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Tetrahedron Letters 49 (2008) 1062–1065

Tetrahedron Letters

Carbonyl ylide reactions of α-benzylidene-β-dicarbonyl compounds: competitive formation of dihydrofurans and dihydrobenzoxepines

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Received 15 October 2007; revised 19 November 2007; accepted 30 November 2007
Available online 4 December 2007

Abstract

α-Benzylidene-β,β′-biscarbonyl compounds were reacted with dimethyl diazomalonate using Cu(II) acetylacetonate as a catalyst. Dihydrofurans or mixtures of dihydrofurans and dihydrobenzoxepines were obtained depending on the nature of the carbonyl group present in the starting material.

Keywords: Carbene; 1,5-Electrocyclization; 1,7-Electrocyclization; Dihydrofuran; Dihydrobenzoxepine

During the past decade, we have been studying the formal 1,5-electrocyclization reactions of carbonyl ylides derived from metallo-carbenoid species and α,β-unsaturated carbonyl compounds with alkyl or aryl groups as a β-substituent.[1] Cu(II) acetylacetonate catalyzed decompositions of diacyl diazo compounds, such as dimethyl diazomalonate, in the presence of α,β-unsaturated carbonyl compounds, such as α,β-unsaturated ketones and esters, were reported to yield mainly dihydrofuran derivatives. For the reactions to proceed as described, it was reported that the unsaturated carbonyl compounds must be monosubstituted at their β-position with *trans* geometry. For the formation of dihydrofurans, they should favor the s-*cis* conformation. The products were reported to be capable of further reactions, as well. Similar formal electrocyclizations were also reported by the Hamaguchi group[2] and more recently by Sliwinska and Warkentin[3] Our results with esters were in contrast to the results of other researchers who obtained only cyclopropanes[4] and other products.[5] Since furan derivatives are among the most significant heterocycles in natural products, these reactions possess synthetic value. In recent articles by our group, we reported an unusual 1,3-dioxole formation from a strained bicyclic ketone.[6] We realized that the reactions of α,β-enaminones[7] were in contrast to the studies of Maas and Müller;[8] we reported the presence of significant amounts of dihydrofurans under our reaction conditions. Novel 3-anilino-4-oxo-1,4-dihydronaphthalene derivatives were also obtained from an unusual insertion into the benzoyl ring in the case of aniline derivatives. In this study, we compared the reactivities of α,β-unsaturated esters and ketones in these reactions with ylides.

Z- and *E*-ethyl acetobenzylidene acetates **1a** and **1b**[9] were treated with dimethyl diazomalonate (*dmdm*) in the presence of Cu(acac)$_2$ to compare the reactivities of conjugated ketone and ester functions toward ylide formation and the reactivities of these ylides in the formal 1,5-electrocyclization reactions. Product distributions were determined by GC–MS and ^{1}H NMR spectroscopy. The experiments were also repeated using two other *E*/*Z* mixtures (1:1.9 and 2.5:1 by NMR). We obtained the same two products **3a** and **4a** (which are identical to **2b** and **5b**, respectively) only, approximately in the same ratios (Scheme 1 and Table 1). Contrary to our previous experience, **2a** (or **3b**), which would result from the respective keto-ylides, was not found in the reactions. On the other

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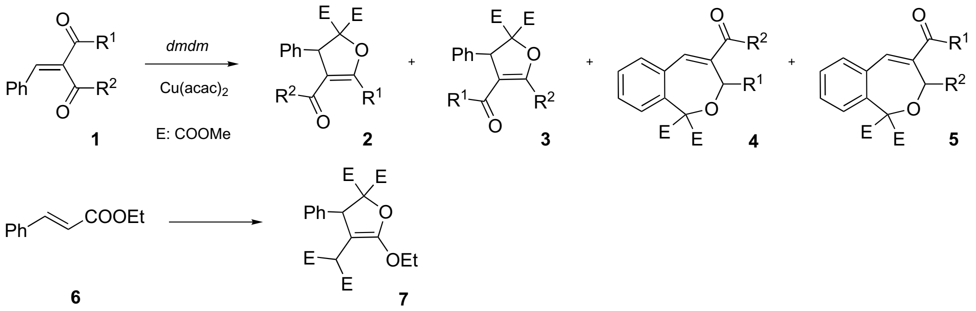
doi:10.1016/j.tetlet.2007.11.197



Scheme 1. The reactions of bis-carbonyl compounds and *dmdm*.

Table 1
Product distribution in the reactions of bis-carbonyl compounds and *dmdm*

Enone	R^1	R^2	Product distribution			
			2	**3**	**4**	**5**
1a	Me	OEt	—	1.0 (=**2b**)	1.0 (=**5b**)	—
1b	OEt	Me	1.0 (=**3a**)	—	—	1.0 (=**4a**)
1c	OEt	OEt	1.0 (=**3c**)[1d]	(**2c**)	—	—
1d	Me	Me	1.0 (=**3d**)	(**2d**)	1.5 (=**5d**)	(**4d**)
6	Ethyl cinnamate	**7**:1.0			—	

hand, the formation of a dihydrobenzoxepine product showed that a 1,7-electrocyclization also took place under these conditions, obviously via the corresponding *E*-keto-ylides. This was not observed in our previous studies.[1] The reactions of the ene–diester **1c** (diethyl benzylidene-malonate) did not yield dihydrobenzoxepines.[1d] We performed the same reaction using ethyl cinnamate (**6**), a simpler mono-ester analogue, and the results were unchanged (Table 1). This suggested that the formation of dihydrobenzoxepines is restricted to substrates with ketone functions only.

To gain more information on this novel dihydrobenzoxepine formation, we reacted benzylidene acetylacetone (**1d**) with *dmdm* under the same conditions and obtained **4d** as the major product. The structure of **4d** was determined by crystallographic analysis[†] (Fig. 1).

According to our previous proposals, the transformations **1a**→**3a** and **1b**→**3b** are not expected unless the reaction proceeds in a stepwise manner. In other words, **1b** should only yield **2b** (**3a**) and no products originating from a keto-ylide. At this point, we eliminated the possibility of *E*–*Z* interconversion.[10] In light of this data, we propose that the overall reaction steps for the formation of compounds **4a** and **4d** are as follows: (i) formation of a keto-ylide, (ii) rotation around formal C═C bonds in the fully conjugated dicarbonyl derivatives (not observed in the corresponding mono-carbonyls) (Scheme 2), (iii) 1,7-cyclization, and (iv) a [1,5]-hydrogen shift. The evidence for the rotation of the carbonyl ylides came from the fact that both *E*- and *Z*-acetoacetates yielded the same mixture of products with the same ratios.

The 1,7-cyclization step is most likely a concerted reaction[11,12] (but in such strongly polarized systems, charge control may also be a possibility). If the cyclization step is a pericyclic mechanism, then there is competition between the 6π 1,5- and the 8π 1,7-cyclization of the conjugated carbonyl ylide intermediates derived from the ester- and keto-ylides, respectively, to the β- or *ortho* carbon of the phenyl ring. As discussed,[11–13] if the possibility of both

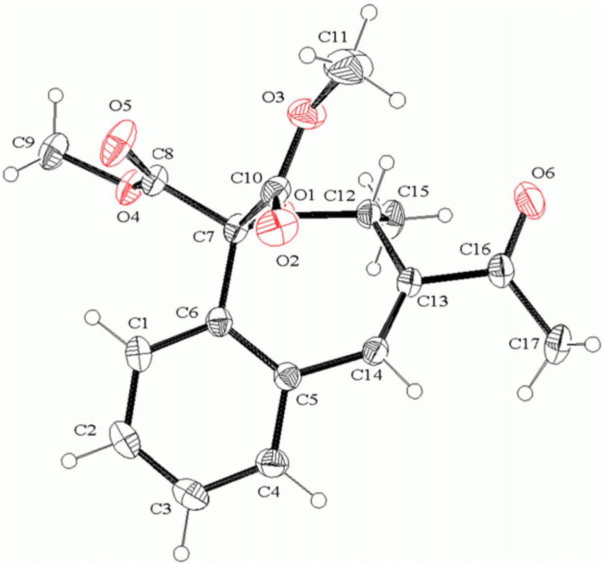
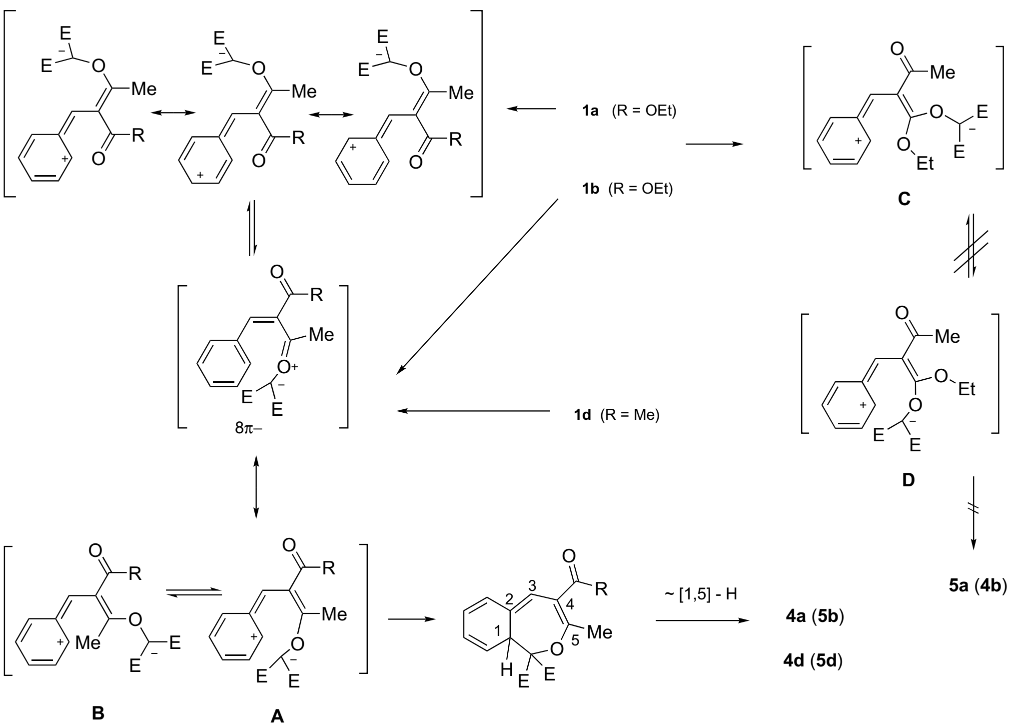


Fig. 1. The X-ray structure of **4d**.

[†] CCDC-662876 (**4d**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Scheme 2. Formation of dihydrobenzoxepines from conjugated dicarbonyls.

1,5- and 1,7-electrocyclization existed, the latter is often preferred because of the larger orbital coefficients at the termini of the conjugated system involving the 8π electrons. According to our results, the ester–ylides preferred formation of dihydrofurans, whereas keto-ylides showed preference for 7-membered rings.[14] In conclusion, we suggest that these initially formed carbonyl-ylides are highly polarized and need not undergo electrocyclization reactions directly, but may rather undergo a rotation around their C(α)–C(β) bonds leading to the two different ring closure reaction products.

Typical procedure[1] for the reaction of α-benzylidene β-dicarbonyl compounds with *dmdm*: To a solution of the enone substrate (1.5 equiv) in benzene (10 mL) was added Cu(acac)$_2$ (0.007 equiv), and the mixture was heated at reflux. A solution of *dmdm* (1 equiv) in benzene (4 mL) was added to this solution over 2.5 h under an N$_2$ atmosphere. When the IR spectrum of the reaction mixture indicated total consumption of dimethyl diazomalonate (absence of the characteristic diazo band at 2130 cm^{-1}), the mixture was filtered, evaporated, and purified by column chromatography or preparative TLC.

Acknowledgments

The authors would like to thank *the I.T.U. Research Fund* (32003) and *The Scientific and Technological Research Council of Turkey* (TUBITAK) (TBAG-105T418).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.197.

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9. Ethyl acetobenzylidene acetate was obtained as a mixture of *Z* and *E* isomers (1.90:1) after distillation. After chromatographic separation,

the structures of the *E*- and *Z*-isomers were clarified from their NOESY spectra.

10. We determined that (*E*)-**1b** was only partially (ca. 10%) converted to (*Z*)-**1a** at room temperature after seven months. Refluxing pure (*Z*)-**1a** in benzene for 5 h also resulted in negligible amounts of conversion. Besides, the 65:35 *Z*/*E* ratio observed after the distillation in the synthetic procedure also indicates that the starting compound alone did not exhibit a facile *Z* to *E* conversion.
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14. Preliminary geometry optimization studies suggested that the probable structure **C** was significantly more stable than structure **D** in Scheme 2, whereas structures **A** and **B** in Scheme 2 had just about the same energies.