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A Novel One-Pot Pseudo-Five-Component Synthesis of 4,5,6,7-Tetrahydro-1*H*-1,4-diazepine-5-carboxamide Derivatives

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A novel one-pot pseudo-five-component synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives starting from simple and readily available inputs including 2,3-diaminomaleonitrile, a cyclic or acyclic ketone, an isocyanide, and water in the presence of a catalytic amount of *p*-toluenesulfonic acid in aqueous medium at ambient temperature in high yields is described.

Sequential transformations and one-pot multicomponent reactions (MCRs) are always resource effective and environmentally acceptable and thus greener as compared to multistep reactions.[1] They offer significant advantages over conventional linear step syntheses, by reducing time and saving money, energy, and raw-materials thus resulting in both economical and environmental benefits. At the same time, diversity can be achieved for building up libraries by simply varying each component.[1] Because of the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (I-MCRs) are among the most versatile, in terms of the number and variety of compounds which can be generated.[1]

Spirocyclic structures are found in wide range of natural compounds isolated from various sources.[2] The complexity of these ring structures is represented by the quaternary carbon center and two fused rings. Stereoselective methodologies for the construction of the spirocenter have allowed total syntheses of many spirocenter-containing natural compounds over the years. On the other hand, spirocyclic systems are structurally interesting.[3]

2,3-Diaminomaleonitrile (DAMN)[4] was considered as one of the versatile precursors for the synthesis of various types of nitrogen heterocycles such as imidazoles,[5] oxazoles,[6] purines,[7] pyrroles,[8] pyrimidines,[9] pyrazines,[10] diazepines,[11] and triazepines.[5,12] Although many reactions of DAMN have been reported under classical two-component reactions,[4] to the best of our knowledge, only one reaction of it with isocyanides under MCR strategy has been studied.[13a]

In continuing our interest in I-MCRs,[13] here we report a hitherto unknown reaction that affords 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives **5a**−***l*** especially spirocyclic 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide-2,3-

TABLE 1. Synthesis of 4,5,6,7-Tetrahydro-1*H*-1,4-diazepine-5-carboxamide Derivatives 5a−*l*

entry	ketone	isocyanide	product	time (h)	yield[a] (%)
1	cyclohexanone	cyclohexyl	**5a**	16	92
2	cyclohexanone	*tert*-butyl	**5b**	18	84
3	cyclopentanone	cyclohexyl	**5c**	20	82
4	cyclopentanone	*tert*-butyl	**5d**	20	80
5	4-*tert*-butylcyclohexanone	cyclohexyl	**5e**	16	85
6	cyclohexanone	benzyl	**5f**	24	85
7	cyclopentanone	1,1,3,3-Tetramethyl-butyl	**5g**	24	80
8	acetophenone	cyclohexyl	**5h**	24	82
9	4′-methylacetophenone	cyclohexyl	**5i**	24	84
10	4′-bromoacetophenone	cyclohexyl	**5j**	22	90
11	acetone	cyclohexyl	**5k**	20	92
12	acetone	*tert*-butyl	**5l**	20	90

[a] Isolated yield.

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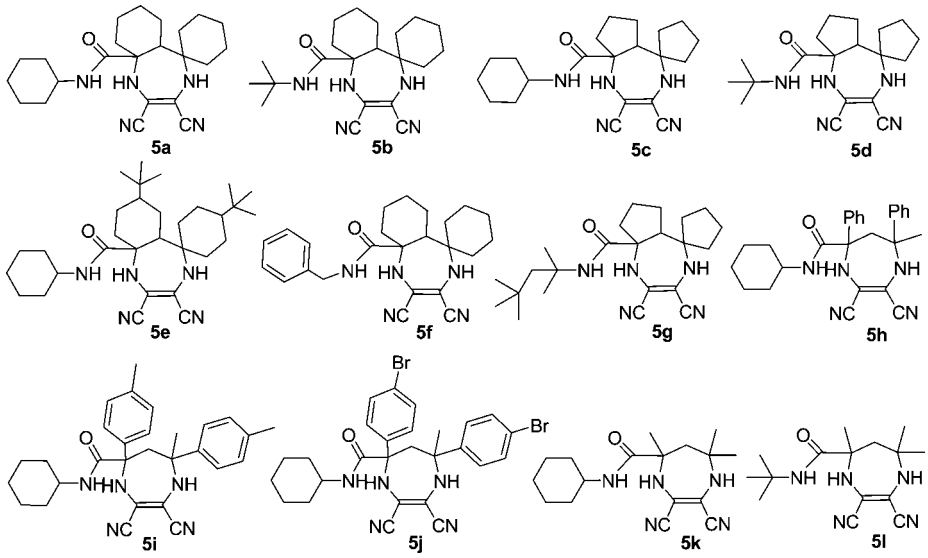
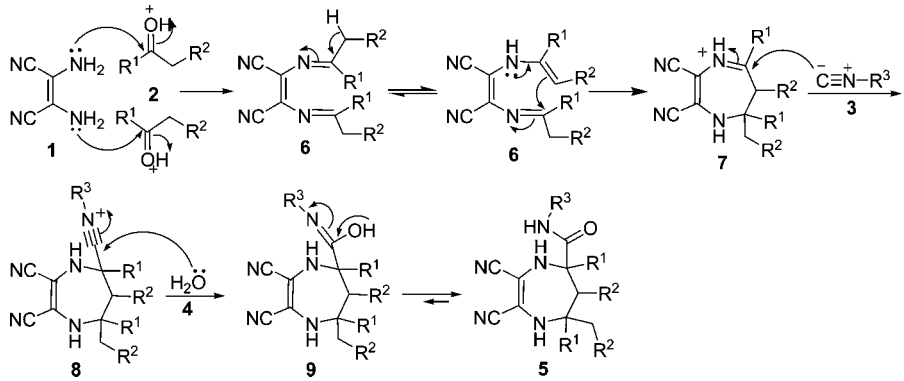
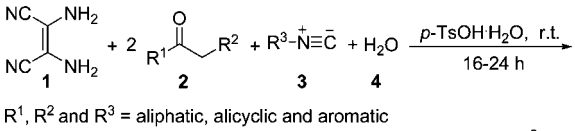


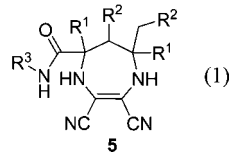
FIGURE 1. The structure of products **5a**−*l*.

SCHEME 1. Possible Mechanism for the Formation of Products 5a−*l*



dicarbonitriles **5a**−**g** via the one-pot pseudo-five-component condensation of 2,3-diaminomaleonitrile **1**, a cyclic or acyclic ketone **2**, an isocyanide **3**, and water **4** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in water at ambient temperature in high yields (eq 1).





(1)

In a pilot experiment, 2,3-diaminomaleonitrile and cyclohexanone were stirred in water at room temperature with a catalytic amount of *p*-toluenesulfonic acid. The progress of the reaction was monitored by TLC. After 4 h, cyclohexyl isocyanide was added to the reaction mixture and stirring was continued for 12 h. After completion of the reaction, an aqueous workup afforded compound **5a** in 92% yield.

In view of the success of the above reaction, we explored the scope of this promising reaction by varying the structure of the ketone and isonitrile component (Table 1). The reaction proceeds very cleanly under mild conditions at room temperature and no undesirable side reactions were observed under these reaction conditions. Representative structures of products are shown in Figure 1.

The possible mechanism for the formation of products **5a**−*l* is shown in Scheme 1. It is conceivable that the initial event is the formation of diimine **6** from condensation between DAMN and ketones.[1,14] Then an intramolecular imine−enamine cyclization of **6** affords seven-membered ring **7**.[5c,10a,15] On the basis of the well-established chemistry of reaction of isocyanides with imines,[1] intermediate **8** was produced by nucleophilic attack of isocyanide **3** to iminium **7** followed by nucleophilic attack of an H_2O molecule on the nitrilium moiety and production of compound **9**. Finally, tautomerization of intermediate **9** produces the 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives **5a**−*l*.

It is important to note that the proposed mechanism is supported by characterization of isolated seven-member-ring intermediate **7** by mass spectroscopy, IR, ^{1}H NMR, and ^{13}C NMR spectra (see the Supporting Information). Finally, the structure of **5a** was confirmed unambiguously by single-crystal X-ray analysis (see the Supporting Information).[16]

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The ^{1}H NMR of crude product of **5a** showed only one stereoisomer. The molar ratio of the second stereoisomer of compounds **5h** to **5j** was negligible to estimate its molar ratio by ^{1}H NMR.

In conclusion, we have discovered a novel pseudo-five-component condensation reaction leading to 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives starting from simple and readily available precursors. This novel reaction can be regarded as a new approach for the preparation of synthetically and pharmaceutically relevant spirocyclic systems. This reaction includes some important aspects like the use of water as a reaction component and a "green" reaction medium, high atom economy, and mild reaction conditions.

Experimental Section

Typical Procedure for the Synthesis of Compound 5a. First, a solution of DAMN (0.108 g, 1 mmol) and cyclohexanone (0.196 g, 2 mmol) in the presence of *p*-TsOH.H_2O (0.095 g, 5 mol%) was stirred for 4 h in 5 mL of H_2O at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2/1; R_f 0.45), cyclohexyl isocyanide (0.109 g, 1 mmol) was added to the reaction mixture. Then the resulting mixture was stirred for 12 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1; R_f 0.35), the product was filtered off, washed further with water, and then crystallized from acetone to give **5a** as colorless crystals (0.363 g, 92%): mp 181−184 °C. IR (KBr) cm^{-1} 3382, 3295, 2933, 2853, 2220, 2202, 1634, 1617, 1543, 1446. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 1.00−2.00 (28H, m), 2.20−2.30 (1H, m), 3.55 (1H, m), 4.68 (1H, m), 5.87 (1H, m), 7.00 (1H, br s). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.1, 21.4, 21.5, 23.9, 25.2, 25.6, 25.7, 26.0, 32.3, 32.6, 36.3, 38.6, 47.6, 48.2, 59.8, 65.0, 105.7, 113.4, 117.0, 118.0, 174.6. MS *m*/*z* 396 ($M^+ + 1$, 30), 298 (100), 269 (84), 208 (15), 98 (18), 81 (22), 67 (20), 55 (50), 41 (55). Anal. Calcd for $C_{23}H_{33}N_5O$: C, 69.84; H, 8.41; N, 17.71. Found C, 69.81; H, 8.43; N, 17.72.

Typical Procedure for the Synthesis of Compound 5*l*. First, a solution of DAMN (0.108 g, 1 mmol) and acetone (0.116 g, 2 mmol) in the presence of *p*-TsOH.H_2O (0.095 g, 5 mol%) was stirred for 5 h in 5 mL of H_2O at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2/1; R_f 0.50), *tert*-butyl isocyanide (0.083 g, 1 mmol) was added to the reaction mixture. Then the resulting mixture was stirred for 15 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1; R_f 0.40), the product was filtered off, washed further with water, and then crystallized from acetone to give ***5l*** as colorless crystals (0.260 g, 90%): mp 164−166 °C. IR (KBr) cm^{-1} 3415, 3320, 2978, 2927, 2857, 2216, 1664, 1622, 1511, 1453. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 1.07−1.24 (18H, m), 1.50 (1H, d, J = 13.9 Hz), 2.40 (1H, d, J = 14.2 Hz), 5.75 (2H, br s), 6.81 (1H, br s). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 28.7, 28.9, 29.6, 32.1, 47.9, 50.8, 54.5, 62.5, 108.6, 111.2, 117.2, 117.8, 173.9. MS *m*/*z* 290 ($M^+ + 1$, 10), 234 (2), 189 (100), 133 (60), 59 (24), 43 (50). Anal. Calcd for $C_{15}H_{23}N_5O$: C, 62.26; H, 8.01; N, 24.20. Found C, 62.33; H, 7.94; N, 24.35.

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Supporting Information Available: Crystallographic data for **5a** (CIF), experimental procedures, and mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **5a**−***l*** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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