Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5053-5056, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01015-5

Selectivity in the Rearrangements of Oxonium Ylides

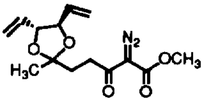
John B. Brogan,[1] Cary B. Bauer,[2] Robin D. Rogers,[2] and Charles K. Zercher[1]*

Department of Chemistry, University of New Hampshire, Durham, NH 03824
Department of Chemistry, Northern Illinois University, DeKalb, IL 60115

Abstract: Oxonium ylides were formed via an intramolecular reaction between a series of dioxalanes and metallocarbenes. The substitution patterns present in the ketals greatly affect the rearrangements of the oxonium ylides. It was also demonstrated that electron-deficient copper (II) species are superior catalysts for these systems. Copyright © 1996 Elsevier Science Ltd

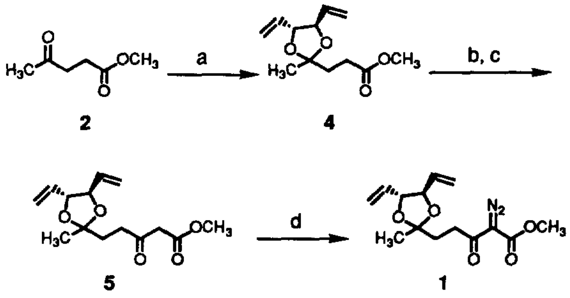
Prompted by methods for the facile generation of metal carbenoids, the formation and subsequent synthetic chemistry of oxonium ylides has received significant attention the past fifteen years.[3] However as a subset of these studies, oxonium ylides derived from ketals have been the focus of far less attention. The initial report by Gutsche on the rearrangement of a presumed oxonium ylide derived from ethyl diazoacetate and 2-phenyl dioxalane appeared to stimulate very little new chemistry.[4] In 1984 Doyle reported the identification of products proposed to be formed from an oxonium ylide generated from the dimethyl acetal of acrolein and the carbenoid of ethyl diazoacetate.[5] A few years later Roscamp and Johnson demonstrated the first intramolecular example of oxonium ylide formation involving a ketal.[6]

We were interested in exploring, in more detail, the chemistry of ketal-derived oxonium ylides. Specifically, we desired to explore the relationship between oxonium ylide ring size, substitution patterns of the ketal, and product distribution. We selected compound **1** as our synthetic target for we felt this substrate provided a system which could address a number of questions. For example, we were interested to determine whether formation of a six-membered ring ylide would be competitive with C-H insertion, which of the two diastereotopic oxygens would become involved in oxonium ylide formation, and whether 1,2- or 2,3-shifts would predominate in this system.



1

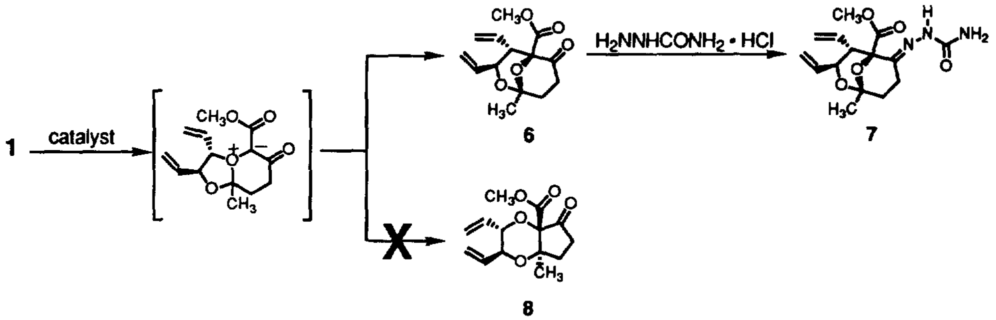
Methyl levulinate **2** was exposed to a mixture of isomers of 3,4-dihydroxy-hexa-1,5-diene **3** in the presence of p-TsOH and trimethylorthoformate. The desired d,l-isomer **4** was separated by careful column chromatography, saponified, and converted into a β-keto ester **5** using the procedure of Masamune.[7] The diazo functionality of **1** was incorporated through the application of p-carboxybenzenesulfonazide.[8]



a) mix of d,l and meso diols **3**, $(CH_3O)_3CH$, p-TsOH, (separate d,l-isomer by chromatography), 40%; b) i) KOH/CH_3OH; ii) H_3O^+, 95%;
c) i) carbonyl diimidazole, ii) $Mg^{2+}(O_2CCH_2CO_2CH_3)_2$, 74%;
d) p-carboxybenzenesulfonazide, Et_3N, 95%.

Scheme 1

A variety of catalytic systems have been used to promote ylide formation. Based upon analogy with the work by Roscamp and Johnson,[6] we chose to expose compound **1** to $Rh_2(OAc)_4$ (Scheme 2). Analysis by ^{1}H- and ^{13}C-NMR revealed that the product **6** was a single diastereomer and that it was derived from a 1,2-shift, yet questions remained about the connectivity and the stereochemical relationships within the molecule. Since compound **6** was a thick oil, a crystalline semicarbazone-derivative **7** was prepared. Analysis of the crystal structure of **7**[9] revealed that compound **6** was the result of a 1,2-shift from a proposed intermediate oxonium ylide. While we were not surprised that the oxonium ylide was formed by carbenoid interaction with the least sterically hindered oxygen, it was interesting to note that this 1,2-shift had occurred to the exocyclic, allylic position rather than to the ketalic position as required for the generation of **8**. This result was interesting in light of the results reported by Roscamp and Johnson[6] where intramolecular formation of an oxonium ylide involving an unsubstituted dioxalane resulted in the formation of a ring-fused 1,4-dioxane product.



Scheme 2

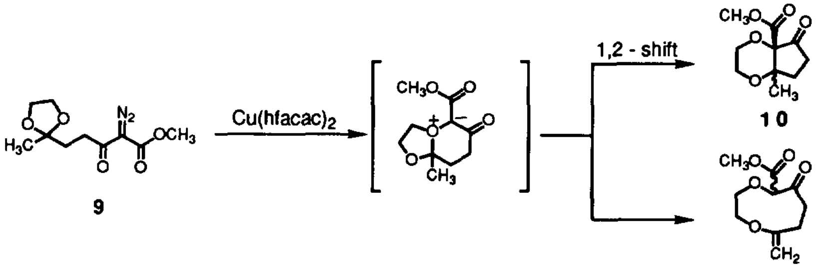
A variety of reaction conditions were screened (Table 1) and it was found that the electron deficient copper species $Cu(hfacac)_2$ provided the best yield of a product **6**. Suggestions have been made in the literature that ylide formation is promoted by electron-deficient copper (II) species.[10] Our studies appear to reinforce that conclusion.

TABLE 1

Substrate	Catalyst	Temp	Yield of 6
1	$Rh_2(OAc)_4$	25°	34%
1	$Rh_2(OAc)_4$	80°	30%
1	$Cu(hfacac)_2$	25°	NR
1	$Cu(hfacac)_2$	80°	64%
1	$Cu(acac)_2$	80°	40%

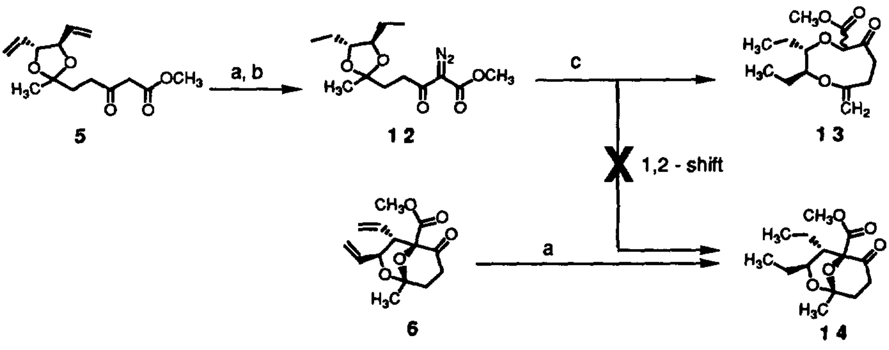
Two differences exist between compound **1** and the system studied by Roscamp and Johnson. The first difference is the presence of vinyl substituents on the dioxalane **1**, while the second is the ring size generated upon bicyclic oxonium ylide formation. We undertook a study to determine the role of these vinylic groups in biasing the 1,2-shift to the exocyclic position.

Preparation of the unsubstituted dioxalane derivative **9** via the same sequence of reactions as indicated in Scheme 1 provided us with another substrate for study. Exposure of **9** to the identical reaction conditions generated a complex reaction mixture which contained the stereochemically undefined ring-fused product compound **10** (18%) and a compound identified as the β-elimination product **11** (57%). The yield of diastereomerically pure **10** was eventually optimized at 51% through the use of anhydrous catalyst.[11] Since the β-elimination product **11** was eliminated through the use of catalyst which was very carefully dried, it is quite possible that water acts as a base to promote formation of the β-elimination product. (Scheme 3)



Scheme 3

Compound **12** was prepared (Scheme 4) by the catalytic reduction of the vinyl groups in compound **5** followed by the introduction of the diazo functionality through the use of p-carboxybenzenesulfonazide. The 4,5-diethyl-substituted dioxalane ring in compound **12** provided a third ketal suitable for investigating oxonium ylide formation and rearrangement. An authentic sample of the exocyclic 1,2-shift product **14** was prepared by catalytic reduction. Exposure of compound **12** to $Cu(hfacac)_2$ resulted in the formation of a product mixture from which it was immediately apparent that a 1,2-shift did not take place. The identification of an exocyclic olefin in the ^{1}H-NMR suggested that the β-elimination process dominated the chemistry of this substrate. The treatment of **9** and **12** with $Rh_2(OAc)_4$ yielded no ylide-derived products, further indication of the ylide-selectivity of $Cu(hfacac)_2$.



a) H_2/10% Pd/C, 50%; b) p-carboxybenzenesulfonazide, Et_3N, 95%; c) cat. $Cu(hfacac)_2$, benzene, 80°, 23%;

Scheme 4

We have concluded that intramolecular ylide formation generated from carbenoids and dioxalanes takes place on the least sterically hindered oxygen. No evidence was observed for a 2,3-sigmatropic shift involving the vinylic dioxalanes, nor were C-H insertion products identified. The regioselective 1,2-shifts of the proposed oxonium ylides were quite dependent upon the substitution patterns on the dioxalane. A 1,2-shift to the exocyclic position was facilitated by the presence of allylic stabilization, while the 1,2-shift to form the ring-fused product **10** occurred with, at best, modest efficiency using an unsubstituted dioxalane. The placement of sterically demanding and poorly cation-stabilizing substituents on the dioxalane, as with **12**, resulted in a predominance of β-elimination. The extension of this work to other ketals and a more detailed investigation of the factors which control this reaction and its selectivity are under investigation.

REFERENCES AND NOTES

---

[1] University of New Hampshire

[2] Northern Illinois University

[3] a) Nakai, T., Mikami, K., *Chem. Rev.*, **1986**, *86*, 885. b) Pirrung, M. C., Werner, J. A., *J. Am. Chem. Soc.*, **1986**, *108*, 6060. c) Doyle, M. P., Tamblyn, W. H., Bagheri, V., *J. Org. Chem.*, **1981**, *46*, 5094. d) Moody, C. J., Taylor, R. J., *Tetrahedron Lett.*, **1988**, *29*, 6005. e) Davies, H. M. L., Crisco, L. Van T., *Tetrahedron Lett.*, **1987**, *28*, 371.f) Doyle, M. P., Bagheri, V., Harn, N. K., *Tetrahedron Lett.*, **1988**, *29*, 5119. g) Padwa, A., Hornbuckle, S. F., *Chem. Rev.*, **1991**, *91*, 263. h) Doyle, M. P., *Chem. Rev.*, **1986**, *86*, 919. i) Clark, J. S., *Tetrahedron Lett.*, **1992**, *33*, 6193. and references contained therein.

[4] Gutsche, C. D., Hillman, M., *J. Am. Chem. Soc.* **1954**, *76i, 2236.*

[5] Doyle, M. P., Griffin, J. H., Chinn, M. S., van Leusen, D., *J. Org. Chem.*, **1984**, *49*, 1917.

[6] Roscamp, E. J., Johnson, C. R., *J. Am. Chem. Soc.* **1986**, *108*, 6062.

[7] Brooks, D. W., Lu, L. D-D., Masamune, S., *Angew. Chem., Int. Ed. Eng.* **1979**, *18*, 72.

[8] Hendrickson, J. B., Wolf, W. A., *J. Org. Chem.*, **1968**, *33*, 3610.

[9] Details of the crystal structure will be reported in a full account of this work.

[10] Ye T., McKervey, M. A., *Chem. Rev.* **1994**, *94*, 1091.

[11] The catalyst was dried under vacuum (0.5 mm) in the presence of H_2SO_4.

(*Received in USA* 22 *March* 1996; *revised* 21 *May* 1996; *accepted* 22 *May* 1996)