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Novel Syntheses of Tetrahydrobenzodiazepines and Dihydropyrazines via Isocyanide-Based Multicomponent Reactions of Diamines

Ahmad Shaabani,*,† Ali Maleki,† Fatemeh Hajishaabanha,† Hamid Mofakham,† Mozhdeh Seyyedhamzeh,† Mojtaba Mahyari,† and Seik Weng Ng‡

Department of Chemistry, Shahid Beheshti University, 19396-4716, Tehran, Iran, and Department of Chemistry, University of Malaya, 50603, Kuala Lumpur, Malaysia

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In this work, two novel isocyanide-based multicomponent reactions of 1,2-diamine compounds with diketene have been developed as efficient strategies for the synthesis of 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamides with regiochemical control and 1,6-dihydropyrazine-2,3-dicarbonitriles in good to excellent yields at ambient temperature.

Introduction

Benzodiazepines[1] and pyrazines[2] are widely used in medicinal chemistry. Benzodiazepines as one of the most widely prescribed class of psychotropics,[3] which have remarkable central nervous system depressant activity,[4] with various biological interest[5] have been extended to various diseases such as cancer,[6] viral infection (HIV),[7] and cardiovascular disorders.[8] Pyrazines, which are biosynthesized from amino acids, are common units in a wide variety of marine natural products showing cytostatic and antitumor properties,[9] and pyrazinamides[10] as well as pyrazinesters[11] have been successfully evaluated in vitro and in vivo for antituberculosis activity. 2,3-Dicyanopyrazines are very useful starting materials for subsequent heterocyclization such as azaphthalocyanines,[12] tetrazoles,[13] and nucleophilic substitutions of a nitrile and polycyclic quinoxalines.[14]

Diazepam **I** is the first marketed drug of benzodiazepine derivatives possessing anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, and amnestic properties.[15] The benzodiazepine core is indeed a "privileged scaffold"[16] found in compounds active against a variety of target types including therapeutic and prophylactic agent for diabetes, diabetic nephropathy, or glomerulosclerosis **II**[17] and peptide hormones **III**.[18] CB1 Cannabinoid receptor antagonists **IV**[19] are another example of six-membered ring analogs from pyrazine heterocycles (Figure 1).

Recently, benzodiazepines have been the object of intense investigations in organic synthesis and medicinal chemistry and several approaches have been reported for the synthesis of this heterocyclic compounds.[20] However, the development of new synthetic routes for the preparation of pyrazine and benzodiazepine derivatives acquired relevance in recent years.

In view of our current studies on isocyanide-based multicomponent reactions (IMCRs) of diamines[21] and diketene,[22] herein, we wish to report two hitherto unknown IMCRs which afford 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]-diazepine-2-carboxamides **4** with regiochemical control via a condensation reaction between an isocyanide **1**, diketene **2**, and an aromatic 1,2-diamine (AD) **3**. Alternatively, using 2,3-diaminomaleonitrile (DAMN) **5** instead of AD produces 1,6-dihydropyrazine-2,3-dicarbonitriles **6** in good to excellent yields at ambient temperature (Scheme 1).

Results and Discussion

In a pilot experiment, *o*-phenylenediamine, diketene, and cyclohexyl isocyanide were stirred in acetonitrile at room temperature. The progress of the reaction was monitored by TLC until *o*-phenylenediamine as limiting reactant of the reaction was consumed after 4 h. However, in the event, seven-membered ring compound **8a** was generated and nucleophilic attack by isocyanide did not occur. On the other hand, the predicted mechanism was not observed under the given reaction conditions, and the isolated product was 4-methyl-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one **8a**.

It is interesting to note that compound **8a** in the presence of *p*-TsOH·H_2O was reacted with isocyanide and produced the compound **4a** (Scheme 2).

To evaluate the use of this interesting approach, a variety of ADs carrying electron-releasing groups such as CH_3 (**4d**−**j**), electron-withdrawing groups such as COPh (**4k**) and halogenated diamines (**4l**−**n**), and aliphatic, alicyclic, and aromatic isocyanides were reacted under similar circumstances. The results are summarized in Table 1. The two-step reaction proceeded very efficiently under mild conditions at room temperature to produce the corresponding 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide derivatives **4a**−**n** in high yields. The structures of compounds **4a**−**n** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectral data.

The first step of this reaction was highly regioselective. It may be explained that the selectivity is due to the electronic effect of the electron-releasing groups such as CH_3 at the para position is activated exclusively, and product **8A** (not

* Corresponding author. E-mail: a-shaabani@cc.sbu.ac.ir.
† Shahid Beheshti University.
‡ University of Malaya.

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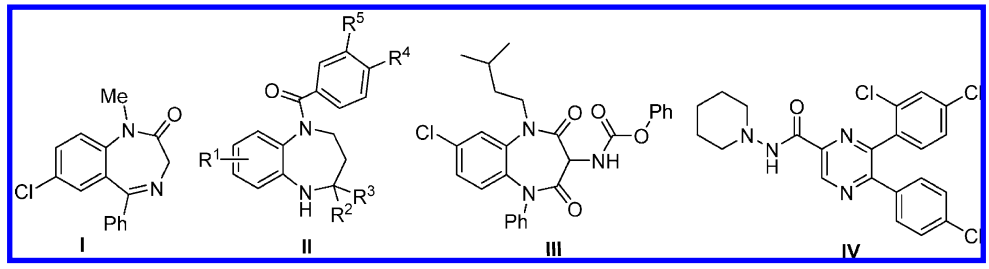
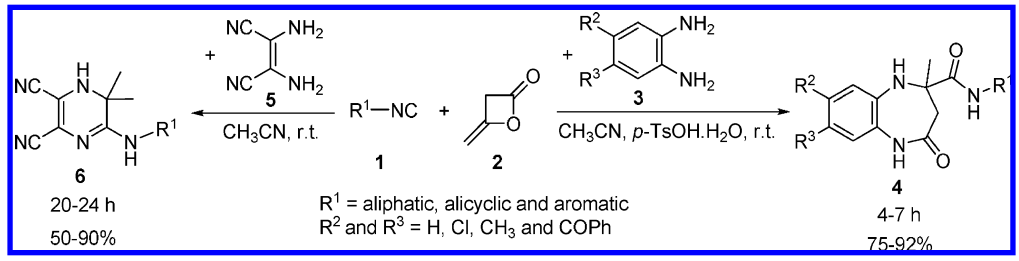


Figure 1. Examples of medicinal benzodiazepine and pyrazine derivatives.

Scheme 1. Synthesis of 2,3,4,5-Tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamides **4** and 1,6-Dihydropyrazine-2,3-dicarbonitriles **6**



Scheme 2. Synthesis of Compound **4a**

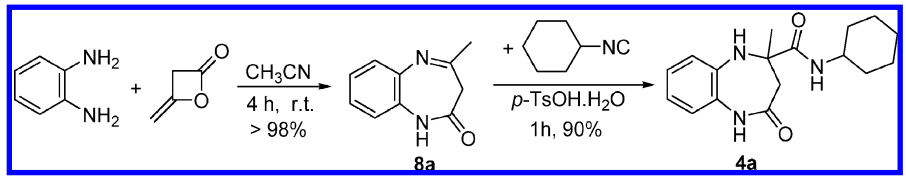


Table 1. Synthesis of 2,3,4,5-Tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamides **4a**−**n**

entry	isocyanide	diamine	product	time (h)	yield[a] (%)
1	cyclohexyl isocyanide	*o*-phenylenediamine	**4a**	5	90
2	*tert*-butyl isocyanide	*o*-phenylenediamine	**4b**	6	82
3	1,1,3,3-tetramethylbutyl isocyanide	*o*-phenylenediamine	**4c**	6	80
4	cyclohexyl isocyanide	4,5-dimethyl-*o*-phenylenediamine	**4d**	4	92
5	*tert*-butyl isocyanide	4,5-dimethyl-*o*-phenylenediamine	**4e**	4	88
6	1,1,3,3-tetramethylbutyl isocyanide	4,5-dimethyl-*o*-phenylenediamine	**4f**	5	80
7	2,6-$(Me)_2$phenyl isocyanide	4,5-dimethyl-*o*-phenylenediamine	**4g**	5	86
8	benzyl isocyanide	4,5-dimethyl-*o*-phenylenediamine	**4h**	5	85
9	cyclohexyl isocyanide	4-methyl-*o*-phenylenediamine	**4i**	5	90
10	benzyl isocyanide	4-methyl-*o*-phenylenediamine	**4j**	6	85
11	cyclohexyl isocyanide	3,4-diaminobenzophenone	**4k**	7	75
12	cyclohexyl isocyanide	4,5-dichloro-*o*-phenylenediamine	**4l**	7	87
13	1,1,3,3-tetramethylbutyl isocyanide	4,5-dichloro-*o*-phenylenediamine	**4m**	7	80
14	benzyl isocyanide	4,5-dichloro-*o*-phenylenediamine	**4n**	7	80

[a] Isolated yield.

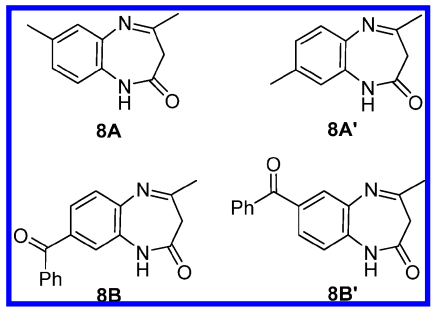


Figure 2. Structure of intermediate products.

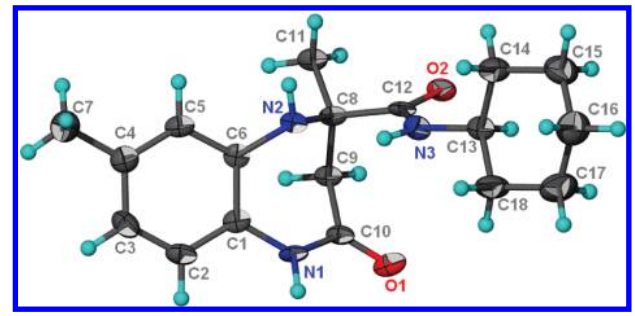


Figure 3. ORTEP diagram for **4i**.

8A′) is formed. While in the case of electron-withdrawing groups such as COPh, which deactivate the para amino group, the reaction is initiated by the meta amino group to give **8B** (not **8B′**) as the favored product (Figure 2).

The structure of the product **4i** was confirmed unambiguously by single-crystal X-ray analysis (Figure 3).

In addition, three substituents in the products can be varied to yield diversity of molecules for chemical library. Representative examples of this reaction are shown in Figure 4.

The suggested mechanism for the formation of products **4a**−**n** is illustrated in Scheme 3. It is conceivable that, the initial event is the formation of β-keto amide **7** from

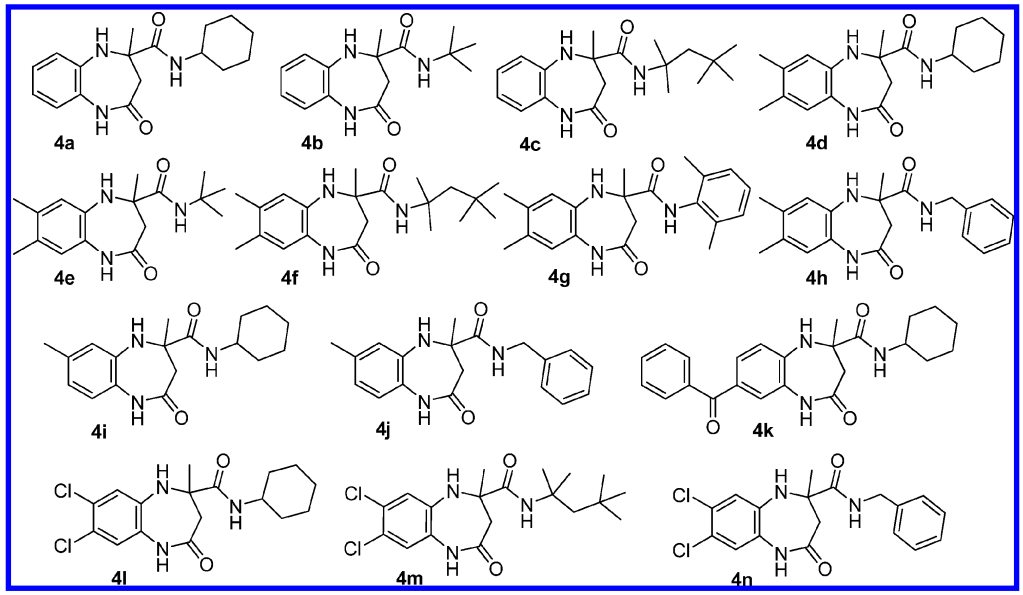
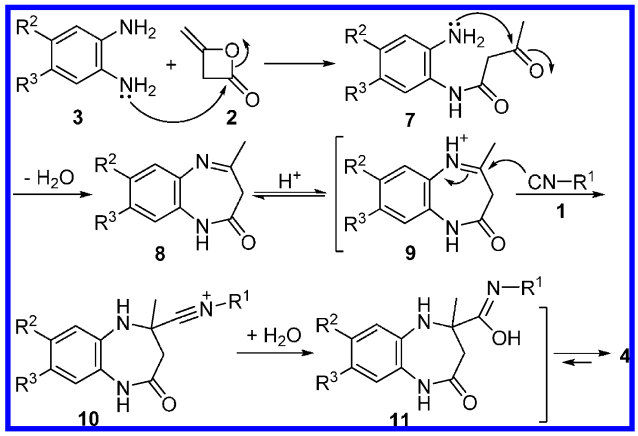


Figure 4. Structure of 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamides **4a**−**n**.

Scheme 3. Possible Mechanism for the Formation of Products **4a**−**n**



nucleophilic attack of **3** to the carbonyl (lactone) site of **2**. The product **8** was formed by intramolecular nucleophilic attack of amine to ketone. On the basis of the well-established chemistry of reaction of isocyanides with imines,[23] intermediate **10** was produced by nucleophilic attack of isocyanide **1** to activated iminium **9** followed by nucleophilic attack of an H_2O molecule on the nitrilium moiety and production of compound **11**. Finally, tautomerization of intermediate **11** produces 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide derivatives **4a**−**n**.

In order to investigate the scope and limitations of this reaction, we decided to extend it to 2,3-diaminomaleonitrile (DAMN) instead of aromatic 1,2-diamines (ADs). In this regard, DAMN, diketene, and cyclohexyl isocyanide in acetonitrile were stirred at room temperature. The progress of the reaction was monitored by TLC. After 20 h, the reaction was completed and 5-(cyclohexylamino)-6,6-dimethyl-1,6-dihydropyrazine-2,3-dicarbonitrile **6a** was obtained in 90% yield. To evaluate the use of this approach, a variety of aliphatic, alicyclic, and aromatic isocyanides as a third component of this reaction was condensed under similar circumstances. The results are shown in Table 2, and the structures of the products 1,6-dihydropyrazine-2,3-dicarbonitriles **6a**−**e** are demonstrated in Figure 5.

Table 2. Synthesis of 1,6-Dihydropyrazine-2,3-dicarbonitrile Derivatives **6a**−**e**

entry	isocyanide	product	time (h)	yield[a] (%)
1	cyclohexyl isocyanide	**6a**	20	90
2	*tert*-butyl isocyanide	**6b**	24	85
3	1,1,3,3-tetramethylbutyl isocyanide	**6c**	24 (15)[b]	50 (85)[b]
4	ethyl 2-isocyanoacetate	**6d**	24	85
5	benzyl isocyanide	**6e**	24	85

[a] Isolated yield. [b] Under refluxing conditions.

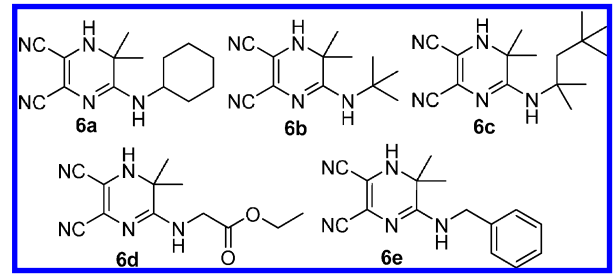
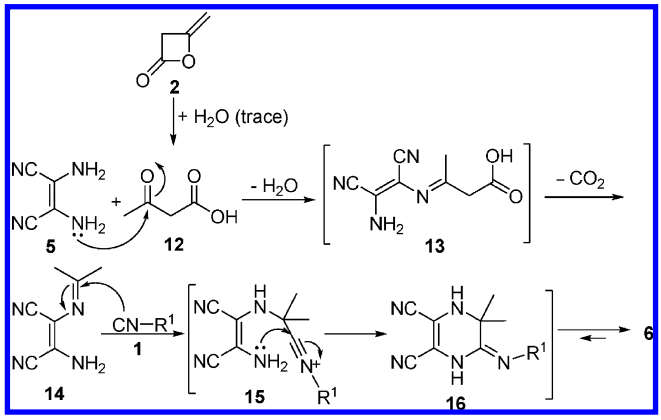


Figure 5. Structure of 1,6-dihydropyrazine-2,3-dicarbonitriles **6a**−**e**.

This reaction proceeded very cleanly under mild conditions at room temperature and no undesirable side reactions were observed. The reaction was compatible with a wide range of isocyanides. Treatment of *tert*-butyl-, 2,6-dimethylphenyl-, and benzyl isocyanides, and ethyl 2-isocyanoacetate with DAMN in the presence of diketene in acetonitrile at ambient temperature led to the formation of the corresponding 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in high yields. Only, in the case of 1,1,3,3-tetramethylbutyl isocyanide after 24 h, the reaction yield was 50%. It is important to note that, when this reaction was performed under reflux conditions in CH_3CN, yield of the reaction increased to 85% after 15 h (Table 2, entry 3).

The possible mechanism for the formation of products **6a**−**e** is shown in Scheme 4. It is very interesting that the initial event is the formation of acetoacetic acid **12** from the reaction of diketene **2** with trace water of the reaction media.[24] Then, the intermediate **13** was produced from the nucleophilic attack of DAMN **5** to the ketone site of **12**.

Scheme 4. Possible Mechanism for the Formation of Products **6a**−**e**



Imine **14** was obtained through decarboxylation of **13**.[24] On the basis of the well established chemistry of the reaction of isocyanides with imines,[23] intermediate **15** was produced by nucleophilic attack of isocyanide **1** to imine **14**, followed by an intramolecular nucleophilic attack by the NH_2 group on the activated nitrile moiety, intermediate **16** is produced. Finally, imine-enamine tautomerization of intermediate **16** produces 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives **6a**−**e**.

Conclusions

In summary, we have developed a novel one-pot two-step protocol for the synthesis of 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide derivatives with regiochemical control and a novel one-pot IMCR for the synthesis of 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives from condensation reactions between diketene, various isocyanides, and aromatic 1,2-diamines or 2,3-diaminomaleonitrile, respectively. We showed that diketene participates in two different ways in reactions with diamines and isocyanides. These two novel reactions can be regarded as efficient approaches for the preparation of pharmaceutically relevant tetrahydrobenzodiazepine and dihydropyrazine derivatives in good to excellent yields at ambient temperature.

Experimental Section

Typical Procedure for the Synthesis of *N*-Cyclohexyl-2-methyl-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide (4a). A solution of *o*-phenylenediamine (0.108 g, 1 mmol) and diketene (0.084 g, 1 mmol) was stirred in 3 mL of CH_3CN for 4 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2/1), cyclohexyl isocyanide (0.109 g, 1 mmol) and *p*-TsOH·H_2O (0.195 g, 1 mmol) were added to the mixture. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1) after 1 h, the compound **4a** was produced. After that, the precipitate was filtered off and washed with water, and then crystallized from acetone to give **4a** as colorless crystals. mp 263−265 °C. IR (KBr) cm^{-1}: 3347, 3295, 3200, 3139, 3087, 2926, 2851, 1675, 1634, 1597, 1526, 1449, 1376. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00−1.70 (13H, m, $5CH_2$ of cyclohexyl and CH_3), 2.39 (2H, br s, CH_2), 3.52 (1H, m, CH of cyclohexyl), 5.34 (1H, br s, NH), 6.85 (2H, br s, H−Ar), 6.95 (2H, br s, H−Ar), 7.64 (1H, br s, NH−CO), 9.55 (1H, br s, NH−CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.9, 25.0, 25.6, 26.6, 32.6, 32.8, 43.4, 48.2, 67.7, 121.9, 122.0, 122.6, 125.0, 131.3, 138.7, 170.4, 173.2. MS *m*/*z*: 302 ($M^+ + 1$, 30), 175 (100), 133 (85), 55 (14), 41 (23). Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94; found C, 67.65; H, 7.74; N, 13.84.

Typical Procedure for the Synthesis of 5-(Cyclohexylamino)-6,6-dimethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (6a). A solution of DAMN (0.108 g, 1 mmol), diketene (0.084 g, 1 mmol), and cyclohexyl isocyanide (0.109 g, 1 mmol) in 3 mL of CH_3CN was stirred for 20 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), the precipitate was filtered off, and then crystallized from acetone to give **6a** as colorless crystals. mp 252−254 °C. IR (KBr) cm^{-1}: 3343, 3081, 2931, 2852, 2217, 1579, 1539, 1451, 1391. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00−2.10 (16H, m, $5CH_2$ of cyclohexyl and $2CH_3$), 3.69 (1H, m, CH of cyclohexyl), 6.86 (1H, d, J = 7.6 Hz, NH), 7.12 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.3, 25.2, 25.7, 31.9, 49.6, 50.0, 110.2, 110.8, 114.9, 118.4, 155.8. MS *m*/*z*: 257 (M^+, 20), 242 (25), 175 (25), 160 (100), 133 (22), 57 (45), 41 (75). Anal. calcd for $C_{14}H_{19}N_5$: C, 65.34; H, 7.44; N, 27.22; found C, 65.28; H, 7.33; N, 27.20.

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Supporting Information Available. Experimental procedures, Mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4a**−**n**, **6a**−**e**, and **8d**−**h**, and crystallographic data for **4f** and **4i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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