Multicomponent Arylation

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Phenol Ugi–Smiles Systems: Strategies for the Multicomponent N-Arylation of Primary Amines with Isocyanides, Aldehydes, and Phenols

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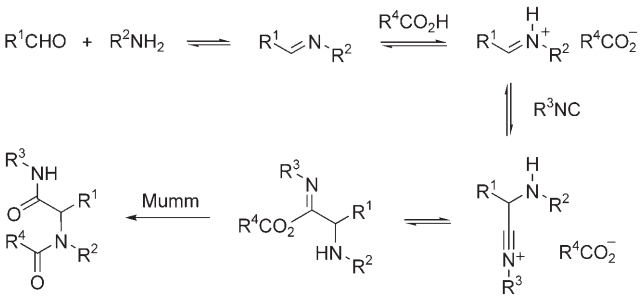
Since the pioneering work of Passerini and Ugi, the use of isocyanides has been strongly associated with the success achieved by multicomponent reactions (MCRs) in the creation of molecular diversity.[1] The high efficiency of isocyanides in MCRs lies in their ability to create bonds in a reversible manner by extending their valence. In the Ugi four-component reaction (U-4CR), equilibria between primary amines, isocyanides, carbonyl compounds, and carboxylic acids are displaced by a final irreversible Mumm-type rearrangement (Scheme 1).



Scheme 1. Ugi reaction mechanism.

The replacement of the carboxylic acid by other acidic compounds has found limited success since the discovery of the reaction. The ideal surrogate for the carboxylic acid should be sufficiently acidic to activate the imine toward the moderately nucleophilic isocyanide, and its counter anion should give a reversible addition to the nitrilium intermediate and induce an irreversible rearrangement in the final step. Ultimately, the acidic compound has to be integrated in the structure so that the final adduct retains sufficient stability (to heat, and for compounds of biological interest, to enzymatic hydrolysis).

Besides carboxylic acids, the most useful acidic components (water, hydrazoic acid, carbonic acid monoesters,

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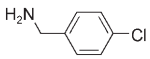
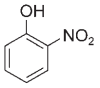
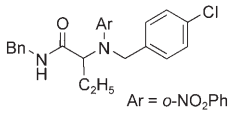
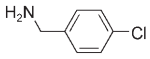
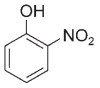
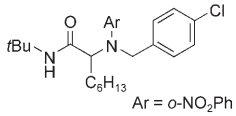
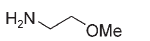
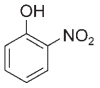
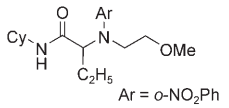
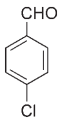
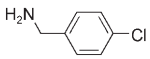
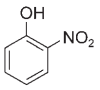
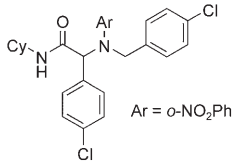
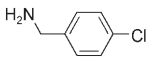
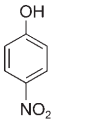
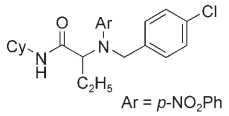
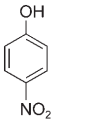
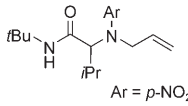
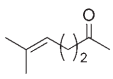
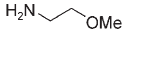
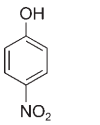
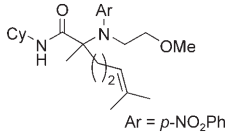
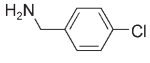
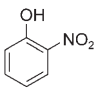
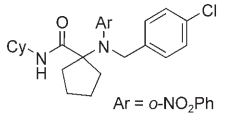
hydrogen sulfide, hydrogen selenide, cyanate,[2] thiocyanate,[2] and thiosulfate[2])[3] were examined by Ugi shortly after his description of the U-4CR process. Recently, in analogy to the formation of carbonic acid from CO_2 and alcohols, COS and CS_2 have also been employed for the preparation of thio derivatives.[4] More significantly, the use of thio acids has led to some elegant heterocyclic syntheses.[5] There has since been no major development in this direction.

The scope of MCRs using isocyanides has been widely extended through the intramolecular trapping of the nitrilium intermediates. Among the most recent and useful examples, the [4+1] cycloaddition of 2-iminopyridines[6] and the formation of isoxazole from isocyanoacetamides[7] are worth noting. In these cases, intramolecular conditions and final aromatization allow good yields even with nucleophiles that perform poorly in the normal U-4CR process (oxygen atoms of amides for instance). However, their intramolecular nature limits the scope of these reactions to three-component couplings with a consequent lower molecular diversity.[8] Herein, we report a highly flexible multicomponent reaction between electron-deficient phenols, amines, carbonyl compounds, and isocyanides to form *N*-aryl amines in phenol Ugi–Smiles systems.

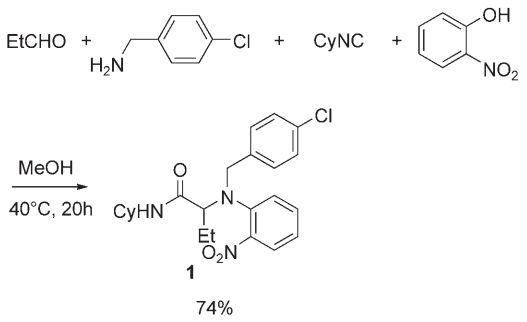
While searching for new acidic partners in the Ugi reaction, we thought that a suitable electron-withdrawing group on a phenol could trigger both the imine activation and the irreversible rearrangement in the key step of the reaction. Indeed, we were delighted to find that *o*-nitrophenol reacts with cyclohexyl isocyanide (1 equiv), *p*-chlorobenzylamine (1 equiv), and propionaldehyde (1 equiv) by a very efficient four-component reaction. This reaction proceeds smoothly at 40 °C in methanol (1 M) within a few hours to provide the desired *N*-aryl amine **1** in 74 % yield (Scheme 2).

The high yield, simple reaction protocol, and originality of this tandem process prompted us to explore the reaction more widely (Table 1). Aliphatic aldehydes are good substrates for this process and react with various amines and isocyanides. Aromatic aldehydes give the expected adducts in moderate

Table 1: The reagents used in the multicomponent reactions and the resulting products.

Entry	RCHO	Amine	RNC	Phenol	Reaction time	Product	Yields[%][a]
1	EtCHO		BnNC		4 h		96
2	$C_6H_{13}CHO$		*t*BuNC		4 h		79
3	EtCHO		CyNC		4 h		71
4							35
5			CyNC		20 h		73[b]
6	EtCHO		CyNC		16 h		72
7	*i*BuCHO		*t*BuNC		48 h		98[c]
8			CyNC		10 days		46[c]
9			CyNC		6 days		33[c]

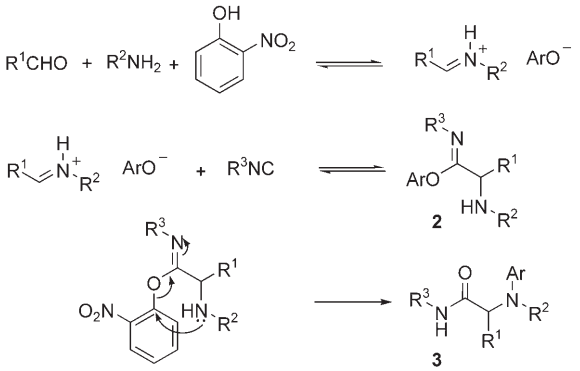
[a] Yields of isolated product. [b] A catalytic amount (15 mol %) of $MgClO_4$ was added. [c] The mixture was heated at 60 °C in methanol. Cy = cyclohexyl.



Scheme 2. Multicomponent N-arylation of chlorobenzylamine with nitrophenol. Cy = cyclohexyl.

yields under these conditions. However, the use of a catalytic amount (15 mol %) of magnesium perchlorate improves the yield considerably (entries 4 and 5, Table 1). *p*-Nitrophenol, which has a comparable acidity, undergoes this coupling process equally efficiently (entries 6 and 7, Table 1). Ketones are less reactive than aldehydes and need much longer reaction times to afford the desired products in moderate yield (entries 8 and 9, Table 1).

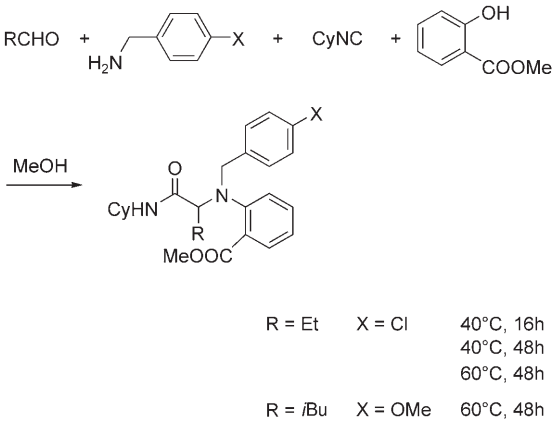
Although no detailed mechanistic studies have been carried out, a reaction sequence leading to *N*-aryl amines can be proposed (Scheme 3). It seems that the acidity of nitrophenols (pK_a values from 7 to 9) provokes sufficient



Scheme 3. Proposed mechanism for the phenol Ugi–Smiles reaction.

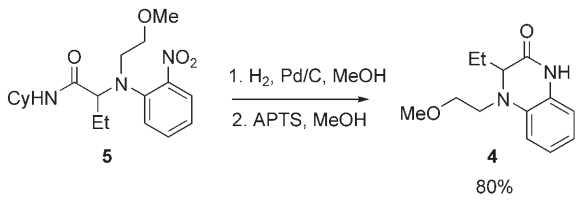
protonation of the imine to induce isocyanide addition. The phenoxide is nucleophilic enough to trap the resulting nitrilium intermediate, thus forming imidate **2**. At 40 °C, the latter undergoes a Smiles rearrangement[9] to provide the more stable *N*-aryl amine **3** (Scheme 3). This last rearrangement probably constitutes the only irreversible step in the whole process, and drives all the preceding equilibria toward the desired product in high yields.

Imidates are known to undergo a Mumm-type rearrangement or an electrocyclic reaction (in the case of hydrazoic acid).[10] However, to the best of our knowledge, this reaction constitutes the first example of a Smiles rearrangement intervening in an Ugi-type reaction. Moreover, the reaction can be extended to other weak phenolic acids. As an example, the reaction of methyl salicylate, propionaldehyde, cyclohexyl isocyanide, and *p*-chlorobenzylamine provides the desired *N*-aryl amine in 74 % yield (Scheme 4). The reaction proceeds smoothly in methanol at 60 °C within 2 days. This result indicates that a wide range of phenols could participate successfully in this new four-component reaction.



Scheme 4. Salicylic ester as the phenol in the Ugi–Smiles reaction. Cy = cyclohexyl.

The presence of the nitro or ester group on the final adduct allows interesting applications to heterocyclic synthesis. Thus, we accomplished an efficient one-pot synthesis of benzopyrazinone **4** by hydrogenolysis (H_2, Pd/C, methanol) and subsequent acidic cyclization (*para*-toluenesulfonic acid (TsOH), methanol) of the aryl amine **5** (Scheme 5).



Scheme 5. Application to the synthesis of benzopyrazinone. Cy = cyclohexyl.

In conclusion, we have developed a novel and very efficient four-component reaction from readily available substrates. The creation of four bonds that should be reasonably resistant to hydrolysis makes this process particularly attractive for the design of pharmaceutical and agrochemical libraries. Moreover, a straightforward elaboration of these adducts gives easy access to various heterocyclic structures. Further studies are under way to examine more thoroughly the scope and limitations of this MCR system.

Experimental Section

Synthesis of benzopyrazinone **4**: 2-Methoxy-1-ethylamine (1.0 equiv), cyclohexyl isocyanide (1.0 equiv), and *o*-nitrophenol (1.0 equiv) were added to a solution of propionaldehyde in methanol (1 M). The resulting mixture was stirred at 40 °C under an inert atmosphere for 20 h and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

A catalytic amount of Pd/C (10%) was added to a solution of the resulting aryl amine in methanol (0.3 M), and the mixture was stirred at room temperature (RT) under a hydrogen atmosphere for 24 h. Hydrogen was then replaced by argon and a catalytic amount of *p*-toluenesulfonic acid was added. The resulting mixture was stirred at RT for 24 h. After addition of a saturated aqueous solution of $NaHCO_3$, filtration, and extraction with diethyl ether, the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (80:20 ether/petroleum ether) to give the desired benzopyrazinone **4** in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.62$ (br s, 1H), 7.02–6.96 (m, 1H), 6.80–6.70 (m, 3H), 3.86 (t, 1H, $J = 6.8$ Hz), 3.73–3.63 (m, 1H), 3.57 (t, 2H, $J = 6.8$ Hz), 3.37 (s, 3H), 3.41–3.31 (m, 1H), 1.72–1.60 (m, 2H), 0.95 ppm (t, 3H, $J = 7.3$ Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 168.9$, 134.2, 126.7, 124.5, 119.1, 115.9, 113.5, 70.5, 64.6, 59.4, 50.1, 24.1, 10.4 ppm. IR (thin film): $\tilde{\nu} = 3200$, 2925, 1675, 1117, 745 cm^{-1}. MS (DI, CI NH_3) *m*/*z* 235.

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Keywords: amines · arylation · multicomponent reaction · phenols · rearrangement

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[10] Formation of tetrazoles when performing Ugi reactions with azides involves the cyclization of an azidoimidoyl intermediate. For a recent example using $TMSN_3$ (trimethylsilyl azide), see: T. Nixey, M. Kelly, D. Semin, C. Hulme, *Tetrahedron Lett.* **2002**, *43*, 3681–3684.

