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O-Silylative Passerini Reaction: A New One-Pot Synthesis of α-Siloxyamides

Takahiro Soeta,* Yuuki Kojima, Yutaka Ukaji, and Katsuhiko Inomata*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

soeta@se.kanazawa-u.ac.jp; inomata@se.kanazawa-u.ac.jp

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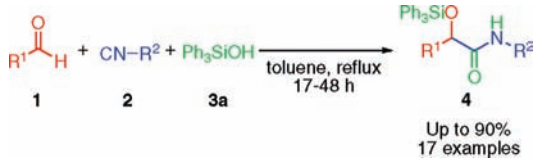
ABSTRACT



A new method for the highly effective synthesis of α-siloxyamides is described. The addition of isocyanide to aldehyde proceeded smoothly in the presence of silanol to give the corresponding α-siloxyamides in high yields. A wide range of aldehydes and isocyanides are applicable in this reaction.

Multicomponent reactions of isocyanides are powerful synthetic tools for the preparation of diverse complex molecules in practical, time-saving one-pot operations through combinatorial strategies or parallel synthesis. Classically, the reaction of isocyanide with aldehyde and carboxylic acid, named the Passerini reaction, is one of the most important multicomponent reactions to synthesize α-acyloxy amides.[1] After being discovered in 1921, various modifications have been developed;[2] however, the use of other components instead of carboxylic acid has not been realized until recently.

One of the reasons carboxylic acid is crucial in this reaction depends on the reaction mechanism. The mechanism of the Passerini reaction has been widely examined; activation of aldehyde by carboxylic acid followed by addition of isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate affords the final product by migration of the acyl group onto the oxygen atom originated from aldehyde.

Therefore, a carboxylic acid is generally necessary in the reaction of isocyanide with aldehyde or imine in the Ugi reaction. In other words, the use of a carboxylic acid limits application of this reaction to the construction of a broad range of molecules. Only two examples using other components instead of carboxylic acid have been reported so far. An *O*-aryrative Passerini reaction using nitrophenol derivatives has been developed by El Kaim, Grimaud, and co-workers in 2006.[3] Taguchi reported the direct alkylative Passerini reaction of aldehyde, isocyanide, and a free aliphatic alcohol catalyzed by In(III).[4] Acetals and ketals are also useful for the reaction of isocyanide catalyzed by Lewis or Brønsted acid, affording α-alkoxyimidates.[5]

As described above, the acyl group in a carboxylic acid consequently acts as an electrophile and the OH group works as a nucleophile to the nitrilium intermediate in the Passerini

(1) Passerini, M. *Gazz. Chem. Ital.* **1921**, *51*, 126–181.

(2) For recent enantioselective Passerini-type reactions, see: (a) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384–8385. (b) Yue, T.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454–9457. (c) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388–391. (d) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667–9676. (e) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231–4233. (f) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021–4024. (g) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825–7827.

(3) (a) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180. (b) El Kaim, L.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2006**, *8*, 5021–5023.

(4) Yanai, H.; Oguchi, T.; Taguchi, T. *J. Org. Chem.* **2009**, *74*, 3927–3929.

(5) (a) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437. (b) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697–3699.

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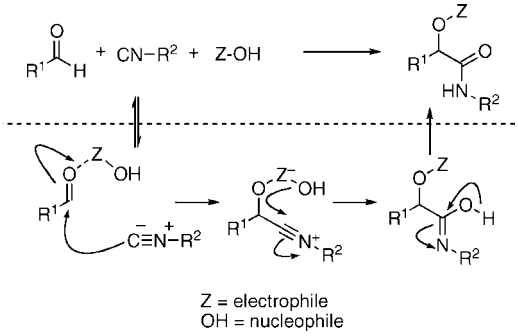
reaction. We tried to survey such molecules that have the same function as the carboxylic acid. If the molecule potentially possesses an electrophilic and a nucleophilic groups (Z-OH), it could act like a carboxylic acid in the Passerini reaction (Scheme 1).

Scheme 1. A Working Hypothesis



At first, we examined whether silanol can induce the three-component coupling reaction with aldehyde and isocyanide to afford the corresponding α-siloxyamides.

α-Siloxyamide or α-hydroxyamide derivatives[6] are versatile synthetic intermediates of biologically active peptide mimics.[7] Only one example for the preparation of α-siloxyamides in a one-pot reaction was reported by Nemoto, where the reaction of aldehyde, amine, and "masked acyl cyanide (MAC)" gave the α-siloxyamides in high yields.[8] Herein, we wish to describe the first example for *O*-silylative Passerini reaction consisting of aldehyde, isocyanide, and silanol to give the corresponding α-siloxyamides in high yields.

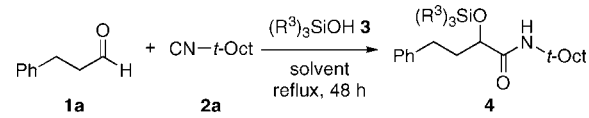
Our initial studies began using aldehyde, isocyanide, and silanol in benzene or toluene (entries 1 and 2 in Table 1). To our delight, triphenylsilanol (**3a**) (1.0 equiv) cleanly reacted with phenylpropionaldehyde (**1a**) and *tert*-octyl isocyanide (**2a**) in toluene at 110 °C to afford the expected α-siloxyamides **4aaa** in 48% yield after 48 h. This reaction proceeded smoothly in aromatic solvents and dichloroethane (DCE) to afford **4aaa** in moderate yields (entries 1−4); however, polar solvents and cyclic ethers were less effective (entries 5−7). In the case of methanol, which has been used in the Ugi reaction as a protic solvent, the reaction was very sluggish and only trace amount of the product was obtained (entry 8). Although the yield of the product was low to moderate, little or no side products were obtained under these conditions.

(6) (a) Greco, M. N.; Zhong, H. M.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4959–4962. (b) Maryanoff, B. E.; Greco, M. N.; Zhang, H.-C.; Adrade-Gordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225–1239.

(7) (a) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472. (b) Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 82–84. (c) Sakurai, M.; Higashida, S.; Sugano, M.; Komai, T.; Yagi, R.; Ozawa, Y.; Handa, H.; Nishigaki, T.; Yabe, Y. *Bioorg. Med. Chem.* **1994**, *2*, 807–825.

(8) Nemoto, H.; Ma, R.; Suzuki, I.; Shibuya, M. *Org. Lett.* **2000**, *2*, 4245–4247.

Table 1. Reaction Conditions for the *O*-Silylative Passerini Reaction



t-Oct = 1,1,3,3-tetramethylbutyl

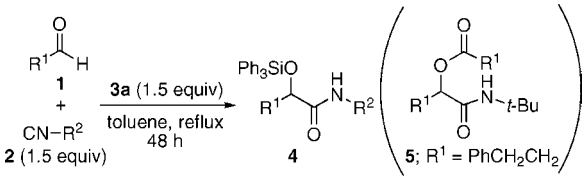
entry	**2a** (equiv)	**3a** (equiv)	solv	$(R^3)_3$-Si	**4** yield (%)
1	1.0	1.0	benzene	Ph_3 (**3a**)	37 (**4aaa**)
2	1.0	1.0	toluene	Ph_3 (**3a**)	48 (**4aaa**)
3	1.0	1.0	xylene	Ph_3 (**3a**)	45 (**4aaa**)
4	1.0	1.0	DCE	Ph_3 (**3a**)	40 (**4aaa**)
5	1.0	1.0	EtCN	Ph_3 (**3a**)	33 (**4aaa**)
6	1.0	1.0	dioxane	Ph_3 (**3a**)	32 (**4aaa**)
7	1.0	1.0	THF	Ph_3 (**3a**)	25 (**4aaa**)
8	1.0	1.0	MeOH	Ph_3 (**3a**)	trace (**4aaa**)
9	2.0	2.0	toluene	Ph_3 (**3a**)	90 (**4aaa**)
10	2.0	1.0	toluene	Ph_3 (**3a**)	76 (**4aaa**)
11	1.0	2.0	toluene	Ph_3 (**3a**)	76 (**4aaa**)
12	1.5	1.5	toluene	Ph_3 (**3a**)	87 (**4aaa**)
13	1.5	1.5	toluene	*i*-Pr_3 (**3b**)	nr
14	1.5	1.5	toluene	Et_3 (**3c**)	20 (**4aac**)
15	1.5	1.5	toluene	*t*-$BuPh_2$ (**3d**)	42 (**4aad**)

A significant increase in yield was observed when 2.0 equiv of isocyanide and silanol were used, and the product **4aaa** was isolated in 90% yield (entry 9). By decreasing the amount of isocyanide or silanol to 1.0 equiv, the yields were lowered to 76%, respectively (entries 10 and 11). Finally, the desired product was obtained in 87% yield when 1.5 equiv of isocyanide and silanol were used in this reaction (entry 12).

As an efficient method for an *O*-silylative Passerini reaction was established, we set out to evaluate silanols bearing other substituents (entries 13−15). Using trialkylsilanol **3b** and **3c**, yields of the product were poor (0% and 20%), respectively. In the case of *tert*-butyldiphenylsilanol **3c**, the product was obtained in moderate yield. These results indicated that the Lewis acidity of the Si atom is crucial for the reaction to proceed efficiently.

It was attempted to expand the scope of isocyanides and aldehydes applicable to the present *O*-silylative Passerini reaction utilizing triphenylsilanol (**3a**) as shown in Table 2. In these reactions, the optimal amounts of aldehydes **1a**−**g** (1.0 equiv) and isocyanides **2a**−**h** (1.5 equiv) were used in the presence of 1.5 equiv of triphenylsilanol (**3a**). From these results, we found that the conditions were applicable to a wide variety of aldehydes and isocyanides, and most reactions were completed within 48 h. The reaction of aliphatic isocyanides (R^2 = *t*-Oct, Bn, and *c*-Hex) with **1a** and **3a** gave the product in high yields (entries 1−3). Aldehyde **1a** was consumed in 17 h when cyclohexylisocyanide (**2c**) was used, giving the product in 89% yield (entry 3). In the case of *tert*-butylisocyanide (**2d**), although the reaction gave the desired product in 53% yield, Passerini product **5** was also obtained in 20% yield, probably due to partial oxidation of **1a** even though the reaction was carried out after degassing

Table 2. Scope of Aldehydes and Isocyanides



entry	R^1	R^2	yield %
1	$PhCH_2CH_2$ (**1a**)	*t*-Oct (**2a**)	87 (**4aaa**)
2	$PhCH_2CH_2$ (**1a**)	Bn (**2b**)	83 (**4aba**)
3	$PhCH_2CH_2$ (**1a**)	*c*-Hex (**2c**)	89[a] (**4aca**)
4	$PhCH_2CH_2$ (**1a**)	*t*-Bu (**2d**)	53[b] (**4ada**)
5	$PhCH_2CH_2$ (**1a**)	Bn, OTBS (**2e**)	83[c] (**4aea**)
6	$PhCH_2CH_2$ (**1a**)	*i*-Pr, OTBS (**2f**)	84[c] (**4afa**)
7	$PhCH_2CH_2$ (**1a**)	4-BrC_6H_4 (**2g**)	85 (**4aga**)
8	$PhCH_2CH_2$ (**1a**)	4-$MeOC_6H_4$ (**2h**)	84 (**4aha**)
9	*c*-Hex (**1b**)	*c*-Hex (**2c**)	83 (**4bca**)
10	*t*-Bu (**1c**)	*c*-Hex (**2c**)	61 (**4cca**)
11	PhCH=CH (**1d**)	*c*-Hex (**2c**)	15 (**4dca**)
12	4-$(Me_2N)C_6H_4$ (**1e**)	*c*-Hex (**2c**)	nr
13	C_6H_5 (**1f**)	*c*-Hex (**2c**)	37 (**4fca**)
14	4-$NO_2C_6H_4$ (**1g**)	*c*-Hex (**2c**)	44 (**4gca**)

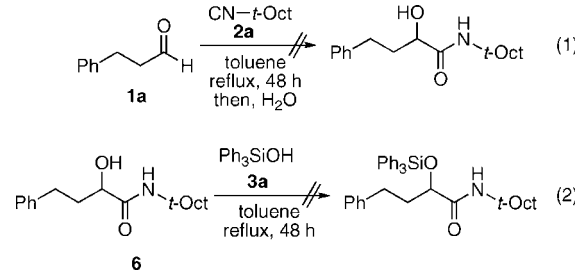
[a] The reaction was completed in 17 h. [b] 20% Passerini product **5** was also obtained. [c] An almost 1:1 ratio of diastereomers was obtained.

(entry 4). Chiral isocyanides **2e** and **2f**, which were prepared from the corresponding amino acids, gave the products in high yields; however, no chiral induction was observed (entries 5 and 6).

Aromatic isocyanides bearing an electron-withdrawing or -donating group at the *para* position also afforded the corresponding α-siloxyamides in high yields (entries 7 and 8).

Reactivity toward various aldehydes using cyclohexylisocyanide (**2c**) was next examined. Aliphatic aldehydes **1b** and **1c** gave the product in 83% and 61% yields, respectively (entries 9 and 10). Cinnamaldehyde (**1d**) was less reactive and afforded the product in only 15% yield (entry 11). Aromatic aldehydes also showed low reactivities (entries12−14). Desired product was not obtained at all when 4-(*N*,*N*-dimehyl)benzaldehyde (**1e**) possessing an electron-donating group was employed, and the starting materials were recovered. However, benzaldehyde (**1f**) and 4-nitrobenzaldehyde (**1g**), which is activated by an electron-withdrawing group, reacted with **2c** and **3a**, giving the products in moderate yields (entries 13 and 14).

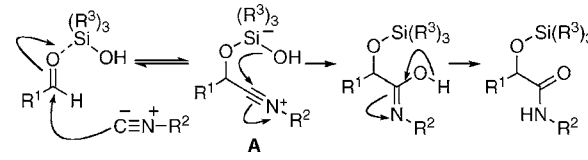
To reveal the reaction mechanism, we conducted some control experiments.



The addition reaction of isocyanide **2a** to aldehyde **1a** in the absence of triphenylsilanol (**3a**) did not proceed in refluxing toluene for 48 h (eq 1). When the reaction of α-hydroxyamide **6** with silanol **3a** was carried out in refluxing toluene, no α-siloxyamide was obtained and **6** was recovered (eq 2). These results indicate that the α-siloxyamide can not be formed by dehydration between α-hydroxyamide **6** and silanol.

On the basis of these results, we propose the reaction mechanism of the present *O*-silylative Passerini reaction as shown in Scheme 2. Aldehyde was activated by silanol

Scheme 2. Proposed Mechanism



through coordination of carbonyl oxygen to the silicon atom. Subsequently, nucleophilic attack of isocyanide to carbonyl group provides a nitrilium intermediate **A**. The hydroxy group on the silanol rearranges to the nitrilium intermediate, which tautomerizes to afford the corresponding α-siloxyamide (Scheme 2)

In summary, we developed a direct *O*-silylative Passerini reaction consisting of aldehydes, isocyanides, and silanols. This reaction is the first example of the isocyanide-based multicomponent reaction using a silanol instead of a carboxylic acid component, giving the corresponding α-siloxyamides in high yields. A wide range of aldehydes and isocyanides are applicable to this reaction. Further studies on this reaction are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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