J.; de Dominguez, N. G.; Gut, J.; Rosenthal, P. J. *J. Med. Chem.* **2005**, *48*, 3654−3658. (j) Opacic, N.; Barbaric, M.; Zorc, B.; Cetina, M.; Nagy, A.; Frkovic, D.; Kralj, M.; Pavelic, K.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Raic-Malic, S.; Mintas, M. *J. Med. Chem.* **2005**, *48*, 475−482. (k) Suzuki, T.; Nagano, Y.; Kouketsu, A.; Matsuura, A.; Maruyama, S.; Kurotaki, M.; Nakagawa, H.; Miyata, N. *J. Med. Chem.* **2005**, *48*, 1019−1032. (l) Varaprasad, C.; Johnson, F. *Tetrahedron Lett.* **2005**, *46*, 2163−2165.

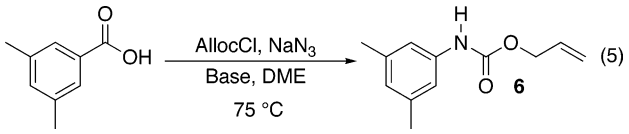
(11) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2157. (c) Murato, K.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1738−1740. (d) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515−3518. (e) Wolff, O.; Waldvogel, S. R. *Synthesis* **2004**, 1303−1305. (f) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219−7223.

nitro, and halides were not tolerated, and the corresponding anilines were isolated in less than 25% yield.

We hypothesized that the full equivalent of base generated from the reaction between di-*tert*-butyl dicarbonate and sodium azide could be the source of the problem, leading to undesired side reactions with these functional groups.

We turned our attention to the use of chloroformates, another class of reagent that could also lead to azidoformate upon reaction with sodium azide. In this case, the byproduct of the reaction is sodium chloride. When benzoic acid was reacted with a mixture of allylchloroformate and sodium azide in DME at 75 °C, 25% of carbamate **6** was obtained (Table 3, entry 1).[15]

Table 3. Curtius Rearrangement of Benzoic Acid: Optimization of the Reaction Conditions with Allylchloroformate (Equation 5)[a]

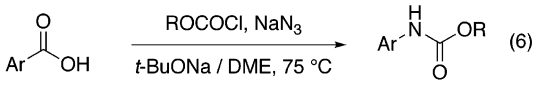


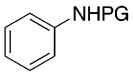
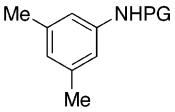
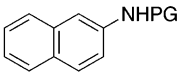
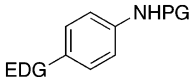
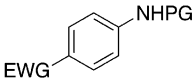
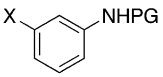
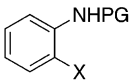
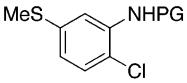
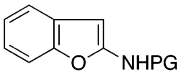
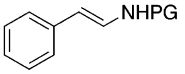
entry	base	conversion (%)[b]
1	none	25
2	pyridine	<5
3	DMAP	<5
4	K_2CO_3	<5
5	NaOAc	90
6	NaH	90
7	***t*-BuONa**	**95**
8	*t*-BuONa[c]	43

[a] Conditions: AllocCl (1.1 equiv), NaN_3 (1.5 equiv), base (15 mol %), 16 h. [b] Conversion by GC-MS. [c] The solvent was dioxane.

The use of pyridine bases or potassium carbonate did not lead to any product (entries 2−4). Conversely, 15 mol % of sodium acetate or sodium hydride promoted the reaction and led to 90% conversion of carbamate **6** (entries 5 and 6). The optimal base was found to be potassium *tert*-butoxide (entry 7). The reaction was also performed in dioxane but led to carbamate **6** in a lower yield. Clearly, a small amount of base is required to promote the reaction.[16] Whereas the generation of a full equivalent of base was found to be deleterious for the functional group compatibility, the use of a catalytic amount was well tolerated, and a variety of carbamates were prepared in high yields (Table 4). Both allyl and benzyl chloroformate were sucessfully used to generate Alloc- and CBz-protected anilines. Electron-rich benzoic acids led to the formation of the corresponding carbamates in 45−77% yields (entries 1−4). The reaction is faster with substrates containing an electron-withdrawing group, suggesting that the addition of the nucleophile to the isocyanate intermediate to form the carbamate is the slowest step of the process. Indeed *p*-nitro and *p*-acetyl benzoic acid substrates provided the desired carbamate in 66−84% yields (entry 5). Halides are also well tolerated, and *o*-iodo benzoic

Table 4. Curtius Rearrangement of Aromatic Carboxylic Acids Using Azidoformates (Equation 6)[a]



entry	carbamate	PG	yield (%)[b]
1		Alloc (**4**)	57
		CBz (**5**)	64
2		Alloc (**6**)	66
		CBz (**7**)	58
3		Alloc (**8**)	77
		CBz (**9**)	55
		EDG	
4		Alloc, OMe (**10**)	45
		t-Bu (**11**)	56
		CBz, OMe (**12**)	62
		t-Bu (**13**)	62
		EWG	
5		Alloc, NO_2 (**14**)	78
		Ac (**15**)	66
		CBz, NO_2 (**16**)	84
		Ac (**17**)	80
		X	
6		Alloc, Cl (**18**)	66
		Br (**19**)	52
		CBz, Cl (**20**)	67
		Br (**21**)	72
		X	
7		Alloc, Br (**22**)	83
		I (**23**)	72
		CBz, Br (**24**)	91
		I (**25**)	93
		Troc, I (**26**)	71[c]
8		Alloc (**27**)	82
		CBz (**28**)	81
9		Alloc (**29**)	69
		CBz (**30**)	80
10		Alloc (**31**)	52
		CBz (**32**)	51

[a] Conditions: ROCOCl (1.1 equiv), NaN_3 (1.7 equiv), *t*-BuONa (15 mol %), 16 h. [b] Isolated yield. [c] 85 °C.

(12) Alternative procedures using solid-phase synthesis: (a) Richter, L. S.; Andersen, S. *Tetrahedron Lett.* **1998**, *39*, 8747−8750. (b) Sunami, S.; Sagara, T.; Ohkubo, M.; Morishima, H. *Tetrahedron Lett.* **1999**, *40*, 1721−1724. (c) Lu, Y.; Taylor, R. T. *Tetrahedron Lett.* **2003**, *44*, 9267−9269.

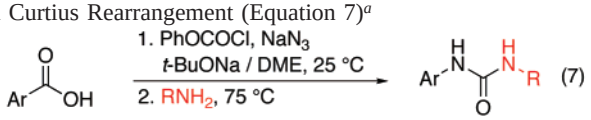
(13) Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107−4110.

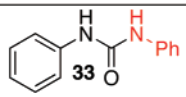
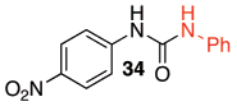
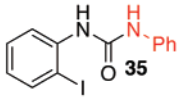
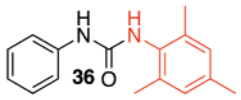
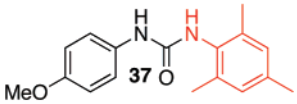
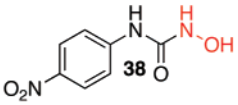
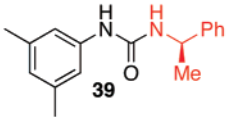
(14) Furthermore, the reaction mixture is completely insoluble when dioxane is used as solvent.

(15) The rest of the material was the isocyanate.

(16) A control experiment was run with chloroformate, sodium azide, and carboxylic acid at room temperature and showed the formation of acyl azide, suggesting that the base is not essential for the formation of this intermediate. The base is probably involved in the formation of the carbamate from the isocyanate, by trapping the proton of the nucleophile.

Table 5. Synthesis of Ureas from Aromatic Carboxylic Acids via Curtius Rearrangement (Equation 7)[a]



entry	urea	yield (%)[b]
1		89
2		74
3		59
4		80
5		61
6		54[c]
7		63[d]

[a] Conditions: PhOCOCl (1.1 equiv), NaN_3 (1.5 equiv), *t*-BuONa (15 mol %), RNH_2 (1.5 equiv). [b] Isolated yield. [c] $NH_2OH{\cdot}HCl$ (2 equiv). [d] The reaction mixture was heated to 75 °C prior to the addition of the amine (see Supporting Information for details).

acid is one of the most reactive substrates (entries 6 and 7). In this case, the use of the less nucleophilic alcohol, trichloroethanol, as the nucleophile is possible leading to the Troc carbamate **26** in 71% yield. Furthermore, the reaction conditions are compatible with thiomethyl ether and benzofuran (entries 8 and 9). Finally, although aliphatic carboxylic acids were not reactive under these reaction conditions, the use of other sp^2-substituted carboxylic acids is possible, as cinnamic acid provided the Alloc and Cbz carbamates **31** and **32** in 52% and 51% yields, respectively.

If one could use nucleophiles other than the alkoxide generated from the chloroformate, this would certainly increase the versatility of this method. The use of phenyl chloroformate that contained a less nucleophilic alcohol was envisioned to achieve this task. Indeed, a mixture of phenyl chloroformate, sodium azide, and carboxylic acid led to the formation of the acyl azide. The reaction was then heated at 75 °C to promote the formation of the isocyanate while adding an amine to trap this intermediate and form the corresponding urea (Table 5). Good yields were obtained for the formation of aromatic ureas via the addition of another aniline (entries 1−5). Furthermore, the addition of hydroxylamine allowed the formation of hydroxyurea **38** in 54% yield (entry 6). Finally, aliphatic amines can also be added with good yields, such as in the case of the formation of urea **39** (entry 7).

In conclusion, we have developed a very efficient process for the Curtius rearrangement that allows the direct conversion of *aromatic* carboxylic acids into carbamates and ureas. This process is based on the use of various commercially available chloroformates and sodium azide, which presumably generate the corresponding azidoformate. The formate serves to activate the carboxylic acids and as a source of nucleophilic alkoxide. Finally, the synthesis of aromatic ureas is also possible as amines can be used as nucleophiles, when using phenyl chloroformate and sodium azide as reagents.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^1H spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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