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Isocyanide-based multicomponent reactions: synthesis of 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives

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ABSTRACT

A new isocyanide-based multicomponent reaction between an aromatic aldehyde, malononitrile, an isocyanide, and acetic acid efficiently provides 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives in excellent yields in ethanol at 70 °C. This reaction led to the construction of two carbon–carbon bonds and one amide group in a single synthetic step.

Multicomponent reactions (MCRs) are very efficient synthetic methods. They offer significant advantages over classical stepwise approaches allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates.[1] MCRs that involve isocyanides are powerful tools in the modern drug discovery process and allow rapid, automated, and high-throughput generation of organic compounds.[2] The pharmaceutical industry has focused more and more on diversity-oriented and biased combinatorial libraries.[3] Furthermore, the discovery of novel isocyanide-based multicomponent reactions (IMCRs) can be considered an interesting research topic that also satisfies the practical interest of applied science.[4] As a result, the number of new IMCRs reported in recent years has grown rapidly.[4]

The most versatile of all IMCRs so far is the Ugi four-component condensation (U-4CC) of an acid, an amine, an aldehyde, or a ketone and an isocyanide.[5] The U-4CC is applicable to a broad range of starting materials including bifunctional examples and plays an important role in the isocyanide-based synthesis of organic compounds. However, to our knowledge, the U-4CC using malononitrile instead of amine components has not been described.

Due to above-mentioned reasons, and as a part of our ongoing research on isocyanide-based MCRs,[6] we report herein the synthesis of 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives **4** via a three-component condensation reaction of aldehydes **1**, malononitrile (**2**), isocyanides **3**, and acetic acid in ethanol at 70 °C (Scheme 1). In this reaction, the role of the carboxylic acid is not only to trap the nitrilium intermediate, but also to activate the alkene and aldehyde toward nucleophilic attack.

For optimization of this reaction, we investigated the effect of solvent, amount of acetic acid, and temperature on the yield and selectivity between the formation of product **4** and intermediate **5**. The reaction of malononitrile, benzaldehyde, and acetic acid with cyclohexyl isocyanide was selected as a model reaction and various solvents were screened under different reaction conditions (Table 1). When the reaction was carried using the aprotic solvents benzene, toluene, acetonitrile, and dichloromethane, the dominant product was intermediate **5** (Table 1, entries 1–4). However, when the reaction was carried out using protic solvents such as water, methanol and ethanol, the major product was **4a** (Table 1, entries 5–11). Ethanol proved to be the best solvent (Table 1, entry 7).

Next, we studied the model reaction in ethanol at different temperatures (Table 1, entries 9–11). The reaction rate increased as the temperature was raised. At 70 °C, the maximum yield (97%) was obtained in a reaction time of 12 h (Table 1, entry 7).

The model reaction in ethanol at 70 °C was also studied using different amounts of acetic acid. The best results were obtained with 100 mol % of acetic acid. Acetic acid is an important component of the reaction acting as both reagent and catalyst. Further work indicated that the best results were obtained when the reaction was carried out at 70 °C for 12 h in ethanol using 100 mol % of acetic acid (Table 1, entry 7).

With optimized conditions established, we next attempted to extend the process to three different isocyanides: cyclohexyl isocyanide, *tert*-butyl isocyanide, and 1,1,3,3-tetramethylbutyl

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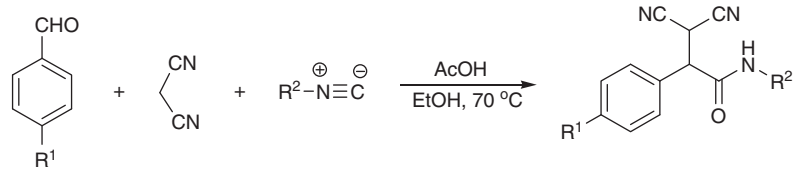
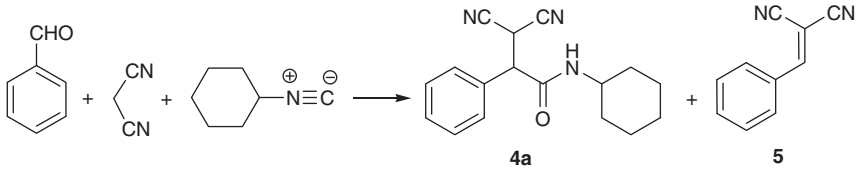


Scheme 1. Synthesis of 3,3-dicyano-*N*-alkyl-2-arylpropanamides **4.**

Table 1
Optimization of the three-component reaction



Entry	Solvent	Acetic acid (mol %)	Product	Temperature (°C)	Yield (%)
1	Benzene	100	**5**	70	70
2	Toluene	100	**5**	70	80
3	CH_2Cl_2	100	**5**	25	50
4	MeCN	100	**5**	70	80
5	H_2O	100	**4a**	70	50
6	MeOH	100	**4a**	70	75
7	EtOH	100	**4a**	70	97
8	EtOH	70	**4a**	70	65
9	EtOH	40	**4a**	70	35
10	EtOH	100	**4a**	50	85
11	EtOH	100	**4a**	25	70

Table 2
Synthesis of 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives

Entry	R^1	R^2	Product	Yield (%)
1	H	Cy	**4a**	97
2	4-O_2N	Cy	**4b**	95
3	4-CH_3O	Cy	**4c**	98
4	4-H_3C	Cy	**4d**	96
5	4-Cl	Cy	**4e**	97
6	H	1,1,3,3,-Tetramethylbutyl	**4f**	99
7	4-H_3C	1,1,3,3,-Tetramethylbutyl	**4g**	91
8	4-H_3C	*tert*-Butyl	**4h**	98

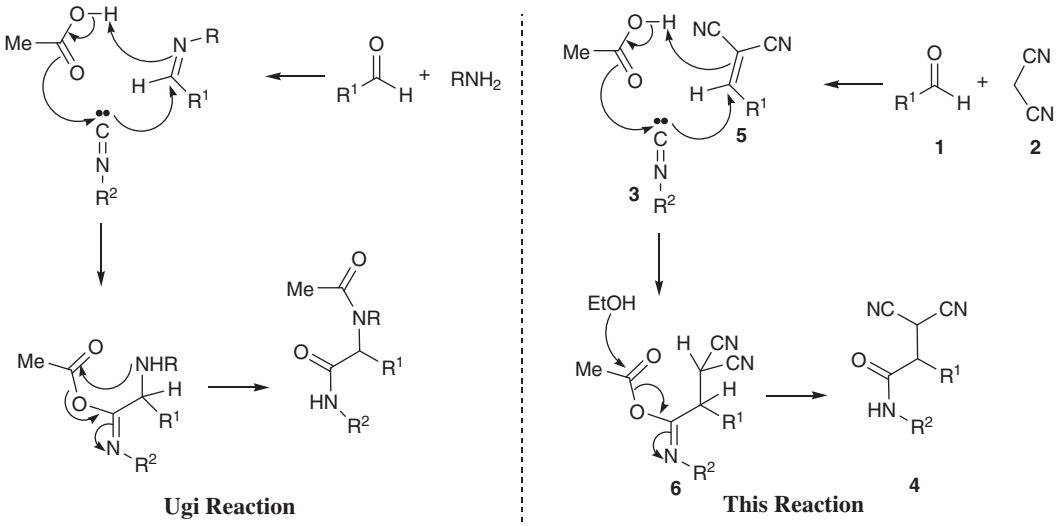
isocyanide, and various aromatic aldehydes. The results are summarized in Table 2. The structures of the products were established by spectroscopic methods. In all cases, excellent yields were obtained, regardless of the nature of the substituent present on the aldehyde (electron-donating or electron-withdrawing). This confirms the reliability of the synthetic method.

The structures of the products were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring protons (δ = 1.03–1.96), a multiplet for the N–C*H* cyclohexyl proton (δ = 3.77–3.89), two doublets for the CH–C*H*(CN)$_2$ (δ = 4.00, $^3J_{HH}$ = 7.6 Hz) and C*H*–CH(CN)$_2$ (δ = 4.65, $^3J_{HH}$ = 7.6 Hz) protons, a doublet for the CH–N*H* (δ = 5.39, $^3J_{HH}$ = 7.3 Hz) proton, and a multiplet for the aromatic protons (δ = 7.39–7.51). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances, partial assignment of these resonances is given in the experimental section.

The reaction mechanism can be regarded as a special case of the Ugi four-component reaction. Mechanistically, it is conceivable that the reaction involves the initial formation of the activated alkene, benzylidenemalonodinitrile[7] **5** through knoevenagel condensation of malononitrile (**2**) and the aldehyde **1**. Intermediate **5** undergoes nucleophilic addition with the isocyanide **3** followed by nucleophilic attack on the isocyanide by the carboxylate to afford intermediate **6**. Subsequently, intermediate **6** undergoes nucleophilic addition with ethanol to afford 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives **4** (Scheme 2). To clarify the proposed mechanism, first, the activated alkene **5** was synthesized by condensation of malononitrile (**2**) and aldehyde **1**. Next, reaction of **5** with the isocyanide and acetic acid in ethanol afforded the corresponding 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives. Also, for further clarification, the reaction was studied in the absence of acetic acid. Under these conditions, no product was obtained even after 24 h.

It should be noted that the reaction between the activated alkene (2-methylenemalononitrile) and isocyanides in methanol to afford 2-[(*E*)-2-methoxybut-2-enyl]malononitrile was published more than 30 years ago.[8] Recently, Mironov et al. reported the reaction between benzylidenemalonodinitrile, an isocyanide and phenol in the presence Et_3N/Py.[9] Also, Shaabani et al. reported the reaction between an activated alkene (Meldrum's acid), an aldehyde, an isocyanide and an amine or alcohol in dichloromethane.[10]

In conclusion, we have developed a new and efficient approach for the synthesis of a wide range of 3,3-dicyano-*N*-alkyl-2-arylpropanamide derivatives from aldehydes, malononitrile, isocyanides, and acetic acid. The reaction has been shown to display good functional group tolerance, is high yielding and product isolation is very straightforward.



Scheme 2. The typical Ugi reaction mechanism and the proposed overall mechanism for this reaction.

Typical procedure for the preparation of 3,3-dicyano-*N*-cyclohexyl-2-phenylpropanamide (4a)

A solution of benzalaldehyde (0.106 g, 1 mmol), malononitrile (0.066 g, 1 mmol) and acetic acid (0.060 g, 1 mmol), in EtOH (10 mL) was stirred at 70 °C. After 30 min, cyclohexyl isocyanide (0.109 g, 1 mmol) was added and the mixture stirred for 12 h at 70 °C. After completion of the reaction, as indicated by TLC, H_2O (10 mL) was added and the resulting precipitate washed with H_2O to afford the product **4a** as a yellow powder (0.27 g, yield 97%); mp 185–187 °C. IR (KBr) (ν_{max}/cm^{-1}): 3279 (NH), 3084, 2928, 2850, 2250 (CN), 1644, 1563. MS, *m/z* (%): 282 (M^++1, 50), 200 (15), 155 (20), 129 (25), 126 (20), 83 (100), 55 (50), 41 (25). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H (ppm) 1.03–1.96 (10H, m, $5CH_2$ of cyclohexyl), 3.77–3.89 (1H, m, C*H*–NH of cyclohexyl), 4.00 (1H, d, $^3J_{HH}$ = 7.6 Hz, –CH–C*H*$(CN)_2$), 4.65 (1H, d, $^3J_{HH}$ = 7.6 Hz, –C*H*–$CH(CN)_2$), 5.39 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH–N*H*), 7.39–7.51 (5H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.6, 24.7, 25.3, 32.5, 32.7 (*C*-cyclohexyl), 26.9 (–CH–*C*H$(CN)_2$), 49.4 (–*C*H–$CH(CN)_2$), 53.0 (CH–NH), 111.5, 112.1 (2CN), 128.6, 129.7, 130.0, 132.5 (C–Ar), 166.2 (C=O). Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.50; H, 6.75; N, 14.83.

3,3-Dicyano-*N*-cyclohexyl-2-(4-nitrophenyl)propanamide (4b)

Yellow powder (0.31 g, yield 95%); mp 160–162 °C. IR (KBr) (ν_{max}/cm^{-1}): 3273 (NH), 2926, 2850, 2215 (CN), 1646, 1524, 1349. MS, *m/z* (%): 327 (M^++1, 25), 326 (M^+, 5), 245 (25), 201 (25), 150 (50), 126 (30), 83 (100), 81 (65), 43 (85). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H (ppm) 1.07–2.11 (10H, m, $5CH_2$ of cyclohexyl), 3.81–3.87 (1H, m, C*H*–NH of cyclohexyl), 4.11 (1H, d, $^3J_{HH}$ = 8.3 Hz, –CH–C*H*$(CN)_2$), 4.67 (1H, d, $^3J_{HH}$ = 8.3 Hz, –C*H*–$CH(CN)_2$), 5.49 (H, d, $^3J_{HH}$ = 6.4 Hz, CH–N*H*), 7.67 (2H, d, $^3J_{HH}$ = 8.7 Hz, H–Ar), 8.35 (2H, d, $^3J_{HH}$ = 8.7 Hz, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.7, 24.8, 25.5, 32.2, 32.5 (*C*-cyclohexyl), 26.6 (–CH–*C*H$(CN)_2$), 48.7 (–*C*H–$CH(CN)_2$), 50.1 (CH–NH), 113.5, 113.6 (2CN), 124.3, 130.3, 142.1, 148.1 (C–Ar), 166.2 (C=O). Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 63.00; H, 5.52; N, 17.21.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.013.

References and notes

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. Weber, L. *Curr. Med. Chem.* **2002**, *9*, 1241.
3. (a) Schreiber, S.-L. *Science* **2000**, *287*, 1964; (b) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, 1998.
4. (a) Dömling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318; (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306; (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53; (d) Weber, L. *Drug Discovery Today* **2002**, *7*, 143; (e) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471; (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (h) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
5. (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1959**, *71*, 386; (b) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.
6. (a) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 2185; (b) Shaabani, A.; Soleimani, E.; Khavasi, H. R.; Hoffmann, R. D.; Rodewald, U. C.; Poättgen, R. *Tetrahedron Lett.* **2006**, *47*, 5493; (c) Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031; (d) Shaabani, A.; Soleimani, E.; Maleki, A.; Moghimi-Rad, J. *Mol. Divers.* **2009**, *13*, 269; (e) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett.* **2008**, *10*, 2581; (f) Shaabani, A.; Soleimani, E.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 442; (g) Shaabani, A.; Soleimani, E.; Moghimi-Rad, J. *Tetrahedron Lett.* **2008**, *49*, 1277; (h) Shaabani, A.; Sarvary, A.; Soleimani, E.; Rezayan, A. H.; Heidary, M. *Mol. Divers.* **2008**, *12*, 197; (i) Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3968.
7. (a) Jones, G. *Org. React.* **1967**, *15*, 204; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (c) Leelavathi, P.; Kumar, S. R. *J. Mol. Catal. A Chem.* **2004**, *240*, 99; (d) Reddy, T. I.; Varma, R. S. *Tetrahedron Lett.* **1997**, *38*, 1721.
8. Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H.; Takaishi, N. *Tetrahedron* **1971**, *27*, 27.
9. Mironov, M. A.; Ivantsova, M. N.; Mokrushin, V. S. *Synlett* **2006**, 615.
10. Shaabani, A.; Teimouri, M. B.; Bazgir, A.; Bijanzadeh, H. R. *Mol. Divers.* **2003**, *6*, 199.