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# Efficient Approach to 1,2-Diazepines via Formal Diazomethylene Insertion into the C–C bond of Cyclobutenones

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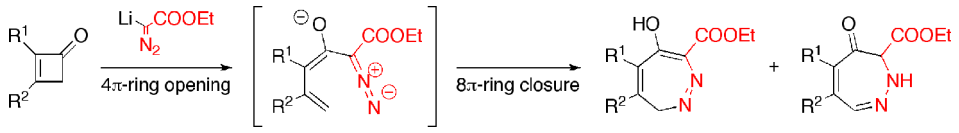
## ABSTRACT




**Efficient monocyclic 1,2-diazepine formation via a tandem electrocyclization reaction of cyclobutenones with lithiodiazoacetate is demonstrated. The reaction proceeds through an oxy anion-accelerated 4π-ring opening of cyclobutene followed by an 8π-ring closure of the resultant oxy anion-substituted diazo-diene under mild conditions to furnish a 1,2-diazepine via formal diazomethylene insertion into the C–C bond of cyclobutenone.**

Diazepines are one of the most important classes of heterocyclic nuclei, and a large number of the derivatives have been reported to exhibit significant biological activities.[1] For example, 1,4-benzodiazepines have been used clinically as tranquilizers, and the 2,3-benzodiazepine nucleus has been demonstrated to play an important role as the core structure for anticonvulsants and neuroprotective agents.[2] To date, structure–activity relationship studies of these drug candidates have been performed extensively. On the other hand, rather less attention has been paid to the monocyclic diazepine core from a biological point of view. However, several unfused 1,2-diazepine derivatives have recently been reported to exert significant progesterone receptor antagonist activity and have high potential for a novel drug candidate,[3] thus increasing the necessity for developing efficient and general methods to provide a variety of monocyclic 1,2-diazepine derivatives.

As with fused derivatives,[4] several methods for the synthesis of unfused monocyclic 1,2-diazepines have been

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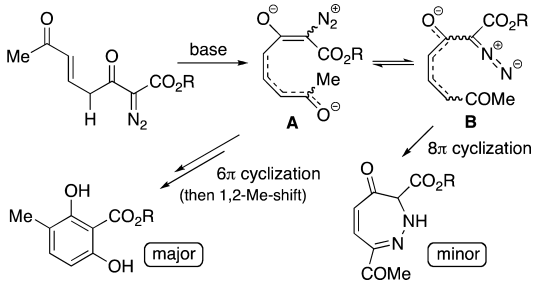
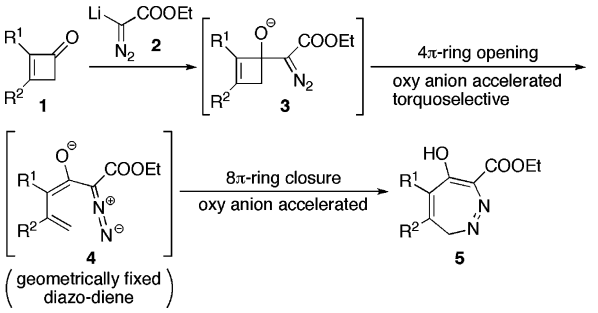
reported, using thermal or photochemical approaches,[5] most notably in the pioneering work by Moore and co-workers.[5a] In addition, subsequent chemical transformations such as dimerization,[6] fragmentation,[5k] rearrangement,[7] and the pericyclic reaction[8] have been carried out to elucidate the interesting chemical properties of these compounds.[9] Among these conventional studies, 1,7-electrocyclization approaches for the 1,2-diazepine nucleus using conjugated diazo-diene compounds as a substrate seem to be a promising method to construct this heterocyclic system. Earlier works by Sharp et al. accomplished syntheses of various 1,2-diazepine derivatives utilizing the 1,7-(8$\pi$)-electrocyclization,[5g] and then Ohno and Eguchi et al. reported 1,2-diazepine-forming reactions from diazo-diene compounds generated by ring cleavage of squaric acid derivatives.[5l] Both of these reactions, however, required thermal activation for cyclization progress and often suffered from side reactions with nitrogen extrusion and 1,5-(6$\pi$)-cyclization (pyrazole formation) to affect the yields of 1,2-diazepines. Recently, electrocyclization reactions of zwitterionic diazo-dienolate have been reported,[5m] which involve competitive 6$\pi$ and 8$\pi$ cyclizations to produce resorcinols and 1,2-diazepines, from **A** and **B** respectively, and the former reaction mode is a predominant pathway over the 1,2-diazepine formation. While these findings provide potential for the 8$\pi$ cyclization strategy for 1,2-diazepine syntheses, it has been stated that the lack of geometric fixation of the diazo-dienolate **B** would be partly responsible for the limited applicability for the efficient formation of 1,2-diazepines (Scheme 1).

**Scheme 1.** Previously Reported 1,2-Diazepine Formation *via* 8$\pi$ Cyclization




**Scheme 2.** Strategy for 1,2-Diazepine Syntheses in This Work




We have previously developed a novel methodology for the syntheses of 2,3-benzodiazepines, involving a tandem 4$\pi$−8$\pi$ electrocyclization system via a highly reactive *o*-quinodimethane intermediate, utilizing benzocyclobutenones and the diazomethylene anion as starting materials.[10] Provided that the tandem system works well in the case of monocyclic cyclobutenones, it can be a powerful strategy for synthesis of unfused 1,2-diazepine derivatives (Scheme 2). This strategy is characterized by the significant acceleration effect of the oxy anion in the intermediate **3** and **4** toward the electrocyclization process and exclusive outward torquoselectivity of the oxy anion substituent in the 4$\pi$-ring opening stage.[11] Therefore, this approach would be superior to prior methods in the following ways: (1) oxy anion acceleration for both electrocyclic reactions enables extremely mild reaction conditions (*without thermal activation*), leading to suppression of undesired nitrogen extrusion, and (2) strong outward rotation of the oxy anion in **3** completely dictates the orientation of the diazo group, which is crucial for the next 8$\pi$-ring closure (*geometric fixation of the diazo-diene intermediate*). We report herein an efficient approach to 1,2-diazepines utilizing a formal diazomethylene insertion reaction into the C−C bond of cyclobutenones via a successive 4$\pi$−8$\pi$ electrocyclization process.

The investigation began with the reaction between 3-(4-methylphenyl)cyclobutenone (**1a**) and 2 equiv of ethyl lithiodiazoacetate generated in situ using LDA as a base (Table 1).[12] In ethereal solvents, the tandem electrocyclic reaction proceeded smoothly to give desired 1,2-diazepine products as a mixture of **5a** and its tautomer **6a** (entries 1−3). The $^1$H NMR spectra of the crude reaction mixture indicated that both **5a** and **6a** were produced in the same ratio as that in Table 1 under reaction conditions,

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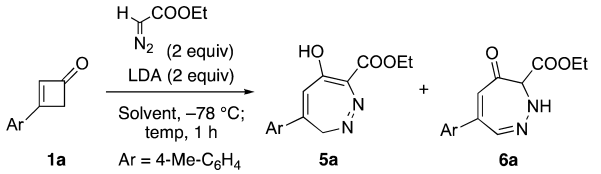
**Table 1.** Optimization of Reaction Conditions




| entry | solvent | temp | yield (%)[a] | 5a:6a |
|---|---|---|---|---|
| 1 | THF | rt | 73 | 51:49 |
| 2 | CPME[b] | rt | 47 | 40:60 |
| 3 | $Et_2O$ | rt | 65 | 45:55 |
| 4 | THF | 0 °C | 44 (51)[c] | 37:63 |
| 5 | THF | 45 °C | 47 | 34:66 |
| 6[d] | THF | rt | 85 | 82:18 |

[a] Isolated yields. [b] CPME = cyclopentyl methyl ether. [c] Yield in parentheses are based on recovered starting materials. [d] The crude reaction mixture was analyzed by $^1$H NMR in benzene-$d_6$ instead of $CDCl_3$ before purification.

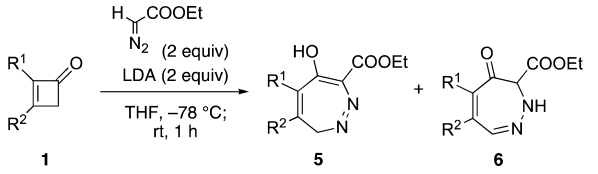
suggesting the isomerization did not occur during a purification process. Note that **5a** and **6a** could be separated easily by column chromatography and isolated as stable compounds despite the interrelation as simple tautomers.[13] Although the reaction in THF afforded the best yield (entry 1), reactions conducted at a lower or a higher temperature did not increase the yield (entries 4 and 5). In entry 6, the deuterated solvent for $^1$H NMR measurement of the crude reaction mixture was changed from $CDCl_3$ to benzene-$d_6$, leading to an improvement in the yield and ratio of tautomers. This indicated these products were labile or interconvertible under the influence of acidic impurities.

Once the optimal reaction conditions were obtained, the reaction was applied to various cyclobutenones as shown in Table 2. 3-Phenylcyclobutenone (**1b**) afforded **5b** and **6b** in good yield (entry 1). Cyclobutenones with an electron-donating group (4-MeO-$C_6H_4$) and an electron-deficient group (4-F-$C_6H_4$) also gave corresponding 1,2-diazepines (**5c** and **6c**, **5d** and **6d**), respectively (entries 2 and 3). Sterically demanding substituents on the cyclobutenones did not affect the reaction (entries 4 and 5). Furthermore, the reaction with mesityl-substituted cyclobutenone **1g** proceeded uneventfully to furnish the desired products **5g** and **6g** (entry 6). These reaction conditions were also applicable to the 2,3-diphenyl-substituted substrate **1h** (entry 7). In addition, 3-alkyl-substituted cyclobutenone **1i** gave **5i** and **6i** in moderate yield (entry 8). In all cases, the reaction predominantly afforded **5** with a small amount of **6**. Thus, it was demonstrated that the 1,2-diazepine-forming reaction examined above would have broad generality and high efficiency.

During the investigation, we noticed that tautomer **5** could isomerize into **6** under some conditions, and not

(13) Similar findings on isolation of 1,2-diazepine tautomers and their alkoxide-mediated isomerization have been reported. Pleiss, M. G.; Moore, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 1369. And see also, ref 4a and 4f.

**Table 2.** Tandem Electrocyclization of Various Cyclobutenones

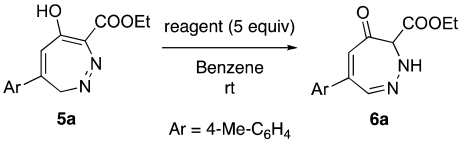



| entry | 1 | $R^1$ | $R^2$ | yield (%)[a] | 5:6 |
|---|---|---|---|---|---|
| 1 | **1b** | H | Ph | 84 | 86:14 |
| 2 | **1c** | H | 4-MeO-$C_6H_4$ | 77 | 77:23 |
| 3 | **1d** | H | 4-F-$C_6H_4$ | 71 | 90:10 |
| 4 | **1e** | H | 1-Naph | 78 | 72:28 |
| 5 | **1f** | H | 2-Me-$C_6H_4$ | 77 | 73:27 |
| 6 | **1g** | H | Mes | 59 | 58:42 |
| 7 | **1h** | Ph | Ph | 69 | 81:19 |
| 8 | **1i** | H | *n*-Bu | 64 | 88:12 |

[a] Isolated yields.

vice versa, suggesting that tautomer **6** was more stable than **5**. To improve the product selectivity in the present 1,2-diazepine-forming reaction, optimization of the isomerization conditions of **5a** into **6a** was examined (Table 3). While **5a** gradually decomposed under acidic conditions (entry 1), the isomerization to **6a** was greatly accelerated under basic conditions,[13] and the isomerization was confirmed to be very sluggish under neutral conditions. A primary or secondary amine, such as $BnNH_2$ or *i*-$Pr_2NH$, caused the rapid isomerization of **5a** to **6a**, although it was accompanied by significant decomposition (entries 2 and 3). The tertiary amine, $Et_3N$, was more effective at providing **6a** within 1.5 h in relatively good yield (entry 4), and pyridine was the best base for the isomerization (81%, entry 5). In contrast, the addition of highly nucleophilic or sterically congested bases produced a moderate yield with several unidentified side products (entries 6 and 7).

**Table 3.** Optimization of Isomerization Reaction of **5a** to **6a**

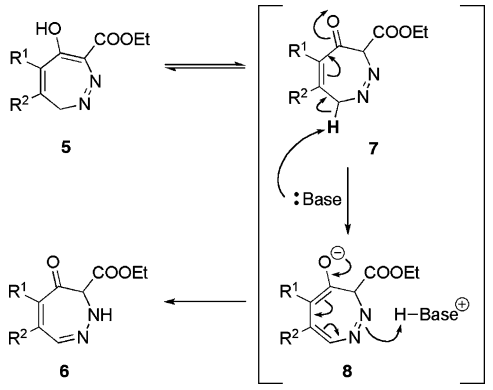



| entry | reagent | time (h) | yield (%) |
|---|---|---|---|
| 1 | 10% HCl aq | 21 | – |
| 2 | *i*-$Pr_2NH$ | 0.75 | 59 |
| 3 | $BnNH_2$ | 0.75 | 41 |
| 4 | $Et_3N$ | 1.5 | 70 |
| 5 | pyridine | 7 | 81 |
| 6 | DMAP | 0.5 | 61 |
| 7 | 2,6-lutidine | 4 | 67 (10)[a] |

[a] Value in parentheses is the recovery of starting material **5a**.

These observations led to the proposed reaction mechanism for the isomerization as shown in Scheme 3. Enone **7**, which would be in tautomerism with **5**, is deprotonated by the base to form the conjugated enolate **8**, and then the nitrogen atom of **8** is protonated to give **6**. Alternatively, this isomerization can also be explained by the base-promoted 1,5-hydrogen shift of **5**, which would directly produce the enolate anion **8**.[13]

**Scheme 3.** Plausible Reaction Mechanism for Isomerization of **5**




On the basis of these findings, we finally examined the selective synthesis of the tautomers **5** and **6**, with suitable modifications of the reaction conditions and procedures (Scheme 4). The substrate **1a** was subjected to lithiodiazoacetate under the same conditions as those in Table 2, and the crude mixture was treated with pyridine in benzene at rt to give the 1,2-diazepine **6a** as the sole product in 57% overall yield. On the other hand, the reaction of **1c** with lithiodiazoacetate generated using *n*-BuLi as a base[14] successfully produced **5c** as a sole product in 84% isolated yield. In this case the isomerization of **5** to **6** could be circumvented, because in situ generation of *i*-$Pr_2NH$, which would cause the isomerization in the reaction medium, was avoided by use of *n*-BuLi instead of LDA.

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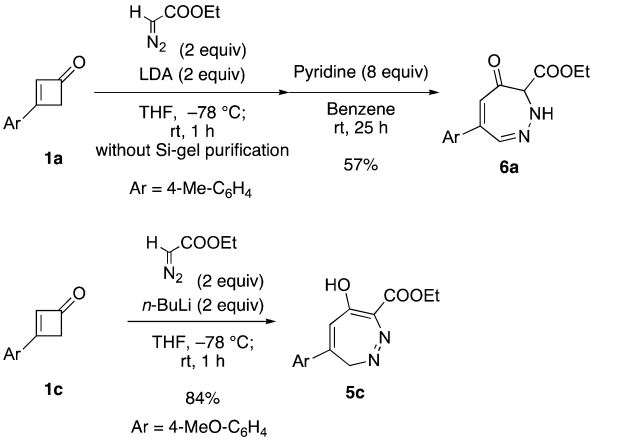
**Scheme 4.** Selective Synthesis of Both Tautomers **5** and **6**




In conclusion, an efficient synthetic method for unannulated 1,2-diazepines was developed via a tandem electrocyclic reaction of cyclobutenones with lithiodiazoacetate under mild conditions. Compared with recent 8$\pi$-electrocyclic approaches to 1,2-diazepines from squaric acid derivatives or linear diazoketone derivatives; our synthesis is more practical and achieved selective preparation of two tautomers. Further computational studies for the rationale of the isomerization and biological evaluation of the 1,2-diazepines are ongoing in our group.

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**Supporting Information Available.** Experimental procedures and $^1H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.