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Boc-Protected Amines via a Mild and Efficient One-Pot Curtius Rearrangement

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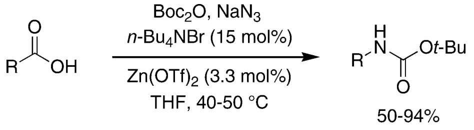
ABSTRACT



The reaction of a carboxylic acid with di-*tert*-butyl dicarbonate and sodium azide allowed the formation of an acyl azide intermediate, which undergoes a Curtius rearrangement in the presence of tetrabutylammonium bromide and zinc(II) triflate. The trapping of the isocyanate derivative in the reaction mixture led to the desired *tert*-butyl carbamate in high yields at low temperature. These reaction conditions are compatible with a variety of substrates, including malonate derivatives, which provide access to protected amino acids.

The Curtius rearrangement describes the degradation of an acyl azide into an isocyanate through a concerted mechanism.[1] The isocyanate can be trapped by a variety of nucleophiles, including alcohols, which provides the corresponding carbamate. It is one of the most widely used methods to synthesize amine derivatives, and over 1000 references can be found in the literature related to the Curtius rearrangement. A number of methods have been developed to access acyl azides from carboxylic acid derivatives, such as hydrazides,[2] acyl chlorides,[3] and mixed anhydrides.[4,5] In these cases, acyl azides are isolated, and the rearrangement is then performed in a separate step. However, acyl azides are well-known to be unstable; thus, one-pot processes that allow the direct conversion of carboxylic acids into carbamates have become very popular.[6,7] The most widely used reagent for this purpose is diphenylphosphorazidate.[8,9] However, there are a number of drawbacks associated with the use of this reagent, including the high temperature and the difficulty to purify the desired product from the phosphorus

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(1) (a) Smith, P. A. S. *Org. React.* **1946**, *3*, 337−349. (b) Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 795. (c) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368.

(2) Selected examples: (a) Jean, L.; Baglin, I.; Rouden, J.; Maddaluno, J.; Lasne, M. C. *Tetrahedron Lett.* **2001**, *42*, 5645−5649. (b) Nettekoven, M. *Synlett* **2001**, 1917−1920. (c) Macor, J. E.; Mullen, G.; Verhoest, P.; Sampognaro, A.; Shepardson, B.; Mack, R. A. *J. Org. Chem.* **2004**, *69*, 6493−6495.

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residues.[10] Herein, we wish to disclose a new process to perform the Curtius rearrangement starting with a carboxylic acid, di-*tert*-butyl dicarbonate, and sodium azide to form the corresponding *tert*-butyl carbamate in high yields. Furthermore, the use of transition-metal complexes and Lewis acids as catalysts for the Curtius rearrangement will be presented.

Our initial goal was to develop an efficient one-pot process for the synthesis of carbamates from carboxylic acids through the Curtius rearrangement. The optimal reagent should include both the azide and the *tert*-butoxy moiety while activating the carboxylic acid substrate. *tert*-Butyl azidoformate or BocN$_3$ appears as the reagent of choice for this purpose.[11] However, the isolation of this reagent is not an easy task, since detonation during the required distillation under reduced pressure has been reported. Furthermore, neat *tert*-butyl azidoformate is sensitive to both heat and shock. Conversely, we found that we could safely prepare BocN$_3$ as a solution in THF from di-*tert*-butyl dicarbonate and an excess of sodium azide in the presence of a phase transfer catalyst. Moreover, addition of 1-adamantanecarboxylic acid to this reaction mixture led to the formation of the corresponding acyl azide **1** (eq 1). When the reaction mixture was heated to 80 °C, the Curtius rearrangement occurred and led to the desired carbamate **2** quantitatively (Table 1, entry 2).

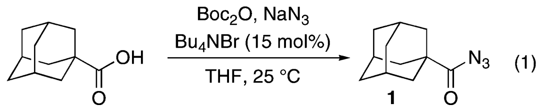
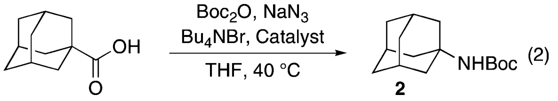


Table 1. Curtius Rearrangement of 1-Adamantanecarboxylic Acid: Catalyst Optimization (eq 2)[a]



entry	catalyst	conv[b] (%)	entry	catalyst	conv[b] (%)
1	none	≤5	11	Pd$_2$(dba)$_3$	55
2	none	95[c]	12	La(OTf)$_3$	55
3	HCl	20	13	Sc(OTf)$_3$	≤5
4	HOTf	25	14	CuCl	≤5
5	BF$_3$·OEt$_2$	≤5	15	Cu(OTf)$_2$	5[d]
6	MgBr$_2$	≤5	16	Cu(OAc)$_2$	40
7	TiCl$_4$	≤5	17	CuCl$_2$	35
8	Fe(acac)$_3$	60	18	AgOTf	20
9	Rh$_2$(OAc)$_4$	55	19	ZnCl$_2$	90
10	ClRh(PPh$_3$)$_3$	≤5	20	Zn(OTf)$_2$	≥95

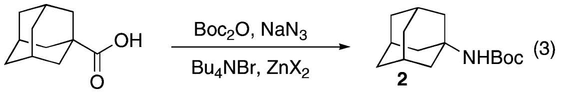
[a] Conditions: Boc$_2$O (1.1 equiv), NaN$_3$ (7 equiv), Bu$_4$NBr (15 mol %), catalyst (3.3 mol %), 24 h. [b] Conversion by GC−MS; acyl azide and isocyanate are the remaining product. [c] The reaction was run at 80 °C. [d] Catalyst loading was 5 mol %.

Although acyl azide **1** formed the corresponding isocyanate at 40 °C, carbamate **2** was only obtained with a low yield (entry 1). This observation suggested that the addition of the *tert*-butoxy moiety to the isocyanate intermediate was slow at 40 °C.

We postulated that the addition of a transition metal or a Lewis acid complex as a catalyst could favor the formation of carbamate **2** from 1-adamantane carboxylic acid.[12,13] Indeed, the addition of protic acids led to the formation of carbamate **2** in 20−25% yields (entries 3 and 4), while strong Lewis acids showed no activity (entries 5−7). Some late transition metal and lanthanide complexes catalyzed the formation of carbamate **2** with modest yields (entries 8−13), similarly to copper and silver salts (entries 14−18). Conversely, zinc complexes were very efficient at promoting the Curtius rearrangement and the formation of carbamate **2** directly from 1-adamantanecarboxylic acid (entries 19 and 20).

Further optimization showed that the most efficient catalyst was zinc triflate, although zinc chloride and zinc bromide still provided the desired carbamate in 60−70% yield (Table 2, entry 5 vs 2 and 3).

Table 2. Zinc-Catalyzed Curtius Rearrangement (eq 3)[a]



entry	ZnX$_2$	conditions	conv[b] (%)
1	ZnF$_2$	THF, 40 °C	40
2	ZnCl$_2$	THF, 40 °C	60
3	ZnBr$_2$	THF, 40 °C	70
4	ZnI$_2$	THF, 40 °C	20
5	**Zn(OTf)$_2$**	**THF, 40 °C**	**≥95**
6	Zn(OTf)$_2$	THF, 30 °C	5
7	Zn(OTf)$_2$	THF, 40 °C	30[c]
8	Zn(OTf)$_2$	TABI (15 mol %), THF, 40 °C	≤5[d]
9	Zn(OTf)$_2$	TBACl·H$_2$O (15 mol %), THF, 40 °C	70[d]
10	Zn(OTf)$_2$	TBAF (15 mol %), THF, 40 °C	≤5[d]
11	Zn(OTf)$_2$	DME, 40 °C	≤5[d]
12	Zn(OTf)$_2$	dioxane, 40 °C	20[d]

[a] Conditions: Boc$_2$O (1.1 equiv), NaN$_3$ (3.5 equiv), Bu$_4$NBr (15 mol %), ZnX$_2$ (3.3 mol %), 24 h. [b] Conversion by GC−MS; acyl azide and isocyanate are the remaining product. [c] NaN$_3$ (2.5 equiv). [d] Reaction time: 15 h.

No Curtius rearrangement occurred at 30 °C (entry 6), and lower yields were obtained when less than 3 equiv of sodium azide was used (entry 7). Tetrabutylammonium bromide could be substituted with the corresponding chloride, although the reaction did not reach completion (entry 9). In contrast, no reaction was observed with tetrabutylammonium iodide or fluoride, which is consistent with the result obtained with the zinc salts (entries 8−10 vs 1−4). The solvent proved instrumental, as low conversions were observed with solvents other than THF (entries 10−12).

A variety of substrates were tested under the optimal reaction conditions using 1.1 equiv of di-*tert*-butyl dicar-

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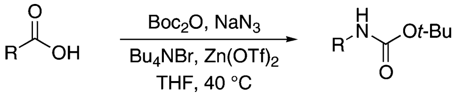
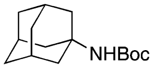
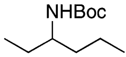
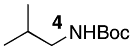
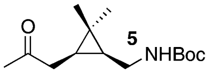
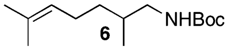
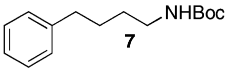
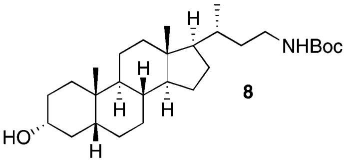
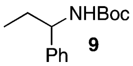
Table 3. Zinc-Catalyzed Curtius Rearrangement (eq 4)[a]



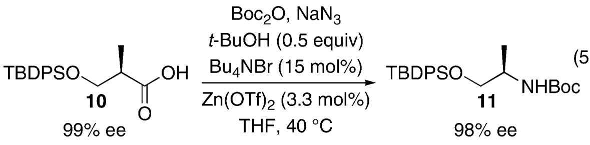
(4)

entry	carbamate	yield (%)[b]
1	 **2**	90
2	 **3**	94
3	 **4**	77
4	 **5**	68
5	 **6**	80
6	 **7**	57
7	 **8**	72
8	 **9**	58

[a] Conditions: Boc$_2$O (1.1 equiv), NaN$_3$ (3.5 equiv), Bu$_4$NBr (15 mol %), Zn(OTf)$_2$ (3.3 mol %), 16−24 h. [b] Isolated yield.

bonate, 3.5 equiv of sodium azide, 15 mol % of tetrabutylammonium bromide, and 3.3 mol % of zinc triflate (Table 3). The reaction proceeded very well with tertiary and secondary carboxylic acids to provide carbamates **2** and **3** in more than 90% isolated yield (entries 1 and 2). Primary protected amines were also obtained in good yields (entries 3−7). Furthermore, the reaction conditions are compatible with unprotected ketones and alcohols; thus carbamates **5** and **8** were isolated in 68% and 72% yield, respectively (entries 4 and 7). 2-Phenylbutanoic acid led to the formation of carbamate **9** together with the corresponding *tert*-butyl ester, which probably resulted from the addition of the *tert*-butoxy moiety onto the corresponding ketene, generated from the elimination of hydrazoic acid (entry 8).[14]

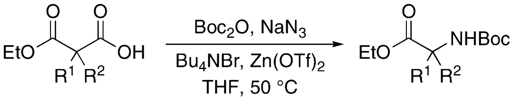
We have examined our new reaction conditions for the Curtius rearrangement of chiral enantioenriched α-substituted carboxylic acid **10** (eq 5). Indeed, the rearrangement proceeded with retention of configuration. However, under the standard reaction conditions described before, carbamate **11** was recovered with only 91% ee (49% yield) indicating an erosion of the enantiomeric excess during the process.[15] To decrease the basicity of the reaction mixture, 0.5 equiv of *tert*-butyl alcohol was added; under these new reaction conditions, the desired product was obtained in 49% yield and with almost no loss in the enantiomeric excess.[16]



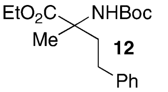
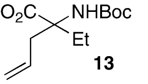
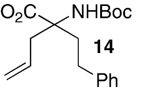
(5)

Malonate derivatives are interesting substrates for the Curtius rearrangement as they lead to the formation of protected amino acids.[17,] Monosaponification of 2,2-disubstituted malonates[18] led to the formation of the corresponding monoester malonic acid, the requisite substrate to perform the Curtius degradation. The rearrangement is slower with these types of substrates and it was required to increase the temperature of the reaction mixture. We found that under the standard reaction conditions using di-*tert*-butyl dicarbonate and sodium azide but at 50 °C, racemic α,α-disubstituted protected amino acids were efficiently prepared in 60−75% yields (Table 4).

Table 4. Zinc-Catalyzed Curtius Rearrangement of Malonate Substrates (eq 6)[a]



(6)

entry	carbamate	yield (%)[b]
1	 **12**	75
2	 **13**	65
3	 **14**	60

[a] Conditions: Boc$_2$O (1.1 equiv), NaN$_3$ (3.5 equiv), Bu$_4$NBr (15 mol %), Zn(OTf)$_2$ (3.3 mol %), 48 h. [b] Isolated yield.

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In conclusion, we have developed a very efficient process for the Curtius rearrangement which allows the direct conversion of carboxylic acids into carbamates. The use of a mixture of di-*tert*-butyl dicarbonate and sodium azide allows the transformation of aliphatic carboxylic acids into alkyl azides, which rearrange spontaneously at 40 °C to produce the corresponding isocyanate. Our inital studies established that the zinc catalyst is not involved in this step. Conversely, the addition of *tert*-butyl alcohol onto the isocyanate is the slowest step of the process and is accelerated by heating the reaction mixture or adding a mixture of tetrabutylammonium bromide and zinc triflate (presumably through the formation of a zinc carbamoyl bromide species). Studies are currently underway to establish the exact kinetics and the mechanism of this reaction, and the results of these studies will be reported in due course.

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

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(14) The corresponding *tert*-butyl ester was the major product formed under the thermal reaction conditions (at 80 °C without $Zn(OTf)_2$), and only 33% of carbamate **9** was isolated.

(15) Similar erosion of the ee for compound **11** (86%) was observed when the reaction was performed at 80 °C without $Zn(OTf)_2$. However, carbamate **11** was obtained with only 20% yield.

(16) The enantiomeric excess was determined by supercritical-fluid chromatography (SFC) using a Chiracel OD, and a difference of 1% ee is within the experimental error.

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