JOC Note

Brønsted Acidity of Substrates Influences the Outcome of Passerini Three-Component Reactions

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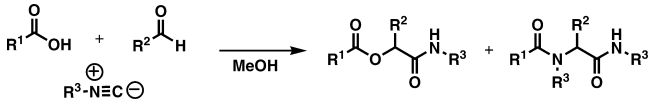


Passerini three-component reactions of aldehydes, isocyanides, and strong carboxylic acids (i.e., pK_a < 2) yield α-acyloxycarboxamides and/or α-acylaminocarboxamides, the characteristic products of Ugi four-component reactions. We propose that α-acylaminocarboxamide formation with these substrates is a consequence of in situ Brønsted acid-catalyzed reaction of the isocyanide and aldehyde to yield an imine that participates in an Ugi-type reaction. The apparent transfer of the isocyanide α-carbon to protic solvents as a formyl group during imine formation is indicative of new isocyanide reactivity.

Isocyanide-based multicomponent reactions are used extensively in targeted oriented and diversity oriented organic synthesis.[1] These one-pot reactions are known for the ease with which they are performed, their high yields, and their predictable outcomes. The most widely known and best characterized of the isocyanide-based multicomponent reactions are the Passerini three-component reaction (Passerini 3CR) and the Ugi four-component reaction (Ugi 4CR).[1] In the Passerini 3CR, an isocyanide, a carboxylic acid, and either an aldehyde or a ketone react with one another to yield an α-acyloxycarboxamide (Scheme 1).[2] In contrast, an isocyanide, a carboxylic acid, an amine, and either an aldehyde or a ketone react to yield an α-acylaminocarboxamide in the Ugi 4CR (Scheme 1).[3] Generally, the Passerini 3CR and Ugi 4CR have these characteristic outcomes regardless of the identities of the substrates.[1] Curiously, we found that under typical Passerini conditions, carboxylic acids with a pK_a < 2 reacted with aldehydes and isocyanides to yield varying amounts of α-acylaminocarboxamides, the characteristic products of the Ugi 4CR. Our observations are reminiscent of those reported by Dai and Li where

SCHEME 1. Proposed Mechanisms of the Passerini 3CR and the Ugi 4CR

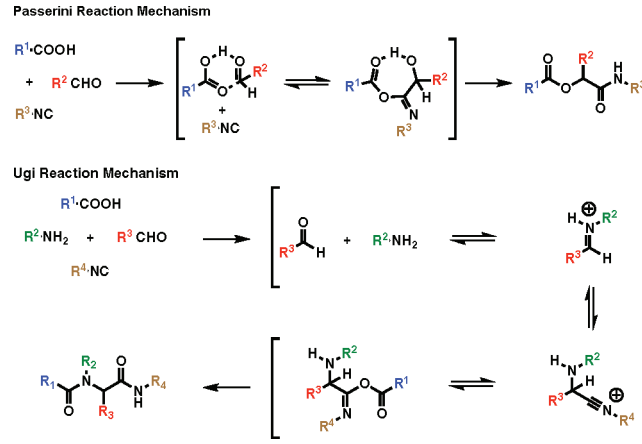
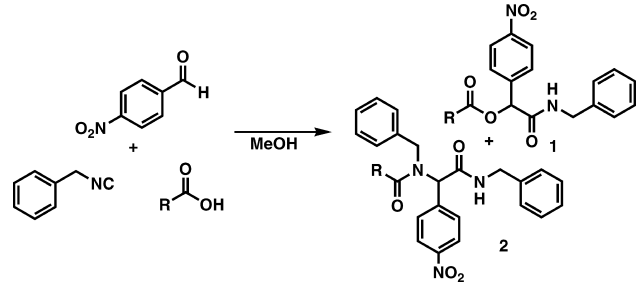
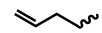
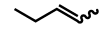


TABLE 1. Dependence of α-Acylaminocarboxamide Formation on the Carboxylic Acid Identity[a]



Entry	R	Yield (%) 1	Yield (%) 2
a		83	0
b		78	0
c		79	0
d		24	68
e		18	75
f		0	12

[a] All reactions were performed in methanol at 1.0 M for 12 h at room temperature. The stoichiometry of aldehyde:isocyanide:acid was 1:2:1. Products were isolated by flash chromatography. Yields were calculated based on the carboxylic acid.

Lewis acids catalyze the formation of Ugi 4CR products from Passerini 3CR substrates.[4] We propose that this unanticipated reaction outcome is a consequence of in situ Brønsted acid-catalyzed generation of imines from isocyanides and aldehydes via transfer of the isocyanide α-carbon to protic solvents as a formyl group.

(1) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(2) (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964.
(3) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Rosendahl, F. K.; Bondesheim, F. *Liebigs Ann. Chem.* **1963**, *666*, 54.
(4) Dai, W.-M.; Li, H. *Tetrahedron* **2007**, *63*, 12866–12876.

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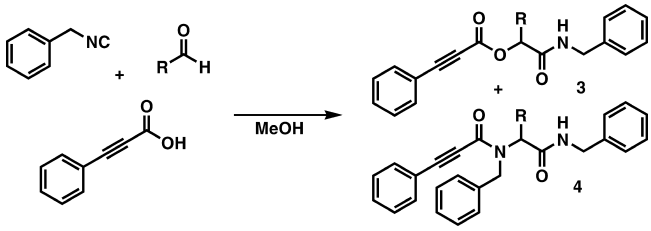
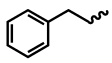
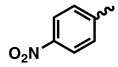
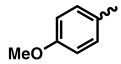
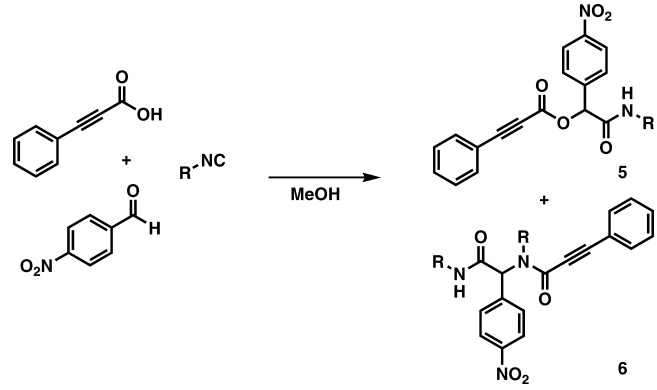
TABLE 2. Dependence of α-Acylaminocarboxamide Formation on the Identity of Carbonyl Substrate[a]

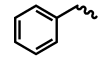
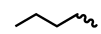


Entry	R	Yields (%) 3	4
a		77	14
b		49	32
c		4	80
d		24	68
e		11	62
f		6	58
g		2	58

[a] All reactions were performed in methanol at 1.0 M for 12 h at room temperature. The stoichiometry of aldehyde:isocyanide:acid was 1:2:1. Products were isolated by flash chromatography. Yields were calculated based on the carboxylic acid.

TABLE 3. Dependence of Product Distribution on the Isocyanide Identity[a]



Entry	R	Yields (%) 5	6
a		24	68
b		27	46
c		29	53
d		29	10

[a] All reactions were performed in methanol at 1.0 M for 12 h at room temperature. The stoichiometry of aldehyde:isocyanide:acid was 1:2:1. Products were isolated by flash chromatography. Yields were calculated based on the carboxylic acid.

In an analysis of the correlation between the rate of the Passerini 3CR and the pK_a of the carboxylic acid substrate, we found that reaction of phenyl propiolic acid (p$K_a \approx 1.8$),[5] *p*-nitrobenzaldehyde, and benzyl isocyanide in methanol yielded two distinct products in significant quantities. NMR spectroscopic and mass analyses of the minor product confirmed its identity as the expected α-acyloxycarboxamide, the Passerini 3CR product. On the basis of several spectral features including the presence of two sets of benzylic protons and its molecular mass, we hypothesized that the major product of the reaction was an α-acylaminocarboxamide. The identity of the major product in this reaction was confirmed by its independent synthesis via an Ugi 4CR employing phenyl propiolic acid, *p*-nitrobenzaldehyde, benzyl amine, and benzyl isocyanide. The ^{1}H NMR spectra of both products were superimposable and their masses were identical.

The formation of an α-acylaminocarboxamide from substrates of a Passerini 3CR is novel. Because α-acylaminocarboxamides and α-acyloxylcarboxamides cannot interconvert under the reaction conditions, we suspected that the products result from distinct reaction pathways. We hypothesized that the result of the low pK_a of phenyl propiolic acid played a critical role in α-acylaminocarboxamide formation. Its pK_a is 2 to 3 orders of magnitude lower than those of the carboxylic acids generally used as substrates in Passerini 3CRs. Consistent with this hypothesis was our observation that only α-acyloxycarboxamides were isolated from Passerini 3CRs that used carboxylic acid substrates with a pK_a higher than 2 (Table 1, entries a−c). Furthermore, Passerini 3CRs with propiolic acids and trifluoroacetic acid (carboxylic acids with a pK_a < 2) as substrates yielded α-acylaminocarboxamides (Table 1, entries d−f).

To gain further insights into α-acylaminocarboxamide formation under Passerini 3CR conditions, we reacted phenyl propiolic acid with a variety of isocyanides and carbonyl compounds. Significant quantities of α-acylaminocarboxamides were isolated from reactions of phenyl propiolic acid, benzyl isocyanide, and various aldehydes or a ketone (Table 2). The yields of α-acylaminocarboxamides were notably higher in reactions with aromatic and conjugated aldehydes than those with aliphatic aldehydes. These observation suggest that aliphatic aldehydes are better substrates in the competing Passerini 3CR than aromatic aldehydes (Table 2, entries c−f). In the reactions of phenyl propiolic acid and *p*-nitrobenzaldehyde with different isocyanides, there was a correlation between the degree of substitution of the isocyanide and the product distribution (Table 3). Specifically, the proportion of α-acylaminocarboxamide in the products decreased as a function of the substitution of the isocyanide. For instance, the α-acylaminocarboxamide was isolated in 68% yield from a reaction with benzyl isocyanide (Table 3, entry a), while the yields of the α-acyloxycarboxamide and the α-acylaminocarboxamide from the reaction with *tert*-butyl isocyanide were 29% and 10%, respectively (Table 3, entry d).[6]

(5) *CRC Handbook of Chemistry and Physics*, 85th ed.; Lide, D. R. Editor-in-Chief; CRC Press: Boca Raton, FL, 2004−2005.

(6) Substituents are known to influence the reactivity of isocyanides via sterics and/or inductive effects. See: Portal, C.; Launay, D.; Merritt, A.; Bradley, M. *J. Comb. Chem.* **2005**, *7*, 554.

SCHEME 2. Proposed Mechanism for the Brønsted Acid-Catalyzed Formation of an Imine from an Isocyanide

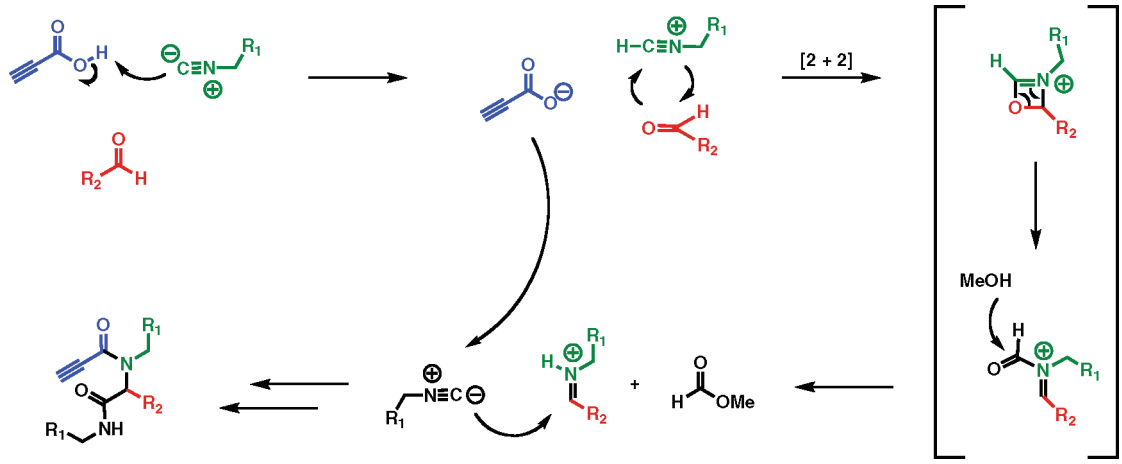
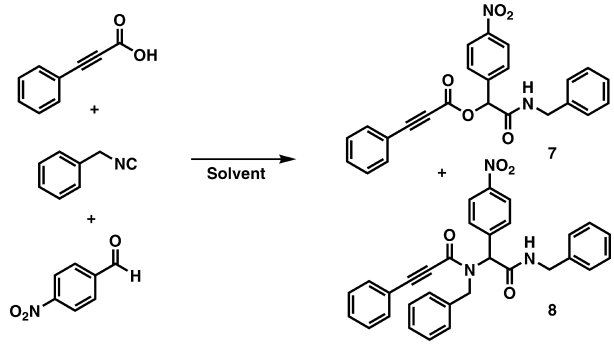


TABLE 4. Solvent Dependence of α-Acylaminocarboxamide Formation[a]



		yields (%)	
entry	solvent	**7**	**8**
a	CH_2Cl_2	76	0
b	$CHCl_3$	75	0
c	CH_3CN	69	0
d	MeOH	24	68
e	CH_2Cl_2 + 2 equiv MeOH	46	34

[a] All reactions were performed in methanol at 1.0 M for 12 h at room temperature. The stoichiometry of aldehyde:isocyanide:acid was 1:2:1. Products were isolated by flash chromatography. Yields were calculated based on the carboxylic acid.

Because the rate of the Passerini 3CR is reported to differ in protic and aprotic solvents,[7] the outcome of the reaction of phenyl propiolic acid, *p*-nitrobenzaldehyde, and benzyl isocyanide was assessed in a variety of solvents. Interestingly, the reactions in aprotic, organic solvents exclusively yielded the canonical products whereas reactions in protic solvents yielded mixtures of α-acyloxycarboxamides and α-acylaminocarboxamides (Table 4, entries a−c). The inclusion of stoichiometric quantities of methanol in the reaction of phenyl propiolic acid, *p*-nitrobenzaldehyde, and benzyl isocyanide in CH_2Cl_2 resulted in the formation of a significant amount of α-acylaminocarboxamide. These observations suggested that a nucleophilic alcohol participates in the reaction pathway that yields α-acylaminocarboxamides. Indeed, *p*-nitrobenzyl formate and α-acylaminocarboxamide were formed in a 1.2:1 molar ratio in the reaction of phenylpropiolic acid, *p*-nitrobenzaldehyde, benzyl isocyanide, and *p*-nitrobenzyl alcohol (see the Supporting Information). The most likely source of the formyl group is the isocyanide α-carbon.

The formation of an α-acylaminocarboxamide and a formate ester from substrates of a Passerini 3CR is indicative of an atypical reaction of isocyanides. There are two main possibilities. One possibility is hydrative conversion of an isocyanide into a formamide, followed by formyl transfer to an alcohol yielding a formyl ester and an amine that participates in an Ugi 4CR. We rule out this possibility because hydration of isocyanides typically requires aqueous mineral acids and the Passerini 3CRs with phenyl propiolic acid yielding α-acylaminocarboxamides were performed in anhydrous solvents under inert atmosphere. A mechanism involving hydrative consumption of isocyanides is further ruled out because benzyl formamide is absolutely stable in the presence of alcohols and phenyl propiolic acid.[8] In the alternative possibility, a *C*-protonated isocyanide and the aldehyde undergo a formal [2+2] cycloaddition followed by cycloreversion and alcoholysis yielding an imine and a formate ester (Scheme 2). The imine intermediate subsequently reacts with a molecule of isocyanide and phenyl propiolic acid to yield an α-acylaminocarboxamide, as in the Ugi 4CR (Schemes 1 and 2). There are many reports of cycloadditions involving isocyanides in the heterocycle literature,[9] but this is the first proposal of a [2+2] cycloaddition involving an isocyanide and an aldehyde. A [2+2] cycloaddition between an isocyanide and a carboxylic acid was considered by Danishefsky, Houk, and co-workers to explain the formation of *N*-formyl amides.[10,11] The proposed mechanism is an alternative to that invoked by Dai and Li (i.e., conversion of the nitrilium intermediate into an aziridine that rearranges to yield an imine) to explain a related observation.[4]

In conclusion, the inclusion of carboxylic acids with low pK_a values as substrates in Passerini three-component reactions results in the formation of Ugi four-component reaction products through a peculiar transformation of isocyanides. This transformation is another addition to a growing list of new reactions of isocyanides.[4,10−12]

(7) Ugi, I.; Meyr, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.

(8) Benzyl formamide and phenyl propiolic acid were stirred in methanol overnight. GC-MS of the solution showed no significant degradation of benzyl formamide. Only benzyl formamide and phenyl propiolic acid were detected.

(9) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141.

(10) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *108*, 5446.

(11) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093.

(12) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 2185.

Experimental Section

General Procedure for Passerini 3CRs. The aldehyde (0.125 mmol, 1 equiv), isocyanide (0.25 mmol, 2 equiv), and carboxylic acid (0.125 mmol, 1 equiv) were added to 125 μL of the solvent in a half dram glass vial and stirred overnight. After removal of solvent in vacuo, the reaction products were purified by flash column chromatography. In reactions where an alcohol was included, 2 equiv of the alcohol was added along with the starting materials at the start of the reaction.

Isolation and characterization of compound 1a (Table 1): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.23 (d, $J = 8.8$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 2H), 7.38−7.32 (m, 3H), 7.25 (d, $J = 5$ Hz, 2H), 6.71 (br, 1H), 6.23 (s, 1H), 5.83−5.74 (m, 1H), 5.06−5.95 (m, 2H), 4.48 (d, $J = 5.8$ Hz, 2H), 2.60 (td, $J = 7.26$, 2.76 Hz, 2H), 2.42 (q, $J = 6.9$ Hz, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.9, 167.0, 148.1, 142.5, 137.3, 136.1, 128.9, 128.1, 127.9, 127.8, 123.9, 116.2, 74.4, 43.5, 33.3, 28.6; LRMS calcd for $C_{20}H_{20}N_2O_5$ 368.38, obsd 391.5 $[M + Na]^+$.

Acknowledgment. We thank Dr. Tun-Li Shen for mass spectrometric analyses. This work was generously supported by funds from Brown University and a 2009 Salomon Award sponsored by the Office of Vice President of Research at Brown.

Supporting Information Available: Detailed experimental procedures, compound characterization data, spectra, and expanded discussion of peripheral findings. This material is available free of charge via the Internet at http://pubs.acs.org.

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