Reaction of 1,6-Dioxo-2,4-diene with Aziridine and Secondary Amine

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The (2*E*,4*E*)- and (2*E*,4*Z*)-1-phenyl-1,6-dioxo-hepta-2,4-diene reacts with aziridine to give aziridine-cyclopentenol **3**. This product arises from an intermolecular Michael addition of a nitrogen lone pair to the less reactive enone, followed by an intramolecular aldol reaction of the enol with ketone. Furthermore, the initially formed enol did not undergo nucleophilic attack onto the aziridine ring to form heterocycles. Interestingly, the reaction with secondary amine did not give the cyclopentenol adduct, and this only leads to the isomerization of (2*E*,4*Z*)-1-phenyl-1,6-dioxo-hepta-2,4-diene to the more stable (2*E*,4*E)*-1-phenyl-1,6-dioxo-hepta-2,4-diene by addition to the more reactive enone.

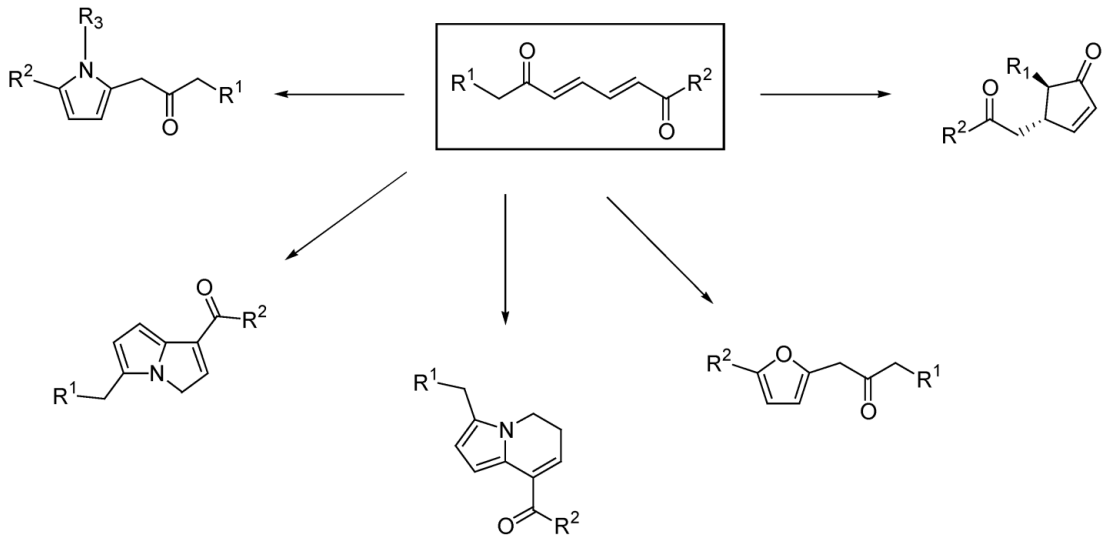
Keywords: 1,6-Dioxo-2,4-diene; Aziridine; Secondary amine.

INTRODUCTION

The 1,6-dioxo-2,4-diene can be readily synthesized using the following methods: (i) transition metal-catalyzed reaction of monosubstituted furans with aromatic diazo ketones,[1] (ii) electrophilic substitution of 1,4-bis(trimethylsilyl)buta-l,3-diene with acyl chlorides,[2] and (iii) palladium-catalyzed isomerization of ynone.[3] Our previous studies have demonstrated polyaromatic furan, pyrrole and pyrrolizine and indolizine derivatives[4] (Scheme I). This involved the sequential intermolecular 1,2- or 1,4-addition of nucleophiles to the dienone followed by an intramolecular cyclization reaction.

The chemistry of aziridines continues to attract the attention of the synthetic community.[5-13] We were interested in utilizing an aziridine derivative as the nucleophile for addition to 1,6-dioxo-2,4-diene. Although there have been no reports of this reaction, it was believed that the aziridine adduct might undergo a further ring opening reaction by the generated enol or enolate to form new heterocycles.

Scheme I The synthetic application of 1,6-dioxo-2,4-diene derivatives



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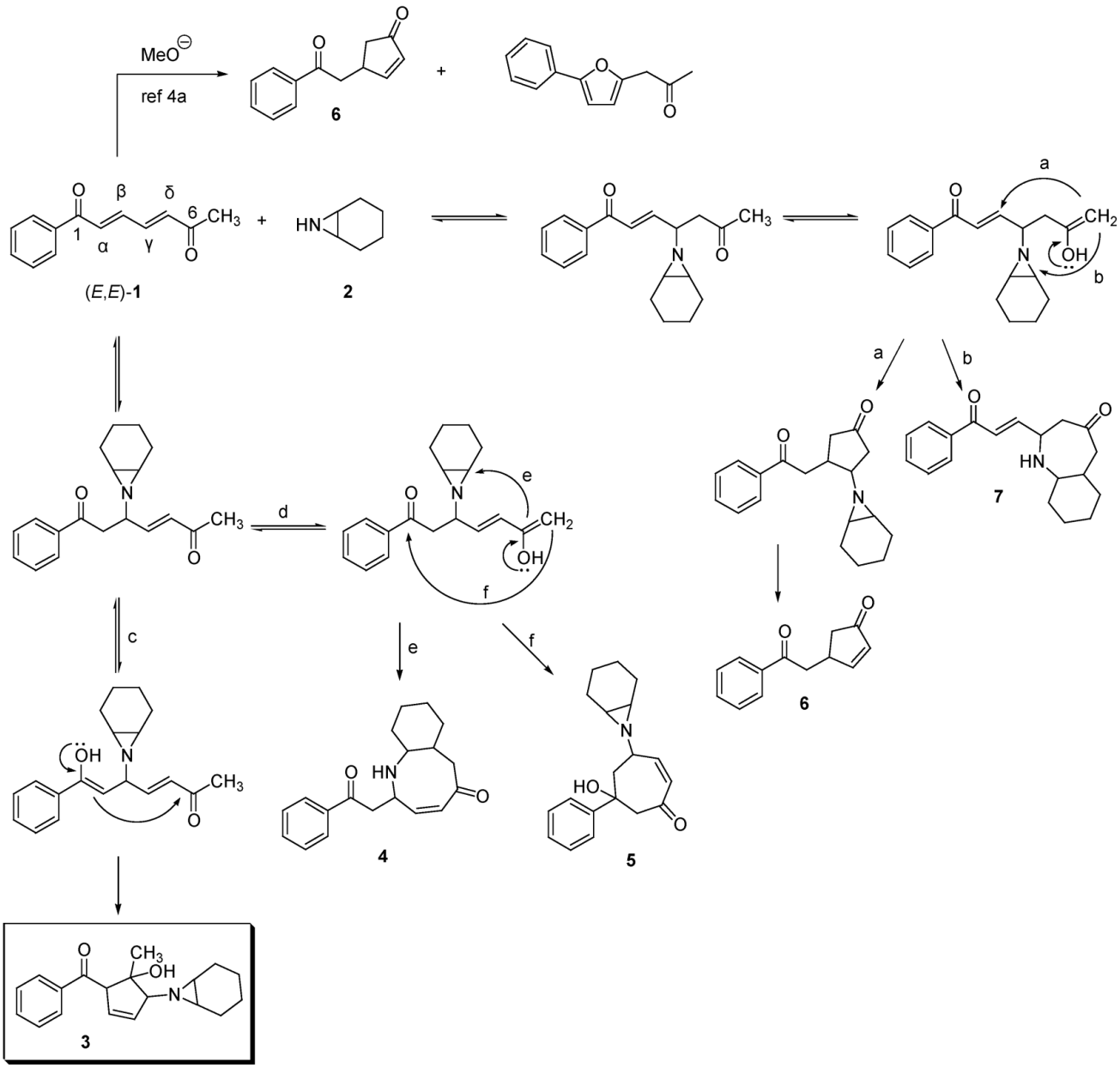
RESULTS AND DISCUSSION

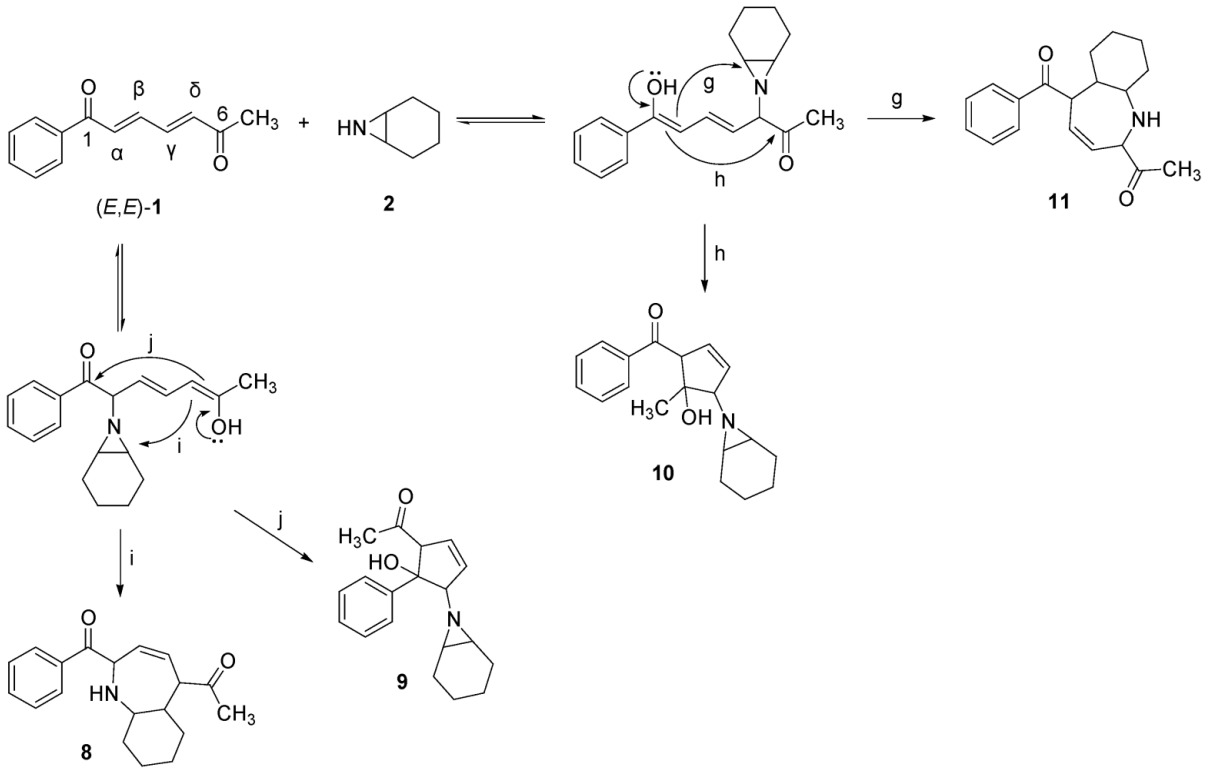
We have recently reported that aromatic 1,6-dioxo-2,4-diene can be converted to 4,5-disubstituted cyclopentenone by methoxide anion through a tandem intermolecular Michael addition, followed by an intramolecular Michael addition of the enolate generated.[4a] In light of this result, we reasoned that aziridine would undergo a similar reaction with aromatic 1,6-dioxo-2,4-diene to generate an enol or enolate, but this might undergo a further attack on the aziridine ring. The products that might arise from the intermolecular 1,4- and 1,6-addition of aziridine, followed by either an intramolecular aldol or aziridine ring opening reaction are illustrated in Scheme II and Scheme III, respectively.

The desired 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**) was readily prepared as reported.[4] Next, the symmetric 7-azabicyclo[4,1,0]heptane, (**2**), was prepared from

Scheme II Proposed possible products from the 1,4-addition of aziridine to 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**)



Scheme III Proposed products from the 1,6-addition of aziridine to 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**)



cyclohexene oxide by the ring-opening reaction with sodium azide followed by the ring-closure reaction with PPh_3.[14] Aziridine (**2**) was chosen because of the ease of preparation, and it is not volatile and thus can be easily handled. Treatment of 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**) with aziridine (**2**) under basic conditions using ^{t}BuOK resulted in a great number of unidentifiable products and could not be separated by chromatography. Consequently, the reaction was carried out in the absence of base. Indeed, when 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**) was used directly to react with aziridine (**2**) in methanol at 0 °C, a major product in 46% yield was obtained after purifying by chromatography on an aluminum oxide column. The ^{1}H-NMR of this major product showed peaks at δ 5.86 and 5.73 for an unconjugated double bond. Thus, we were able to exclude those products having a α,β-unsaturated ketone. The most likely structures were thus those containing an isolated double bond in Scheme II and Scheme III. We were not able to unambiguously assign the structure from the NMR data. Luckily, we were able to obtain a single crystal suitable for an X-ray analysis. The X-ray structure is shown in Fig. 1, and this unambiguously proves the structure of the product to be **3**. Interestingly, the neutral aziridine (**2**) adds to the less reactive aromatic enone to give a more stabilized enol, which undergoes an intramolecular aldol reaction to give cyclopentenol **3**. We did not isolate the enone **6** from this reaction. This is in contrast with the methoxide anion which adds to the more reactive nonaromatic enone to give enone **6**.[4a] This result showed the inertness of the aziridine ring to undergo an intramolecular ring opening reaction by the enol. This is conceivable as there has not yet been any report of such reactions. Futhermore, our result excludes the 1,6-addition shown in Scheme III.

In order to determine the generality of the above reaction for 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**) with secondary amine, several commercially available second-

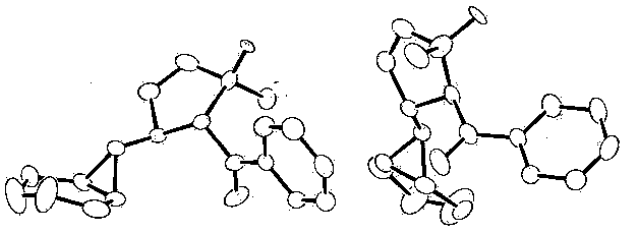
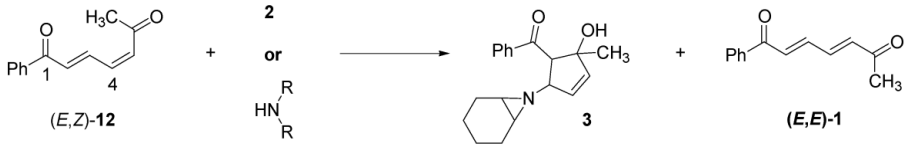


Fig. 1. The X-Ray structure of the compound **3**.

Table 1. The reaction of 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*Z*)-diene (**12**) with aziridine (**2**) and secondary amine



Entry	Reactant	Condition	Temp.	Product	Yield
1	**2**	^{t}BuOK / THF	0 °C	A[a]	x
2	**2**	CH_3OH	0 °C	**3**	46%
3	R=Ethyl	^{t}BuOK / THF	0 °C	A[a]	x
4	R=Ethyl	CH_3OH	0 °C or RT	**1**	100%
5	R=Isopropyl	^{t}BuOK / THF	0 °C	A[a]	x
6	R=Isopropyl	CH_3OH	0 °C or RT	**1**	100%
7	R=Phenyl	^{t}BuOK / THF	0 °C	A[a]	x
8	R=Phenyl	CH3OH	0 °C or RT	**1**	100%

[a] A represents the great number of unidentifiable product.

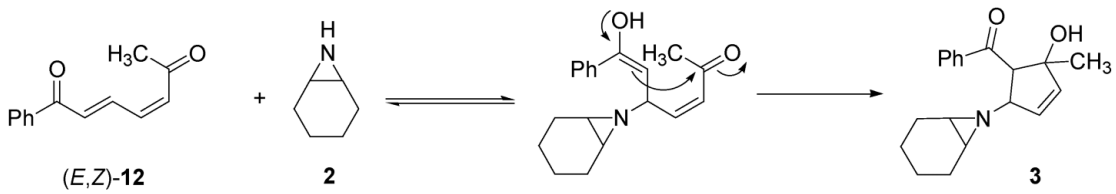
ary amines were studied. The reaction of 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**) with secondary amines such as diethylamine, diisopropylamine or diphenylamine under similar conditions resulted in the recovery of (**1**). The failure of the desired reaction to form cyclopentenol could be attributed to two possibilities: (i) the addition of these amines to the less reactive aromatic enone did not undergo an aldol reaction, or a retro-aldol took place, and this is followed by the elimination of the secondary amine to regenerate the starting materials; (ii) reaction of these amine at the more reactive enone, but this did not undergo aldol reaction with the more stable aromatic carbonyl and undergo elimination to regenerate starting material.

We decided to probe the mechanism further. It was hoped that the use of 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*Z*)-diene (**12**) could provide some insight into the reaction. We were able to obtain the initially formed 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*Z*)-diene (**12**) from the reaction of phenyl diazo ketone with 2-methylfuran in the presence of catalyzed copper sulfate by recrystallization from ether. Purification by chromatography on a silica gel column gave the more stable 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**). Reaction of (*E*,*Z*)-(**12**) with aziridine (**2**) also gave the same cycolpentenol product **3** (Scheme IV). The reaction of diethylamine, diisopropylamine or diphenylamine with 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*Z*)-diene (**12**) was found to induce isomerization of the (*Z*)-double bond in (**12**) to give 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*E*)-diene (**1**). These results are summarized in Table 1. The possible mechanism of this isomerization is shown in Scheme V. This strongly suggested that these secondary amines also react at the more reactive (*Z*)-enone to allow isomerization after rotation of the single bond, followed by elimination of the disubstituent amine to form the (*E*,*E*)-(**1**). Thus the 1,4-addition of secondary amine is similar to that of the reported methoxide anion.[4a]

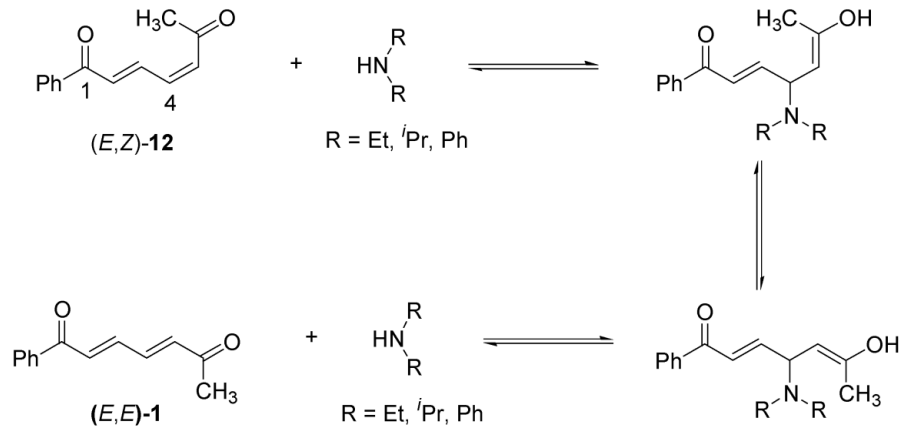
CONCLUSION

In conclusion, we have shown that the reaction of aziridine with 1-phenyl-1,6-dioxo-hepta-2,4-diene differs

Scheme IV The formation of the cyclopentenol **3** from 1,6-dioxo-2,4-(*E*,*Z*)-diene (**12**)



Scheme V The isomerization of (*E*,*Z*)-**12** to (*E*,*E*)-**1**



from the reaction with secondary amines and methoxide anion. Aziridine was found to give cyclopentenol *via* an intermolecular 1,4-addition to the less reactive aromatic enone, followed by an intramolecular aldol reaction. The failure of secondary amines to undergo a similar reaction has led us to investigate the differences of their reactivities with respect to aziridine. More work will be carried out in the future to induce the aziridine ring opening reaction in the presence of metal catalysis.[13]

EXPERIMENTAL SECTION

Compounds **1**, **12**[1] and **2**[14] were prepared according to previously reported methods.

[5-(7-Aza-bicyclo[4.1.0]hept-7-yl)-2-hydroxy-2-methyl-cyclopent-3-enyl]-phenylmethanone 3

To a solution of 1-phenyl-1,6-dioxo-hepta-2,4-(*E*,*Z*)-diene (**12**) (0.5 g, 2.5 mmol) and 7-azabicyclo[4,1,0]heptane (**2**) (0.24 g, 2.5 mmol) in 20 mL methanol at 0 °C was stirred overnight. The reaction mixture was concentrated to give the crude product. The crude product was purified by chromatography (Al_2O_3, Hexane:Ethyl Acetate = 10:1) to afford cyclopentenol **25** (340 mg, 46%) as a white solid. Mp.: 143-144 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.17 (d, 1H, *J* = 7.0 Hz), 7.59 (t, 1H), 7.50 (t, 1H), 5.86 (dd, 1H, *J* = 2.0, 5.5 Hz), 5.73 (dd, 1H, *J* = 1.5, 5.5 Hz), 4.16 (d, 1H, *J* = 5.0 Hz), 3.23 (d, 1H, *J* = 5.0 Hz), 3.07 (br, 1H), 1.77-1.81 (m, 3H), 1.55-1.64 (m, 3H), 1.24-1.31 (m, 2H), 1.10-1.15 (m, 2H), 1.07 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 200.6 (C), 138.6 (C), 138.0 (CH), 133.2 (CH), 131.7 (CH), 129.0 (CH × 2), 128.6 (CH × 2), 84.7 (C), 75.6 (CH), 65.1 (CH), 37.8 (CH), 37.7 (CH), 24.1 (CH_2 × 2), 23.8 (CH_3), 20.4 (CH_2), 20.1 (CH_2). LRMS (EI^+, *m/z*): 296 [$(M-1)^+$]. HRMS (EI^+) calcd for $C_{19}H_{23}NO_2$ [M^+]: 297.1729; found $C_{19}H_{23}NO_2$ [M^+]: 297.1731.

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