Isocyanide-Based Multicomponent Reaction 'without' Isocyanides

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Abstract: We present here a one-pot, four-component sequence that affords Ugi-type adducts starting from simple benzyl or allyl bromides. The isocyanides are prepared in situ under alkylation of silver cyanide salts and the resulting mixture is directly used in a Ugi–Smiles coupling.

Key words: isocyanides, synthesis, alkylation, silver cyanide, Ugi– Smiles, multicomponent reaction

Although discovered more than a century ago when Lieke treated allyl bromide with silver cyanide,¹ the isocyanide family has remained a chemical curiosity for years, even with the disclosure of the Passerini reaction.² It is only in the 1960s that the synthetic versatility of the isocyanides began to be exploited,³ due to the development of efficient methods to generate them. Nowadays, two leading procedures are used for their preparation: the carbylamine reaction⁴ under phase-transfer catalysis,⁵ and the treatment of N-substituted formamides by a chlorinated reagent (POCl₃, SOCl₂, COCl₂, etc.) in the presence of a base.⁶ Apart from these two methods, various procedures⁷ such as the reduction of isocyanates or isothiocyanates,⁸ an oxidation-reduction condensation with phosphonates,9 an opening of oxazoles,¹⁰ or an epoxide ring opening with trimethylsilylcyanide¹¹ have been reported but they are still of limited use.

In spite of all these methods, many chemists unfamiliar with isocyanides remain reluctant to prepare the compounds that are not commercially available. More than their suspected toxicity, it is the smell of most of these products that is probably an important barrier for their wider synthesis and subsequent use. A sensible way to bypass this obstacle would be to find an efficient preparation of isocyanides that would allow one-pot, multicomponent processes directly from the synthetic precursors of the isocyanide. As a further proof of the interest of such an approach, we decided that the second step of the sequence would be a four-component-type reaction. The dehydration of formamides, often regarded as the most efficient preparation of isocyanides, is, however, hampered by the use of an excess of chlorinated reagents and thus poorly compatible with the following additions of the inputs for the Ugi reaction. In terms of mildness of reaction and nature of side products, the preparation of isocyanide from metal cyanide as reported at the early age of isocyanide chemistry by Lieke¹ and Gautier^{12,13} seemed more promising. Metal cyanides, such as iron¹⁴ and silver,¹⁵ have indeed been used with iodo or bromo derivatives and even tertiary alcohols¹⁶ as starting materials. The fact that some of these metals have been shown to catalyze a few multicomponent reactions involving isocyanides was a vital indication for the success of this chemical journey.¹⁷

Table 1 Synthesis of Isocyanides

\rightarrow	Br -	KCN (1 ec solvent (1	uiv)	NC
Entry	Cyanide source	TEBAC (mol%)	Conditions	Yield (%)
1	AgCN	-	MeOH (60 °C, 3 d)	-
2	AgCN	_	DMF (60 °C, 3 d)	_
3	AgCN	-	DCE (60 °C, 3 d)	15
4	AgCN	_	MeCN (80 °C, 2 d)	45
5	KAgCN ₂	-	MeCN (80 °C, 2 d)	30 ^a
6	AgCN	20	MeCN (80 °C, 2 d)	75 ^b
7	AgCN	20	NMP (110 °C, 1 d)	90
8	ZnCN ₂	20	MeCN (80 °C, 72 h)	_
9	K ₃ FeCN ₆	20	MeCN (80 °C, 72 h)	_
10	K ₄ FeCN ₆	20	MeCN (80 °C, 1 d)	_
11	K ₄ FeCN ₆	20	NMP (110 °C, 1 d)	80
12	CuCN	20	MeCN (80 °C, 1 d)	-

^a The reaction was performed without additional potassium cyanide. ^b The reaction was quantitative when performed overnight at a 3 M concentration.

The starting point of our study was the high-yielding procedure described by Songstad and co-workers.¹⁸ In this previous work, the isocyanide formation was performed via the alkylation of freshly prepared onium dicyanoargentate salts in acetonitrile. In order to devise a more convenient procedure, with simple commercial reagents, we first tested the reaction using stoichiometric amounts of *tert*-butyl benzyl bromide, silver cyanide, and potassium cyanide in various polar solvents. Inspired by Songstad's results, we then progressively added bulky ammonium salts to the mixture. Without any onium salt, we obtained the expected isocyanide in modest yield, with acetonitrile

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at 80 °C showing the best results (Table 1, entries 1–4). The introduction of triethylbenzylammonium chloride allows for the formation of a dicyano ammonium silver salt of increased nucleophilicity and solubility. To our delight, we observed that a small amount of this salt (20 mol%) was sufficient to dramatically raise the yields, up to 75% when the mixture was heated overnight in acetonitrile (Table 1, entry 6). With these promising conditions in hand, a brief metal-salt survey was carried out to confirm that silver was the best choice (Table 1, entries 8–12).

However, it is worth noticing that similar results were obtained using iron(II) cyanide in *N*-methyl pyrrolidone at $110 \,^{\circ}$ C (Table 1, entry 11).¹⁹ These results could be further improved if the reaction is performed at higher concentration. Indeed, at 3 M concentration, a quantitative formation of isocyanide was observed with silver salts. With this convenient method in hands, we next evaluated the one-pot four component process.

R ¹ Br	$\xrightarrow{\text{AgCN}} \begin{bmatrix} \text{KCN} \\ \text{MeCN, 80 °C} \end{bmatrix} = \begin{bmatrix} \text{R}^1 \text{NC} \end{bmatrix}$	OH NO ₂ R ² CHO R ³ NH ₂ MeCN, 80 °C	H R^2 NO_2 N R^3	
Entry	\mathbf{R}^1	\mathbb{R}^2	R ³	Product (yield, %)
1	2-CNBn	<i>i</i> -Bu	All	
2	4-t-BuBn	<i>i-</i> Bu	All	t-Bu H N O All
3	4- <i>t</i> -BuBn	<i>i-</i> Bu	All	t-Bu H H H N H N N N N NO2
4	4- <i>t</i> -BuBn	<i>i</i> -Bu	4-ClBn	81 $t \cdot Bu$ H H H H H H H H H H
5	4- <i>t</i> -BuBn	Et	All	78 $t \to H$ H H H H H H H
6	Bn	<i>i</i> -Bu	All	
7	Bn	<i>i-</i> Bu	All	$\begin{array}{c} 42 \\ H \\ $
8	4-MeOBn	<i>i-</i> Bu	All	$H \xrightarrow{i-Bu}_{O} NO_{2}$

 Table 2
 Ugi–Smiles Coupling

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 Table 2
 Ugi–Smiles Coupling (continued)

As part of our ongoing program,²⁰ we next investigated the possibility to perform a Ugi–Smiles coupling using this in situ preparation of the isocyanide partner. After completion of its formation (checked by ¹H NMR analysis of an aliquot), stoichiometric amounts of an aldehyde, a primary amine, and a nitrophenol were added. The resulting mixture was stirred in acetonitrile²¹ for two days at 80 °C. Benzyl bromides bearing electron-withdrawing groups reacted slowly with silver salts (*para*-nitrobenzyl bromide turned out to be unreactive) and did not perform the four-component coupling (Table 2, entry 1). On the contrary, benzyl derivatives with various electron-donating substituents reacted smoothly in this one-pot, two-step

process, and the desired adducts were isolated in modest to good yields (Table 2, entries 2–11). Unfortunately, no reaction occurred when using secondary or tertiary halogeno alkyl derivatives. As such, this method is still limited to activated bromides. Indeed, cinnamyl bromide was coupled successfully as well (Table 2, entries 14 and 15). Allyl bromide turned out to be less reactive and yields did not exceed 50% for the whole sequence. However, its extremely foul odor prevents its direct use, therefore this method constitutes a very convenient way to synthesize allylamide-substituted Ugi–Smiles adducts (Table 2, entries 12 and 13). To the best of our knowledge, it is the first time that an isocyanide can be synthesized and used without further purification in a four-component process.²² The operational simplicity of the present protocol, combined with the extreme foul odor of several isocyanides, which probably deterred many groups from working with them, makes the method potentially attractive. We are still exploring the scope of this process to develop further isocyanide-based multicomponent reaction (IMCR) chemistry without intermediate purification of isocyanides.

Typical Procedure for the Product of Table 2, Entry 6

To a 3 M solution of bromide derivative (1.0 mmol, 1.0 equiv) in MeCN were added AgCN (134 mg, 1.0 mmol, 1.0 equiv), KCN (65 mg, 1.0 mmol, 1.0 equiv), and Et₃NBnCl (46 mg, 0.20 mmol, 20 mol%). The mixture was then stirred at 80 °C in a sealed vial overnight. After completion of the formation of the isocyanide (checked via ¹H NMR analysis), the aldehyde (1.0 mmol, 1.0 equiv), the amine (1.0 mmol, 1.0 equiv), and the nitrophenol (1.0 mmol, 1.0 equiv) were added to the mixture, which was then stirred at 80 °C for 3 d. After checking the completion of the reaction via TLC, the reaction was quenched with the addition of a 1 M NaOH soln, and diluted with CH₂Cl₂. The aqueous phase was washed several times with CH₂Cl₂, the organic phases were then collected, dried over anhyd MgSO₄, and concentrated in vacuo. Finally, a flash column chromatography on SiO₂ afforded the desired product as a yellow solid (42%); mp 131–132 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.00 (d, J = 9.3 Hz, 2 H), 7.32–7.27 (m, 3 H), 7.21 (d, J = 7.1 Hz, 2 H), 6.71 (d, J = 9.3 Hz, 2 H), 6.54 (br s, 1 H), 5.83 (ddt, J = 17.2, 10.3, 5.3 Hz, 1 H), 5.24 (d, J = 10.3 Hz, 1 H), 5.21 (d, J = 17.2 Hz, 1 H), 4.45–4.40 (m, 3 H), 4.10 (dd, J = 17.4, 5.1 Hz, 1 H), 4.01 (dd, *J* = 17.4, 5.1 Hz, 1 H), 2.10 (ddd, *J* = 14.1, 7.3, 5.8 Hz, 1 H), 1.79– 1.59 (m, 2 H), 0.96 (d, J = 6.3 Hz, 3 H), 0.93 (d, J = 6.3 Hz, 3 H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 171.1, 153.3, 138.6, 138.2, 133.4, 129.1, 128.2, 128.0, 126.4, 118.7, 112.8, 62.2, 51.0, 44.2, 38.5, 25.6, 23.2, 22.7. IR (thin film): 2958, 1655, 1593, 1505, 1306, 1264, 1204, 1171, 1114 cm⁻¹. HRMS: *m/z* calcd 381.2052; found: 381.2057.

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