Tetrahedron Letters 51 (2010) 385–386

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A modified Curtius reaction: an efficient and simple method for direct isolation of free amine

Bin Ma *, Wen-Cherng Lee *

BiogenIdec Inc., 12 Cambridge Center, Cambridge, MA 02142, USA

ARTICLE INFO

Article history:
Received 29 October 2009
Accepted 9 November 2009
Available online 13 November 2009

Keywords:
Curtius reaction
NaOTMS
DPPA
Amine
Carboxylic acid

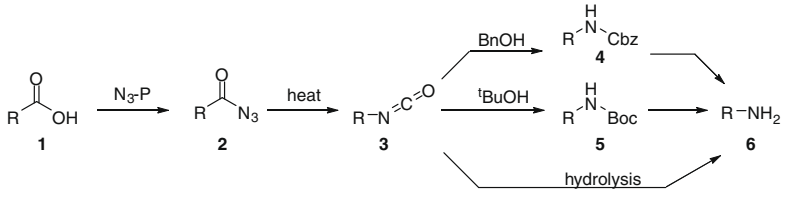
ABSTRACT

The Curtius rearrangement and related reactions are often used to convert carboxylic acids to the corresponding primary amines. However, this reaction often requires harsh conditions for hydrolysis of the isocyanate intermediates to amines, and can also be contaminated by the formation of corresponding ureas due to the reactive nature of the intermediates. We have discovered that by quenching the isocyanate intermediates with sodium trimethylsilanolate, the free amines can be isolated after aqueous workup. This mild and fast procedure provides free amines in one pot with good yields.

Amines are important functional groups in a variety of biologically interesting materials, including biopolymers, drugs, and dyes.[1] Among a number of methods developed to synthesize amines, the Curtius rearrangement is particularly popular as it provides an efficient means to amines from readily available carboxylic acids, especially for the synthesis of sterically hindered amines.[2] Discovered in 1890 by Theodor Curtius,[3] this reaction involves the formation of an unstable acyl azide (**2**) from a carboxylic acid (**1**), followed by the rearrangement to an isocyanate (**3**) with the loss of a N_2. The isocyanate can be trapped by a variety of nucleophiles. When the reaction is performed in the presence of benzyl alcohol, the reaction generates Cbz-protected amines (**4**),[4] while Boc-protected amines are formed with *tert*-butanol (**5**).[5] Free amines (**6**) can be obtained after deprotection of the Cbz- or Boc-protected amines (Scheme 1).

The hydrolysis of isocyanate (**3**) with water should give primary amines (**6**) directly. However, this hydrolysis either requires long reaction times, high temperatures, or the use of strong acids or base, particularly for sterically hindered precursors.[6] Often, the hydrolyzed product may be contaminated with the corresponding urea[7] due to the reactive nature of the isocyanate intermediate. A mercuration–demercuration method has been reported.[8]

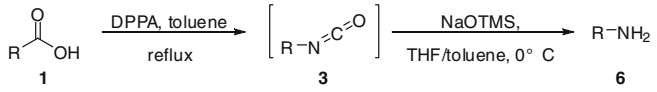
In this Letter, we now report a very simple modification of Curtius reaction by quenching the isocyanate intermediates (**3**) with sodium trimethylsilanolate (NaOTMS), which provides an efficient one-pot method for direct isolation of free amines. The experiment was designed as a two-stage process. First, diphenylphosphoryl azide (DPPA)[9] was selected to convert the carboxylic acid into an isocyanate with minimal accumulation of the unstable acyl azide, and the isolation of isocyanate was avoided. Next, workup with NaOTMS hydrolyzes the isocyanate to free amine.[10] Based on this strategy, toluene was found to be a suitable solvent for both steps, and the free amine can be isolated after aqueous workup (Scheme 2).



Scheme 1.

* Corresponding authors. Tel.: +1 617 914 4955; fax: +1 617 679 3635.
E-mail addresses: bin.ma@biogenidec.com (B. Ma), wen-cherng.lee@biogenidec.com (W.-C. Lee).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.038



Scheme 2.

Table 1
NaOTMS-modified Curtius reaction of carboxylic acids[a]

Entry	Carboxylic acid	Amine	Yield[b] (%)
1	Bu^tO_2C CO_2H **1a**	Bu^tO_2C NH_2 **6a**	56
2	CO_2H O_2N **1b**	NH_2 O_2N **6b**	87
3	MeO CO_2H **1c**	MeO NH_2 **6c**	88
4	Boc N CO_2H **1d**	Boc N NH_2 **6d**	76[c]
5	CO_2Me CO_2H **1e**	CO_2Me NH_2 **6e**	63, 79[c]
6	CO_2H **1f**	NH_2 **6f**	70
7	CO_2H **1g**	NH_2 **6g**	45[d]
8	OH O **1h**	NH_2 **6h**	76
9	OBu^t O OH O **1i**	OBu^t O NH_2 **6i**	67 ,76[c]
10	OBu^t O OH O **1j**	OBu^t O NH_2 **6j**	58

[a] Conditions: DPPA (1.0 equiv), Et_3N (1.2 equiv), toluene, reflux, 2–3 h; NaOTMS (2.0 equiv, 1 M in THF), 0 °C or rt.
[b] Yield after column chromatography purification.
[c] Crude yield, after the acidic/basic extraction.
[d] Hydrolysis complete within 6 h at room temperature.

The following is a typical procedure. To a solution of acid (**1i**, 44 mg, 0.20 mmol) in toluene (3 mL) were added Et_3N (34 μL, 0.24 mmol) and diphenylphosphoryl azide (45 μL, 0.20 mmol), and then the reaction mixture was heated to reflux for 2–3 h. After cooling to 0 °C, a 1 M solution of sodium trimethylsilanolate in THF (0.4 mL) was added and the mixture was stirred for 20 min at room temperature. After quenching with 5% citric acid (5 mL), the mixture was concentrated to half-volume, and then was washed with Et_2O (2 times). The remained aqueous solution was made basic with 1 N NaOH, and then extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried, and concentrated. The crude product was very clean, and could be further purified by chromatography to give the pure product **6i** (26 mg, 67% yield).

These conditions worked very well for aliphatic amines, including sterically hindered amines (Table 1).[11] A variety of functional groups were well tolerated (Table 1, entries 1–5). Aromatic amines were also accessible, though the hydrolysis required a longer time at room temperature (Table 1, entry 7). In addition to being a mild and fast reaction, there was no epimerization for the conversion of chiral carboxylic acids into the corresponding chiral amines (Table 1, entries 8–10). For example, when the commercially available acid **1h** (99% ee) was treated under these conditions, **6h** was obtained with greater than 78:1 dr as determined by its Mosher ester derivatives.

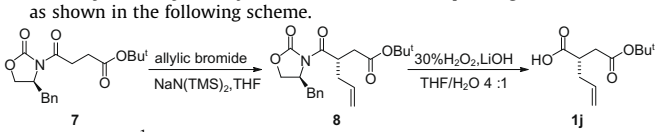
In conclusion, we have shown that the NaOTMS-modified Curtius reaction can be used to convert a variety of carboxylic acids directly to the corresponding primary amines with good functional group tolerance. This one-pot procedure is simple, mild, and efficient, and is expected to be applied to the synthesis of structurally more complicated molecules.

Acknowledgement

We thank Professor John K. Snyder for reviewing this manuscript.

References and notes

1. (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811. and references cited therein; (b) Miriyala, B.; Bhattacharyya, S.; Williamson, J. *Tetrahedron* **2004**, *60*, 1463–1471. and references cited therein.
2. Selected reviews: (a) Smith, P. A. S. *Org. React.* **1946**, *3*, 337–349; (b) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
3. (a) Curtius, T. *Ber.* **1890**, *23*, 3023–3041; (b) Curtius, T. *J. Prakt. Chem.* **1894**, *50*, 275; (c) Curtius, T. *J. Prakt. Chem.* **1915**, *91*, 39–102.
4. Selected examples: (a) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164–2167; (b) Ende, D. J. A.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Proc. Res. Dev.* **1998**, *2*, 382–392.
5. Selected examples: (a) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E.. In *Organic Syntheses*; Wiley: New York, 1988; Vol. VI; (b) Nettekoven, M.; Jenny, C. *Org. Process Res. Dev.* **2003**, *7*, 38–43; (c) Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107–4110.
6. Selected examples: (a) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511; (b) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733–10741; (c) Fairweather, K. A.; Mander, L. N. *Org. Lett.* **2006**, *8*, 3395–3398.
7. Selected examples: (a) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515–3518; (b) Earley, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G. P.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046–18053; (c) Yue, T.-Y.; McLeod, D. D.; Albertson, K. B.; Beck, S. R.; Deerberg, J.; Fortunak, J. M.; Nugent, W. A.; Radesca, L. A.; Tang, L.; Xiang, C. D. *Org. Process Res. Dev.* **2006**, *10*, 262–271.
8. Malanga, C.; Urso, A.; Lardicci, L. *Tetrahedron Lett.* **1995**, *36*, 8859–8860.
9. (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) Wolff, O.; Waldvogel, S. R. *Synthesis* **2004**, 1303–1305.
10. Using NaOH the produced amine contaminated with urea, and a much higher temperature and long reaction time were required for hydrolysis.
11. All starting carboxylic acids were purchased from commercial sources, except **1i** and **1j**. **1i** and **1j** were synthesized from the corresponding Evan's auxiliaries as shown in the following scheme.



Compound **8**: ^1H NMR (300 MHz, $CDCl_3$): 7.33–7.18 (m, 5H), 5.85–5.71 (m, 1H), 5.11–5.05 (m, 2H), 4.72–4.64 (m, 1H), 4.23–4.06 (m, 3 H), 3.25 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.79 (dd, *J* = 17.0, 11.0 Hz, 1H), 2.67 (dd, *J* = 13.3, 9.9 Hz, 1H), 2.45 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.40 (dd, *J* = 17.0, 3.9 Hz, 1H), 2.22 (dt, *J* = 13.7, 7.6 Hz, 1H), 1.39 (s, 9H).Compound **1j**: ^1H NMR (300 MHz, $CDCl_3$): 5.79–5.66 (m, 1H), 5.11–5.05 (m, 2H), 2.88 (m, 1H), 2.58 (dd, *J* = 16.7, 9.1 Hz, 1H), 2.23–2.48 (m, 3H), 1.41 (s, 9H).Compound **6j**: ^1H NMR (300 MHz, $CDCl_3$): 5.81–5.67 (m, 1H), 5.11–5.05 (m, 2H), 3.20 (m, 1H), 2.37 (dd, *J* = 15.9, 4.2 Hz, 1H), 2.00–2.21 (m, 3H), 1.64 (s, 2H), 1.42 (s, 9H). The dr of the Mosher's ester derivatives was greater than 60:1.