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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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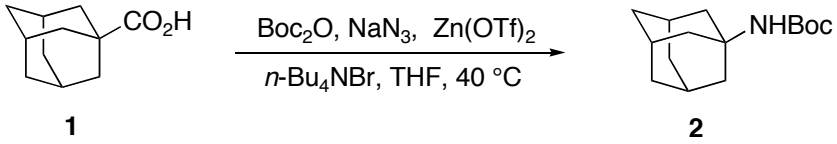
MILD AND EFFICIENT ONE-POT CURTIUS REARRANGEMENT: PREPARATION OF *N*-*tert*-BUTYL ADAMANTANYL-1-YL-CARBAMATE



1 **2**

Submitted by Olivier Leogane and Hélène Lebel.[1]
Checked by Kay M. Brummond, Thomas O. Painter, and Matthew Klinge.

1. Procedure

Caution ! The reaction should be conducted in a well-ventilated hood.

N-tert-Butyl adamantan-1-yl-carbamate (**2**). A flame-dried 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer and fitted with a thermometer and a rubber septum with an argon inlet is charged with adamantane-1-carboxylic acid (**1**, 5.40 g, 30.0 mmol) (Note 1), sodium azide (3.90 g, 60.0 mmol, 2.0 equiv)) (Note 2), tetra-*n*-butyl ammonium bromide (0.870 g, 2.70 mmol. 0.09 equiv) (Note 3), and finally zinc triflate (0.220 g, 0.60 mmol, 0.02 equiv) (Note 4). The flask is then purged with argon. After 10 min, 150 mL of THF (Note 5) is added via a syringe and the flask is heated in an oil bath at 40 °C. Once the internal temperature has reached 40 ºC, the di-*tert*-butyl dicarbonate (7.58 mL, 33.0 mmol, 1.1 equiv) is added (Note 6). The reaction mixture is then stirred under argon at 40 °C until >95% conversion to product is observed by GC analysis (Note 7). The reaction mixture is cooled to room temperature and quenched with a 50 mL portion of a 10% aqueous solution of $NaNO_2$ (Note 8). The biphasic mixture is stirred 30 min at room temperature and transferred to a 500-mL separatory funnel. The reaction flask is washed with hexanes and water and the two layers are separated. The aqueous layer is extracted twice with hexanes (2 x 40 mL) and the combined organic layers are washed successively with saturated aqueous NH_4Cl (75 mL), brine (75 mL), and then dried over Na_2SO_4 (50 g). The organic solution is filtered into a round-bottomed 250-mL flask and concentrated at 40 °C by rotary evaporation (12–14 mmHg) to afford a white solid. The 250-mL flask is then equipped with a reflux condenser and the solid dissolved in a boiling mixture (T = 75 °C) of hexanes (90 mL) and ethyl acetate (2 mL) (Note 9). The suspension is

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heated in an oil bath at reflux for 20 min, complete dissolution of the solid occurs, along with the formation of a sluggish orange oil. The clear, colorless solution is decanted away from this orange residue into a 250 mL Erlenmeyer flask fitted with a 24/40 glass joint and then concentrated at 40 °C by rotary evaporation (12–14 mmHg) then under high vacuum (< 3 mmHg) for 30 min to afford a white solid, which is recrystallized from a mixture of hexanes (< 50-60 mL), and chloroform (< 2 mL) (Note 10). The resulting crystalline product is collected on a fritted funnel, the filtrate is washed with 10–15 mL of cold hexanes, and excess solvent is removed under vacuum to yield 6.03 g of product. The mother liquor is concentrated at 40 °C by rotary evaporation (12–14 mmHg) then under high vacuum (< 3 mmHg), and the resulting white solid recrystallized (Note 11) from hexanes (< 10 mL) to yield 0.55 g of additional product after filtration as above. The solids are combined to provide 6.58 g (87%) of the title compound as a crystalline white solid (Notes 12 and 13).

2. Notes

1. Adamantane-1-carboxylic acid, 99% was purchased from Alfa Aesar, and was used without further purification.

2. NaN_3, 99% was purchased from Alfa Aesar, and was ground prior to use.

3. Tetra-*n*-butyl ammonium bromide, 99% was purchased from Aldrich Chemical Company, Inc. and stored in a desiccator filled with drierite.

4. The checkers purchased $Zn(OTf)_2$, 98% from Strem Chemicals and stored it in a glove-box under a nitrogen atmosphere upon receipt. $Zn(OTf)_2$ was weighed into a two-necked round-bottomed flask, sealed, then equipped with an argon inlet upon removal from the glove-box. $Zn(OTf)_2$ was quickly transferred to the reaction mixture by pouring it from the two-necked flask under an argon flow. The submitters report that for their best results, the $Zn(OTf)_2$ was purchased from Aldrich Chemical Company, Inc., handled under an argon atmosphere in a glove-box and was used without further purification affording an 85% yield. The checkers found that the $Zn(OTf)_2$ purchased from Aldrich resulted in incomplete reactions. The submitters report that $Zn(OTf)_2$ from Strem Chemicals is compatible with the reaction conditions (81% yield for **2**) but also comment that very low yields were observed if $Zn(OTf)_2$ from Alfa Aesar was used.

5. Anhydrous 99.9%, inhibitor free tetrahydrofuran was purchased from Aldrich and purified with alumina using the Sol-Tek ST-002 solvent purification system directly before use. The submitters report that THF was purified with a Glass Contour Seca Solvent Purification System.

6. Boc_2O, 99% was purchased from Aldrich Chemical Company, Inc and stored in the refrigerator. For convenience, the bottle of Boc_2O was warmed in a water bath to reach the melting point, and the colorless oil was then transferred quickly to the reaction flask via a syringe.

7. The internal reaction temperature must be maintained between 39 and 41 °C during the entire process. This was accomplished using a temperature controller and thermocouple connected to a variac and oil bath. After 120 hours, 96% conversion was observed by GC analysis in the first full scale reaction. The second full scale check did not reach >95% conversion until 240 hours. The submitters report that after 48 hours, 85% conversion for the desired carbamate was observed by GC - MS analysis. The product appeared to crystallize in the reaction mixture.

8. $NaNO_2$, 99% was purchased from Aldrich Chemical Company, Inc. and was used without further purification. Sodium nitrite is used to quench any residual azide derivatives from the reaction mixture.

9. Hexanes and ethyl acetate were purchased from EMD Chemicals and distilled prior to use. The submitters report that hexanes and ethyl acetate (ACS grade) were purchased from Fisher Scientific and were used as received.

10. Chloroform (ACS grade) was purchased from Fisher Scientific and was used as received. For the recrystallization, the white solid is dissolved in a boiling solution (75 °C) of hexanes (50–60 mL) and chloroform (< 2 mL) in a 250-mL Erlenmeyer flask. The mixture is heated on a hot plate until complete dissolution of the solid occurs. The solution is then concentrated with heating on the hot plate to a volume of less than 25 mL. The mixture was cooled to room temperature over 10 min, then placed into a cold room at 4 °C overnight.

11. The solution was concentrated to less than 5 mL by heating on a hot plate.

12. The physical properties of the purified material **2** are as follows: mp 114-115 ºC; R_f 0.49 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6, 70 °C) δ: 1.46 (s, 9 H), 1.50 (s, 6 H), 1.86 (s, 9 H), 4.10 (s (br), 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.4, 29.4, 36.3, 41.9, 50.4, 78.5 (br), 154.1 (br); IR (neat) 3321, 2977, 2906, 2851, 1685, 1526, 1362, 1172, 1054, 874

cm^{-1}; HMRS (EI) calcd for $C_{15}H_{25}NO_2$ $[M]^+$: 251.1885. Found: 251.1883. Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57; O, 12.73; found C, 71.69; H, 10.20; N, 5.57.

13. A second run on the same scale provided 6.06 g (80%) of product with the same physical characteristics and melting point. The submitters reported a yield of 6.41 g (85%).

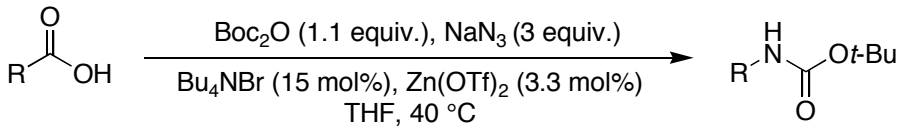
Safety and Waste Disposal Information

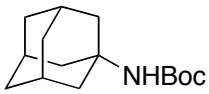
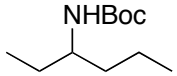
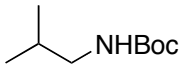
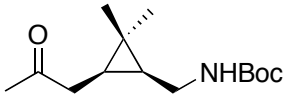
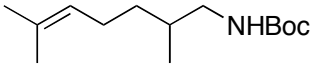
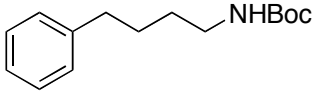
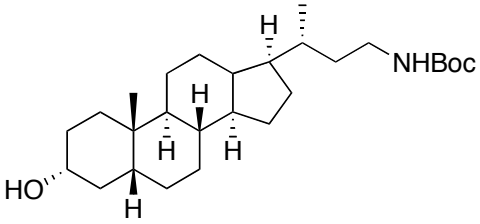
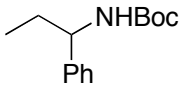
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The Curtius rearrangement involves the concerted degradation of an acyl azide into an isocyanate, which can be trapped by a variety of nucleophiles (such as alcohols), providing a convenient method to synthesize amine derivatives (such as carbamates). Although a number of methods have been reported for the preparation of acyl azides, such a starting material is unstable and difficult to handle. Diphenylphosphorazidate (DPPA) was the first reagent reported for the direct conversion of carboxylic acids into carbamates, in a one-pot process without isolation of the acyl azide intermediate.[2] However, many drawbacks are associated with the use of this reagent including the requirement for high temperatures and the difficult separation of the desired product from phosphorus residues. The procedure described herein provides a practical and efficient method for the synthesis of aliphatic Boc-protected amines by one-pot zinc-catalyzed Curtius rearrangement starting from a variety of carboxylic acids (Table 1).[3] The method uses readily and commercially available reagents. A mixture of sodium azide, di-*tert*-butyl dicarbonate and an aliphatic carboxylic acid produces sodium *t*-butoxide and the corresponding acyl azide, which spontaneously rearranges at 40 °C to the corresponding isocyanate. In the presence of catalytic amounts of $Zn(OTf)_2$ and tetrabutyl ammonium bromide, the *tert*-butoxide species then reacts with the isocyanate intermediate to form the carbamate derivative.

Table 1. Curtius Rearrangement of Carboxylic Acids



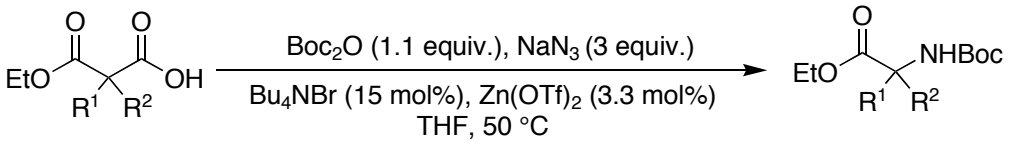
entry	carbamate	isolated yield (%)
1		90 (85)[a]
2		94
3		77
4		68
5		80 (86)[a]
6		57
7		72
8		58 (45)[a]

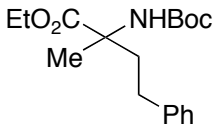
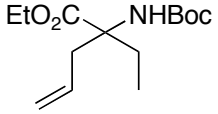
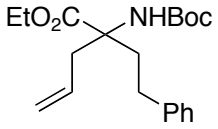
[a] In parenthese, yields for 10 mmol scale.

The by-products are easy to eliminate, thus the purification proceeds efficiently. Compared to the original procedure,[3] the catalyst loading of $Zn(OTf)_2$ was decreased to 2 mol % and only 2 equivalents of sodium azide were necessary, when the reaction was run on 30 mmol scale. Although azide species are known to be potentially explosive and hazardous compounds, the experimental procedure described here is safe at the temperatures described. Indeed, TGA (thermogravimetric analysis) showed decomposition of the reaction mixture at temperatures >100 ºC. This new methodology was also used with malonates derivatives, giving access to

unnatural 2,2-disubstituted protected amino acids (Table 2). Finally, an alternative procedure for the synthesis of anilines from aromatic carboxylic acids has been recently disclosed.[4]

Table 2. Curtius Rearrangement of Malonate Derivatives



entry	carbamate	isolated yield (%)
1		75 (70)[a]
2		65
3		60

[a] In parentheses, yields for 30 mmol scale.

1. Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal (Québec), Canada, H3C 3J7. Helene.lebel@umontreal.ca

2. (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) Shioiri, T.; Yamada, S-i. *Org. Synth.* **1984**, *62*, 187-190.

3. Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107-4110.

4. Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717-5720.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-*tert*-Butyl adamantan-1-yl-carbamate: Carbamic acid, tricyclo[3.3.1.13,7]dec-1-yl-, 1,1-dimethylethyl ester**; (**151476-40-3)
Sodium azide; (26628-22-8)
Adamantine-1-carboxylic acid: Tricyclo[3.3.1.13,7]decane-1-carboxylic acid; (828-51-3)
Tetra-*n*-butyl ammonium bromide; (1643-19-2)
Zinc triflate; (54010-75-2)
Di-*tert*-butyl dicarbonate: Dicarbonic acid, C,C'-bis(1,1-dimethylethyl) ester; (24424-99-5)

Hélène Lebel received her B.Sc. degree in biochemistry from the Université Laval in 1993. She conducted her Ph.D. studies in organic chemistry at the chemistry department of the Université de Montréal under the supervision of professor André B. Charette as a 1967 Science and Engineering NSERC Fellow. In 1998, she joined the research group of professor Eric Jacobsen at Harvard University as a NSERC Postdoctoral Fellow. She started her independent career in 1999 at the Université de Montréal, where her research program focuses on the development of novel synthetic methods.

Olivier Leogane is from Guadeloupe in the West Indies. He received a B.Sc. degree in chemistry in 2002 from Université de Nantes. He then pursued his Ms.C in organic chemistry at Université de Paris VI in 2003. His Ph.D. studies were conducted under supervision of Hélène Lebel at Université de Montréal where he developed new catalyzed-methodologies for the Curtius Rearrangement. He is currently an industrial NSERC Postdoctoral Fellow at Tranzyme Pharma.

Thomas Painter was born in 1980 in Pittsburgh, Pennsylvania. During his undergraduate studies he interned at Valspar Corporation in 2002, and obtained his B.S. degree in chemistry from the University of Pittsburgh in 2003. He is currently finishing graduate studies as a Bayer Fellow in the laboratory of Professor Kay Brummond at the University of Pittsburgh. His graduate research has included work on the synthesis of electron- deficient trienones and ε-lactams, and progress toward bicyclic analogs of irofulven using rhodium(I)-catalyzed cycloisomerization reactions. He will be pursuing future research endeavors as a post-doctoral associate under the guidance of Professor Jeffrey Aubé at the University of Kansas.

Matthew Klinge was born in 1986 in Erie, Pennsylvania. He is currently pursuing undergraduate studies at the University of Pittsburgh with a declared major in biology, and a minor in chemistry. He conducted undergraduate research in the laboratory of Professor Kay Brummond at the University of Pittsburgh during the 2007-2008 academic year. He looks forward to graduating from the University of Pittsburgh in April of 2009, and wishes to attend medical school following graduation.

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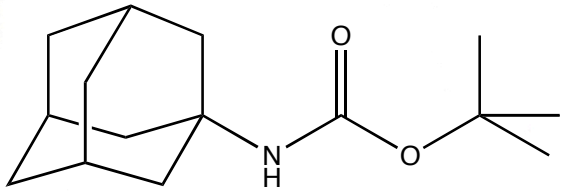

2

tp OS149 C6D6 1H (500 MHz) 70 C nmr500 5/6/08