Pergamon

Tetrahedron Letters, Vol. 38, No. 19, pp. 3319-3322, 1997

0040-4039/97 $17.00 + 0.00

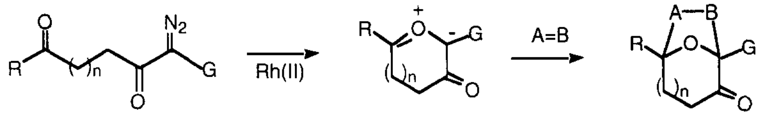
PII: S0040-4039(97)00617-5

Cyclization of Rhodium Carbenoids Using Ester and Amido Carbonyl Groups

*Erin A. Curtis, Kimberly J. Worsencroft, and Albert Padwa**
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Abstract: Carbonyl ylide dipoles derived from diazoacetyl esters underwent 4π-electrocyclization to furnish bicyclic epoxides. Reaction of related α-diazoketo amides with rhodium(II) carboxylate catalysts resulted in cyclization on both the oxygen and nitrogen atoms of the amido group to give carbonyl and ammonium ylides. © 1997 Elsevier Science Ltd.

In recent studies,[1] we have described the formation of cyclic carbonyl ylide dipoles by a process involving cyclization of an electrophilic metallo carbenoid onto an adjacent carbonyl group.[2] The general reaction investigated is illustrated below; variations in chain length (n = 0, 1, 2) and nature of the activating group (G) were explored.[1,2] With limited exceptions,[3] alkyl and aryl ketones were employed and dipole **2** was generated by the rhodium(II)-catalyzed decomposition of diazoalkanedione **1** in benzene at 80 °C.[4]

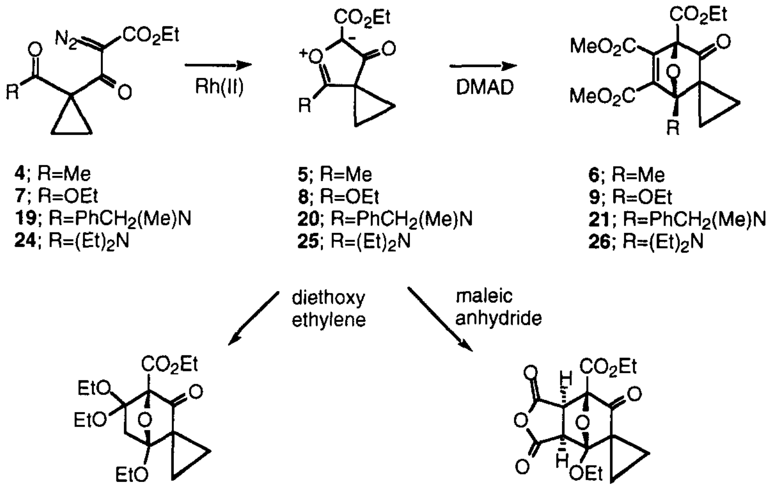


1 **2** **3**

This tandem cyclization-cycloaddition strategy was used as the key step in the synthesis of a number of natural products as it provides for the rapid assembly of the basic core unit of several target molecules having most of the functionality in place.[5-10] In an effort to increase the versatility of the method, we have undertaken a study of the effect of ester and amido groups (R = OR, NR_2) on the efficiency of dipole formation. Details of these cyclizations are the subject of this communication.

The cycloaddition reaction of α-diazoketo ester **4** proceeded in high yield (97%) when dimethyl acetylenedicarboxylate (DMAD) or other electron deficient π-bonds were used as the dipolarophile.[11] With the DMAD reaction as a benchmark, the effect of varying the substituent adjacent to the carbonyl group on the cycloaddition was compared. In this regard, treatment of the related diazoester **7** under the standard Rh(II)-catalyzed conditions resulted in smooth cycloaddition with a variety of dipolarophiles such as DMAD, maleic anhydride, *N*-phenylmaleimide, and 1,1-diethoxyethylene.

Placement of a tethered π-bond on the diazo ester side chain was also examined. Thus, the Rh(II)-catalyzed decomposition of **12** in benzene at 80 °C for 5 h furnished the expected intramolecular



4; R=Me
7; R=OEt
19; R=PhCH$_2$(Me)N
24; R=(Et)$_2$N

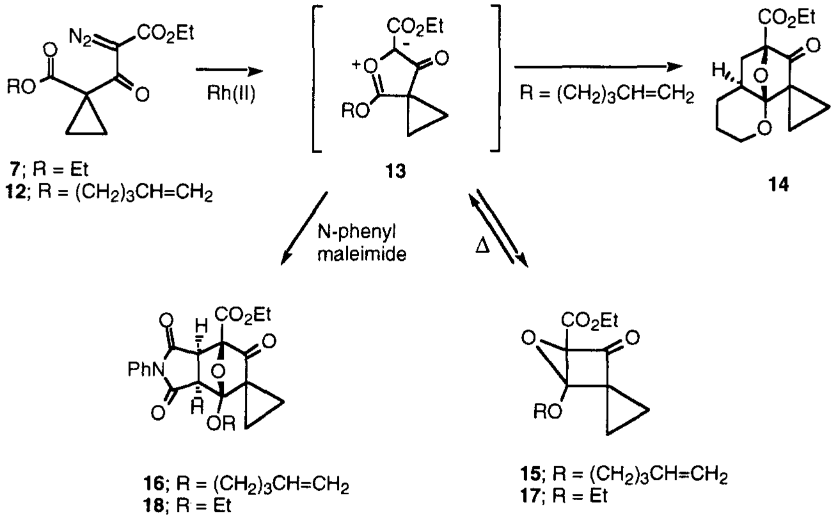
5; R=Me
8; R=OEt
20; R=PhCH$_2$(Me)N
25; R=(Et)$_2$N

6; R=Me
9; R=OEt
21; R=PhCH$_2$(Me)N
26; R=(Et)$_2$N

10

11

cycloadduct **14** as the exclusive product (60%). When the reaction was stopped after 1 h, however, a 1:1-mixture of cycloadduct **14** and bicyclic epoxide **15** was obtained in 84% overall yield. Further heating a sample of **15** at 80 °C afforded cycloadduct **14**. This transformation presumably involves C-C bond cleavage of the strained epoxide[12] followed by intramolecular trapping of the resultant carbonyl ylide intermediate **13**. Additional support for the involvement of dipole **13** comes from heating a sample of **15** in the presence of *N*-phenylmaleimide. In addition to cycloadduct **14** (50%), it was also possible to isolate the bimolecular cycloadduct **16** (13%). It is worthy to note that when the simpler diazoester **7** was subjected to Rh_2OAc_4 decomposition in the absence of a trapping agent, bicyclic epoxide **17** was



7; R = Et
12; R = (CH$_2$)$_3$CH=CH$_2$

13

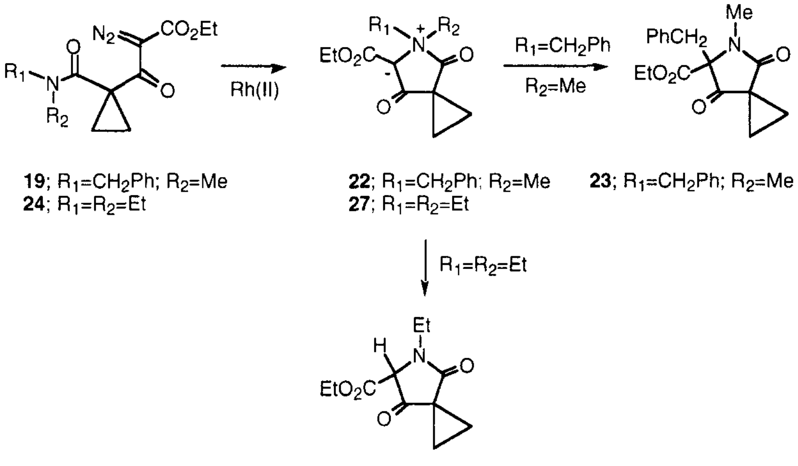
14

16; R = (CH$_2$)$_3$CH=CH$_2$
18; R = Et

15; R = (CH$_2$)$_3$CH=CH$_2$
17; R = Et

obtained in 68% yield as a crystalline solid. Further heating of **17** with *N*-phenylmaleimide (or DMAD) in the absence of the rhodium catalyst afforded the bimolecular cycloadducts **18** (90%) or **9** (85%). More than likely, the enhanced stability of the alkoxy substituted carbonyl ylide allows the relatively rare 4π-electrocyclization reaction to occur.[13]

Next, we subjected the closely related α-diazo ketoamide **19** to the Rh(II)-catalyzed conditions. Our expectation was that the initially formed carbonyl ylide **20** would also undergo the 4π-electrocyclization reaction. We found, however, that the Rh(II)-catalyzed[14] reaction of **19** in the presence of DMAD afforded cycloadduct **21** (57%) together with the totally unexpected lactam **23** (23%). When the reaction of **19** was carried out in the absence of DMAD, the rearranged lactam **23** was isolated in 62% yield. The formation of **23** can be attributed to the initial generation of ammonium ylide **22** followed by a 1,2-benzyl shift. Related 1,2-shifts of cyclic ammonium ylides derived from the reaction of tertiary amines and α-diazo carbonyl compounds have been described by West and coworkers[15] thereby providing good analogy for the suggested mechanism. It would appear as though the highly electrophilic carbenoid center can either attack the lone pair of electrons on the amide nitrogen (ammonium ylide formation) or the lone pair of electrons on the carbonyl oxygen (carbonyl ylide formation).[16]



19; R_1=CH_2Ph; R_2=Me
24; R_1=R_2=Et

22; R_1=CH_2Ph; R_2=Me
27; R_1=R_2=Et

23; R_1=CH_2Ph; R_2=Me

28

Products derived from both a carbonyl ylide and an ammonium ylide were also encountered with diazoketoamide **24**. When the Rh(II)-catalyzed[14] reaction of **24** was carried out in the presence of DMAD, a 2:3-mixture of lactam **28** (27%) and cycloadduct **26** (40%) was obtained. In the absence of a trapping agent, **24** furnished lactam **28** in 75% isolated yield. The formation of this product can readily be rationalized in terms of α,β-fragmentation of ethylene from the transient ammonium ylide **27**.

Further studies are underway to determine whether the product distribution derived from the Rh(II)-

catalyzed decomposition of these diazoketo amides is related to conformational and/or electronic factors and also if the distribution is sensitive to the nature of the ligand groups on the rhodium metal.

Acknowledgment: We gratefully acknowledge support of this work by the National Institutes of Health (CA-26751).

References and Notes

1. Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894. Padwa, A.; Stull, P. D. *Tetrahedron Lett.* **1987**, *28*, 5407. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2877. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
2. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.
3. Dean, D. C.; Krumpe, K. E.; Padwa, A. *J. Chem. Soc., Chem. Commun.* **1989**, 921.
4. Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091.
5. Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635.
6. McMills, M. C.; Zhuang, L.; Wright, D. L.; Watt, W. *Tetrahedron Lett.* **1994**, *35*, 8311.
7. Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185.
8. Curtis, E. A.; Sandanayaka, V. P.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 1989. Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73. Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667.
9. Kinder, F. R., Jr.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965.
10. Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491.
11. All new compounds were completely characterized (IR; ^{1}H-NMR, ^{13}C-NMR and analytical data).
12. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572. Turro, N. J.; Cha, Y. *Tetrahedron Lett.* **1987**, *28*, 1723. Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22. Klärner, F. G.; Golz, T.; Uhlander, C.; Yaslak, S. *Tetrahedron Lett.* **1996**, *37*, 1385.
13. Chateauneuf, J. E.; Liu, M. T. H. *J. Am. Chem. Soc.* **1991**, *113*, 6585.
14. Rhodium(II) perfluorobutyrate was used as the catalyst in these reactions.
15. West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051. West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892.
16. Ammonium ylide *vs.* carbonyl ylide formation has recently been encountered by C. O. Kappe in a study of the Rh(II)-catalyzed decomposition of diazoacetylureas; see accompanying communication.

(*Received in USA* 11 *February* 1997; *accepted* 24 *March* 1997)