

Metal-Promoted Variants of the Passerini Reaction Leading to Functionalized Heterocycles

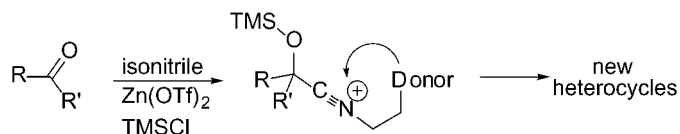
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ABSTRACT



The effect of replacing the Brønsted acid in classic Passerini reactions with a mild Lewis acid has been studied. Triggered by metal-promoted silylation, condensations of aliphatic or aromatic carbonyl compounds with appropriately substituted isonitriles capable of neighboring group donation afford α-hydroxyamides, substituted oxazoles, and other useful heterocycles.

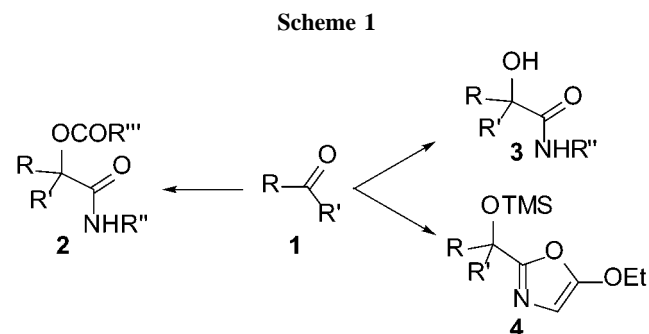
The Ugi and Passerini reactions play a central role in the development of combinatorial chemistry.¹ These and other multiple-component condensation reactions make possible versatile synthetic routes to collections of chemical substances sharing common structural features.

The normal Passerini reaction of a carbonyl compound **1**, an isonitrile, and a carboxylic acid leads to an α-acyloxy-carboxamide **2** (Scheme 1). Over the past 35 years, several

acidic conditions, a recently developed modification employs TFA in the presence of mild bases and is more compatible with acid-sensitive functionality.⁵

We have been interested in developing milder Lewis acids to expand the scope and generality of the Passerini reaction. Here we report that use of Zn(OTf)₂ and chlorotrimethylsilane (TMSCl) can direct the condensation to afford either α-hydroxycarboxylic acid amides **3** or disubstituted oxazoles **4** in synthetically useful yields, depending on the choice of isonitrile. Moreover, structure/reactivity studies provide fresh insights into the role of the isonitrile component in these metal-promoted Passerini variations.

Although not widely appreciated, most Passerini reactions are sluggish and afford products in low yields unless either strong carboxylic acids (CF₃CO₂H, HCO₂H) or unusually electrophilic carbonyl compounds are used. For example, 2-(morpholinoethyl)isonitrile **5** and benzaldehyde fail to



two-component variants have been developed in which a Brønsted² or Lewis acid^{3,4} replaces the carboxylic acid to form α-hydroxyamides **3**. As an alternative to these highly

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- (2) Hagedorn, I.; Eholzer, U. *Chem. Ber.* **1965**, *98*, 936–940.
- (3) BF₃-etherate: (a) Müller, E.; Zeeh, B. *Liebigs Ann. Chem.* **1968**, *715*, 47–51. (b) Müller, E.; Zeeh, B. *Liebigs Ann. Chem.* **1966**, *696*, 72–80.
- (4) TiCl₄: (a) Carofiglio, T.; Cozzi, P. G.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 2726–2736. (b) Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber.* **1988**, *121*, 507–517.
- (5) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769–2772.

undergo the Passerini reaction, even with excess acetic acid. By contrast, the corresponding four-component Ugi reactions of **5**, which involve more electrophilic iminium ions formed in situ, are known.⁶ These findings underscore the importance of carbonyl activation.

Consistent with that observation, Seebach et al. obtained hydroxyamide **6a** (R= H, R'= Ph, 67% yield) from the reaction of **5** with benzaldehyde using stoichiometric TiCl₄.^{4b} Although initially thought to activate the isonitrile component, the titanium reagent was later shown to promote condensation by enhancing the electrophilicity of the carbonyl compound.^{4a} Thus, it became of interest to examine the effect of other carbonyl-activating reagents on Passerini reactions of simple carbonyl compounds.

We first investigated whether silylation of the carbonyl component might promote Passerini condensations in the absence of a protic acid. Silylations using TMSCl can be markedly enhanced by various tin(II) and zinc(II) salts. In fact, the combination of zinc triflate and TMSCl, a mixture known to promote glycoside formation,⁷ successfully transformed **5** to the desired benzaldehyde adduct **6a**. Control experiments showed that no reaction took place between **5** and benzaldehyde either in the presence of stoichiometric quantities of TMSCl alone or in the presence of zinc triflate alone.

The highest yield of **6a** (77%, Table 1) was obtained using 0.3 equiv of Zn(OTf)₂ and 3 equiv of TMSCl in CH₂Cl₂ (24

Table 1. Metal-Promoted Passerini Condensations Using **5**

entry	carbonyl cmpd	product	% yield
1	PhCHO ^a	6a R = H, R' = Ph	77
2	PhCHO ^b	6a	68
3	PhCH ₂ CH ₂ CHO ^a	6b R = H, R' = Ph(CH ₂) ₂	74
4	(<i>E</i>)-PhCH=CHCHO ^a	6c R = H, R' = (<i>E</i>)-PhCH=CH-	61
5	(<i>E</i>)-PhCH=CHCHO ^b	6c	73
6	CH ₃ (CH ₂) ₈ CHO ^a	6d R = H, R' = <i>n</i> -C ₇ H ₁₅	60
7	CH ₃ (CH ₂) ₈ CHO ^b	6d	24
8	cyclohexanone ^a	6e R, R' = (CH ₂) ₅	57

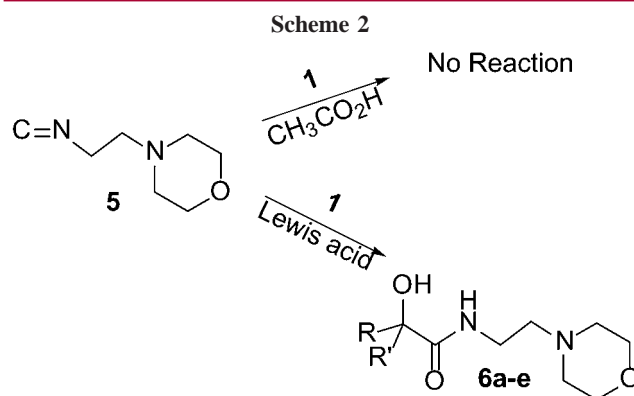
^a Method A, using Zn(OTf)₂ (0.3 equiv) and TMSCl (3 equiv).

h, rt, followed by aqueous workup to promote desilylation). As indicated (entries 1, 3, 4, 6, 8), the method proved to be general in scope, successfully affording the desired condensation product using a number of representative carbonyl compounds.

We also tested whether Passerini reactions of **5** might be promoted by trimethylsilyltriflate, which could be generated in situ by the combination of Zn(OTf)₂ and TMSCl. As shown in Table 1 (entries 2, 5, and 7), preformed TMSOTf (2.1 equiv) did afford the desired products, although the yield

(6) Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959–4962.

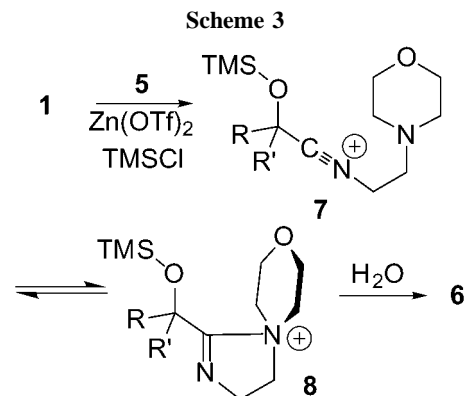
(7) (a) Susaki, H.; Higashi, K. *Chem. Pharm. Bull.* **1992**, *40*, 2019–2022. (b) Susaki, H.; Higashi, K. *Chem. Pharm. Bull.* **1993**, *41*, 201–204. (c) Susaki, H. *Chem. Pharm. Bull.* **1994**, *42*, 1917–1918.



of hydroxyamide **6d** from octanal was significantly higher (entry 7) using Zn(OTf)₂/TMSCl. Similar advantages of Zn(OTf)₂/TMSCl as a silylating agent were also noted in earlier work.^{7c}

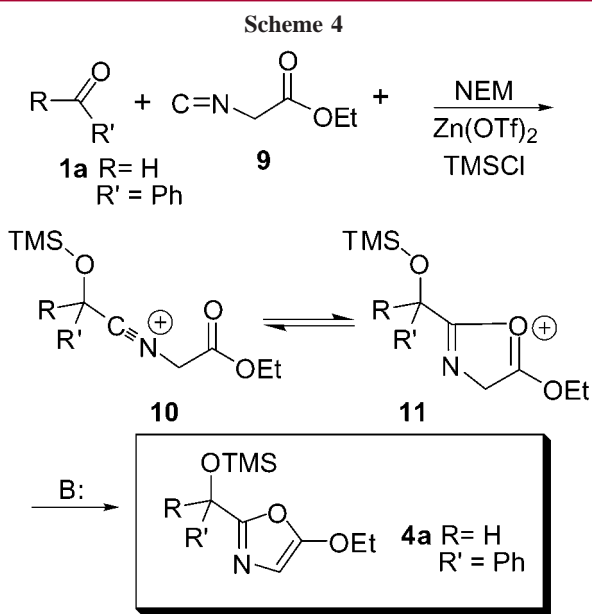
To our surprise, none of the condensations shown in Table 1 occurred when **5** was replaced with cyclohexylisocyanide. While reminiscent of limitations in the classical Passerini reaction, the failure of simple isocyanides to react by either Method A or B led us to suspect that the morpholine ring in **5** may have played some role in promoting successful condensations.

Specifically, nitrilium ion **7** (Scheme 3) generated by the condensation of **1** with **5** gains added stabilization through



lone pair donation by the proximal morpholine nitrogen, as in **8**, prior to hydrolytic workup. Attempts to enhance the reactivity of simple isocyanides by adding a tertiary amine were unsuccessful. No reaction occurred when benzaldehyde and cyclohexyl isocyanide were stirred with *N*-ethylmorpholine (NEM, 1 equiv) under the conditions of Method A.

The effect of other donor groups on the isocyanide was probed. An ether analogue of **5**, 2-(methoxyethyl)isonitrile, failed to react with benzaldehyde (Method A). However, ethyl isocyanoacetate **9** (Scheme 4) afforded a new product, 2-(α -silyloxyalkyl)-5-ethoxyoxazole **4a** (R= Ph, R'= H) in 9% yield. The yield of **4** was improved to 53% by using 0.5 equiv of Zn(OTf)₂ and 3 equiv of NEM. A plausible



mechanism (Scheme 4) invokes a similar neighboring group effect, leading to stabilization of the initial nitrilium ion **10** as oxonium ion **11**.⁸ Deprotonation of **11** by *N*-ethylmorpholine would likely give **4a**.

The scope and utility of this new condensation are shown in Table 2. The process successfully afforded the expected

Table 2. Metal-Promoted Passerini Condensations Using **9**; A New Synthesis of 4-Alkoxyoxazoles

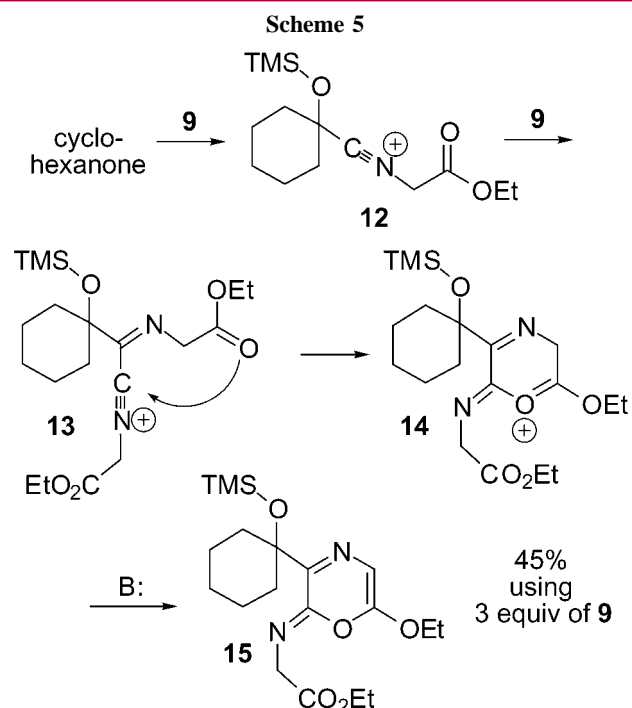
entry	carbonyl compd	product ^a	% yield
1	PhCHO	4a R = H, R' = Ph	53
2	PhCH ₂ CH ₂ CHO	4b R = H, R' = Ph(CH ₂) ₂	58
3	(<i>E</i>)-PhCH=CHCHO	4c R = H, R' = (<i>E</i>)-PhCH=CH-	54
4	CH ₃ (CH ₂) ₈ CHO	4d R = H, R' = <i>n</i> -C ₉ H ₁₉	47
5	cyclohexanone	4e R, R' = (CH ₂) ₅	64

2-(α -silyloxyalkyl)-5-alkoxyoxazoles in good yield using a range of aliphatic and aromatic carbonyl compounds.

In the case of cyclohexanone, formation of oxazole **4e** was accompanied by a minor product **15** (Scheme 5) representing a 2:1 isonitrile/ketone adduct.

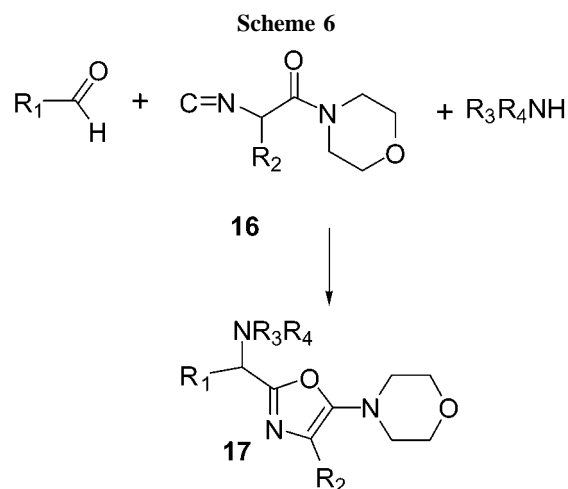
The formation of **15**, an unusual substituted 2*H*-1,4-oxazin-2-one, likely involved trapping of the initially formed nitrilium ion **12** (Scheme 5) with a second molecule of isonitrile **9** leading to **13**. Cyclization of the carboethoxy group in **13** to **14** followed by deprotonation gave **15**. The structure of **15** was assigned on the basis of spectroscopic data. In particular, the electrospray ionization mass spectrum of **15** exhibited an $M + H^+$ peak at m/z 397, which

(8) A related mechanism has been proposed for the cyclization of α -ketoimidoyl chlorides to 2-acyl-5-ethoxyoxazoles: Huang, W.-S.; Zhang, Y.-X.; Yuan, C.-Y. *Synth. Commun.* **1996**, *26*, 1149–1154.



established the overall molecular weight and the presence of two nitrogens. The yield of **15** could be increased to 45% by boosting the quantity of **9** to three equiv.

Very recently, Sun et al. described a related route to 2-(α -aminoalkyl)-5-aminoxazoles **17** by the reaction of isocyanacetamides **16** with aldehydes in the presence of primary or secondary amines (Scheme 6).⁹ No promoter or



^b Method B, using TMSOTf (2.1 equiv).

catalyst was needed, apparently because the in situ generated iminium ions were more electrophilic than the uncharged carbonyl compounds. In attempts to develop a hybrid condensation for the synthesis of 2-(α -aminoalkyl)-5-alkoxyoxazoles, we replaced isonitrile **16** with **9** under the condi-

tions reported by Sun et al. However, only slow ammonolysis of **9** was observed, and no oxazole was formed.

The results summarized in Tables 1 and 2 indicate that it is possible to implement Passerini-like reactions under aprotic conditions using mild silylation conditions instead of strong Brønsted or Lewis acids to activate the carbonyl electrophile. Such mild conditions will be of interest to pharmaceutical chemists, for example, in preparing next-generation libraries of aspartyl protease-directed norstatine derivatives.¹⁰ With the appropriate choice of isonitrile, these variants can also lead to the synthesis of novel heterocyclic systems.

Our findings also indicate that in the absence of a carboxylic acid, nucleophilic addition of an isonitrile to a carbonyl is promoted by appropriately positioned electron-donating groups. Such donor groups may capture the incipient nitrilium ion normally intercepted by the carboxyl nucleophile in standard Passerini condensations.

Substituted 5-alkoxyoxazoles are known to be useful in the synthesis of oxazolines,¹¹ pyrrolopyridines,⁹ and other

pharmaceutically interesting heterocycles.¹² Moreover, Evans et al. have recently reported that enantioselective aldol condensations of 5-alkoxyoxazoles lead to the asymmetric synthesis of syn and anti β -hydroxy- α -amino acids.¹³ It therefore appears that substituted 5-alkoxyoxazoles are broadly useful targets around which new combinatorial libraries may be designed.

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Supporting Information Available: Representative experimental procedures for the synthesis of new isonitrile adducts described in Tables 1 and 2, as well as supporting spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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