Tetrahedron Letters No. 33, pp 2915 - 2916, 1975. Pergamon Press. Printed in Great Britain.

PYRIMIDINE SYNTHESIS FROM METHYL 2,2-DIMETHYLACETOACETATE

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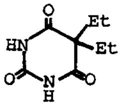
(Received in UK 27 June 1975; accepted for publication 7 July 1975)

It is well known that diesters of disubstituted malonic acids (1a) react with urea, thiourea and their derivatives to form pyrimidines, such as 5,5-diethylbarbituric acid[1] (2). Corresponding disubstituted cyanoacetates (1b) and malononitriles (1c) are also reported[2] to undergo similar reactions. However, we are unaware of any reports in the literature, prior to the present work, relating to the synthesis of pyrimidines from disubstituted β-keto-esters (such as 3).

R^1R^2CXY

1 a, X = Y = CO_2R
b, X = CN, Y = CO_2R
c, X = Y = CN

R^1,R^2 = alkyl or aryl



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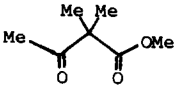

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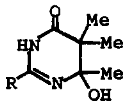
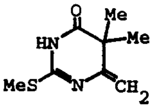


4 a, R = SMe
b; R = SEt
c; R = OMe



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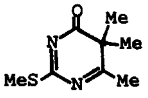

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Methyl 2,2-dimethylacetoacetate[3] (3) reacts with S-methylisothiourea in aqueous solution at 20° to give the 5,6-dihydropyrimidine derivative (4a) in 70% yield. The latter compound (m.p 146-147°) was characterized[4] on the basis of its n.m.r. [$\tau(CD_3OD)$ 7.55 (3H, s), 8.64 (3H, s), 8.80 (3H, s), 8.84 (3H, s)], i.r. [$\nu_{max}^{CHCl_3}$ 3590w, 3380w, 1705s, 1630s cm^{-1}] and mass [M^+ at m/e = 202.0766 (calc. 202.0775)] spectra and its elemental composition.[5] Methyl 2,2-dimethylacetoacetate (3) reacts in the same way with S-ethylisothiourea and

O-methylisourea to give (4b) and (4c), respectively The latter compounds have also been isolated as crystalline solids and fully characterized[6].

When (4a) is sublimed under reduced pressure or treated with methanesulphonyl chloride and triethylamine in dichloromethane solution, its dehydration product (5) [τ(CDCl$_3$) 4.98 (1H, s), 5,20 (1H, s), 7.49 (3H, s), 8 60 (6H, s); M^+ at *m/e* = 184 0665 (calc 184 0671)] is obtained and may be isolated crystalline (m p. 108-109°) in modest yield The formation of its tautomer (6) is not observed under either set of reaction conditions.

Acknowledgment One of us (S.R.J) thanks the S R C for the award of a research studentship.

REFERENCES AND FOOTNOTES

[1] E. Fischer and A Dilthey, *Annalen* **335**, 334 (1904)

[2] D J Brown, "The Pyrimidines", Interscience, New York and London, 1962, pp 68, 73

[3] K v Auwers, *Chem. Ber* **46**, 494 (1913)

[4] The preferred tautomeric structure of (4a), *i e* whether the N-H proton is situated on *N*(1) or *N*(3), has not been determined.

[5] Satisfactory microanalytical data have been obtained for all the new compounds described

[6] (4b) has m p 150-151°, τ(CD$_3$OD) 6 97 (2H, q, J = 7Hz), 8 66 (3H, s), 8 69 (3H, t, J = 7Hz 8 81 (3H, s), 8.85 (3H, s), M^+ at *m/e* = 216 0939 (calc. 216.0933)

(4c) has m p 132-133°, τ(CD$_3$OD) 6 18 (3H, s), 8 61 (3H, s), 8 80 (3H, s), 8 90 (3H, s), M^+ at *m/e* = 186 1010 (calc 186 1004)