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Anomalous behaviour of Rh(II)-generated carbonyl ylides: entry into functionalized spiro dioxa-bridged polycyclic frameworks

Sengodagounder Muthusamy,* Srinivasarao Arulananda Babu and Chidambaram Gunanathan

Silicates and Catalysis Discipline, Central Salt and Marine Chemicals Research Institute, Bhavnagar 364 002, India

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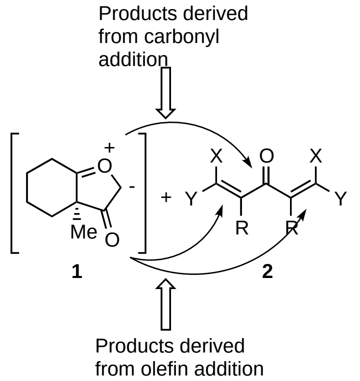
Abstract—A series of symmetrical α,β-unsaturated ketone systems having multiple π-bonds were synthesized. To generate five-membered-ring carbonyl ylides as intermediates, the rhodium(II)-catalyzed reactions of α-diazo ketones were carried out and the carbonyl ylides reacted with the π-bonded α,β-unsaturated ketone systems. Functionalized spiro dioxa-bridged polycyclic ring systems were produced with high regio- and chemoselectivity in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

α-Diazo ketones are intermediates in that they undergo very useful transformations in a highly productive manner and continue to be the subject of considerable interest and intensive investigation in synthetic organic chemistry.[1] Intramolecular carbenoid–carbonyl group cyclizations have been recognized as one of the most effective methods for generating carbonyl ylides; subsequent 1,3-dipolar cycloadditions with π-bonds to construct novel hetero/carbocyclic ring systems are well documented.[2] Based on this tandem cyclization–cycloaddition strategy, the synthesis of many natural products such as brevicomin,[3] illudins,[4] phorbol ester derivatives,[5] zaragozic acid A[6] and various alkaloids[7] have been ingeniously approached. As a result, there has been growing interest in the use of rhodium(II)-generated carbonyl ylides as 1,3-dipoles for the construction of many important natural/unnatural derivatives. Their inter- or intramolecular 1,3-dipolar cycloaddition reactions with the C=C bond of various dipolarophiles have been well established.[1,2] Further, the intermolecular formation of carbonyl ylides from α-diazo ketones with aldehydes,[3,6a,8] ketones,[9] α,β-unsaturated ketones[10] and quinones[11] have also been reported. However, the intermolecular carbonyl ylide reactions with dipolarophiles having multiple π-bonded systems[12] have received little attention.

It was of interest to us to consider the reactions of carbonyl ylide **1** with symmetrical systems having multiple π-bonds **2** including a carbonyl group. Either of the two different potential dipolarophilic functionalities, i.e. C=C and C=O in compound **2**, could participate in 1,3-dipolar cycloaddition reactions. Many regio- as well as diastereomeric products could be expected in the reaction of carbonyl ylide **1** and dipolarophiles such as **2** (Scheme 1). To the best of our knowledge, there has been only one recent relevant report;[13a] nitrilimine dipoles cycloadds to both exocyclic C=C bonds of (*E*,*E*)-2,6-bis(arylmethylidene)cyclohexanones, but not to the C=O group. Also, there are some reports in which the formation of bis- or mono-cycloadducts were observed as a result of the cycloaddition reactions of dipoles to C=C bonds of bis(arylmethylidene)ketones.[13b,c,d] As part of our ongoing research program[14] to study the reactivity profile of carbonyl ylides and the synthesis of epoxy-bridged polycyclic ring systems, we wish to report a novel stereoselective reaction involving cyclic carbonyl ylides **1** with dipolar-



Scheme 1.

Keywords: carbonyl ylides; chemoselectivity; cycloaddition; diazo carbonyl compounds; polycycles; rhodium acetate; spiro compounds.

* Corresponding author. Tel.: +91 278 567760; fax: +91 278 567562; e-mail: salt@csir.res.in

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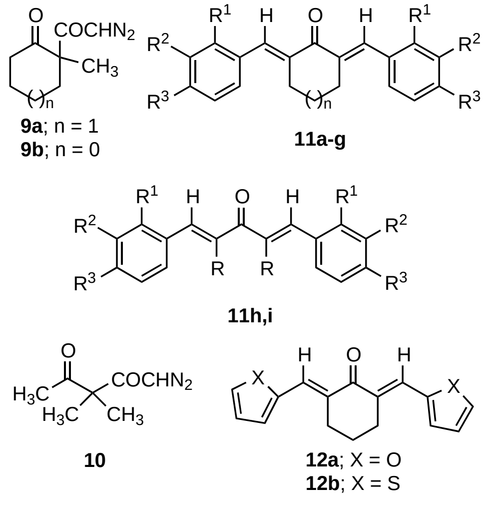
ophiles having multiple π-bonded systems **2** using rhodium(II) acetate dimer as catalyst.

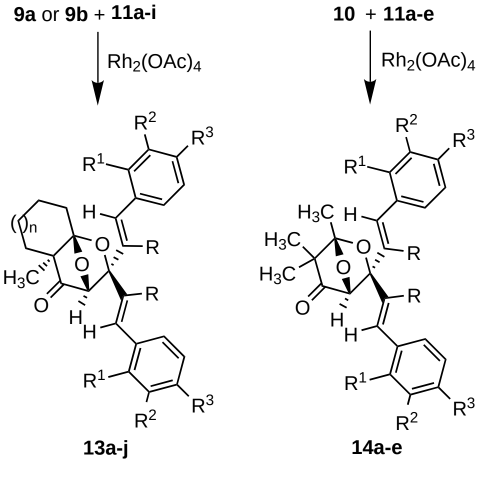
The required starting materials, α-diazo carbonyl compounds[14a] **9**/**10**, bis(arylmethylidene)ketones[15] **11** and bis(heteroarylmethylidene)ketones **12**, were prepared according to literature procedures (Scheme 2).

Initially, we investigated the rhodium(II)-catalyzed behaviour of α-diazo ketones **9**/**10** and (*E*,*E*)-2,6-bis(arylmethylidene)cycloalkanones **11a**–**g** as multiple π-bonded dipolarophiles. A solution of an equimolar amount of α-diazo ketone **9a** and 2,6-dibenzylidenecyclohexanone (**11a**) with 1 mol% of rhodium(II) acetate dimer catalyst in dry dichloromethane was stirred at room temperature under an argon atmosphere for 3 h. The reaction was followed by TLC until the disappearance of starting α-diazo ketone **9a** was found; concentration followed by purification through silica gel column chromatography afforded product **13a**[16a] in 79% yield (Scheme 3, Table 1).

This reaction surprisingly revealed that the cyclic carbonyl ylide **1** derived from α-diazo ketone **9a** underwent cycloaddition only to the C=O group of dipolarophile **11a** in a chemoselective manner. We have not isolated any other products from C=C addition. The proton NMR spectrum of the crude reaction mixture also revealed the presence of only one product **13a**, in the reaction mixture. Next, we performed the reaction of α-diazo ketone **9a** with a variety of dipolarophiles having multiple π-bonds **11b**–**g** in the presence of rhodium(II) acetate dimer catalyst to furnish the respective cycloadducts **13b**–**g** (Scheme 3, Table 1).



Scheme 2.



Scheme 3.

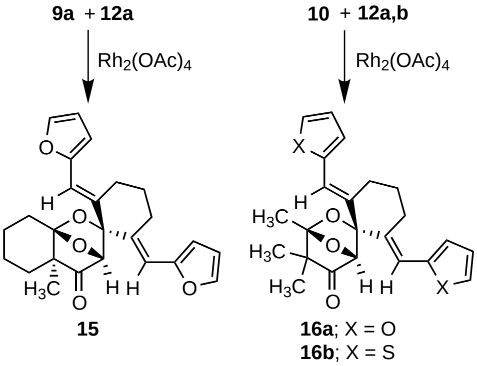
Reaction of diazo ketone **10** with dipolarophiles **11a**–**e** in the presence of rhodium(II) acetate dimer catalyst in dry dichloromethane afforded the corresponding products **14a**–**e** chemoselectively and in good yields (Scheme 3, Table 1). The product **14c** has been unequivocally characterized by single-crystal X-ray analysis.[16b] Interestingly, the reaction of diazo carbonyl compound **9a** with acyclic bis(arylmethylidine)ketones **11h**,**i** furnished the corresponding products **13h**,**i** in good yield. Diazo carbonyl compound **9b** reacted with dipolarophile **11a** giving **13j**. Neither electron-withdrawing nor electron-donating groups as substituents in the aromatic ring of dipolarophiles **11a**–**i** ($R^1/R^2/R^3$) altered the reaction profile (Table 1). Interestingly, the yield of products **13** and **14** was quantitative based on the recovery of the starting material (dipolarophile).

Next, we wished to investigate the reactions of carbonyl ylides with heteroarylmethylideneketones **12a**,**b** as dipolarophiles. α-Diazo ketone **9a** and heteroarylmethylideneketone **12a** in dry dichloromethane was allowed to react with rhodium(II) acetate dimer. The reaction was followed by TLC until the disappearance of starting α-diazo ketone **9a**. Concentration followed by chromatographic purification on an alumina column of the crude reaction mixture furnished product **15** in 74% yield (Scheme 4). We also performed a similar reaction using diazo ketone **10** with heteroarylmethylideneketones **12a**,**b** to afford the corresponding novel products **16a**,**b** in 72 and 73% yields, respectively (Scheme 4). Thus, here too the formation of C=O cycloaddition products was observed in a chemoselective manner. It has been reported that the C=C bond of the furan ring

Table 1. Synthesis of spiro-dioxa bridged compounds **13** and **14**

Entry	*n*	R	R^1	R^2	R^3	Yield[a] (%)	
						13	**14**
a	1	$-(CH_2)_3-$	H	H	H	79	77
b	1	$-(CH_2)_3-$	H	H	OMe	78	75
c	1	$-(CH_2)_3-$	H	H	Cl	70	71
d	1	$-(CH_2)_2-$	H	H	Cl	71	72
e	1	$-(CH_2)_3-$	OMe	H	OMe	76	75
f	1	$-(CH_2)_4-$	H	H	Cl	55	–
g	1	$-(CH_2)_3-$	$-(CH=CH)_2-$		H	76	–
h	1	H	H	H	OMe	74	–
i	1	H	H	H	Me	73	–
j	0	$-(CH_2)_3-$	H	H	H	74	–

[a] Yields (unoptimized) of pure and isolated compounds **13** and **14**.

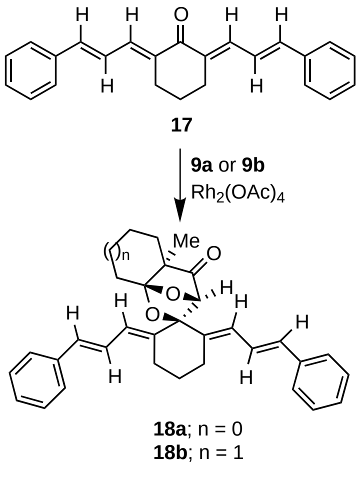


Scheme 4.

is known[17] to undergo cycloaddition with isomünchnone dipoles. It is worth mentioning that the furan as well as thiophene rings remained intact in our experiments.

Enthusiastically, we now decided to study the reactivity of cyclic carbonyl ylides with the systems having conjugated C=C bonds in dipolarophiles **11**. To this end, we synthesized 2,6-bis-(3-phenylallylidene)cyclohexanone **17** from *trans*-cinnamaldehyde and cyclohexanone. A solution of dipolarophile **17** was allowed to react with diazo carbonyl compounds **9a** or **9b** in the presence of rhodium(II) acetate dimer, followed by purification of the crude reaction mixture by neutral alumina column chromatography giving the products **18a**,**b** in 74 and 69% yield, respectively (Scheme 5). These reactions also afforded products **18** in a chemoselective manner as a result of cycloaddition only to the C=O group of dipolarophile **17**.

Interestingly, these dioxa-bridged ring skeletons are present in many natural products such as amberketal,[18a] austalide B,[18b] frontalin,[18c] levoglucoseneone,[18d] brevicomin[3] and zaragozic acid A.[6] It is worth noting here that exocyclic C=C bonds exclusively served as dipolarophiles with other dipoles in the presence of the C=O group.[19] It is evident that all the above reactions furnished functionalized spiro dioxa-bridged polycyclic ring systems in a highly regio- and chemoselective manner. These reactions did not afford any cycloaddition products as a result of addition to C=C bonds. It is very important to note that starting from a relatively simple precursor and a dipolarophile, these tandem cycloaddition–cyclization reactions resulted in the formation of one C–C and two C–O bonds in a stereoselective manner.



Scheme 5.

In summary, we have discovered that rhodium(II)-generated carbonyl ylides underwent exclusive cycloaddition to the C=O group of a variety of multiple π-bonded dipolarophiles. Even though the C=C cycloaddition processes of carbonyl ylides are well known, the 1,3-dipolar cycloaddition of five-membered-ring carbonyl ylides underwent only to the carbonyl group, no matter how many C=C bonds were present in the dipolarophiles. This method provides a synthesis of various spiro dioxa-bridged systems having multiple π-bonds with high regio- and chemoselectivity. Currently, we are engaged in the application of this stereoselective method to the synthesis of natural products having oxygen containing heterocyclic systems.

Acknowledgements

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16. (a) All new compounds exhibited spectral data consistent with their structures. Selected spectral data **13a**: Mp 182–184°C; IR (KBr) 2956, 2933, 2858, 1761, 1491, 1443, 1375, 1285, 1032, 919 cm^{-1}; ^{1}H NMR (200 MHz, CDCl_3) δ 7.36–7.21 (m, 10H, Arom-*H*), 6.92 (s, 1H, =C*H*), 6.89 (s, 1H, =C*H*), 5.00 (s, 1H, OC*H*), 3.19–3.00 (m, 2H), 2.40–1.30 (m, 12H), 1.32 (s, 3H, CH_3); ^{13}C NMR (50 MHz, CDCl_3) δ 212.5 (*C*=O), 141.1 (*quat*-*C*), 140.2 (*quat*-*C*), 138.2 (*quat*-*C*), 137.6 (*quat*-*C*), 129.6 (=*C*H), 129.3 (=*C*H), 128.6 (=*C*H), 128.5 (=*C*H), 127.1 (=*C*H), 126.9 (=*C*H), 124.8 (=*C*H), 124.3 (=*C*H), 113.7 (*quat*-*C*), 88.6 (*quat*-*C*), 86.0 (O*C*H), 53.6 (*quat*-*C*), 33.0 (*C*H_2), 28.9 (*C*H_2), 28.3 (*C*H_2), 27.9 (*C*H_2), 27.3 (*C*H_2), 23.5 (*C*H_2), 20.5 (*C*H_2), 15.0 (*C*H_3); MS (EI) m/z (%): 426 (M^+, 13), 316 (24), 315 (100), 287 (16), 275 (72), 273 (22), 141 (13), 123 (82); anal. calcd for $\text{C}_{29}\text{H}_{30}\text{O}_3$: C, 81.66; H, 7.09. Found: C, 81.60; H, 7.13%. (b) The X-ray crystal structure analysis will be reported elsewhere.
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