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FORMATION OF A REARRANGED β,γ-ENONE FROM REACTION OF AN ACYCLIC β,γ-UNSATURATED CARBOXYLIC ACID WITH METHYL LITHIUM

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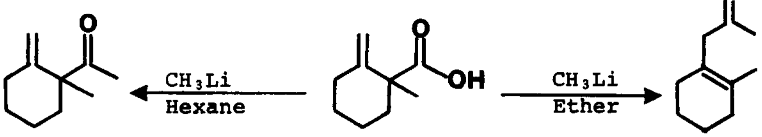
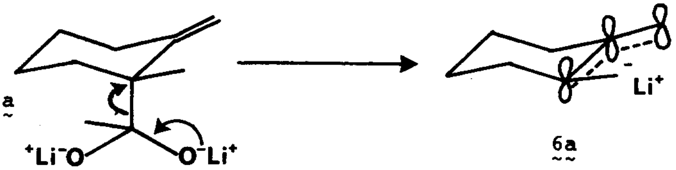
We have recently reported that reaction of β,γ-unsaturated carboxylic acid **1a** with methyl lithium yields, after work-up, unrearranged β,γ-unsaturated ketone **2a** in hexane and rearranged β,γ-unsaturated ketone **3a** in ether (eqn. 1).[1] Formation of rearranged enone **3a** in ether was rationalized by the mechanism given in the Scheme.



(1)

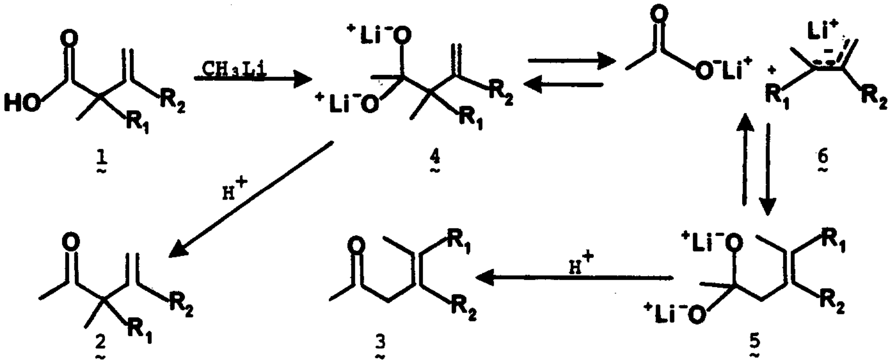
2a **1a** **3a**

The fragmentation of dilithio intermediate **4a** to give an allyl lithium **6a** and lithium acetate presumably occurs in ether but not in hexane because of the greater Lewis basicity of ether.[2] Although there is precedent for fragmentation of dilithio intermediates such as $YRC(OLi)_2$ to Y^-Li^+ and RCO_2Li when formation of stable anions is possible, e.g., $Y^- = CF_3^-$, this was the first report of the occurrence of such a fragmentation and rearrangement in the reaction of a β,γ-unsaturated carboxylic acid (Y = allyl anion) with an organolithium reagent. We suggested that the fragmentation of **4a** in ether was favored both by relief of steric crowding and by the fact that when the dilithio group in **4a** is axial, the molecule benefits from maximum allylic anion resonance stabilization as the fragmentation occurs (see eqn. 2).[1] Presumably the rearrangement has not been observed with other sterically crowded, i.e., α,α-disubstituted, β,



4a **6a**

$+ CH_3CO_2Li$ (2)

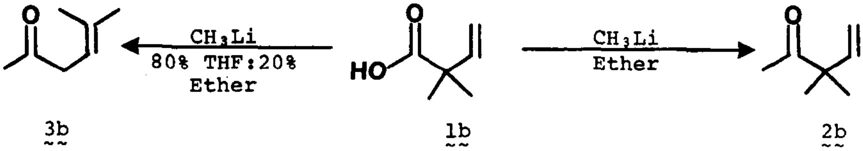


Scheme

a: $R_1, R_2 = (CH_2)_4$ b: $R_1 = CH_3$; $R_2 = H$

γ-unsaturated carboxylic acids because the acids lacked the cyclohexane ring system which in one chair conformation "holds" dilithio intermediate 4a in the optimum orientation for fragmentation. If conditions could be found which promote fragmentation of β,γ-unsaturated dilithio intermediates lacking the special cyclohexane stereochemistry, then clearly the potential of this rearrangement for synthesis of β,γ-unsaturated ketones would be considerably enhanced. We report here the first example of formation of a rearranged β,γ-enone from reaction of an acyclic β,γ-unsaturated carboxylic acid with methyl lithium. Treatment of 2,2-dimethyl-3-butenoic acid, 1b, with methyl lithium yields unrearranged ketone 2b in ether and rearranged ketone 3b in 80% tetrahydrofuran: 20% ether.

Approximately two equivalents of methyl lithium (Alfa, 1.8 M in ether) were added dropwise to an ethereal solution of 2,2-dimethyl-3-butenoic acid,[4,5] 1b, at 0° under nitrogen. The reaction mixture was next stirred for 4 hrs at 0° and then refluxed for 2 hrs. Acidic work-up gave a 55% yield[6] of the unrearranged β,γ-unsaturated ketone, 3,3-dimethyl-4-penten-2-one,[7] 2b (eqn. 3). No formation of rearranged enone, 5,5-dimethyl-4-penten-2-one,[8] 3b, was observed. Thus, while reaction of acid 1a with CH_3Li in ether cleanly yields rearranged ketone 3a, acid 1b under the same conditions gives only unrearranged 2b. This observation is consistent with literature reports of formation of only unrearranged β,γ-enones upon treatment of β,γ-unsaturated acids other than 1a with methyl lithium in ether.[9]



(3)

Since tetrahydrofuran (THF) is a better Lewis base than ether, fragmentation of dilithio intermediates such as 4a and 4b should be more rapid in THF or mixtures of THF and ether than in ether.[2] Therefore, a THF-ether mixture was tried as solvent for the reaction of methyl lithium with 2,2-dimethyl-3-butenoic acid. Dropwise addition of approximately two equivalents of methyl lithium (Alfa, 1.8 M in ether, 5 ml) to a 20 ml solution of 2,2-dimethyl-3-butenoic acid, 1b, in THF at 0° under nitrogen followed by 4 hrs stirring at 0° and then 2 hrs at reflux gave, after acidic work-up, a 50% yield of rearranged β,γ-unsaturated ketone, 5,5-dimethyl-4-penten-2-one,[8] 3b (eqn. 3). No formation of unrearranged enone 2b was observed. Thus simply switching solvents from ether to 80% THF:20% ether converts the reaction from an efficient synthesis of β,γ-enone 2b to an efficient synthesis of β,γ-enone 3b. This dramatic solvent effect is consistent with promotion of fragmentation of dilithio intermediate 4b by the more basic THF-ether solvent mixture.[10] The fact that only rearranged ketone 3b is isolated when fragmentation of 4b occurs, suggests that dilithio intermediate 5b is considerably more stable than dilithio intermediate 4b, presumably in part because of steric crowding caused by the two α-methyls in 4b.[11]

In summary, we have shown that the special stereochemistry of the cyclohexyl ring system is not required for the reaction of β,γ-unsaturated acids with CH_3Li to yield rearranged β,γ-unsaturated ketones. Although acyclic 2,2-dimethyl-3-butenoic acid, 1b, requires more vigorous reaction conditions to promote rearrangement than does 2-methyl-2-carboxymethylenecyclohexane, 1a, clean formation of either rearranged or unrearranged β,γ-unsaturated ketones can be effected for both acids by selection of the proper solvent. This suggests that it will generally be possible to find conditions that promote fragmentation of sterically crowded β,γ-unsaturated dilithio intermediates. Thus the formation of rearranged β,γ-enones from the reactions of β,γ-unsaturated carboxylic acids with alkyl lithiums may be a synthetically useful reaction.

Acknowledgement

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References

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2. Increasing the Lewis basicity of the solvent enhances its ability to solvate Li$^+$, thus leading to greater ionic character in O-Li and C-Li bonds and a higher fraction of free ions or solvent-separated ion pairs rather than contact ion pairs. Such changes should increase the reactivity of dilithio intermediates such as **4a** toward fragmentation. See, for example: (a) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307 (1966); and (b) R. A. Benkeser and W. E. Broxterman, *J. Amer. Chem. Soc.*, **91**, 5162 (1969).
3. M. T. Jorgenson, *Org. Reactions*, **18**, 26-28 (1971) and references therein.
4. Prepared by hydrolysis of the analogous ethyl ester, which was obtained from a Reformatsky reaction with ethyl 2-bromoisobutyrate and acetaldehyde followed by dehydration.
5. W. E. Parham and S. H. Groen, *J. Org. Chem.*, **31**, 1694 (1966).
6. Product yields were determined by glpc using a 25' x 1/4" 30% FFAP on Chromosorb W column. Dodecane was used as an internal standard.
7. N. F. Cywinski and H. J. Hepp, *J. Org. Chem.*, **30**, 3814 (1965).
8. (a) R. Heilmann, G. de Gaudemaris, P. Arnaud and G. Scheuerbrandt, *Bull. Chem. Soc. France*, 112 (1957); (b) N. C. Yang and M. J. Jorgenson, *Tetrahedron Letts.*, 1203 (1964).
9. For a review, see Reference 3.
10. Exclusive formation of rearranged enone **3b** is also observed when the THF-ether solution is heated at 35°, the reflux temperature of ether, for 2 hrs. This eliminates the possibility that the somewhat higher reflux temperature of the THF-ether solution is causing the fragmentation and rearrangement.
11. See Reference 2b for a related example in which relief of steric compression is the driving force for fragmentation and rearrangement of an adduct formed by reaction of an allylic Grignard reagent and a ketone.