"Isocyanide-free" Ugi reactions†

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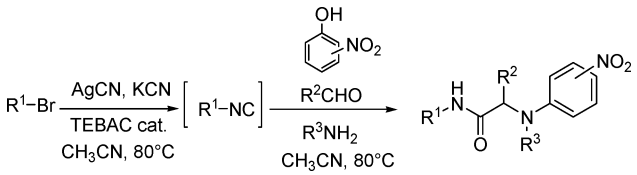
High-yielding Ugi reactions have been carried out with *in situ*-prepared isocyanides, derived from the reaction of bromide derivatives with silver and potassium cyanide, thus alleviating the burden of the preparation, purification and subsequent use of isocyanides in multicomponent reactions.

Considered as the most famous coupling among multicomponent reactions, the Ugi reaction[1] has seduced many organic chemists, especially in the middle of the 1990s, when the demand for molecular diversity and for huge libraries of pharmaceutical scaffolds grew considerably. For the scientists who are unfamiliar with this chemistry, the main issue rests with the isocyanide synthesis, because of their (wrongly) suspected toxicity and the strongly unpleasant smell associated with the most representative ones.

Above all, very few compounds are commercially available, and among the various preparative methods reported in the literature[2], the preferred processes are either the carbylamine reaction[3], or the dehydration of formamides.[4] Both syntheses are impaired by the use of chlorinated agents in excess and by the harsh experimental conditions that are not always compatible with functionalized substrates.

Inspired by Songstad and co-workers' modified procedure[5] of the Lieke synthesis of isocyanides[6], we have recently devised a process that involves the reaction of bromide derivatives with silver cyanide and potassium cyanide in the same pot, thereby allowing the formation of several benzylic and allylic isocyanides. We showed that these conditions were compatible with the Ugi–Smiles coupling and we have reported the first one-pot four-component reaction without any manipulation of isocyanide (Scheme 1).[7]



Scheme 1 One-pot sequence: isonitrile synthesis and Ugi–Smiles reaction.

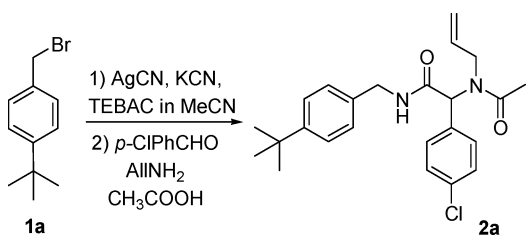
Considering the importance of the Ugi adducts towards organic chemistry, we were eager to test the feasibility of the four-component reaction using an *in situ*-generated isocyanide. An *in situ* alkylation of isocyanide has been reported by Armstrong and co-workers, based on the Schöllkopf reaction, and subsequent Ugi coupling, but the starting point of the reaction remains an isocyanide.[8] We wish to report herein the first (to the best of our knowledge) four-component Ugi reaction using a halogenated compound as an isocyanide substitute.

The alkylation reaction was performed in acetonitrile at 80 °C, using a stoichiometric mixture of silver cyanide and potassium cyanide in the presence of a catalytic amount of an ammonium salt (20% of triethylbenzyl ammonium chloride—TEBAC). We presume that the reactive metal species might be the complex $Ag(CN)_2^-$ $NBn(Et)_3^+$. According to the previous work of the Songstad group, the counter ion should be a bulky ammonium salt to perform the bromide exchange; this explains the beneficial effect of the phase-transfer agent. However, in contrast to Songstad's work, we have been able to reduce the amount of such a salt in the medium from a stoichiometric to a catalytic amount of 20 mol%, preventing the formation of a slurry that would slow down the subsequent reaction.

The brominated compound **1a** in solution in acetonitrile was treated with stoichiometric amounts of silver cyanide and potassium cyanide in the presence of 20 mol% of TEBAC. The resulting mixture was next heated at 80 °C until completion of the reaction (which could be checked by ^{1}H NMR analysis of an aliquot). Allylamine, *para*-chlorobenzaldehyde and acetic acid were then successively added. We observed that an excess of the reactants—imine and carboxylic acid—as well as preformation of the imine noticeably increased the yields (Table 1).

However, quite surprisingly, when performed at room temperature—the usual procedure for this reaction—the Ugi coupling was not complete and isocyanide was still recovered unreacted. Nevertheless, the reaction proceeded smoothly at 40 °C in acetonitrile (2 M) for three days to provide the desired adduct **2a** in 82% yield.

Table 1 Influence of the imine on the yield of the reaction



1a **2a**

entry	amount of imine	formation of imine	yield (%)
1	1.2 equiv.	*in situ*	11
2	1.5 equiv.	*in situ*	50
3	1.5 equiv.	preformed	57
4	2.0 equiv.	preformed	82

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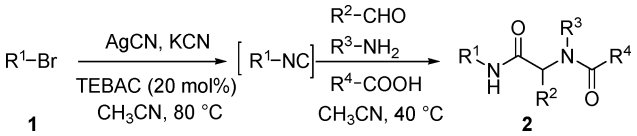
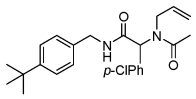
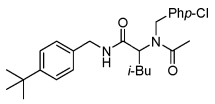
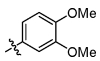
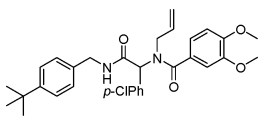
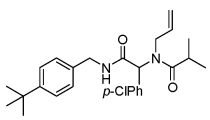
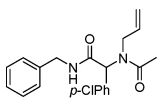
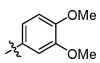
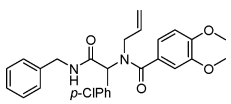
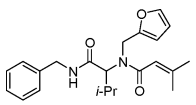
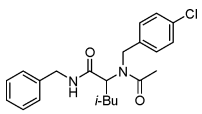
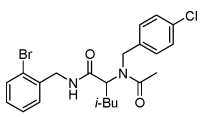
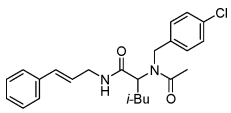
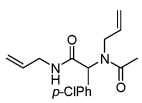
† Electronic supplementary information (ESI) available: Experimental details, ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b908541f

Table 2 Ugi reactions with *in situ*-prepared isocyanides



1 2

entry	R^1	R^2	R^3	R^4	product	yield (%)
1	*p*-*t*BuBn	*p*-ClPh	All	Me	 **2a**	82
2	*p*-*t*BuBn	*i*Bu	*p*-ClBn	Me	 **2b**	84
3	*p*-*t*BuBn	*p*-ClPh	All		 **2c**	44
4	*p*-*t*BuBn	*p*-ClPh	All	*i*-Pr	 **2d**	48
5	Bn	*p*-ClPh	All	Me	 **2e**	97
6	Bn	*p*-ClPh	All		 **2f**	67
7	Bn	*i*Pr	Furfuryl		 **2g**	75
8	Bn	*i*Bu	*p*-ClBn	Me	 **2h**	96
9	*o*-BrBn	*i*Bu	*p*-ClBn	Me	 **2i**	64
10	PhCH=CH–CH_2	*i*Bu	*p*-ClBn	Me	 **2j**	60
11	All	*p*-ClPh	All	Me	 **2k**	47

The high yield and simple experimental protocol of this new tandem process prompted us to explore this reaction more widely (Table 2).‡ Various benzyl isocyanides were synthesized and coupled *in situ* with different aliphatic or aromatic aldehydes and amines (Table 2, entries 1–9). In all the cases, the Ugi adducts were isolated in fair to excellent yields. In order to compare the efficiency of the sequence, we prepared the compound **2g** already reported by Pirrung and Sarma[9], and obtained a similar yield (75% instead of 85% yield) (Table 2, entry 7).

When taking into account the yield of the preparation of the isocyanide, the interest of such a process becomes obvious. Even if allyl isocyanides seem to be less efficient in this sequence (Table 2, entries 10 and 11), this procedure constitutes an attractive way of forming the corresponding adducts, considering the high volatility and strong odour of allyl isocyanide.

To conclude, the burden of isocyanide synthesis has been considerably lightened with the disclosure of this new strategy featuring their synthesis from bromide derivatives, silver and potassium cyanide, followed by their *in situ* use in a multicomponent reaction. This approach has been successfully applied to the Ugi reaction, allowing us to report herein an efficient and time-saving method for preparing peptidic derivatives bearing an allyl or a benzyl amide. This sequence avoids the isolation of volatile and foul-smelling intermediates, providing the desired adduct in yields comparable to those obtained using classical conditions. Further studies to extend such easy-to-handle methods are still in progress in our laboratory.

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Notes and references

‡ **Typical procedure for 2b:** To a 2 M solution of *para-tert*-butylbenzyl bromide (184 μL, 1.0 mmol) in acetonitrile were added silver cyanide (134 mg, 1.0 mmol), potassium cyanide (65 mg, 1.0 mmol) and TEBAC (46 mg, 0.20 mmol). The mixture was then heated at 80 °C for one day. Meanwhile, the imine was preformed by stirring *para*-chlorobenzaldehyde (280 mg, 2.0 mmol) and allylamine (150 μL, 2.0 mmol) at 40 °C for 2 hours. The imine and the acetic acid (120 μL, 2.0 mmol) were added to the mixture and left to react at 40 °C for 3 days. The reaction was quenched by the addition of water and then extracted with dichloromethane (3 × 50 mL). The combined extracts were dried and evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica gel using a 4:6 mixture of petroleum ether and diethyl ether as eluent to give the Ugi adduct (340 mg, 85%) as a yellow solid. m.p. 159–160 °C; ν_{max}/cm^{-1} (thin film) 3272 (NH), 3054 (conj. CH), 2964 (CH), 1674 (CO), 1626 (CO), 1515 (conj. CC), 1491 (conj. CC), 1411 (conj. CC), 1265 (CN). δ_H (400 MHz; $CDCl_3$) 1.31 (9H, s, Me_3), 2.10 (3H, s, COMe), 4.05–3.95 (2H, m, $NCH_2CH{=}CH_2$), 4.39 (1H, dd, *J* 14.7 and 5.2, $ArCH_2$), 4.47 (1H, dd, *J* 14.7 and 5.2, $ArCH_2$), 4.98 (1H, d, *J* 17.4, $NCH_2CH{=}CH_2$), 4.99 (1H, d, *J* 11.4, $NCH_2CH{=}CH_2$), 5.48–5.38 (1H, m, $NCH_2CH{=}CH_2$), 6.13 (1H, s, *p*ClAr*CH*), 6.57 (1H, br t, *J* 5.2, NH), 7.19 (2H, d, *J* 8.1, 2H, H_{Ar}), 7.36–7.28 (6H, m, H_{Ar}). δ_C (100.6 MHz; $CDCl_3$) 22.4 (CO*Me*), 31.7 (Me_3), 34.9 (*C*Me_3), 43.7 ($C_{Ar}CH_2$), 49.8 ($NCH_2CH{=}CH_2$), 60.8 (*p*ClAr*CH*), 117.1 ($NCH_2CH{=}CH_2$), 126.0 (CH_{Ar}), 127.9 (CH_{Ar}), 129.3 (CH_{Ar}), 131.4 (CH_{Ar}), 134.2 ($NCH_2CH{=}CH_2$ and C_{Ar}), 134.9 ($C_{Ar}Cl$), 135.1 ($C_{Ar}CH_2$), 150.9 (C_{Ar}tBu), 169.7 (NH*C*O), 172.7 (*C*OCH$_3$). HRMS (EI) Found: 412.1900, Calc. for $C_{24}H_{29}ClN_2O_2$: 412.1918.

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