Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4315-4318, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00819-1

Efficient 1,3 Ester Shift in α–Disubstituted β–Ketoester Enolates. Remarkable Influence of the Metal Counterion on the Rate of Reaction

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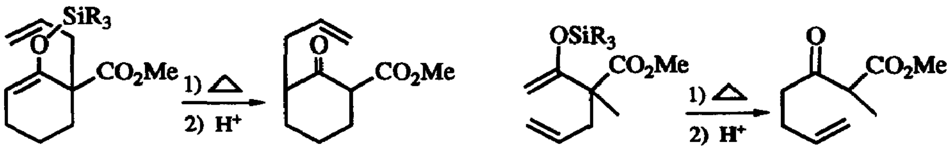
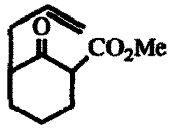
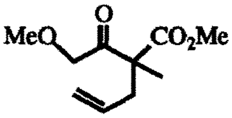
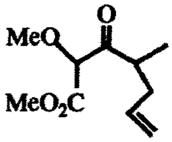
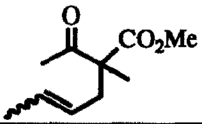
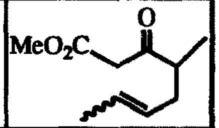
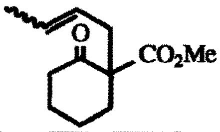
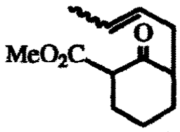
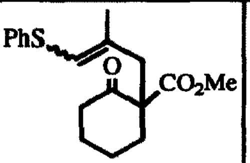
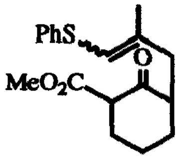
Abstract: The efficient and rapid α to γ rearrangement of the carbalkoxy group in α-disubstituted β–ketoesters is reported. The reaction proceeds at room temperature and in high yields when performed under naked anion conditions. A crossover experiment using appropriately substituted β–ketoesters is consistent with a cyclobutanedione monohemiketal intermediate.

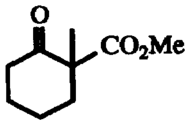
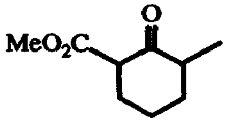
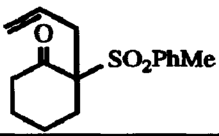
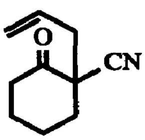
During an ongoing study of the Cope rearrangement of α–allyl β–ketoester silylenolethers of the type represented below,[1]



it was hypothesized that the corresponding enolates might undergo the same reaction at hopefully lower temperatures for reasons similar to those proposed[2] to explain the great rate acceleration of oxyanions in the oxy-Cope rearrangement.[3] In the event, it turned out that metal enolates did give the rearranged product in the first series investigated, and as hoped, temperatures for rearrangement were much lower and, in analogy with the oxyanion Cope rearrangement, there was a marked effect of the nakedness of the anion on the rate of reaction (entries 1 to 7, table 1). What was not anticipated however, was a change in reaction on going from silylenolethers to enolates as became apparent when the aliphatic models (entries 8 and 9, table 1) were studied. Indeed, it rapidly became evident that whereas the silylenolethers reacted *via* a Cope rearrangement, the corresponding metal enolates reacted *via* an α to γ carbomethoxy shift, which unfortunately was not apparent in the first cyclic model studied because of the identity of the product in both cases. Attempted reaction on appropriately substituted cyclic models clearly revealed the carbomethoxy shift (entries 10 to 12, table 1). Although the models of entries 10 and 11 might conceivably have involved a [1,3] sigmatropic schift of the allylic moiety,[4] the model of entry 12 on the other hand bears little ambiguity.[4c] Initial attempts to force the [3,3] sigmatropic shift with a substituted β–ketosulfone or β–ketonitrile failed (entries 13 and 14, table 1); this is

Table 1.

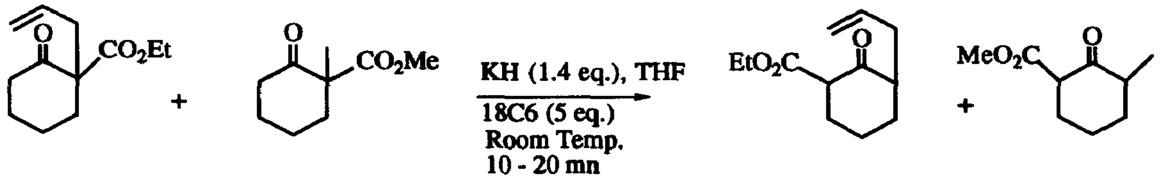
Ent.	Comp.	Base, Solvent	Temp.	Time	Yield	Prod.
1		LDA (1.4 eq), THF	Reflux	24 h	—	No reaction
2	"	LDA (1.4 eq), THF 12 C 4 (1 eq.)	Reflux	20 h	75	
3	"	NaH (1.4 eq), THF	Reflux	24 h	75	"
4	"	NaH (1.4 eq), THF 15 C 5 (1 eq.)	Reflux	2h30 mn	79	"
5	"	KH (1.4 eq), THF	Reflux	15-30 mn	78	"
6	"	KH (1.4 eq), THF 18 C 6 (1 eq.)	Refux	10-20 mn	83	"
7	"	KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	10-20 mn	86	"
8		KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	10-20 mn	60	
9		KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	10-20 mn	65	
10		KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	10-20 mn	81	
11		KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	10-20 mn	80	

12		KH (1.4 eq), THF 18 C 6 (5 eq.)	Room Temp.	15 mn	75	
13		KH (1.4 eq), THF 18 C 6 (1 eq.)	Reflux	48 h	—	No Reaction
14		KH (1.4 eq), THF 18 C 6 (5 eq.)	Reflux	48 h	—	Decomposition

intriguing in view of the great ease of the Claisen enolate rearrangement[5] with which the present system bears some similarity.

As pertains to the observed 1,3 carbomethoxy shift in our model compounds, similar 1,2 to 1,5 ester shifts have been known for a long time and a cyclic mechanism proposed.[6] In the present case, evidence was obtained in favor of the cyclic mechanism through a crossover experiment (scheme 1) and furthermore, the results are consistent with a 1,3 cyclobutanedione monohemiketal intermediate but not the free 1,3-dione itself (scheme 2). This result is perhaps not too surprising in view of the known propensity for highly strained

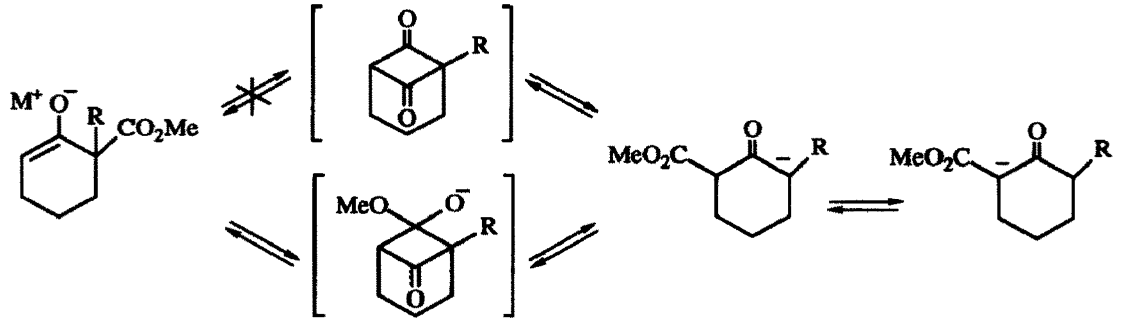
Scheme 1.



ketones to form hydrates and hemiacetals thus relieving angle strain in converting an sp^2 hybridized carbon into an sp^3 hybridized one.[7]

Finally, if one considers the rearrangement in its entirety, one question remains open and that is the rearrangement of the newly formed substituted carbanion into the β–ketoester enolate (last step, scheme 2) which is the lowest energy anion in the equilibrium. Depending on the base and conditions used, it could involve a dianion, be due to an adventitious source of protons or perhaps involve a 1,3 proton shift. Nevertheless, the reaction appears general and the yields are from good to excellent which gives it good synthetic potential. Further work is underway to delineate its scope and limitations.

Scheme 2.



Acknowledgement: Financial support from the Natural Sciences and Engineering Research Council of Canada and FCAR (Québec) is gratefully acknowledged.

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(*Received in USA* 4 *March* 1994; *revised* 19 *April* 1994; *accepted* 21 *April* 1994)