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Direct Access to Heterocyclic Scaffolds by New Multicomponent Ugi–Smiles Couplings

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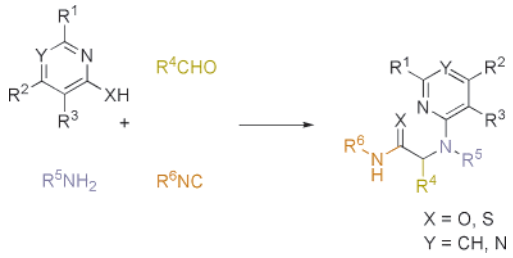
ABSTRACT

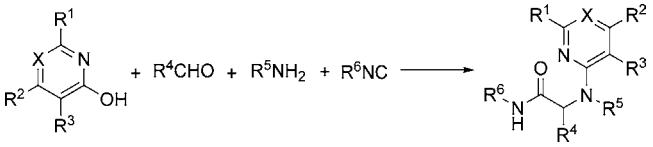


New heterocyclic scaffolds can be easily prepared by the coupling of heteroaromatic phenols (pyridines, pyrimidines) with carbonyl compounds, amines, and isocyanides. This transformation related to the Ugi reaction probably involves a Smiles rearrangement. The scope of this methodology is further extended by the successful use of heterocyclic thiols to form highly functionalized thioamides.

Heterocycles have attracted considerable attention in the design of biologically active compounds.[1] Most marketed compounds belong to this family, and the discovery of small molecular weight scaffolds with a high degree of diversity is becoming a serious bottleneck in the drug discovery process.[2] Among the various heterocycles, *ortho*-amino-substituted nitrogen heterocycles (2-amino pyridines, pyrimidines, etc.) are often considered by medicinal chemists as "priviledged medicinal scaffolds"[3] in line with their relevance to many natural biological systems. Indeed, such amino heterocycles have been reported to be potent therapeutic agents for the treatment of inflammatory diseases (asthma, rheumatoid arthritis, etc.),[4] HBV infection,[5] Creutzfeldt−Jacob disease,[6] epilepsy, cancer, etc.[7] Consequently, such heterocycles remain major targets for the pharmaceutical industry.

As part of our ongoing studies on the chemistry of isocyanides,[8] we have discovered a direct and general access to heterocyclic libraries by new Ugi−Smiles multicomponent couplings (Scheme 1).

Scheme 1. Ugi−Smiles Couplings with Heteroaromatic Phenols



Being aware of the need for an acidic site to activate the nucleophilic addition of the isocyanide onto the intermediate imine, we first examined nitro-substituted 2-hydroxy pyridines (entries 1 and 2, Table 1) which react smoothly in

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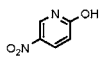
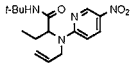
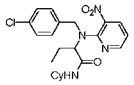
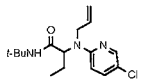
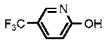
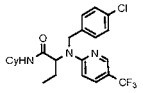
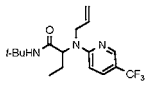
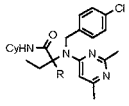
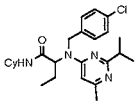
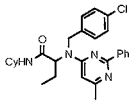
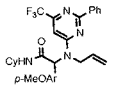
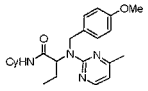
Table 1. Heteroaromatic Phenol Ugi−Smiles Coupling

entry	phenol	product	yield (%)[a]
1			96
2			62
3			54[b]
4			44[b]
5			58[b]
6			A: (R=H) 78 B: (R=Me) 54
7			63
8			89
9			51[c]
10			38[d]

[a] Isolated yields. [b] The reaction mixture was heated at 80 °C in toluene. [c] A catalytic amount (15 mol %) of $MgClO_4$ was added. [d] The hydrochloride salt was neutralized by 1 equiv of NaOMe, generated in situ beforehand.

methanol at 60 °C to give the 2-amino pyridines in good yields. Because many heterocyclic families have been successfully involved in Smiles rearrangements,[9] we surmised that the electrophilic nature of six-membered ring nitrogen heterocycles could perhaps trigger a similar coupling without the need for a strong activating group on the heterocyclic nucleus. This would expand considerably the scope of this approach.

Indeed, we were delighted to find that various 2-hydroxy pyridines and pyrimidines acted as valuable partners in this process (Table 1). In the case of 2-hydroxy pyridines, the best yields were observed when the reactions were performed at 80 °C in toluene as solvent, whereas methanol gave much lower yields (entries 3−5, Table 1). Of particular importance is the possible access to fluorinated scaffolds by the use of trifluoromethyl-substituted heterocycles as starting materials (entries 4−5 and 9, Table 1). This pharmacophore of high medicinal interest[10] enhances furthermore the efficiency of the coupling by increasing the electron deficiency of the heteroaromatic ring.

4-Hydroxy pyrimidines react smoothly in methanol at 60 °C with both aliphatic and aromatic aldehydes in the presence of various amines and isocyanides (entries 6−9, Table 1). Ketones require longer reaction times to afford the desired adducts in moderate yield (entry 6 (R = Me), Table 1). 2-Hydroxy pyrimidines are also potent partners in this multicomponent reaction. The free pyrimidine, generated in situ from its commercial hydrochloride (1 equiv of NaOMe in MeOH), gave the expected 2-amino pyrimidine in moderate yield (entry 10, Table 1). The straightforward and general access to various hydroxy pyrimidines by the condensation of β-dicarbonyl compounds with amidines[11] widens even more the diversity offered by this coupling.

The strength of this process lies in the Smiles rearrangement as an irreversible step in the Ugi reaction cascades (Scheme 2). Classical Ugi transformations with carboxylic acids involve an intramolecular acyl transfer from oxygen to nitrogen (known as the Mumm rearrangement).[12] The conversion of acyl imidate to amide ensures the irreversibility of the rearrangement and thus the efficiency of the Ugi process. Smiles rearrangements (intramolecular nucleophilic displacement on electron-poor aromatic systems) using hydroxy aromatics can operate equally: the higher thermodynamic stability of the amide toward the phenoxy imidate

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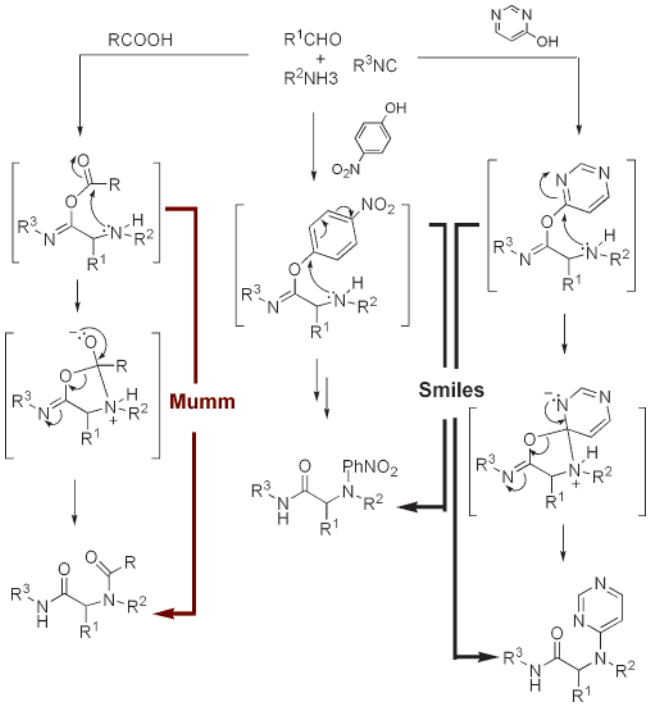
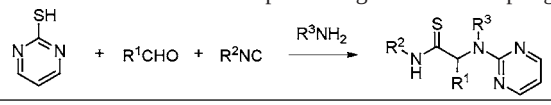
Scheme 2. Smiles vs Mumm Rearrangements in Ugi Processes

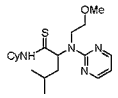
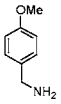
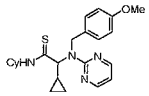
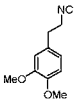
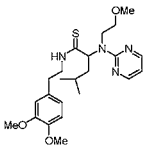
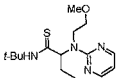


totally displaces the potential equilibrium involving spiro transition states or intermediates. These spiro systems can be observed with simply electron-deficient aromatics (e.g., nitrophenols) but also with heteroaromatics as observed in the Julia−Kocienski reaction.

To explore further the scope of this new multicomponent reaction, we contemplated the use of other acidic heterocyclic derivatives. Among the various possible surrogates[13] for acids in Ugi-type couplings,[14] the potential of thio carboxylic acids has been recognized early and exploited in recent post-condensation heterocyclic syntheses.[15] In this case, the final Mumm-type rearrangement affords an interesting access to thiopeptide analogues. We therefore tested the behavior of heterocyclic thiols in our new Ugi−Smiles sequence. We were pleased to observe the first Ugi−Smiles conversion of thiols with direct formation of heterocyclic thioamides (Table 2). The reaction of 2-mercapto pyrimidines with a carbonyl compound, an isocyanide, and an amine was performed neat at 80 °C to afford the desired adduct in good yields.

Table 2. Heteroaromatic Thiophenol Ugi−Smiles Coupling



entry	R^1CHO	R^2NC	R^3NH_2	product	yield (%)[a]
1	*i*-BuCHO	CyNC			77
2		CyNC			71
3	*i*-BuCHO				75
4	EtCHO	*t*-BuNC			42

[a] Isolated yields.

The substitution of the hydroxy group by a thiol moiety seems to enhance the efficiency of this process as the 2-mercapto pyrimidine gave a coupled product in much better yields.

In conclusion, this study presents a new and direct route to biologically relevant heterocyclic scaffolds by a new Ugi−Smiles multicomponent strategy. The scope of this coupling is further extended by the successful use of heterocyclic thiols to form thioamides that would be difficult to obtain by standard addition−elimination of functionalized amines to chloro heterocycles. Other heterocyclic families as well as the formation of novel fused heterocycles by post-condensations are currently under study.

Acknowledgment. M.G. and J.O. thank the MENR for a fellowship. Financial support was provided by the ENSTA.

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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