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A Novel Isocyanide-Based Three-Component Reaction: Synthesis of Highly Substituted 1,6-Dihydropyrazine-2,3-dicarbonitrile Derivatives

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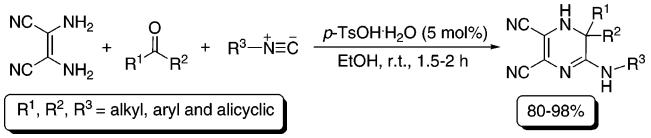

A novel multi-component synthesis of highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives starting from simple and readily available inputs is described. Thus, simply stirring an ethanol solution of 2,3-diaminomaleonitrile, a ketone, and an isocyanide in the presence of a catalytic amount of *p*-toluenesulfonic acid provided highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in good to excellent yields at ambient temperature.

Within the past decade, the resurgence of interest in multi-component reactions (MCRs) has been driven, not only due to their convergent nature, superior atom economy, and straightforward experimental procedures but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies and parallel synthesis. Due to the unique reactivity of the isocyanide functional group, MCRs involving isocyanides are among the most versatile, in terms of the number and variety of compounds which can be generated.[1]

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1] Therefore, it is not surprising that research in the field of synthesis of heterocyclic compounds has received special attention.

2,3-Diaminomaleonitrile (DAMN),[2] a tetramer of hydrogen cyanide, was considered as one of the versatile precursors to the synthesis of various types of nitrogen heterocycles such as imidazoles,[3] oxazoles,[4] purines,[5] pyrroles,[6] pyrimidines,[7] pyrazines,[8] diazepines,[9] and triazepines.[3,10] Although the reaction of DAMN with various carbonyl compounds has been reported under classical two-component reactions, a careful literature search reveals that the reaction of DAMN with carbonyl compounds and isocyanide under a MCR strategy has not been studied.

SCHEME 1. Synthesis of 1,6-Dihydropyrazine-2,3-dicarbonitrile Derivatives 4

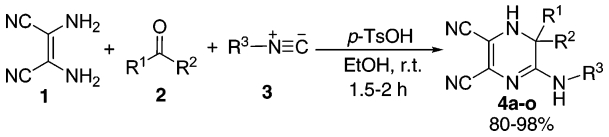

TABLE 1. Synthesis of 1,6-Dihydropyrazine-2,3-dicarbonitrile Derivatives 4a−o

entry	ketone	isocyanide	product	time (min)	yield[a] (%)
1	acetone	cyclohexyl	**4a**	90	90
2	2-butanone	cyclohexyl	**4b**	100	94
3	2-pentanone	cyclohexyl	**4c**	100	98
4	cyclopentanone	cyclohexyl	**4d**	90	88
5	cyclohexanone	cyclohexyl	**4e**	90	82
6	2-methylcyclohexanone	cyclohexyl	**4f**	110	85
7	acetophenone	cyclohexyl	**4g**	110	82
8	4-methylacetophenone	cyclohexyl	**4h**	120	92
9	4-bromoacetophenone	cyclohexyl	**4i**	100	94
10	acetone	*tert*-butyl	**4j**	95	93
11	cyclopentanone	*tert*-butyl	**4k**	110	84
12	4-methylacetophenone	*tert*-butyl	**4l**	120	82
13	2-methylcyclohexanone	2,6-$(Me)_2$-phenyl	**4m**	120	80
14	acetone	1,1,3,3-tetramethylbutyl	**4n**	100	87
15	cyclohexanone	1,1,3,3-tetramethylbutyl	**4o**	120	80

[a] Isolated yield.

In continuing our interest in isocyanide-based multi-component reactions,[11] here we report a hitherto unknown reaction which affords 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives **4** via the three-component condensation of 2,3-diaminomaleonitrile **1**, a ketone **2**, and an isocyanide **3** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in ethanol at ambient temperature in excellent yields (Scheme 1).

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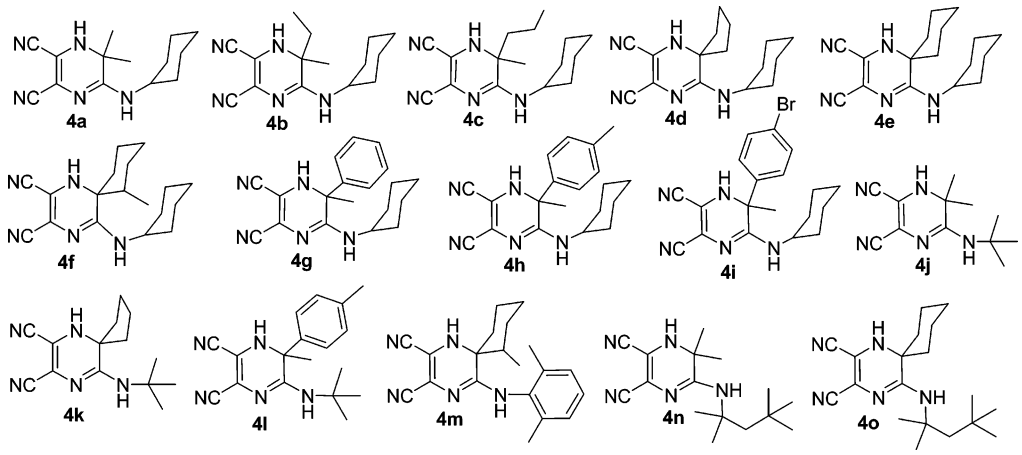
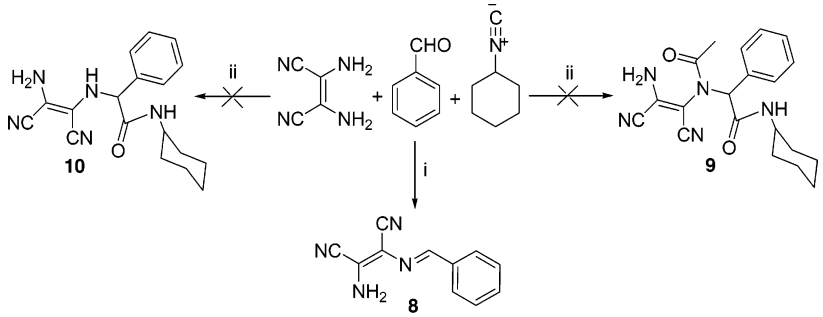


FIGURE 1. The structure of products **4a**−**o**.

SCHEME 2. Reaction of DAMN with Isocyanide and Aldehyde



In a pilot experiment, 2,3-diaminomaleonitrile, acetone, and cyclohexyl isocyanide in EtOH were stirred at room temperature using a catalytic amount of *p*-toluenesulfonic acid. The progress of the reaction was monitored by TLC. After completion of the reaction after 90 min, an aqueous workup afforded 5-(cyclohexylamino)-1,6-dihydro-6,6-dimethylpyrazine-2,3-dicarbonitrile **4a** in 90% yield. To evaluate the use of this approach, a variety of aliphatic, alicyclic, and aromatic ketones were condensed under similar circumstances. The results are shown in Table 1. The reaction proceeds very cleanly at room temperature, and no undesirable side reactions were observed.

In view of the success of the above reactions, we explored the use of various alkyl and aryl isocyanides as a third component in this reaction. Treatment of *tert*-butyl, 2,6-dimethylphenyl-, or 1,1,3,3-tetramethylbutyl isocyanides with DAMN in the presence of ketones in ethanol at ambient temperature led to the formation of the corresponding 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in high yields. The results are summarized in Table 1.

The structures of the products **4a**−**o** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. For example, the ^{1}H NMR spectrum of **4h** consisted of a multiplet of signals for the cyclohexyl ring at δ 1.00−2.01 and two singlets for methyl groups at δ 1.64 and 2.26. A multiplet was observed for the NH−C*H* at δ 3.85, an AB quartet pattern for aromatic protons centered at δ 7.11 and 7.16, a doublet for N*H*−CH at δ 7.36, and a fairly broad singlet was observed for the NH group at δ 7.97. The ^{1}H decoupled ^{13}C NMR spectrum of **4h** showed 18 distinct resonances. Partial assignment of these resonances is given in the Experimental Section.

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Two substituents in the products can be varied independently of each other. Representative examples of this reaction are shown in Figure 1.

We extended this reaction to aldehyde; however, Schiff base **8** was generated from the aldehyde, and nucleophilic attack by isocyanide does not occur. So, the isolated compound was intermediate **8** (Scheme 2).

We have also investigated this reaction under Ugi four-component reaction conditions using DAMN, isocyanide, aldehyde, or acetone in the presence of a stoichiometric amount of HOAc. In both cases, the previously isolated products **4** and **8** were produced, respectively. Neither the classical Ugi four-component product **9** (HOAc as acid component) nor the product **10** (HOAc as catalyst) was observed under the given reaction conditions (Scheme 2).

The possible mechanism for the formation of product is shown in Scheme 3. It is conceivable that the initial event is the formation of iminium **5** from DAMN and an activated

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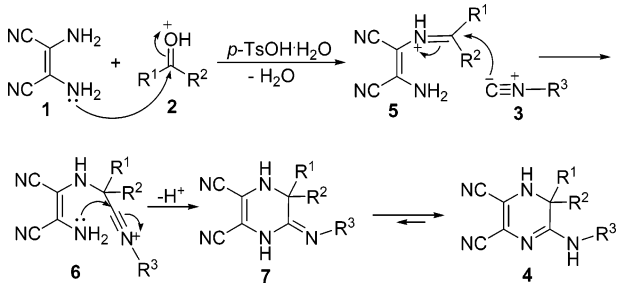
SCHEME 3. Possible Mechanism for the Formation of Products 4a−o



ketone.[12] On the basis of the well-established chemistry of reaction of isocyanides with imines,[1b] intermediate **6** was produced by nucleophilic attack of isocyanide **3** to iminium **5** followed by intramolecular nucleophilic attack by the NH_2 group on the activated nitrile moiety and production of compound **7**. Imine−enamine tautomerization of intermediate **7** produces the product **4**.

In summary, we have discovered a novel multi-component reaction leading to polysubstituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives starting from simple and readily available precursors. This novel reaction can be regarded as a new approach for the preparation of pharmaceutically relevant, highly substituted spiro-1,6-dihydropyrazine-2,3-dicarbonitrile derivatives. The biological activities of prepared 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives **4** are now under study.

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Experimental Section

Typical Procedure for the Synthesis of 5-(Cyclohexylamino)-1,6-dihydro-6-methyl-6-*p*-tolylpyrazine-2,3-dicarbonitrile (4h): To a solution of DAMN (0.108 g, 1 mmol), 4-methylphenylacetone (0.148 g, 1 mmol), and cyclohexyl isocyanide (0.109 g, 1 mmol), in 3 mL of EtOH, was added *p*-TsOH·H_2O (0.095 g, 5 mol %). The resulting mixture was stirred for 2 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), the product was precipitated by addition of 10 mL of water. The precipitate was filtered off and washed with water, and then crystallized from acetone to give **4h** as light yellow crystals (0.310 g, 92%): mp 250−253 °C; IR (KBr, cm^{-1}) ν 3350, 2932, 2854, 2225, 2209, 1564, 1536; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 1.00−2.01 (10H, m), 1.64 (3H, s), 2.26 (3H, s), 3.85 (1H, m), 7.11, 7.16 (4H, AB-q, $^3J_{AB}$ = 7.5 Hz), 7.36 (1H, d, $^3J_{HH}$ = 7.1 Hz), 7.97 (1H, br s); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 20.5, 24.7, 24.8, 25.2, 25.4, 31.3, 31.6, 50.2, 54.9, 109.8, 111.4, 114.2, 117.5, 124.6, 129.0, 137.0, 139.4, 153.0; MS *m/z* 333 (M^+, 24), 318 (47), 251 (20), 236 (100), 209 (20), 160 (20), 117 (27), 91 (25), 65 (15), 55 (54), 41 (70). Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 72.02; H, 6.96; N, 21.02.

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Supporting Information Available: Experimental procedures, mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4a**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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