Acta Chemica Scandinavica B 36 (1982) 529 – 531

Enols of 1,1-Diformylacetone in the Synthesis of 5-Acylpyrimidines

TORE BENNECHE and KJELL UNDHEIM

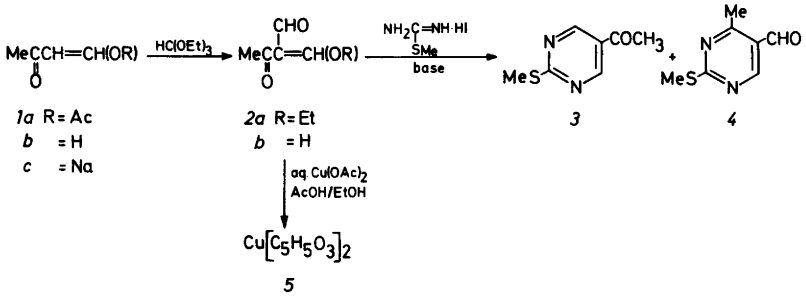
Department of Chemistry, University of Oslo, Oslo 3, Norway

The enol acetate of 3-oxobutanal has been formylated using ethyl orthoformate to provide the enol ether of 1,1-diformylacetone. The latter has been condensed with methylisothiourea to yield isomeric 5-acetyl- and 4-methyl-5-formyl- pyrimidines, the ratio being dependent on the reaction conditions.

Substituted malondialdehydes or their "masked" analogues are useful three-carbon units in the synthesis of 5-substituted pyrimidines.[1] For the preparation of 5-acylpyrimidines without substituents in the 4- and 6-positions, a suitable intermediate acetylmalondialdehyde (1,1-diformylacetone) was required. Thus benzoylmalondialdehyde has been prepared by formylation of 3-oxo-3-phenylpropanal.[2] Other acylmalondialdehydes have been synthesized by the Vilsmeier formylation of ketones and aldehydes.[3,4] In the formylation of acetone by this method, however, the reaction proceeds beyond the 1,1-diformylated acetone *2b* to its triformylated derivative.[5] We describe a synthesis of the desired acetylmalondialdehyde *2b* masked as 4-ethoxy-3-formyl-3-buten-2-one *2a*. This was achieved by formylation of the enol acetate *1a* using triethyl orthoformate and acetic acid catalysis. One half equivalent of acetic acid in the presence of excess ortho ester gave optimal yields. The isomer ratio of (*Z*)- and (*E*)-*2* was close to unity (^{1}H NMR, GLC). The product, an oil, formed a solid adduct with cupric ions (*5*). Formylation as above of the unprotected enol of 3-oxobutanol *1b*, or of its sodium salt *1c*, in the presence of acetic anhydride gave only low yields of the malondialdehyde *2a*.

For the pyrimidine synthesis, 4-ethoxy-3-formyl-3-buten-2-one was condensed with methylisothiourea. A mixture of 5-acetyl-2-methylthiopyrimidine *3* and the isomeric 5-formyl-4-methyl-2-methylthiopyrimidine *4* was obtained, the yields and isomer ratios being dependent on the reaction conditions; in sodium methoxide the yield of isolated product *3* was only 9%, and in DMF using potassium *tert*-butoxide the total yields of *3* and *4* were of the order 50%. The isomer ratio *3*:*4* varied from 45:55 on slow addition of *2a* to a solution of methylisothiourea, to 75:25 for the reverse addition. With acetone as solvent, the ketone *3* was the major isomer (ratio 80:20).

The reaction sequence leading to the cyclic product is rationalized as a Michael type addition of the amino nucleophile with subsequent expulsion of



Scheme 1.

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the RO-substituent and cyclization, the reactivities of the two competitive oxo groups being similar.

By this type of synthesis useful pyrimidine synthons are available due to the ease of substitution of the 2-methylthio substituent and the possibility for transformations of the 5-acyl moiety.

EXPERIMENTAL

(Z)- and (E)-4-ethoxy-3-formyl-3-buten-2-one 2a. *Method A.* Acetic acid (3.0 g, 0.05 mol) was added to a solution of 4-acetoxy-3-buten-2-one[6] (15.0 g, 0.11 mol) in triethyl orthoformate (50 ml) and the mixture heated for 6 h under conditions where the more volatile product distilled from the reaction mixture at 85 °C. When the reaction was over, the excess triethyl formate was removed at reduced pressure and the residue distilled collecting the fraction containing the title compound with b.p. 60 – 68 °C/0.01 mmHg. This fraction was redistilled; yield 6.2 g (40 %), b.p. 62 – 64 °C/0.01 mmHg. GLC gave isomer separation on a 10 % OV-17 column, t = 100 – 250 °C/16 °C per min; ratio 1:1. ^{1}H NMR ($CDCl_3$): δ 1.48 and 4.36 or 4.38 (OEt), 2.32 (COMe), 7.63 (1H,vinyl,s,(*Z*)), 8.00 (1H,vinyl,s,(*E*)), 9.71 (CHO,s), 10.03 (CHO,s). IR (film): 2850 and 2760 (CHO), 1700 – 1660 cm^{-1} (MeCO). MS [70 eV; m/z (% rel.int.)]: 142(0.3,M), 114(6), 100(4), 99(6), 86(12), 43(100).

For elemental analysis the cupric acetate complex was prepared. Thus cupric acetate was added to a solution of a specimen of the above product in ethanol and acetic acid. The complex formed was slowly precipitated in the cold and was recrystallized from methanol, m.p. 211 – 214 °C. Anal. $C_{10}H_{10}O_6Cu$: C,H.

When less than $\frac{1}{2}$ equivalent of acetic acid was used, the yield of *2a* was decreased whereas the yield varied little in the range $\frac{1}{2}$ – 1 equivalent of acetic acid. Invariably, unreacted enol acetate *1a* was recovered (25 – 30 %) from the reaction mixture, but increase in the reaction time also increased polymerization.

Method B: The yields of *2a* were of the order 10 – 15 %, when 3-oxo-butanal[7] or its sodium salt[7] was reacted as above in the presence of one equivalent of acetic anhydride for the *in situ* generation of the enol acetate.

5-Acetyl-2-methylthiopyrimidine 3 *and 4-formyl-4-methyl-2-methylthiopyrimidine* 4. *Method A.* 4-Ethoxy-3-formyl-3-buten-2-one (28.4 g, 0.2 mol) in DMF (100 ml) was added dropwise (105 min) at 5 °C to a stirred mixture from 2-methylisothiouronium iodide (43.4 g, 0.2 mol) and potassium *tert*-butoxide (22.4 g, 0.2 mol) in DMF (200 ml). The mixture was stirred for an additional 1 h at 5 °C, heated gradually to 50 °C over 1 h and stirred at this temperature for 1 h before the solvent was distilled off at reduced pressure. The residue was triturated with water, the solid collected and washed well with water; yield 18.0 g (54 %). GLC analysis on a 10 % IV-17 column at t = 150 – 250 °C/16 °C per min gave composition 47 % of *3* and 53 % of *4*. The isomers were separated by fractional crystallization from methanol, the 5-formyl isomer *4* being the more soluble.

5-Acetyl-2-methylthiopyrimidine: M.p. 133 – 134 °C (MeOH). Anal. $C_7H_8N_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.56 (MeCO), 2.60 (MeS), 8.97 (H-4 and H-6). IR (KBr): 1680 (CO) and 1580 cm^{-1} (Pyr.). MS [70 eV; m/z (% rel.int.)]: 168(100,M), 167(14), 153(36), 125(7), 123(5), 122(19).

5-Formyl-4-methyl-2-methylthiopyrimidine: M.p. 63 – 64 °C (light petrolum). Anal. $C_7H_8N_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.60 (MeS), 2.77 (4-Me), 8.78 (H-6), 10.17 (CHO). IR (KBr): 1690 (CO) and 1580 cm^{-1} (Pyr). MS [70 eV; m/z (% rel.int.)]: 168 (100,M), 167(16), 153(1), 123(5), 122(29), 96(8).

Method B. A mixture from 2-methylisothiouronium iodide (7.0 g, 32 mmol) and potassium *tert*-butoxide (3.6 g, 32 mmol) in DMF (200 ml) was added over 15 min with stirring at room temperature to a solution of 4-ethoxy-3-formyl-3-buten-2-one (4.6 g, 32 mmol) in DMF (100 ml). The mixture was stirred for 1 h at room temperature and for 1 h at 50 °C before the solvent was removed at reduced pressure and the product worked up as above; yield 2.3 g (43 %). The product composition (GLC) was 74 % of *3* and 26 % of *4*.

Method C. A solution of 4-ethoxy-3-formyl-3-buten-2-one (14.2 g, 0.1 mol) in acetone (50 ml) was added over 10 min at 5 °C to a stirred mixture from 2-methylisothioronium iodide (21.7 g, 0.1 mol) in acetone (200 ml) and 1 M potassium *tert*-butoxide in *tert*-butanol (100 ml). The resultant mixture was stirred for 24 h at room temperature before the acetone was distilled off. Part of the 5-acetyl isomer *3* was precipitated and was collected. The filtrate was evaporated at reduced pressure and the remaining *3*-isomer isolated by fractional crystallization of the residue from methanol; yield of *3* 6.7 g (40 %). The methanol solution was subsequently evaporated and the residue subjected to distillation which gave *4* in 12 % (2.0 g) yield; b.p. 88 – 89 °C/0.01 mmHg.

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Received February 12, 1982.

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