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O-Arylative Passerini Reactions

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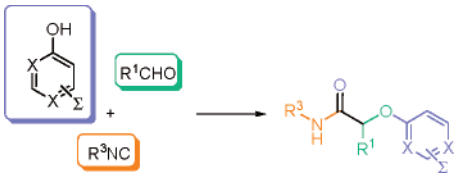
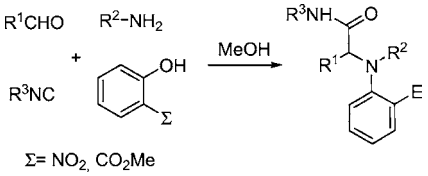
ABSTRACT



The three-component addition of isocyanides to phenol derivatives and aldehydes proceeds easily in methanol to form *O*-arylated compounds in a new Passerini-type reaction. The key step of the conversion lies in an irreversible Smiles rearrangement of intermediate phenoxyimidate adducts. It represents the first use of a Smiles rearrangement in a Passerini reaction.

Along with the Ugi reaction, the Passerini coupling of isocyanides with aldehydes and carboxylic acids represents the most important use of isocyanides in organic synthesis.[1] It shares with the Ugi reaction the same mechanistic features: activation of the aldehyde by the carboxylic acid followed by addition of the moderately nucleophilic isocyanide and trapping of the resulting nitrilium by the carboxylate. All of these reversible additions are finally displaced by a Mumm-type rearrangement to form α-hydroxy amide derivatives. We recently disclosed a novel Ugi-type process involving phenols instead of carboxylic acids, the key step being an irreversible Smiles rearrangement in place of the traditional Mumm acyl transfer.[2] The overall process led to new *N*-arylative Ugi type couplings (Scheme 1).

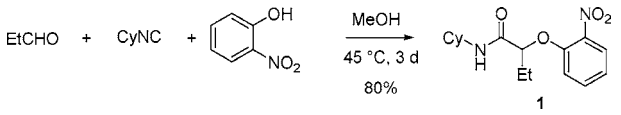
Scheme 1. Phenol−Ugi−Smiles Systems



Knowing that Passerini reactions usually require stronger acidic conditions than Ugi couplings (the iminium intermediates being more reactive),[3] we were eager to test whether nitrophenols would be sufficiently reactive to induce the expected coupling with carbonyl compounds and isocyanides.

To our delight, it appears that *o*-nitrophenol (1 equiv) reacts smoothly at 40 °C in methanol (1 M) with cyclohexyl isocyanide (1 equiv) and propionaldehyde (1 equiv) during 3 days to provide the expected α-aryloxy amide **1** in 80% yield (Scheme 2).

Scheme 2. Phenol−Passerini−Smiles Systems



To explore the scope of this new three-component coupling, we investigated different aldehydes and isocyanides. α-Aryloxy amides are obtained in moderate to good yields for aliphatic aldehydes (entries 1−5, Table 1), even

(1) For recent reviews concerning the Ugi and Passerini couplings, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (b) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1−140. (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144. (d) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53−66. (e) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51−80. (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329. (g) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(2) El Kaim, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7164−7169.

(3) Xia, Q.; Ganem, B. *Org. Lett.* **2002**, *4*, 1631−1634.

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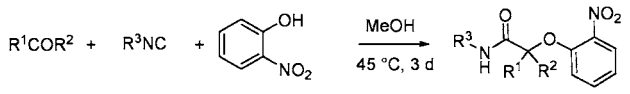
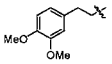
Table 1. *O*-Nitrophenol Passerini−Smiles Coupling



Entry	R^1	R^2	R^3	Yield(%)[a]
1	*i*-Bu	H	Cy	64
2	C_6H_{13}	H	Cy	64
3	Et	H	*t*-Bu	36
4	Et	H		28
5	Cl_3C	H	Cy	50
6	*p*-ClC_6H_4	H	Cy	57
7	*m*-$CF_3C_6H_4$	H	Cy	62
8			Cy	26[b]
9	Me	CH_2Cl	Cy	71
10	Me	CF_3	Cy	74

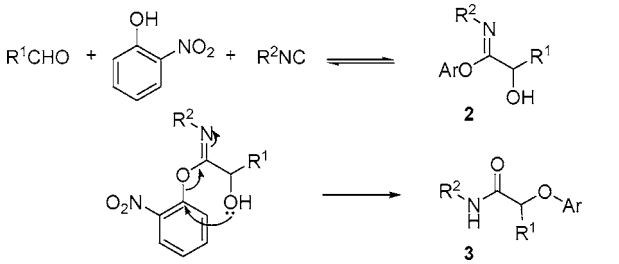
[a] Isolated yields. [b] The reaction mixture was heated for 5 days.

in the case of hindered isocyanides (entry 3, Table 1). Aromatic aldehydes give the desired compounds in similar yields (entries 6 and 7, Table 1). However, no trace of expected product could be detected in the case of α,*β*-unsaturated aldehydes. As in the classical Passerini couplings, nonactivated ketones need longer reaction time (5 days) to afford the expected product in low yields (entry 8, Table 1). In contrast, α-halogenated ketones react within 3 days to afford the desired adducts in good yields (entries 9 and 10). In all cases, the nitrophenol moiety was incorporated, and no trace of α-hydroxy amides could be detected.

As in the phenol Ugi−Smiles coupling we recently described,[2] a final Smiles rearrangement probably displaces all of the equilibria to give the expected α-aryloxy amides. The yields obtained for this reaction are lower than those observed in the four-component reaction. It is consistent with the lower electrophility of the aldehyde compared to the corresponding imine. Although no detailed mechanistic studies have been carried out, it seems that the *o*-nitrophenol (pK_a = 7.2) is acidic enough to activate the carbonyl compound and induce isocyanide addition. The phenoxide is nucleophilic enough to trap the resulting nitrilium, forming imidate **2**. The latter undergoes a Smiles rearrangement to provide the more stable α-aryloxy amide **3** (Scheme 3).

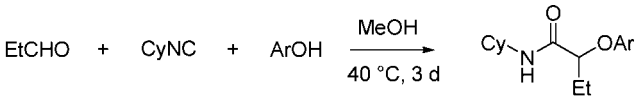
Moreover, to explore further the scope of this reaction we screened the various phenol derivatives that could be used. The presence of a donor substituent on the *o*-nitrophenol has

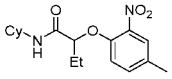
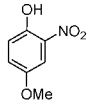
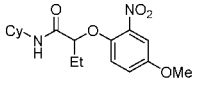
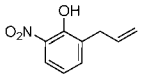
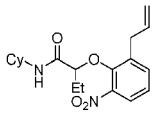
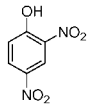
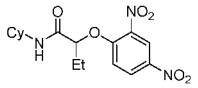
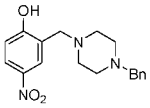
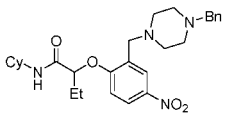
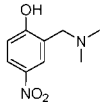
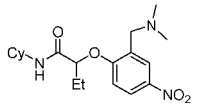
Scheme 3. Proposed Mechanism



no effect on the yields of the reaction (entries 1−3, Table 2). 2,4-Dinitrophenol provides the desired adduct only in

Table 2. Modified Nitrophenol Passerini−Smiles Coupling

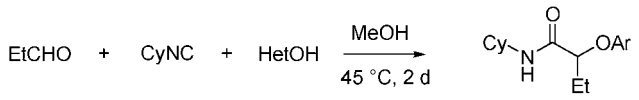


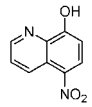
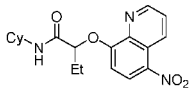
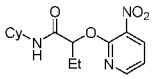
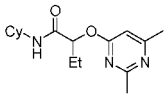
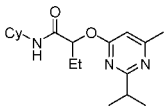
Entry	ArOH	Product	Yield(%)[a]
1			74
2			56
3			72
4			29
5			65
6			59

[a] Isolated yields.

modest yield (entry 4, Table 2). Although with *p*-nitrophenol (efficient acid in the case of the Ugi−Smiles coupling) the reactions are rather sluggish and no desired adduct could be isolated, the Mannich-modified *p*-nitrophenol allows an efficient Passerini−Smiles coupling (entries 5 and 6, Table 2).

Table 3. Heteroaromatic Phenol Passerini−Smiles Coupling



Entry	HetOH	Product	Yield(%)[a]
1			60
2			32
3			60
4			60

[a] Isolated yields.

Since Smiles rearrangements have been observed in many heterocyclic families,[4] these coupling conditions were also tested on various heteroaromatic phenols. Nitro-substituted hydroxyquinolines and -pyridines gave adduct after several days (entries 1 and 2, Table 3). More interestingly, unactivated 4-hydroxypyrimidines are also efficient partners in this multicomponent coupling (entries 3 and 4, Table 3). These heterocycles have also been successfully tested in Ugi−Smiles-type reactions.[5]

This new reaction gives further insight on the potential of Smiles rearrangements in isocyanide chemistry. We are currently exploring the use of Lewis acids to extend the scope of phenols additions as well as further synthetic elaborations of these new Passerini adducts.

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

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(5) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019−4021.