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A New One-Pot Method for the Synthesis of α-Siloxyamides from Aldehydes or Ketones and Its Application to the Synthesis of (−)-Bestatin

Hisao Nemoto,* Rujian Ma, Ichiro Suzuki, and Masayuki Shibuya

Faculty of Pharmaceutical Sciences, The University of Tokushima, 1-78, Sho-machi, Tokushima, 770-8505, Japan

nem@ph2.tokushima-u.ac.jp

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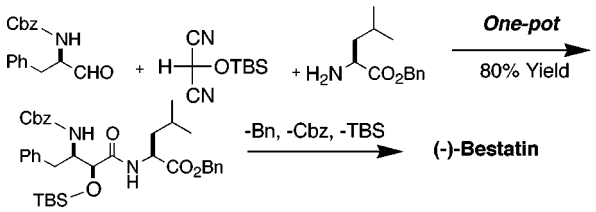
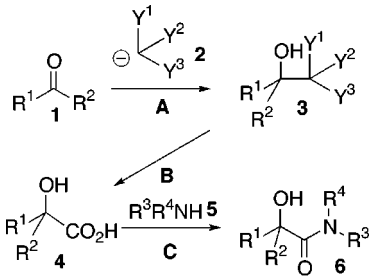
ABSTRACT



A new one-pot method for the synthesis of α-siloxyamides is described. The three substrates, H-C(CN)$_2$O-SiMe$_2$t-Bu, aldehydes or ketones, and primary or secondary amines, are simply mixed in one portion in acetonitrile or ether; the α-siloxyamides are obtained within short peroids in excellent yields in many cases. As a demonstration of our method, the synthesis of (−)-bestatin was carried out.

α-Hydroxyamides and the *O*-protected derivatives[1] are among the most important synthetic intermediates of biologically active peptide mimics.[2] The most direct synthetic methods involving multiple steps are based on the homologation of aldehydes **1** with various masked anions **2** to prepare **3**. This must be subsequently unmasked to give the α-hydroxycarboxylic acids **4**. Amide bond formation of **4** with amines **5** is then carried out to produce **6**[3] as outlined in Scheme 1.[4] In the scheme, the H−C bond of **2** is activated

Scheme 1



and three of C−Y^n bonds are preserved in the first step. The activation of the C−Y^n bonds of **3** is carried out in the next step. Additionally, independent activation of the resulting carbonyl functionality of **4** is required for the following subsequent amide bond formation.[5] Hence, until now, it has been very difficult to carry out these reactions in one pot using ordinary reagents such as **2**.

(1) In the following papers, serious problems were encountered in the protecting reaction of α-hydroxyamides. Therefore, if the *O*-protected derivatives could be directly obtained by an alternative method, they could be efficiently used for further synthetic steps toward the final target molecules. (a) Maryanoff, B. E.; Greco, M. N.; Zhang, H.-C.; Andrade-Gordon, P.; Kaufman, J. A.; Nicolau, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225. (b) Greco, M. N.; Zhang, H. M.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4959.

(2) (a) Babine, R. E.; Bender S. L. *Chem. Rev.* **1997**, *97*, 1359. (b) Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 82. (c) Sakurai, M.; Higashida, S.; Sugano, M.; Komai, T.; Yagi, R.; Ozawa, Y.; Handa, H,; Nishigaki, T.; Yabe, Y. *Bioorg. Med. Chem.* **1994**, *2*, 807.

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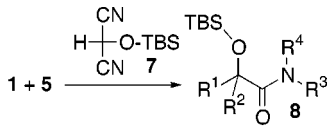
We report a new *one-pot* method to synthesize α-siloxyamides. When an aldehyde (or a ketone) **1**, an amine **5**, and H-MAC[6]-TBS [H-C(CN)$_2$O-TBS] (**7**)[7] are simply mixed *in one portion*, the α-siloxyamides **8** are obtained in good to excellent yields (Scheme 2). Because of the migration of

Scheme 2



the TBS group, cyanide anion is eliminated from the oxymalononitrile moiety to generate the acyl cyanide, which is condensed with amine.[7] It is also noteworthy that we were the first to observe this *migration of O*-protecting group of MAC reagents.[6−8]

We first examined 1.1 equiv of various amines for the reaction of 4-tolualdehyde. In all cases listed in Table 1, the

Table 1. Reaction of 4-$CH_3C_6H_4CHO$ to 4-$CH_3C_6H_4CH$(OTBS)-$CONR^3R^4$ with Various Amines (1.1 equiv) and **7** (1.2 equiv) at 0 °C for 5 min in Acetonitrile

entry	R^3R^4NH	yield (%)
1	$C_4H_9NH_2$	96
2	NH_3[a]	90
3	NH_2OH[b]	78[c]
4	$PhNH_2$[d]	88
5	$H_2N-CH_2-CO_2Me$	88
6	$HOCH_2CH_2NH_2$	94
7	(*R*)-$PhCH(CH_3)NH_2$	89[e]
8	$(C_2H_5)_2NH$	77
9	morphorine	92

[a] 10% aqueous solution was used. [b] 50% of aqueous solution and 1 equiv of triethylamine were used. [c] Carried out at −25 °C for 2 h. [d] 0.1 equiv of DMAP was added. [e] A mixture of diastereomers (1:1) was obtained.

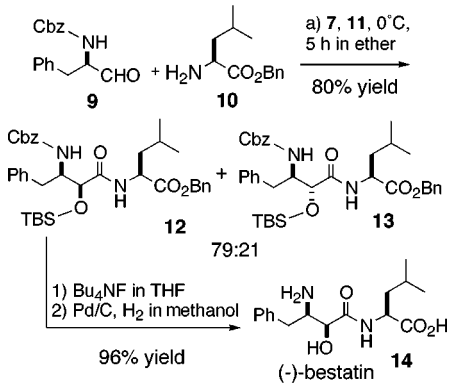
corresponding α-siloxyamides **8** were obtained in excellent yields within 5 min by using 1.2 equiv of **7** at 0 °C in acetonitrile.[9] When weakly basic amines were used, an additional *tert*-amine such as *N*,*N*-dimethyl-4-aminopyridine (DMAP) or triethylamine was added (entries 3 and 4).

Next, the reactions for various aldehydes and ketones were carried out (Table 2). In the case of aromatic aldehydes with an electron-donating, electron-withdrawing, or *ortho*-substituted group and α,*β*-conjugated aldehydes, the desired products were also obtained within 5 min in excellent yields by using a slight excess of H-MAC-TBS and butylamine at 0 °C in acetonitrile (entries 1−7). In contrast, the reactions of 3-phenylpropanal or 2-ethylhexanal, as representative examples of aliphatic aldehydes, gave the corresponding α-siloxyamide in moderate yields, along with the cyanohydrin of the starting aldehyde (entries 8 and 10).

We examined the reaction in various solvents using 2-ethylhexanal[10] as a representative aldehyde and found that formation of the byproduct, the cyanohydrin of the starting 2-ethylhexanal, is effectively inhibited in ether at −25 °C. In ether, the yields of **8** obtained were dramatically increased (entries 9 and 11). Then, we carried out the reaction for various aldehydes and ketones. The easily enolizable diphenylacetaldehyde was also converted to the desired compound in 85% yield in ether (entry 12). In the reaction of pivaldehyde, the best yield obtained was 35% after numerous attempts under various conditions (entry 13). Two typical aromatic ketones, 4-nitroacetophenone and 4-methylacetophenone, were transformed to the corresponding amides in high yields, respectively (entries 14 and 15). In these cases, acetonitrile is more effective than ether. The reaction of cyclohexanone and 3-pentanone proceeded in good to excellent yields (entries 16 and 17). No reaction took place when 3,3-dimethyl-2-butanone was used even under conditions similar to those used for the other entries (entry 18).

We applied the method to the synthesis of (−)-bestatin[3a,5a] **14** according to Scheme 3. A mixture of **7** (0.20 mmol),

Scheme 3



leucine benzyl ester (**10**) (0.12 mmol), and aldehyde **9**, prepared from Cbz-phenylalanine (0.10 mmol),[11] was simply

(3) (a) Chen, J. J.; Coles, P. J.; Arnold, L. D.; Smith, R. A.; MacDonald, I. D.; Carriére, J.; Krantz, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 435. (b) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570. (c) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181. (d) Aggarwal, V. K.; Thomas, A.; Schade, S.; *Tetrahedron* **1997**, *48*, 16213. (e) Katritzky, A. R.; Yang, Z.; Lam. J. N. *Synthesis* **1990**, 666.

(4) Monenschein, H.; Dräger, G.; Jung, A.; Kirschning, A. *Eur. J. Chem. Soc.* **1999**, *5*, 2270.

(5) In recent years, several advanced methods have been reported for the efficient combination of the steps B and C. In those methods, the unmasking reactions directly produce the acyl chlorides or acyl cyanides. (a) Wasserman, H. H.; Xia, M.; Peterson, A. K.; Jorgenson, M. R.; Curtis, E. A. *Tetrahedron Lett*. **1999**, *40*, 6163. (b) Satoh, T.; Onda, K.-I.; Yamakawa, K. *Tetrahedron Lett*. **1990**, *25*, 3567.

(6) MAC is the abbreviation for "masked acyl cyanide". X-MAC-Y means X-[C(CN)$_2$O]-Y. When the X-MAC-Y has a deprotective proton (X = H), we describe them as "MAC reagents". Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40*, 1319.

(7) Synthesis of **7** and the details of the transformation of MAC moiety to amides: Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515.

(8) (a) Kubota, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 7195. (b) Nemoto, H.; Kubota, Y.; Sasaki, N.; Yamamoto, Y. *Synlett* **1993**, 465. (c) Nemoto, H. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 1044. (d) Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161.

Table 2. Preparation α-Siloxyamides **8** from Aldehydes or Ketones with Butylamine and **7**

entry	aldehyde	solvent	temp, °C	**7** (equiv)	butylamine (equiv)	reaction period	yield[a] (%)
1	4-H_3C-C_6H_4-CHO	acetonitrile	0	1.2	1.1	5 min	96
2	2-HO-C_6H_4-CHO	acetonitrile	0	1.2	1.1	5 min	95
3	furan-2-carbaldehyde	acetonitrile	0	1.2	1.1	5 min	94
4	2-Br-C_6H_4-CHO	acetonitrile	0	1.2	1.1	5 min	92
5	4-NC-C_6H_4-CHO	acetonitrile	0	1.2	1.1	5 min	97[b]
6	C_6H_5CH═$CHCHO$	acetonitrile	0	1.2	1.1	5 min	91
7	CH_3CH═$CHCHO$	acetonitrile	0	1.2	1.1	5 min	82
8	$C_6H_5CH_2CH_2CHO$	acetonitrile	0	1.2	1.1	5 min	63[c]
9	$C_6H_5CH_2CH_2CHO$	ether	−25	1.2	1.1	2 h	85
10	2-ethylhexanal	acetonitrile	0	1.2	1.1	5 min	54[c]
11	2-ethylhexanal	ether	−25	1.2	1.1	2 h	94
12	Ph_2CHCHO	ether	−25	1.2	1.1	2 h	84
13	$(CH_3)_3CCHO$	ether	−25	3.0	3.0	20 h	35
14	4-O_2N-$C_6H_4COCH_3$	acetonitrile	0	1.2	1.1	5 min	94
15	4-H_3C-$C_6H_4COCH_3$	acetonitrile	−25	3.0	3.0	2 h	98
16	cyclohexanone	ether	0	1.2	1.1	5 min	96
17	3-pentanone	ether	−25	3.0	3.0	2 h	75
18	$CH_3COC(CH_3)_3$	ether	−25	3.0	3.0	20 h	−25

[a] Isolated yields by silica gel column chromatography. [b] We also carried out the direct synthesis of α-hydroxyamides. The overall yield from 4-NC-C_6H_4-CHO was 94%. See Supporting Information for details. [c] Cyanohydrin of the starting aldehyde was obtained as a byproduct.

stirred at 0 °C for 5 h in the presence of 4-prorridinylpyridine (**11**);[12] a diastereomeric mixture of **12** and **13** (79:21) was then obtained in 80% yield. The major isomer **12** was transformed to (−)-bestatin **14** in 96% yield by the removal of TBS, Cbz, and benzyl groups. It is noteworthy that the overall yield obtained is considerably higher (ca. 61% from Cbz-phenylalanine) than that from the previous synthetic works.[3a,5a]

In conclusion, we have developed an efficient one-pot method for the synthesis of α-siloxyamides. The reactions of various aldehydes or ketones generally proceed in excellent yields within a short period under the mild basic conditions, which can be often produced by a primary or a secondary amine as a substrate. We also demonstrate an efficient synthesis of (−)-bestatin. Work investigating the catalytic stereochemical control by optically active bases is now being carried out.

Acknowledgment. We thank Dr. Yasushi Okamoto of the Eisai Co. Ltd. for significant and important suggestions on this project.

Supporting Information Available: Physical and spectroscopic data for **8** (all the compounds listed in Tables 1 and 2), **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) When another MAC reagent with nonmigratory protecting groups such as ethoxyethyl or methoxymethyl groups are used, acetonitrile is the best solvent for the reaction of aldehydes. (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1665. (b) Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *41*, 1463.

(10) We investigated THF, CH_2Cl_2, toluene, hexane, 1,2-dimethoxyethane, ether, and acetonitrile as reaction solvents. Whereas in the reaction of 4-tolualdehyde the desired product was obtained in excellent yield (92−98%) in all the solvents, other aldehydes revealed a distinct solvent dependence. For example, in the case of 3-phenylpropanal yields were mainly in the range of 60−80% in all the solvents employed. On the other hand, the yields for 2-ethylhexanal in ether were better than in all six other solvents.

(11) 3-Phenyl-2*R*-Cbz-aminopropanal (**11**) was prepared by the known method. Fehrentz, J.-A.; Castro B. *Synthesis* **1983**, 676.

(12) Without the additional base, the desired reaction was quite slow and the yield was very low. By the use of *N*,*N*-dimethyl-4-aminopyridine, imidazole, 2,6-lutidine, and pyridine, the chemical yields and diastereomeric ratio of **12** vs **13** were lower than those from the use of 4-prorridinylpyridine.