Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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.*
Sodium Methoxide-Catalyzed Direct Amidation of Esters

Submitted by Kazushi Agura,¹ Takashi Ohshima,*¹ Yukiko Hayashi,² and Kazushi Mashima*²

¹Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan; ²Department of Chemistry, Graduate School of Engineering Science, Osaka University, Osaka 560-8531, Japan

Checked by Mengyang Fan and Dawei Ma

A. \( \text{N-Hexylbenzamide} \). A 50-mL, one-necked, round-bottomed Schlenk flask equipped with a 2-cm ellipsoidal magnetic stir bar and a septum is connected to Schlenk line and dried with a heat gun under reduced pressure (1.5 mmHg) (Note 1). After the flask cooled to room temperature, it is evacuated and backfilled with argon for three times. The septum is removed and sodium methoxide (17.7 mg, 0.328 mmol, 1 mol%) (Note 2) and an activated powder of 3Å molecular sieve (808 mg) (Note 3) are added quickly to the flask under an argon atmosphere (Note 4). The septum is replaced and the flask is filled with argon and toluene (8.0 mL) (Note 5), n-
HexNH₂ (5.5 mL, 41.6 mmol, 1.3 equiv) (Note 6), and methyl benzoate (4.0 mL, 32.1 mmol, 1.0 equiv) (Note 7) are added via syringe. The reaction mixture is stirred and heated at 55 °C (Note 8) with an oil bath for 20 h under an argon flow conditions. The progress of the reaction is monitored by TLC (Rf = 0.30, hexanes/EtOAc = 4/1). The resulting mixture is quenched by adding aqueous saturated NH₄Cl (30 mL), then EtOAc (30 mL). The biphasic suspension is filtered through a Celite pad (5 g) and the residue is washed with EtOAc (100 mL). The filtered solution is transferred to a 250-mL separatory funnel, and the organic layer is separated, washed with aqueous saturated NH₄Cl (30 mL), brine (30 mL), dried over Na₂SO₄ (10 g), filtered through a cotton plug, and concentrated using a rotary evaporator (30 °C, 4 mmHg). The residue is purified by flash column chromatography (diameter = 6 cm; 550 mL of silica gel; hexanes/EtOAc = 4/1 to 2/1) to give 5.42–5.54 g (82–84% yield) of N-hexylbenzamide (Note 9) as a white solid.

B. (S)-tert-Butyl (1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate. A 50-mL, one-necked, round-bottomed Schlenk flask equipped with a 2-cm ellipsoidal magnetic stir bar and a septum is connected to Schlenk line and dried with a heat gun under reduced pressure (1.5 mmHg) (Note 1). After the flask cooled to room temperature, it is evacuated and backfilled with argon for three times. The septum is removed and sodium methoxide (108 mg, 2.01 mmol, 10 mol%) (Note 2) and an activated powder 3 Å molecular sieve (530 mg) (Note 3) are added to the flask under an argon atmosphere quickly. The septum is replaced and the flask is filled with argon gas and a yellow solution of 4-CF₃-C₆H₄-OH (973 mg, 6.00 mmol, 30 mol%) (Note 10) in toluene (5.0 mL) (Note 5), BnNH₂ (2.8 mL, 26.1 mmol, 1.3 equiv) (Note 11), and (S)-Boc-Leu-OMe (4.95 g, 20.2 mmol, 1.0 equiv) (Note 12) are added. The reaction mixture is stirred and heated at 70 °C (Note 8) with an oil bath for 99 h under argon flow conditions. The progress of the reaction is monitored by TLC (Rf = 0.30, hexanes/EtOAc = 4/1). The resulting mixture is quenched with aqueous saturated NH₄Cl (30 mL). After adding EtOAc (30 mL), the biphasic suspension is filtered through a Celite pad (5 g) and the residue is washed with EtOAc (100 mL). The filtered solution is transferred to a 250-mL separatory funnel, and the organic layer is separated and washed with aqueous saturated NH₄Cl (30 mL), water (30 mL), and brine (30 mL), dried over Na₂SO₄ (10 g), filtered through a cotton plug, and concentrated using a rotary evaporator (30 °C, 4 mmHg). The residue is purified by flash column chromatography (diameter = 6 cm;
550 mL silica gel; hexane/EtOAc = 8/1 to 2/1) to give 5.31–5.47 g (82–85% yield and 98% ee) of (S)-Boc-Leu-NHBn (Note 13) as a white solid.

Notes

1. Maintaining anhydrous conditions is critically important to achieve a high turnover frequency and maintain good reproducibility, because contamination by water decomposes the NaOMe catalyst to NaOH, which further reacts with ester to generate inactive sodium carboxylate. The submitter used a 50-mL, one-necked, round-bottomed flask equipped with a three-way cock. To ensure the anhydrous conditions, the checker used a 50-mL, one-necked, round-bottomed Schlenk flask attached to Schlenk line.

2. From a freshly opened bottle, NaOMe (powder, 95%, purchased from Aldrich) is quickly transferred to a Schlenk tube under a flow of argon and stored under an argon atmosphere.

3. The powder ed 3Å molecular sieves (powder < 50 μm, purchased from Acros) are activated by heating at 200 °C through use of an oil bath under reduced pressure (1.5 mmHg) for 5 h. The activated sieves are stored in a Schlenk tube under argon atmosphere.

4. The submitter used a two-leg glass adapter to transfer the NaOMe or the molecular sieve from the Schlenk tube to the flask. The checkers did not use such apparatus, but connected the flask to an argon line and quickly transferred the NaOMe or the molecular sieve under a flow of argon.

5. The toluene (purchased from Sinopharm Chemical Reagent Co., Ltd) is dried over CaH$_2$ overnight at room temperature and then distilled over CaH$_2$ under standard pressure and stored in a side-arm flask under argon atmosphere.

6. n-HexNH$_2$ (purchased from Aldrich, 99%) is dried over CaH$_2$ overnight at room temperature and then distilled under ordinary pressure and stored in a Schlenk tube under argon atmosphere.

7. Methyl benzoate (purchased from Aldrich, 99%) is dried over CaH$_2$ overnight at room temperature and then distilled at atmospheric pressure and stored in a Schlenk tube under argon atmosphere.

8. The reaction temperature significantly affects the rate of the NaOMe-catalyzed amidation. Although the 8-mmol scale reactions reported in
the original manuscript\textsuperscript{3} are performed at 50 °C (oil bath), for procedures A and B (32.1 mmol scale), the oil bath temperature is increased to 55 °C to improve heat transfer efficiency.

9. The analytical data of N-hexylbenzamide are as follows: white solid; mp 41–43 °C; R\textsubscript{f} = 0.30 (hexanes/EtOAc = 4/1); IR (KBr disk, ν/cm\textsuperscript{-1}) 3324, 2965, 2956, 2921, 2857, 1632, 1577, 1529, 1489, 1481, 1466, 1376, 1350, 1313, 1275, 1078, 928, 859, 805, 718, 695, 634; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ: 0.90 (t, J = 6.8 Hz, 3 H), 1.30-1.44 (m, 6 H), 1.62 (m, 2 H), 3.46 (dt, J = 6.6, 6.0 Hz, 2 H), 6.08 (br s, 1 H), 7.41-7.51 (m, 3 H), 7.76 (d, J = 7.6 Hz, 2 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ: 14.0, 22.5, 26.6, 29.6, 31.5, 40.1, 126.8, 128.5, 131.2, 134.9, 167.5; MS (ESI+) m/z (relative intensity) 206.2 ([M+H\textsuperscript{+}], 100%), 282.2 ([M+Na\textsuperscript{+}], 22%); HRMS (ESI+) m/z calcd. for C\textsubscript{13}H\textsubscript{19}NO 206.1539, found 206.1539; Anal. calcd for C\textsubscript{13}H\textsubscript{19}NO: C, 76.06, H, 9.33, N, 6.82; found: C, 76.09, H, 9.45, N, 6.79.

10. p-Trifluoromethylphenol (purchased from Aldrich, 97%) is dissolved in toluene (Note 4) and stored in a Schlenk tube under argon atmosphere.

11. Benzylamine (purchased from Aldrich, 99%) is dried over CaH\textsubscript{2} overnight at room temperature and then distilled under reduced pressure and stored in a Schlenk tube under argon atmosphere.

12. N-(tert-Butoxycarbonyl)-L-leucine methyl ester ((S)-Boc-Leu-OMe) (97%) was purchased from Sigma-Aldrich and used directly without further purification.

13. The analytical data of (S)-Boc-Leu-NHBn are as follows: white solid; mp 77–79 °C; R\textsubscript{f} = 0.30 (hexanes/EtOAc = 4/1); IR (KBr disk, ν/cm\textsuperscript{-1}) 3294, 3089, 2961, 2870, 1682, 1655, 1534, 1454, 1392, 1366, 1321, 1274, 1247, 1171, 1046, 1027, 714, 695; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ: 0.93 (d, J = 4.5 Hz, 3 H), 0.95 (d, J = 4.5 Hz, 3 H), 1.42 (s, 9 H), 1.46–1.54 (m, 1 H), 1.64–1.78 (m, 2 H), 4.11 (m, 1 H), 4.45 (m, 2 H), 4.84 (br s, 1 H), 6.42 (br s, 1 H), 7.24–7.35 (m, 5 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ: 22.0, 22.9, 24.7, 28.2, 41.2, 43.4, 53.1, 80.0, 127.4, 127.6, 128.6, 138.1, 155.8, 172.5; MS (ESI+) m/z (relative intensity) 343.3 ([M+Na\textsuperscript{+}], 100%), 265.3 (56%); HRMS (ESI+) m/z calcd for C\textsubscript{18}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3} 321.2173, found 321.2166; Anal. calcd for C\textsubscript{18}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3}: C, 67.47, H, 8.81, N, 8.74; found: C, 67.50, H, 8.78, N, 8.73; [α]\textsubscript{D}\textsuperscript{27}= 24.8 (c 1.03 in CH\textsubscript{2}Cl\textsubscript{2}); The enantiomeric excess (%ee) was determined to be 98% by HPLC using CHIRALPAK OD-3 column (2% i-ProOH/hexane, 1.0 mL/min, 254 nm): t\textsubscript{R} (minor, 13.3 min) t\textsubscript{R} (major, 19.3 min). The racemic mixture was prepared through the condensation of rac-Boc-Leu-OH and benzylamine using HOBT and EDCI.
Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011 www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

These procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Amides are one of the most ubiquitous and important functional groups in natural and synthetic organic compounds, and the amide bond formation has been studied intensively in organic synthesis. The most common method of synthesizing amides is the coupling reaction of carboxylic acids and amines using stoichiometric amounts of condensation reagents. Amidation of esters with amines, which is a key transformation in biologic peptide synthesis on ribosomes, is another important synthetic method for amide bond formation due to the environmental benefits of this reaction and the operational benefits of esters, such as their handling ease and high stability as well as their high solubility in most organic solvents compared with carboxylic acid. In non-enzymatic amide formation, however, simple alkyl esters are viewed as an inert scaffold and rather harsh reaction conditions, such as high temperature, high pressure, or the use of more than stoichiometric amounts of strongly basic reagents, are required to promote amidation.

Ester-amide exchange reactions using alkali metal alkoxides such as NaOMe° and KO-t-Bu have been reported, but more than stoichiometric amounts or sub-stoichiometric amounts of these reagents are necessary in
these systems. In contrast, this is the first report that maintenance of the anhydrous conditions successfully promotes the reactions with only a catalytic amount of NaOMe (1-10 mol%). Because this NaOMe-catalyzed amidation proceeds with high efficiency under mild conditions (as low as room temperature), a variety of functionalized aliphatic and aromatic

Table 1. NaOMe-catalyzed amidation with various esters and amine$^{a,b}$

| Reaction condition; A reaction mixture of ester (8.0 mmol), amine (10.4 mmol), NaOMe (0.4 mmol, 5 mol% based on ester) and toluene (2.0 mL) was heated at 50 °C with oil bath under an argon atmosphere.$^{b}$ Isolated yield. $^{c}$ 21% of amino ester was also obtained. |
methyl esters as well as cyclic lactones are smoothly converted to the corresponding amides (Table 1). Furthermore, adding a desiccant such as MS3Å or Drierite can minimize catalyst loading to 1 mol% (Procedure A).

When chiral α-amino ester derivatives are used as the substrate, epimerization is a major problem due to the strongly basic conditions. This severe epimerization is successfully rectified by the addition of the rather acidic alcohol 4-trifluorophenol. Under the optimized conditions using 4-trifluorophenol, a catalytic ester-amide exchange reaction of various N-Boc protected chiral α-amino esters with benzylamine proceeds in high yield without epimerization (Table 2).

**Table 2. NaOMe-catalyzed amidation with various chiral α-amino esters<sup>a,b,c</sup>**

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product Structure</th>
<th>Yield</th>
<th>ee (%)</th>
<th>Temp., Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ph)</td>
<td><img src="image.png" alt="Image of product structure" /></td>
<td>81%</td>
<td>97%</td>
<td>(50 °C, 72 h)</td>
</tr>
<tr>
<td>(Me)</td>
<td><img src="image.png" alt="Image of product structure" /></td>
<td>80%</td>
<td>98%</td>
<td>(50 °C, 72 h)</td>
</tr>
<tr>
<td>(t-BuOOC)</td>
<td><img src="image.png" alt="Image of product structure" /></td>
<td>84%</td>
<td>99%</td>
<td>(70 °C, 99 h)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction condition: A reaction mixture of ester (2.0 mmol), benzyl amine (2.6 mmol), NaOMe (0.2 mmol, 10 mol% based on ester), 4-trifluoromethylphenol (0.6 mmol, 30 mol% based on ester), MS 3Å (50 mg) and toluene (0.5 mL) was heated with oil bath under an argon atmosphere. <sup>b</sup> Isolated yield <sup>c</sup> ee was determined by chiral HPLC analysis. <sup>d</sup> 4.0 equiv of amine was used.
References

1. Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan.
2. Department of Chemistry, Graduate School of Engineering Science, Osaka University, Osaka 560-8531, Japan.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

Benzoic acid, methyl ester; (93-58-3)
Benzenemethanamine; (100-46-9)
Sodium methoxide; (124-41-4)
Benzamide, N-(phenylmethyl)-; (1485-70-7)
1-Hexanamine; (111-26-2)
Benzamide, N-hexyl-; (4773-75-5)
L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-, methyl ester; (63096-02-6)
Phenol, 4-(trifluoromethyl)-; (402-45-9)
Carbamic acid, N-[(15)-3-methyl-1-[[phenylmethyl]amino]carbonyl]butyl]-, 1,1-dimethylethyl ester; (101669-45-8)
Takashi Ohshima received his Ph.D. from The University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. He joined Otsuka Pharmaceutical Co., Ltd. for one year. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997-1999), he returned to Japan and joined Professor Shibasaki’s group in The University of Tokyo as an Assistant Professor. He was appointed as Associate Professor of Osaka University in 2005. In 2010, he was promoted to Professor of Kyushu University. He has received the Fujisawa Award in Synthetic Organic Chemistry (2001), Pharmaceutical Society of Japan Award for Young scientists (2004), The Japanese Society for Process Chemistry Award for Excellence (2008), 9th Green Sustainable Chemistry Award with MEXT Award (2010), and Asian Core Program Lectureship Award (2012).

Kazushi Mashima received his Doctor degree (1986) from Osaka University under the supervision of Professor A. Nakamura. He became an Assistant Professor at Institute for Molecular Science, Okazaki National Institutes in 1983, Faculty of Engineering, Kyoto University in 1989, and then to Faculty of Science, Osaka University in 1991. He was appointed as an Associate Professor at Faculty of Engineering Science, Osaka University in 1994, and then a full Professor at Graduate School of Engineering Science, Osaka University in 2003. He worked with Professor M. A. Bennett, Australian National University in 1992 and Professor W. A. Herrmann, Technisch Universität München in 1993. He has received The Chemical Society of Japan Award for Creative Work for 2008, The 9th Green and Sustainable Chemistry Award, Awarded by the Ministry of Education, Culture, Sports, Science and Technology in 2010, and The Award of the Society of Polymer Science, Japan in 2010.
Kazushi Agura was born in 1986 in Kyoto, Japan. He obtained his Master's degree from Graduate School of Engineering Science, Osaka University, Osaka, Japan, in the laboratory of Professor Kazushi Mashima. He then joined the Ph.D. program at Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, in the laboratory of Professor Takashi Ohshima and is studying the development of new chiral bimetallic catalyst. He then received the Ph.D. from Kyushu University, Fukuoka, Japan, in 2014 under the direction of Professor Takashi Ohshima. He is currently working in Shionogi & Co., Ltd.

Yukiko Hayashi was born in 1986 in Kobe, Japan. After obtaining her B.Sc. degree from Osaka University in 2008, she received Ph.D. from Osaka University in 2013 under the supervision of Prof. Kazushi Mashima. She was Research Fellow of the Japan Society for the Promotion of Science in 2010-2013. She is currently working in Noritake Co., Ltd.

Mengyang Fan was born in 1989 in Xuzhou, China. He obtained his B.Sc. degree from the Department of Chemistry and Chemical Engineering, Southeast University in 2011. He then joined the Ph.D. program in the laboratory of Professor Dawei Ma at Shanghai Institution of Organic Chemistry and is studying transition metal catalyzed C-H bond activation.