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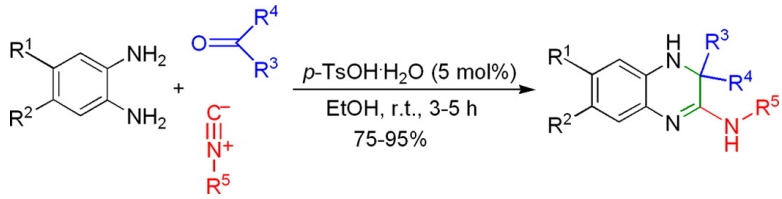

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Novel Isocyanide-Based Three-Component Synthesis of 3,4-Dihydroquinoxalin-2-amine Derivatives

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Synthesis of a novel class of highly substituted 3,4-dihydroquinoxalin-2-amine derivatives including spirocyclic compounds from three-component condensation reaction of *o*-phenylenediamines, diverse carbonyl compounds, and isocyanides in the presence of a catalytic amount of *p*-toluenesulfonic acid in good to excellent yields at room temperature is described.

Introduction

In recent years, the resurgence of interest in multicomponent reactions (MCRs) has been driven not only because of their convergent nature, superior atom economy, and straightforward experimental procedures but also because of their value to the pharmaceutical industry for the generation of a large ensemble of low molecular weight compounds through combinatorial strategy and parallel synthesis. Because of the unique reactivity of isocyanide functional group, MCRs involving isocyanides are among the most versatile, in terms of the number and variety of compounds that can be generated.[1–3]

Quinoxalinones exhibit a wide variety of biological activity, including antidiabetic[4] and antiviral effects, in particular, against retroviruses such as HIV.[5] They also are inhibitors of aldose reductase,[6,7] partial agonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex,[8] and antagonists of the AMPA and angiotensin II receptors.[9] 3,4-Dihydroquinoxalines possess biological activity, for example, as inhibitors of cholesteryl ester transfer proteins.[10]

In continuation of our interest in isocyanide-based multicomponent reactions,[11] herein we report a hitherto unknown reaction that affords 3,4-dihydroquinoxalin-2-amine derivatives **4** via the three-component condensation of a 1,2-diamine **1**, an aldehyde or ketone **2**, and an isocyanide **3** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in good to excellent yields in ethanol at room temperature (Scheme 1).

Results and Discussion

In a pilot experiment, *o*-phenylenediamine, acetone, and cyclohexyl isocyanide in ethanol 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, an aqueous workup afforded *N*-cyclohexyl-3,4-dihydro-3,3-dimethylquinoxalin-2-amine **4a** in 90% yield.

To explore the scope and limitations of this reaction, we extended the procedure to various alkyl, benzyl, and alicyclic isocyanides and aliphatic, alicyclic, and aromatic ketones with aromatic diamines. As indicated in Table 1, the reaction proceeds very efficiently in excellent yields in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in ethanol at ambient temperature and leads to the formation of the corresponding 3,4-dihydroquinoxalin-2-amine derivatives **4a**−**k**. The reaction proceeds very cleanly, and no undesirable side reactions were observed.

We decided to extend this reaction to various aromatic and aliphatic aldehydes with aromatic 1,2-diamines in the presence of cyclohexyl isocyanide. Benzaldehydes with electron-withdrawing and electron-releasing groups at their para positions afforded the desired products **4l**−**o** in high yields. Aliphatic aldehyde also afforded **4p** in high yield (Table 2).

The amine component of the MCR is also variable. To examine the replacement of the aromatic diamine **1** (Scheme 1) with alicyclic 1,2-diamines, we used cyclohexane-1,2-diamine as an alicyclic diamine. The isolated products *N*-cyclohexyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-3,3-dimethylquinoxalin-2-amine **4q** and *N*-*tert*-butyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-3-*p*-tolylquinoxalin-2-amine **4r** were obtained in high yields (Table 3).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. It is noteworthy that five substituents in the products (R^1−R^5) can be varied independently of each other.

The structures of the products **4a**−**r** 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.

Scheme 1. Synthesis of 3,4-Dihydroquinoxalin-2-amine Derivatives **4a**−**p**

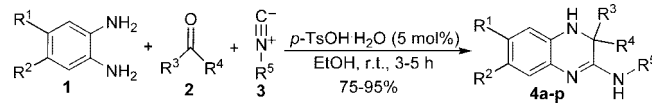

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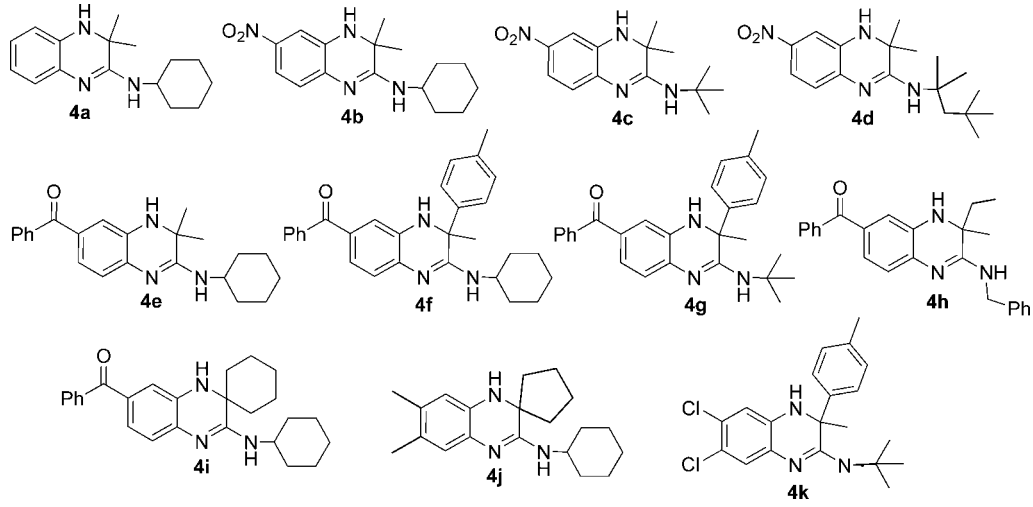
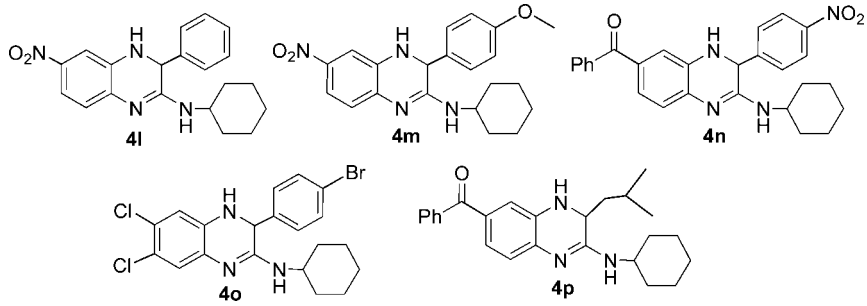
Table 1. 3,4-Dihydroquinoxalin-2-amines Produced from the MCRs of Diamines, Ketones, and Isocyanides



product	time (h)	yield[a] (%)	product	time (h)	yield[a] (%)
4a	4	90	**4g**	4	77
4b	3	87	**4h**	5	90
4c	4	75	**4i**	3	85
4d	3	92	**4j**	5	82
4e	3	95	**4k**	5	80
4f	3	88			

[a] Isolated yield.

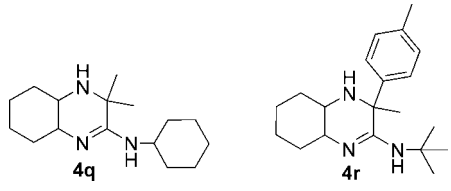
Table 2. 3,4-Dihydroquinoxalin-2-amines Produced from the MCRs of Aromatic Diamines, Aldehydes, and Cyclohexyl Isocyanide



product	time (h)	yield[a] (%)
4l	5	76
4m	4	88
4n	4.5	90
4o	5	75
4p	5	84

[a] Isolated yield.

Table 3. Octahydroquinoxalines Produced from the MCRs of Cyclohexane-1,2-diamine, Ketones, and Isocyanides



product	time (h)	yield[a] (%)
4q	4.5	80
4r	5	77

[a] Isolated yield.

Finally, the structure of **4e** was confirmed unambiguously by single crystal X-ray analysis (Figure 1).

The reaction is in this case highly regioselective, and the X-ray structure shows the favored isomer. We think that this selectivity is the result of the (−R) effect of the benzoyl group, which deactivates the *p*-amino group. Therefore the reaction is initiated by the *m*-amino group to give iminium ion **5** as an intermediate. Finally, the attack of isocyanide to iminium gives the product **4e** as the only isomer. Accordingly we assume that the structures of compounds **4b**−**d**, **4f**−**i**, **4l**−**n**, and **4p** are those depicted in the schemes, on the basis of mechanistic analogies with **4e**.

The possible mechanism for the formation of products **4a**−**r** is shown in Scheme 2. It is conceivable that the initial event is the formation of iminium **5** from diamine **1** and an aldehyde or ketone **2**.[1] On the basis of the well-established chemistry of reaction of isocyanides with imines,[1] intermediate **6** was produced by nucleophilic attack of isocyanide **3** to activated iminium **5** and then by an intramolecular nucleophilic attack of NH_2 group to the activated nitrile moiety to yield **7**. Imine−enamine tau-

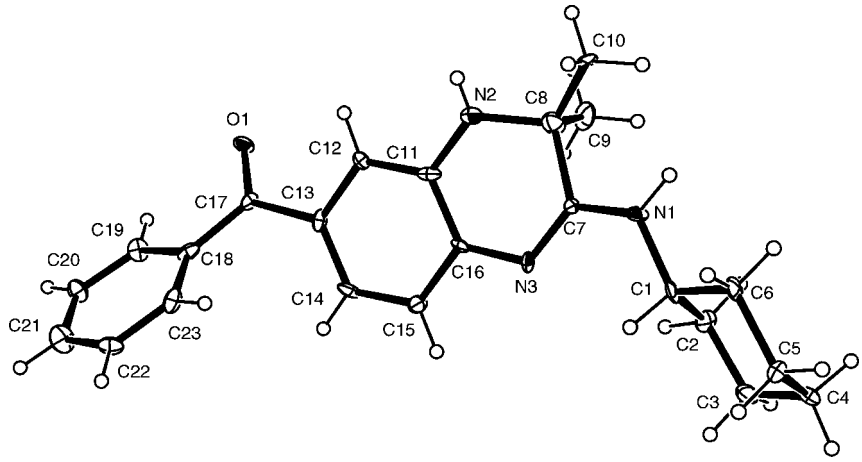
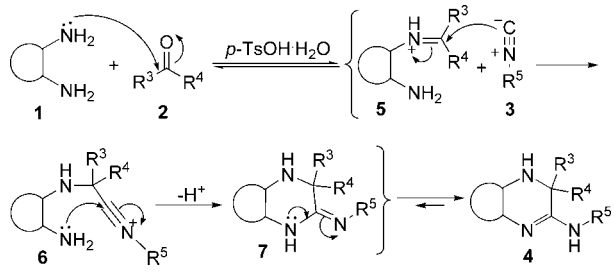


Figure 1. X-ray crystal structure of compound **4e**.

Scheme 2. Proposed Mechanism for the Formation of Products **4a**−**r**



tomerization of intermediate **7** leads to the formation of products **4a**−**r**.

Conclusions

In summary, we have discovered a novel multicomponent reactions leading to diverse polysubstituted 3,4-dihydroquinoxalin-2-amine derivatives starting from simple and readily available precursors like various aromatic and alicyclic diamines, diverse carbonyl compounds, and isocyanides. This novel reaction can be regarded as a new approach for the preparation of pharmaceutical relevant highly substituted 3,4-dihydroquinoxalin-2-amine derivatives, especially spiro ones (**4i** and **4j**). The reaction is easy to perform and allows the introduction of at least five diversity points in the final products and access to thousands of compounds. Work-up procedures were simple, chromatography-free, and allowed to isolate target materials with high purity. The biological activities of products **4a**−**r** are now under investigation.

Experimental Section

Typical Procedure for the Synthesis of *N*-Cyclohexyl-3,4-dihydro-3,3-dimethyl-6-benzoylquinoxalin-2-amine 4e. To a solution of 3,4-diaminobenzophenone (0.212 g, 1 mmol), acetone (0.058 g, 1 mmol), and cyclohexyl isocyanide (0.109 g, 1 mmol) in 3 mL of ethanol was added *p*-TsOH·H_2O (0.095 g, 5 mol%). The resulting mixture was stirred for 3 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane 2/1), the product was precipitated by addition of 10 mL of water. The precipitate was filtered off and washed with 5% sodium hydroxide solution and then with water. The residue was crystallized from ethanol to give **4e** as yellow crystals (0.343 g, 95%): mp 181–182 °C; IR (KBr) cm^{-1} 3281, 2934, 2850, 1650, 1605, 1504, 1460, 1324; ^{1}H NMR (DMSO-d_6) δ 1.10–2.07 (10H, m, 5CH_2 of cyclohexyl), 1.24 (6H, s, 2CH_3), 3.95 (1H, m, CH−N), 5.99 (1H, br s, NH), 6.47 (1H, d, $^3J_{HH}$ = 7.8 Hz, N*H*−CH), 6.84 (1H, d, $^3J_{HH}$ = 8.0 Hz, H_{arom}), 6.98 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.8 Hz, H_{arom}), 7.05 (1H, d, $^4J_{HH}$ = 1.6 Hz, H_{arom}), 7.48–7.65 (5H, m, H_{arom}); ^{13}C NMR (DMSO-d_6) δ 25.4, 25.9 (carbons of cyclohexyl), 26.1 (CH_3), 32.4 (carbon of cyclohexyl), 49.0 (CH−N), 50.5 (*C*−CH_3), 114.2, 121.9, 122.0, 128.6, 129.4, 130.3, 131.7, 136.2, 139.3, 140.7 (C_{arom}), 161.4 (*N* = C−NH), 195.3 (*C*=O); MS *m*/*z* 361 (M^+, 6), 346 (42), 264 (55), 237 (30), 172 (12), 105 (65), 91 (35), 77 (100), 55 (67), 41 (85); Anal. Calcd for $C_{23}H_{27}N_3O$ C 76.42, H 7.53, N 11.62; found C 76.40, H 7.54, N 11.65.

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

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