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DECARBALKOXYLATION OF β-KETO ESTERS - A NEW MILD PROCEDURE[1]

Andrew E. Greene, Alicia Cruz, and Pierre Crabbé
C.E.R.M.O., Université Scientifique et Médicale
38041 Grenoble, France

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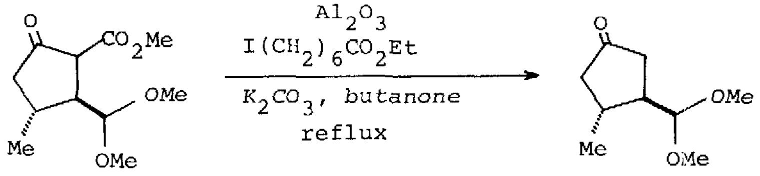
Decarbalkoxylation of β-keto esters, a frequently employed transformation, has received considerable attention in recent years[2].

In the course of our synthesis of 11-methyl-11-desoxy prostaglandin E[3] based on the tropolone approach[4], while attempting to alter the C vs O alkylation ratio, we observed the following facile decarbomethoxylation :

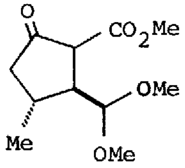


We wish to report that this alumina-assisted reaction has been successfully developed into a convenient, mild method for effecting decarbalkoxylation of β-keto esters in high yield. The best results were obtained using 20 ml of 1.5% aqueous dioxane and 8 g of aluminium oxide[5] (for TLC, basic, type T, Merck) per millimole of keto ester at reflux under nitrogen, followed by simple filtration, evaporation of the solvent, and chromatography when required. This procedure represents a significant improvement over existing methods[2] in that it is easily carried out, requires only moderate temperature and no strong nucleophile, and employs only common reagents. The keto esters that were examined under these conditions, the times that were required to effect the reactions, and the yields[6] that were obtained of the corresponding ketones are indicated below.

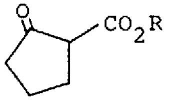
Dioxane was found to be superior to the other solvents examined (DME, acetone, butanone, benzene, methanol, ethyl acetate). All types of wet alumina tested effected the conversion to some degree, but the above type was the most efficacious. Dry alumina in dry solvent gave a significantly slower conversion, indicating a positive effect of water.

The relatively slight differences in reaction rates between corresponding methyl and ethyl esters, the sluggish reaction of the neopentyl ester (10), the hydrolysis of ester (11), and the rapid decarboxylation of keto acid (6) suggest a mechanism[2,7] that involves an alumina co-ordinated hydrolysis of the ester group followed by decarboxylation of the resulting keto acid.

We are currently working to extend the scope of this useful reaction.

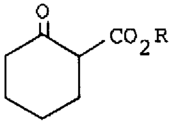


1 ; 3.5 hr, 96%



2 R = Me ; 2 hr, $70\%^{x}$

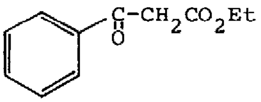
3 R = Et ; 2 hr, $70\%^{x}$



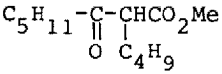
4 R = Me ; 27 hr, $90\%^{x}$

5 R = Et ; 73 hr, $80\%^{x}$

6 R = H ; < 2 hr, $90\%^{x}$

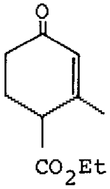


7 ; 16 hr, 89% ($95\%^{x}$)

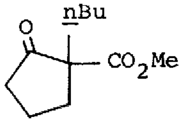


$C_5H_{11}-\underset{\underset{O}{\|}}{C}-\underset{\underset{C_4H_9}{|}}{C}HCO_2Me$

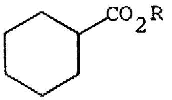
8 ; 29 hr, 95%



9 ; 140 hr, 72% ($80\%^{x}$)



10 ; > 200 hr



11 R = Me
12 R = H
24 hr, 50% 11, 50% 12

Acknowledgements

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1. Contribution n°11 from the Laboratoire de Chimie Organique, CERMO, University of Grenoble ; for n°10, see : P. Crabbé, E. Barreiro, J.M. Dollat, and J.L. Luche, Chem. Comm., 183 (1976).
2. Representative examples of newly developed "non-aqueous" methods include : DMSO-H_2O-(NaCl), 160° - A.P. Krapcho, E.G.E. Jahngen, Jr., A.J. Lovey and F.W. Short, Tetrahedron Letters, 1091 (1974) ; HMPA-NaCN, 75° - P. Müller and B. Siegfried, ibid., 3565 (1973) ; Xylene-Dabco, 165° - B-S. Huang, E.J. Parish and D.H. Miles, J. Org. Chem., 39, 2647 (1974) ; Collidine-LiI, 171° - F. Elsinger, J. Schreiber and A. Eschenmoser, Helv. Chim. Acta, 43, 113 (1960) ; B_2O_3, 150° - J.M. Lalancette and A. Lachance, Tetrahedron Letters, 3903 (1970).
3. A. Cruz, A. Greene and P. Crabbé, manuscript in preparation.
4. A.E. Greene and P. Crabbé, Tetrahedron Letters, 2215 (1975).
5. For other recent developments in the use of alumina in organic chemistry see: G.H. Posner and G.M. Gurria, J. Org. Chem., 41, 578 (1976), and references cited.
6. Yields are based on isolated, pure compounds and/or are established on the crude filtrates by calibrated GLC (noted by an asterisk^{x}) using a column of 5% SE-30. The similarity of retention times of dioxane and cyclopentanone precluded accurate analyses in 2 and 3 and the real yields are, in all probability, substantially higher in these two cases.
7. Cf. J.S. Filippo, Jr., L.J. Romano, C-I. Chern and J.S. Valentine, J. Org. Chem., 41, 586 (1976), and references cited. See also, C.K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, New York, 1953, Chapter XIV.