

A REGIOSPECIFIC SYNTHESIS OF
 α -METHYLENE KETONES

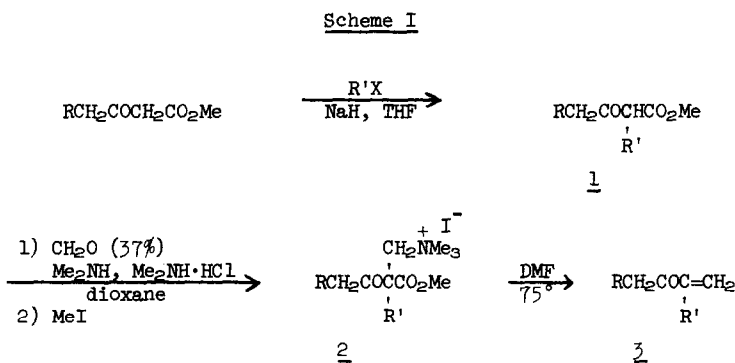
R. Bryan Miller* and Barbara F. Smith

Department of Chemistry, University of California
 Davis, California 95616

(Received in USA 5 September 1973; received in UK for publication 5 November 1973)

A general method for the synthesis of α -methylene ketones involves initial Mannich reaction of the ketone followed by some β -elimination procedure of the dialkylamino function.¹ The major problem with this sequence is the lack of regiospecificity in the Mannich reaction when an unsymmetrical ketone is used.² In the course of a study into a general synthetic approach to α -methylene carbonyl systems³ we have developed a regiospecific synthesis of α -methylene ketones.

The general synthetic approach is shown in Scheme I. The initial alkylation of the β -keto



ester allows the introduction of a wide variety of R' groups being limited only by the availability of the alkylating agent R'X. As others have found with malonic esters,⁴ the use of alkyl iodides or allyl or benzyl bromides as the alkylating agents is necessary to obtain good yields. Mannich reaction of the α -substituted β -keto esters 1⁵ with aqueous formaldehyde, dimethylamine and dimethylamine hydrochloride in dioxane at room temperature for 5 hours gave a

crude Mannich base which was directly quaternized in neat methyl iodide (large excess). The crystalline quaternary ammonium salts $\underline{2}^{5a}$ could easily be separated from unreacted substituted β -keto esters by trituration with anhydrous ether. Heating the quaternary ammonium salts in dimethylformamide at 75°C for 48 hours resulted in clean formation of the desired α -methylene ketones $\underline{3}$.⁵ By use of the activated β -dicarbonyl system the regiospecificity of the Mannich reaction was insured. This control of the site of condensation had been observed nearly fifty years ago by Mannich himself in a study of β -keto acid systems.⁶ The consequence, in our scheme was to allow the ultimate introduction of the α -methylene group cleanly into a known position in unsymmetrical ketones. The results of this study are summarized in Table I.

Table I

R	R'	% Yield $\underline{2}$ ^a	% Yield $\underline{3}$ ^a
H	Et	70 (15) ^b	49 (52) ^c
H	i-Bu	62 (18) ^b	44 (69) ^c
H	i-Pr	23 (60) ^b	36 (37) ^c
H	CH ₂ =C(Me)CH ₂	52 (9) ^b	35 (51) ^c
H	PhCH ₂	90	59
n-C ₅ H ₁₁	Me	77 (22) ^b	67

^a These are isolated yields and represent % conversion.

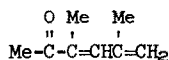
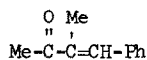
^b This is the amount of unreacted substituted β -keto ester recovered.

^c These are NMR yields determined by integration of vinyl protons using benzene as an internal standard.

The regiospecificity obtained by using the β -keto ester system is dramatically shown in the case where R = H, R' = i-Pr. Mironov^{2a} found that direct Mannich reaction and subsequent decomposition of the hydrochloride of the Mannich base on methyl isobutyl ketone gave a mixture of α -methylene ketones consisting of 5% of $\underline{2}$ (R = H, R' = i-Pr) and 95% of isobutyl vinyl ketone, while our scheme gives exclusively $\underline{3}$ (R = H, R' = i-Pr). This selectivity is also illustrated in the case where R = n-C₅H₁₁, R' = Me. In the use of an unactivated ketone this would involve differentiation between the two α -CH₂ groups of ethyl hexyl ketone and a mixture of α -methylene

ketones would be expected. However using the β -keto ester system the α -methylene group can be exclusively introduced at the carbon bearing the methyl group to give 4 (R = n-C₅H₁₁, R' = Me).

Another point of interest is that only the terminal methylene compound is formed; there was never any detectable amount of the isomeric trisubstituted olefin. This is especially important where R' is methallyl or benzyl. In these cases the isomeric trisubstituted olefins would be fully conjugated, see 4 and 5, and would be the more stable isomers.

45

ACKNOWLEDGMENT. The authors wish to thank the Faculty Committee on Research, University of California, Davis for partial support of this work.

References

1. F. F. Blicke, Org. React., **1**, 303 (1942).
2. For recent examples see: (a) Y. Y. Musabekov, A. F. Moskvin, O. P. Yablonskii, V. V. Vorenenkov and G. S. Mironov, Zn. Org. Khim., **8**, 2288 (1971); (b) T. A. Spencer, D. S. Watt and R. J. Friary, J. Org. Chem., **32**, 1234 (1967); (c) R. A. Cormier, W. L. Schreiber and W. C. Agosta, J. Amer. Chem. Soc., **95**, 4873 (1973).
3. E. S. Behare and R. B. Miller, Chem. Commun., 402 (1970); R. B. Miller and B. F. Smith, Synthetic Commun., **3**, 129 (1973); R. B. Miller and B. F. Smith, Synthetic Commun., in press.
4. P. L. Stotter and K. A. Hill, Tetrahedron Lett., 4067 (1972).
5. Satisfactory (a) nuclear magnetic resonance and infrared spectra and (b) elemental analysis and/or mass spectral data were obtained for these compounds.
6. C. Mannich and M. Bauroth, Ber., **57**, 1108 (1924); C. Mannich and K. Curtaz, Arch. Pharm., **264**, 741 (1926).