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A Novel One-Pot Three-(*in Situ* Five-)Component Condensation Reaction: An Unexpected Approach for the Synthesis of Tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide Derivatives

Ahmad Shaabani,*,† Ali Hossein Rezayan,† Sajjad Keshipour,† Afshin Sarvary,† and Seik Weng Ng‡

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

a-shaabani@cc.sbu.ac.ir

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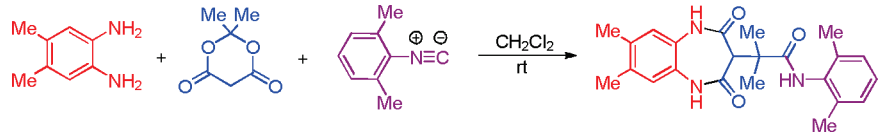
ABSTRACT



A novel and efficient method has been developed for the synthesis of tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide derivatives using an aromatic diamine, Meldrum's acid, and an isocyanide in CH_2Cl_2 at ambient temperature in high yields without using any catalyst or activation. The procedure provides an alternative method for the synthesis of benzo[*b*][1,5]diazepine derivatives. These compounds have closely related ring systems such as triflubazam, clobazam, and 1,5-benzodiazepines, which have a broad spectrum of biological activities.

Benzodiazepines have been an important pharmacophore in the pharmaceutical industry.[1] The therapeutic applications of benzodiazepines include anxiolytics,[2] antiarrhythmics,[3] vasopressin antagonists,[4] HIV reverse transcriptase inhibitors,[5] and cholecystokinin antagonists.[6] Molecules with the 1,5-benzodiazepin-2-one scaffold are privileged substructures exhibiting a range of biological activities. Some of them have been clinically used as anxiolytic agents, such as triflubazam **A**[7] and clobazam **B**.[8] Furthermore, they exhibit activities including interleukin-1β converting enzyme inhibition, such as **C**,[9] and 3-(aryloxycarbonyl)amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine **D**[10] as a cholecystokinin-B receptor antagonists (Figure 1). On the other hand, two recently published patents indicate that tetrahydro-1*H*-1,5-benzodiazepine derivatives carrying carboxamide

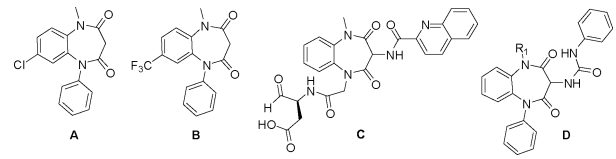


Figure 1. Examples of some biologically active benzodiazepine derivatives.

† Shahid Beheshti University.
‡ University of Malaya.

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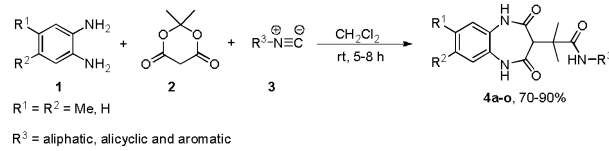
substituents are potentially important as a therapeutic and prophylactic agents for diabetes, diabetic nephropathy, or glomerulosclerosis.[11] Some research has been undertaken on the benzodiazepine-3-carboxamide derivatives. These compounds have been synthesized via multistep approach in the presence of expensive catalysts under sensitive conditions.[1d,7−10] Therefore, development of a synthetic method that could be used to prepare a variety of these templates remains an important task.

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. Such reactions are atom-efficient processes by incorporating the essential parts of the starting materials into the final product. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[12] Recently, the pharmaceutical industries have focused more and more on diversity oriented and biased combinatorial libraries.[13] Furthermore, the discovery of novel MCRs can be considered as an interesting topic for academic research, which also satisfies a practical interest of applied science.[14]

Recently, our reserch group reported the synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamides, 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamides, fully substituted 3,4-dihydrocoumarins, highly substituted quinolizines, 4*H*-furo[3,4-*b*]pyrans, pyrano[2,3-*c*]pyrazoles, amides, fully substituted imino and spiroiminocyclopentenes, 2,5-dihydro-2-methylfuran-3,4-dicarboxylates, and bis(4*H*-chromene-) and 4*H*-benzo[*g*]chromene-3,4-dicarboxylate libraries using isocyanide-based multicomponent reactions.[15]

Herein, we wish to report a novel and efficient method to prepare tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methyl propanamide derivatives **4a**−**o** via the one-pot condensation of an aromatic diamine **1**, Meldrum's acid **2**, and an isocyanide **3** in CH_2Cl_2 at ambient temperature in high yields (Scheme 1). This route permits us to introduce great molecular diversity under mild reaction conditions, including substitution and scaffold diversity. A large number of derivatives can be rapidly synthesized in excellent purity and high yield by using this method.

Scheme 1. Synthesis of Tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide Derivatives **4a**−**o**



The reaction is straightforward, and treatment of various alkyl, aryl, and alicyclic isocyanides and various *o*-phenylenediamines with Meldrum's acid in CH_2Cl_2 at room temperature led to the formation of the tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide derivatives in high yields.

The structure of compounds **4a**−**o** was deduced from their IR, mass,^{1}H NMR, ^{13}C NMR, and HMQC spectra data for **4f**. For example, the ^{1}H NMR spectrum of **4f** exhibited a multiplet for the cyclohexyl ring and two methyl groups at $\delta = 1.19-2.07$, a singlet identified as methyl group at $\delta = 2.27$, a broad singlet at $\delta = 3.46$ for C*H*-NH of cyclohexyl, a multiplet at $\delta = 6.92-7.00$ for H-aromatic and -NH of amide, and a broad singlet at $\delta = 10.26$ for two NH groups. The ^{1}H-decoupled ^{13}C NMR spectrum of **4f** showed 17 distinct resonances in agreement with the proposed structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

Finally, the structure of the product **4a** was confirmed unambiguously by single-crystal X-ray analysis (Figure 2).

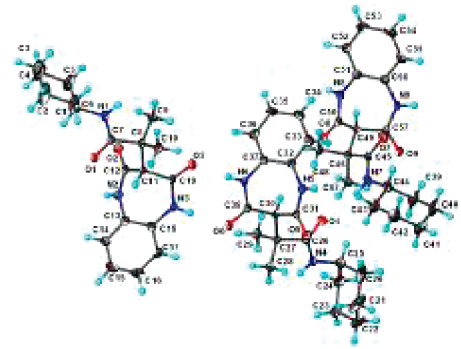


Figure 2. ORTEP diagram for **4a**.

In view of the success of the above-mentioned reaction, we explored the scope of this promising reaction by varying

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the structure of the *o*-phenylenediamine and isocyanide component. As indicated in Figure 3, the reaction proceeds

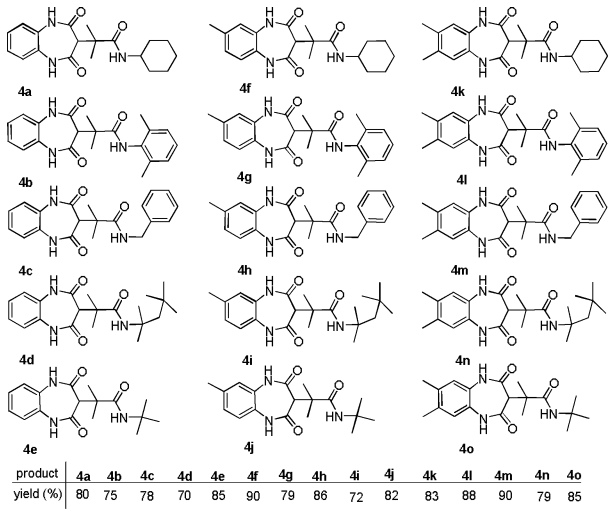
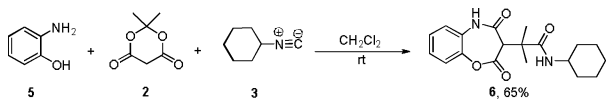


Figure 3. Synthesis of tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide derivatives **4a**−**o**.

very cleanly under mild reaction conditions at room temperature, and no undesirable byproduct was observed. Owing to the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries. In this reaction, when 4-nitrobenzene-1,2-diamine and (3,4-diaminophenyl)(phenyl)methanone were used, the desired reaction did not proceed after 24 h.

The versatility of this multicomponent reaction with respect to the *o*-phenylenediamine **1** was also studied (Scheme 2). As indicated in Scheme 2, 2-aminophenol **5** and

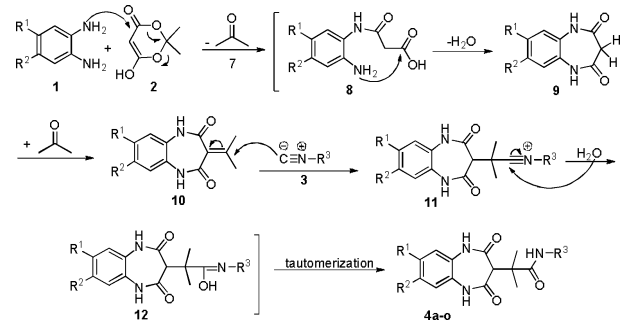
Scheme 2. Use of 2-Aminophenol Instead of *o*-Phenylenediamine



Meldrum's acid **2** with cyclohexyl isocyanides **3** in CH_2Cl_2 led to the formation of *N*-cyclohexyl-2-(2,3,4,5-tetrahydro-7-methyl-2,4-dioxobenzo[*b*][1,5]oxazepin-3-yl)-2-methylpropanamide **6** after 24 h. It should be mentioned that only cyclohexyl isocyanide could participate in this reaction.

A possible mechanism for the formation of products **4a**−**o** is shown in Scheme 3. It is conceivable that the initial event is the formation of 1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione **9**[16a,b] from condensation reaction between *o*-phenylenediamine and Meldrum's acid.[16c] Then, intermediate 1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione **9** under a Knoevenagel condensation reaction with in situ liberated acetone **7** produces the intermediate **10**.[17] On the basis of the well-

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

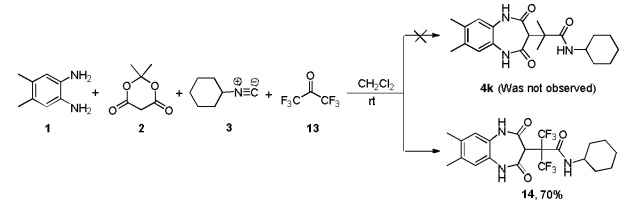


established chemistry of reaction of isocyanides with electron-deficient α,β-unsaturated carbonyl compounds,[18] intermediate **11** was produced by nucleophilic attack of an isocyanide **3** to 3-(propan-2-ylidene)-1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione **10** via a Michael-type addition reaction, followed by nucleophilic attack of a H_2O molecule on the nitrilium moiety to produce compound **12**. Finally, tautomerization of compound **12** produces the 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives **4a**−**o**.

To the best of our knowledge, this is the first report in which Meldrum's acid is decomposed to three parts (1,3-dicarbonyl moiety, acetone, and water) under mild reaction conditions, while all of them participate in the reaction, respectively.

To clarify the mechanism, the reaction of 4,5-dimethylbenzene-1,2-diamine **1**, Meldrum's acid **2**, and cyclohexyl isocyanide **3** in the presence of 1,1,1,3,3,3-hexafluoropropan-2-one **13** under the same reaction conditions was checked. As can be seen from Scheme 4, the desired product **14** was

Scheme 4. Clarification of the Mechanism



obtained. On the other hand, this result shows the 1,1,1,3,3,3-hexafluoropropan-2-one **13** was replaced with liberated acetone **7** from Meldrum's acid.

In conclusion, we have developed a novel one-pot three-(in situ five-)component condensation reaction leading to tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide derivatives starting from simple and readily available inputs under neutral conditions without any activation or modifications. Our literature survey shows that this is the first example in which Meldrum's acid is converted to three components such as 1,3-dicarbonyl moiety, acetone,

and water and all of them recombined in the reaction sequence, respectively. The reaction shows good functional group tolerance and is high-yielding, and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

Acknowledgment. We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supporting Information Available: Experimental procedures, characterization data and spectra of products, IR, mass, ^{1}H and ^{13}C NMR for **4a**−**o**, **6**, **14**, HMQC spectra for **4f**, ^{19}F NMR for **14**, and crystallographic data for **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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