Novel Approach to 1,5-Benzodiazepine-2-ones Containing Peptoid Backbone via One-Pot Diketene-Based Ugi-4CR

Nasrin Zohreh,[†] Abdolali Alizadeh,*[,†] Hamid Reza Bijanzadeh,[†] and Log-Guan Zhu[‡]

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran, and Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

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An efficient and simple route for preparation of substituted 1,5-benzodiazepine-2-one containing peptoid backbone is presented. The classical Ugi reaction is considerably extended by application of *o*-phenylenediamine and diketene as amine and oxo component. 1,3-Dihydro-1,5-benzodiazepine-2-one is generated in situ from these two building blocks combined with isocyanide and aromatic or aliphatic carboxylic acid to assemble the multifunctionalized titled scaffold in high yields. The reaction is performed in the mixture of toluene/CH_2Cl_2 under reflux condition without catalyst. Conformational isomerism is seen in the solution phase because of restricted free rotation around amide and C−CO bands due to steric bulk of substitutions. In single crystal state, the product is found to possess dimeric structure arising from intermolecular hydrogen bonding.

Introduction

The medicinal value of benzodiazepines is well documented. Benzodiazepines[1] have been important pharmacophores in pharmaceutical industry. Some of the therapeutic applications of benzodiazepines include vasopressin antagonists,[2a] HIV reverse transcriptase inhibitors,[2b] and cholecystokinin antagonists.[2c] In this class of compound, the 1,5-benzodiazepin-2-one is a privileged scaffold and compounds containing such substructures exhibit a range of biological activities. For instance, some of them have been clinically used as anxiolytic or antisecretory agents, such as lofendazam **1**[1,3] and telenzepine **2**[4] (Figure 1), respectively. In addition, they exhibit activities including interleukin-1b converting enzyme inhibition, delayed rectifier potassium current blocking,[5] and antiarrhythmic properties.[6] They are also known as active compounds against a variety of target types such as protease inhibitors and 7-TM receptors. For example, compound **3** is a CCK receptor antagonist (Figure 1).[7−9] Actually, less research has been undertaken on the 1,5-benzodiazepin-2-ones, compared to the 1,4-benzodiazepin-2-ones.

Multicomponent reactions (MCRs)[10] are, for their intimate nature, extremely convergent, producing a remarkably high increase of molecular complexity in just one step. The multicomponent reaction story began as far back as in 1850 by the publication of the Strecker reaction.[11] During this one and a half century period, some notable achievements include the discovery of Biginelli,[12] Mannich,[13] and Passerini[14] reactions culminating in 1959 when Ugi published[15] probably the most famous and versatile 4-CR based on the reactivity of isocyanides.[16] U-4CR is known to be one of the most versatile tools for construction of peptoid and mixed peptoid−peptide backbones. Peptoids[17] are a class of oligomeric *N*-alkyl-glycines that mimic the primary natural structure of peptides. Since the pioneering work of Ugi, many acyclic adducts, from the classical versions of this reaction, and interesting heterocyclic structures, using intramolecular variants or MCR coupling with subsequent secondary transformation, have been accessed, taking advantage of additional functionalities suitably placed on its components.[18]

Some of the most important diazepines are prepared using U-4CR.[19] To the best of our knowledge, there is no report for synthesis of 1,5-benzodiazepine-2-ones, which contain an α-amino-amide moiety and are peptoid products of U-4CR. In the context of our ongoing studies, we have devoted our investigations to synthesis of important acyclic and heterocyclic scaffolds via a diketene-based multicomponent reaction. These compounds have unique synthetic and pharmacological applications.[20] In this paper, we would like to report and describe a novel effort toward the synthesis of 1-aryl (or alkyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide **15** in high yield.

Results and Discussion

Recently, our research group reported synthesis of a novel series of 1,5-benzodiazepin-2-one with phosphite ylide **8** or phosphonate **9** substitutions (depending on the reaction conditions) from the reaction of *o*-phenylenediamine **4**, diketene **5**, dialkyl acetylenedicarboxylate **6**, and trialkyl phosphite **7** (Scheme 1).[20g]

We also have investigated synthesis of arylsulfonamide-substituted 1,5-benzodiazepine-2-one **11** by treatment of *o*-phenylenediamine **4** and diketene **5** with arylsulfonyl isocyanates **10** (Scheme 2). However, both of the mentioned reactions were performed under one-pot MCR. We purified and characterized the key intermediate of the two reactions as 1,3-dihydro-1,5-benzodiazepine-2-one **12**.[21]

* To whom correspondence should be addressed.
[†] Tarbiat Modares University.
[‡] Zhejiang University.

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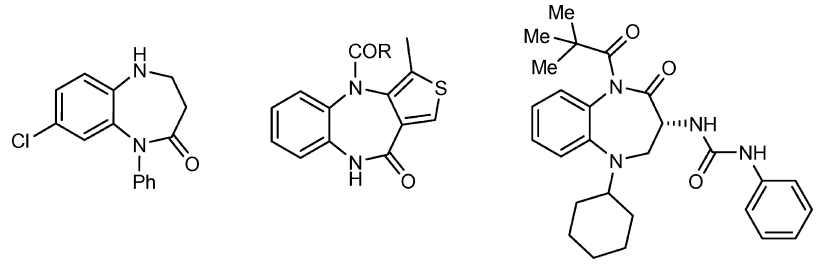
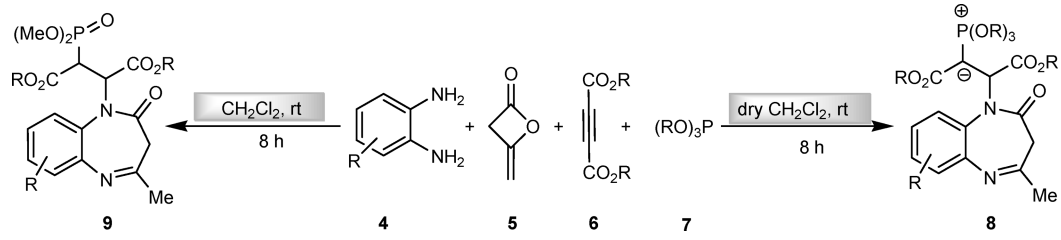
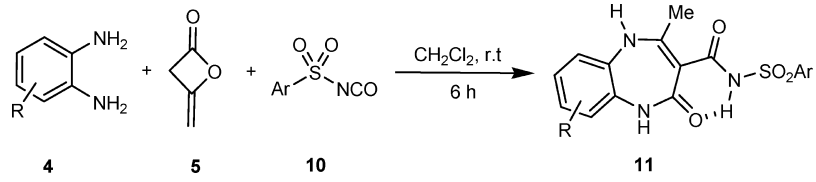


Figure 1. Examples of medicinal 1,5-benzodiazepine-2-one.

Scheme 1. Synthesis of 1,5-Benzodiazepin-2-ones with Phosphite Ylide **8** or Phosphonate **9** Substitutions



Scheme 2. Synthesis of Arylsulfonamide-Substituted 1,5-Benzodiazepine-2-ones



As shown in Figure 2, intermediate **12** is found to possess three different reactive sites. The first is the acidic hydrogen of an amide functional group used to trap the trialkyl phosphite-dialkyl acetylenedicarboxylate zwitterion (Scheme 1). The second is CH_2 nucleophilic carbon which gave rise to arylsulfonamide-substituted 1,5-benzodiazepine-2-one **11**. The other, and maybe the most important reactive site, is the imine functional group. This fact intrigued us to perform a Ugi reaction for preparation of substituted 1,5-benzodiazepine-2-one containing peptoid backbone **15**. As outlined in Scheme 3, the reaction of *o*-phenylenediamine **4** and diketene **5**, as amine and oxo components, with carboxylic acid **13** and cyclohexyl isocyanide **14** proceeds smoothly in the mixture of CH_2Cl_2/toluene at 25−120 °C to afford desired compound **15** in 70−80% yields after 8 h.

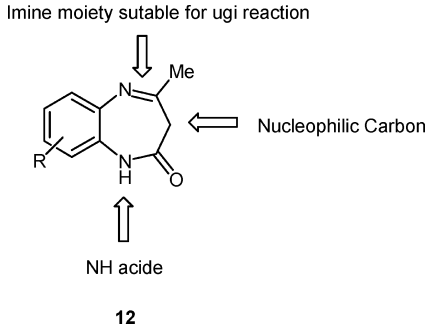


Figure 2. 1,3-Dihydro-1,5-benzodiazepine-2-one **12** as the key intermediate.

To investigate the scope of limitations of the reaction, we first decided to study the effect of the acid component using different types of aliphatic and aromatic carboxylic acid (Table 1, entries 1−5). It was found that the reaction was quite general toward the acid component. In view of the success of the above reactions, we then employed 4-methyl-*o*-phenylenediamine under a similar circumstance to evaluate the substrate scope and especially regioselectivity of this reaction. However, the reaction of 4-methyl-*o*-phenylenediamine, diketene, carboxylic acid, and cyclohexyl isocyanide led to the corresponding 1,5-benzodiazepine-2-one, but the reaction was not regioselective and the mixture of desired

Scheme 3. Synthesis of 1-Aryl (or Alkyl)-2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide **15** from the Reaction of *o*-Phenylenediamine **4**, Diketene **5**, and Carboxylic Acid **13** in the Presence of Cyclohexyl Isocyanide **14**

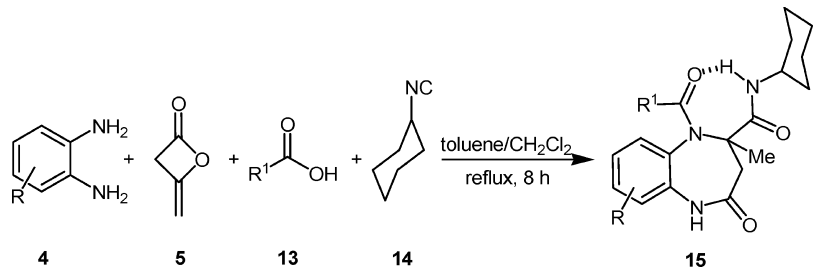


Table 1. 1,5-Benzodiazepin-2-one Derivatives Prepared by the Mentioned Reaction

entry	R	R^1	product	ratio of regioisomers	yield %
1	H	$PhCH_2$	**15a**		80
2	H	PhCH=CH	**15b**		75
3	H	Ph	**15c**		78
4	H	*p*-NO_2−C_6H_4	**15d**		75
5	H	2-Furyl	**15e**		77
6	Me	$PhCH_2$	**15f** and **15g**	67:33	72
7	Me	PhCH=CH	**15h** and **15i**	62:38	70
8	Me	*p*-NO_2−C_6H_4	**15j** and **15k**	60:40	75

1-alkyl (or aryl)-*N*^{2}-cyclohexyl-2,7 and 2,8-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide were produced (Table 1, entries 6−8). Sorrowfully, we were not able to isolate two regioisomers using usual column chromatography and crystallization by different solvent or solvent pairs. Unfortunately, attempts to perform the reaction with tertiarybutyl isocyanide failed to give the desired 1,5-benzodiazepin-2-one, probably because of its lower reactivity compared to cyclohexyl isocyanide.

The steric bulk of CO-R^1 and CO-NHCy substitutions on the 1 and 2 positions of the seven-membered ring of the products is enough to restrict the free rotation around N−CO amide and C−CO single bonds, resulting in conformational isomerism (Figure 3).

The mass spectrum of **15a** displayed a $M^+ + 1$ peak at *m*/*z* 420. Almost, for all of the products, initial fragmentation involved loss of the NH-Cy moiety that for **15a** was shown at 321. In the IR spectrum of **15a**, two absorption bands at 3395 and 3170, a broad band at 1667, and two absorption bands at 1584 and 1490 cm^{-1}, which are related to two NH, three NC=O, and aromatic stretching frequencies, clearly indicated the most significant functional groups of the product. However, the interconversion between these two rotamers is stopped at room temperature, and we were not able to isolate them. The presence of these two rotational isomers in $CDCl_3$ solvent (solution phase) is precisely confirmed by the ^1H and ^{13}C NMR spectra of **15a**−**k** where a set of peaks were detected for each of them. The ^1H NMR spectrum of **15a** exhibited two sharp singlet signals at 1.59 and 2.01 ppm, readily recognized as two methyl groups for two rotamers. Two

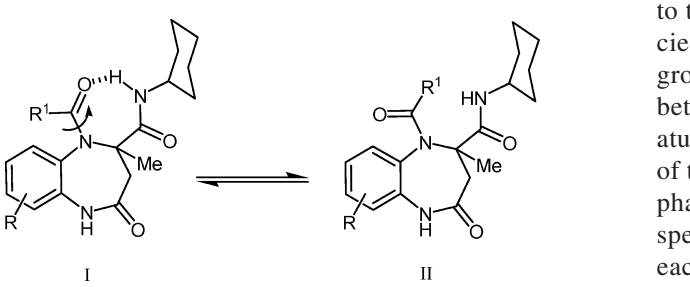


Figure 3. Structure of the two conformational isomerism in solution phase.

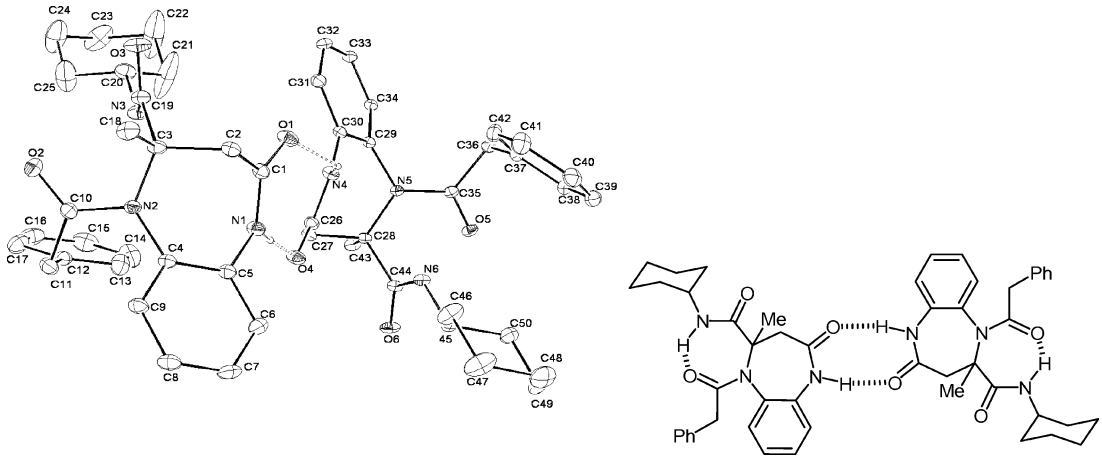
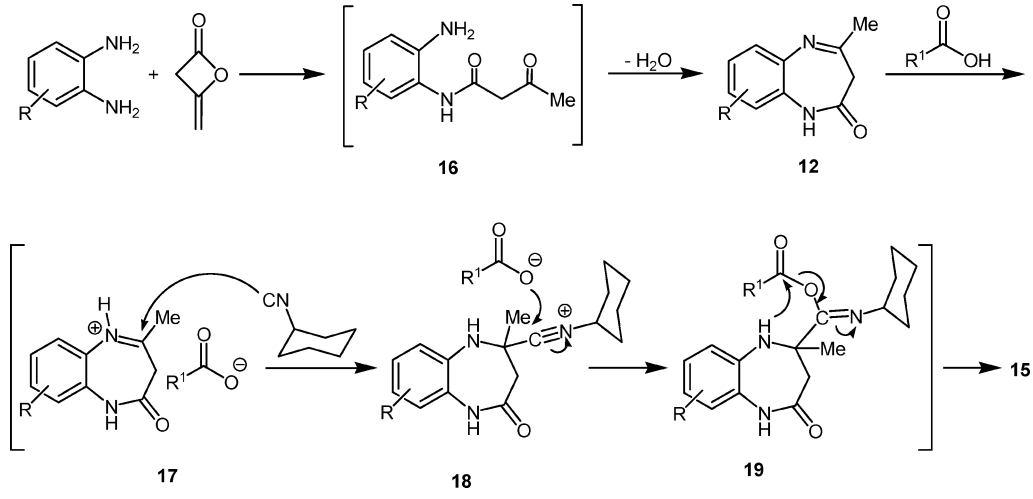


Figure 4. Structure of products in single crystal state and the ORTEP diagram of **15a**.

Scheme 4. Plausible Mechanism for the Formation of Substituted 1,5-Benzodiazepine-2-ones



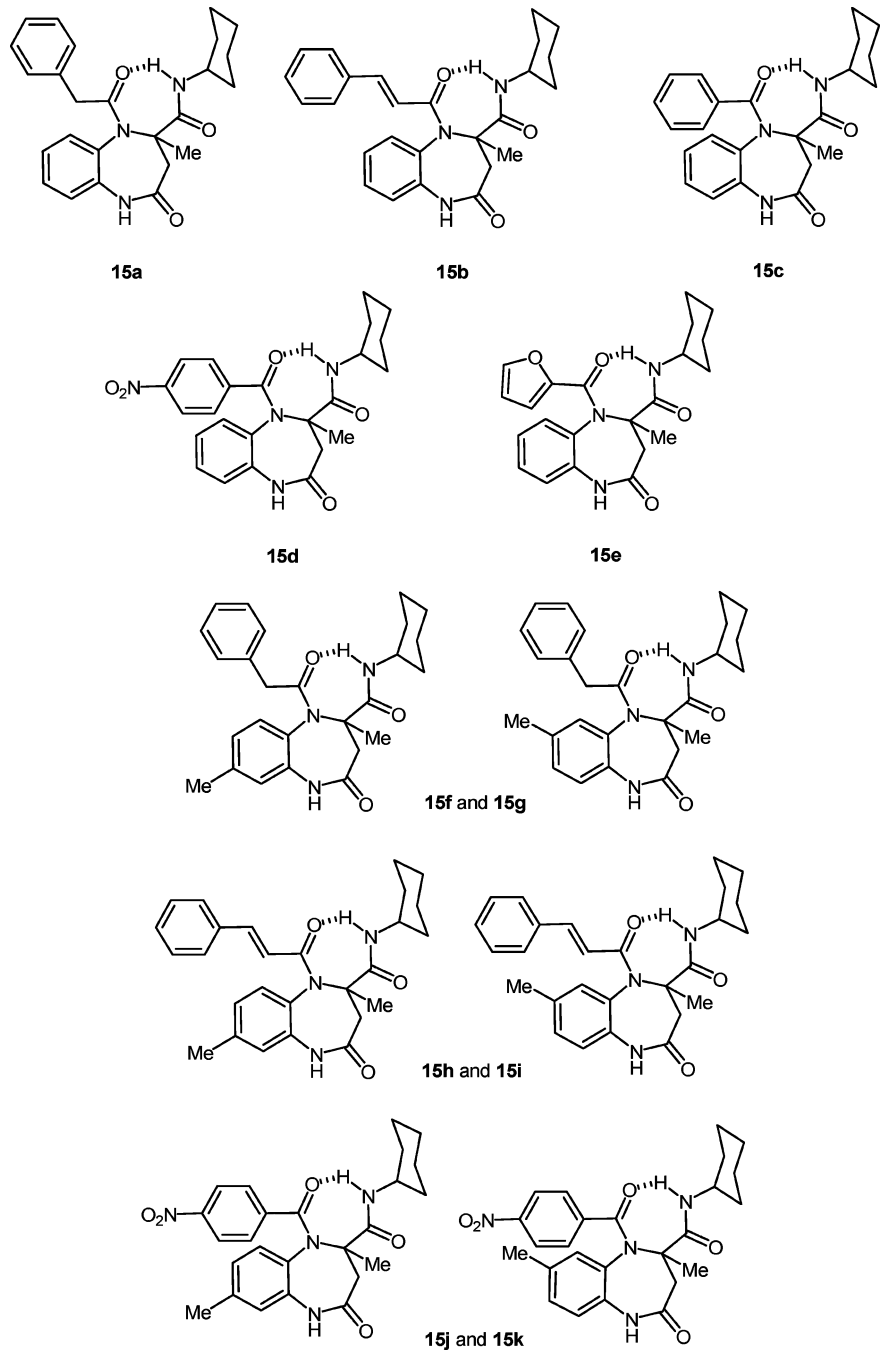


Figure 5. Structure of products **15a**−**k**.

sets of multiplets from 0.66−1.57 ppm and 1.60−1.90 ppm were attributed to the 10 methylenes (CH_2) of the two cyclohexyl groups. The CH_2 group of the seven-membered ring in one of the two rotamers appears as ABq at 2.42 ppm ($^2J_{HH}$ = 17.9 Hz), and the other CH_2 appears as two separated doublet peaks at 2.48 and 3.04 ppm ($^2J_{HH}$ = 14.2 and 13.7 Hz). The spectrum also contains another ABq at 3.32 ($^2J_{HH}$ = 15.1 Hz) and two doublets at 3.41 and 3.58 ppm ($^2J_{HH}$ = 14.1 Hz for both of them), which are attributed to diastereotopic hydrogens of the two CH_2Ph groups. There are two multiplet signals between 6.63 and 3.78 ppm which are related to two CHNH groups of cyclohexyls. For both of the rotamers, the signal corresponding to the NH group attached to cyclohexyl appears as two doublets at 5.50 ($^3J_{HH}$ = 8.0 Hz) and 7.55 ppm ($^3J_{HH}$ = 7.9 Hz). We believe that the last value fits rotamer I, regarding its interamolecular hydrogen bonding. The other two amidic hydrogens resonance at 8.39 and 8.53 ppm as sharp singlet signals. Eighteen aromatic hydrogens of the two rotamers gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **15a** is in agreement with the product structure. In the aliphatic region, there are 18 signals related to two methyls, 12 CH_2 of two cyclohexyls, two CH_2 of the two seven-membered rings, and two CHNH moieties. The quaternary carbon of the two rotamers, which are attached to a methyl group, resonance at 69.80 and 70.99 ppm. The most important region of the spectrum is related to carbonyl groups which produce six C=O signals for the two rotamers. The ^{1}H and ^{13}C

NMR spectra of **15b**−**k** compounds are similar to those of **15a**, except for the group bonded to NC=O which exhibits characteristic signals with appropriate chemical shifts.

It is noteworthy that, in the single crystal state, the product is a dimer due to intermolecular hydrogen bonding of NHC=O in the benzodiazepine rings (Figure 4).

The ^{1}H and ^{13}C NMR of entries 6−8 (Table 1) confirmed the presence of four compounds: two regioisomers, each with a conformational isomerism. For more details of spectroscopic data of entries 1−8 (Table 1), see Supporting Information. The structures of all products are shown in Figure 5.

Regarding the well-documented general mechanism of the Ugi reaction,[18,19] we proposed a five key step plausible mechanism for the mentioned reaction (Scheme 4). Since diketene is a strained β-lacton ring, it is reasonable to propose that the first step begins through a nucleophilic addition of NH_2 to diketene followed by ring-opening and proton transfer to produce *N*-(2-aminophenyl)-3-oxobutanamide **16**.[20g] Then, the other NH_2 condenses with a ketone moiety via an intramolecular process to form 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one **12** that could be converted to iminium salt **17** in the presence of carboxylic acid **13,** a Brønsted acid in the third step. Cyclohexyl isocyanide is subsequently added to the iminium salt **17** to produce the reactive nitrilium intermediate **18**. The reactive *O*-acyl iminolate **19** is formed via the α-addition of carboxylate anion to the nitrilium ion **18**. The final step involves *O*- to *N*-acyl transfer (Mumm rearrangement) to afford the corresponding substituted 1,5-benzodiazepine-2-one **15**.

Conclusion

A concise and efficient one-pot synthesis of substituted 1,5-benzodiazepine-2-ones with a peptoid backbone has been developed based on Ugi-4CR, using *o*-phenylendiamine and diketene instead of amine and aldehyde in a reaction with carboxylic acid and cyclohexyl isocyanide. The product is of potential synthetic and pharmacological interest. This study brings forward a new concept of conformational isomerism in solution phase. In addition, the dimeric structure of the product in the single crystal state may be of theoretical and experimental interest. Easy reaction performance in neutral conditions with no bases or catalysts, high yield, and simple purification of products are the advantages of our work. The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

Supporting Information Available. Experimental procedures, IR, mass, ^{1}H and ^{13}C NMR for all compounds, crystallographic data, and ORTEP/X-ray structure for **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) 4-Methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one: 1H NMR (500.13 MHz, $CDCl_3$) 2.38 (s, 3 H), 2.13 (s, 2 H), 7.06−7.10 (m, 1 H), 7.16−7.18 (m, 2 H), 7.31−7.34 (m, 1 H), 9.59 (s, 1 H).

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