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(E)-Ethyl β-formylacrylate Dimethylhydrazone Methiodide : a Reactive and Convenient Precursor of (E)-Ethyl-β-formylacrylate

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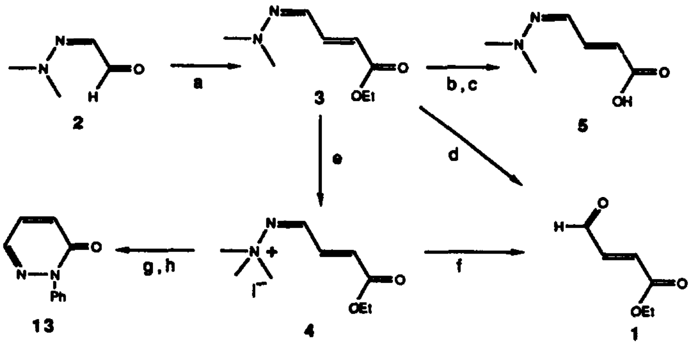
SUMMARY :
The methiodide of (E)-Ethyl-β-formylacrylate dimethylhydrazone is readily prepared in two steps. It gives rise to regioselective 1,4-additions and is a stable and convenient precursor of (E)-Ethyl-β-formylacrylate.

Beta-acylacrylates are polyelectrophilic olefins, widely used in organic chemistry. In particular, the least substituted member of the series, ethyl β-formylacrylate [(E)-4-oxo-2-butenoate] 1[1] is highly reactive,[2] as would expected for a vinylic analog of ethyl glyoxylate.[1] The corresponding free acid is prepared in moderate yields by thermal isomerisation of 5-hydroxy-2-(5H)-furanone.[3] Different masked forms of ethyl β-formylacrylate have been described but their syntheses often suffer from low yields. The most convenient preparations of 1 start from unsymetrical protected glyoxals such as a monothioketal,[4] a monodiethylacetal[5,6] or a N,N-dimethylhydrazone 2.[7]



SCHEME 1

a : K_2CO_3 , $(EtO)_3POCH_2COOEt$, rflx 1h ,85% ; b : same as in a ,24h ; c : H^+ ; d : CHO-CHO ,H^+ ; e : DMF ,MeI ,rt ,48h , 95%
f : H_2O - BENZENE , pTsOH , 65% ; g : NH_2-NH_2 ,A cOH ; h : Ac_2ONa , AcONa ,70%

By condensing this latter reagent either with metallated ethyl acetate or ethyl triphenylphosphoranylidine acetate, Severin et al.[7] obtained ethyl β-formylacrylate as the monohydrazone 3. However, these authors did not succeed in deprotecting this hydrazonoester 3 when an excess of formaldehyde as a N,N-dimethylhydrazine scavenger was used. We modified the above method for the preparation of compound 3 by a Wittig-Horner reaction starting from the glyoxal monohydrazone 2, which proceeds easily and in high yield.

Our attempt to convert the hydrazonoester 3 into the corresponding free ethyl β-formylacrylate 1 failed even when replaced formaldehyde by more electrophilic reagents such as glyoxylic acid or glyoxal.

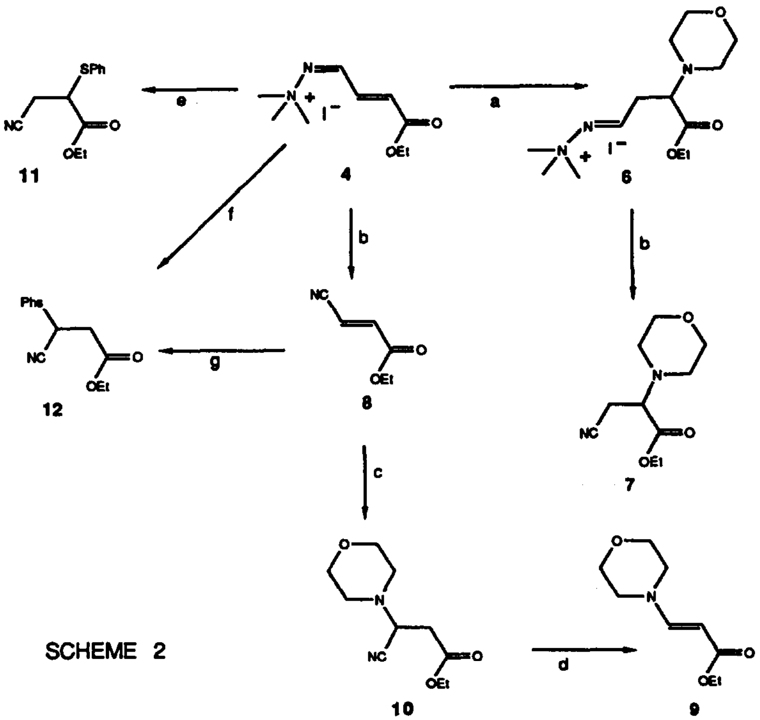
In the search of a stable but more easily hydrolyzed precursor, we investigated the chemical behaviour of a quaternary ammonium salt of compound 3, i.e. the methiodide 4.

The present paper describes the synthesis of compound 4, its use as a synthetic equivalent of 1 in Michael reactions and its easy hydrolysis into β-formylacrylate 1.

The N-N-dimethylmonohydrazone of the glyoxal 2 was reacted with ethyl triethylphosphonoacetate in water in the presence of potassium carbonate, affording an 85 % yield of the hydrazonoester 3 after distillation (85°C/0.2 mm). The corresponding free acid 5 (m.p. 127°C) can be obtained with nearly quantitative yield by extending the reaction time to 24 hours and acidifying the reaction medium. Alkylation of 3 (Scheme 1) with methyliodide in DMF afforded the methiodide 4 (m.p. 140°C) which was recovered by precipitating it with diethyl ether. $^1H(CD_3OD)$ 1.25(t, J=7Hz, 3H), 3.5(s, 9H), 4.20(q, J=7Hz, 2H), 7.00(d, J_{23}=16Hz, H_2), 7.30(dd, J_{32}=16Hz, J_{34}=8Hz, H_3), 8.90(d, J_{43}=8Hz, H_4). It was characterized in NMR spectroscopy by a strong deshielded signal at 8.90 ppm for the H proton of the hydrazonium salt moiety.

As a consequence of its strong electrophilic character the methiodide 4 afforded the morpholino-1,4 addition product 6 (m.p. 148°C) even at room temperature. No reaction was observed with the hydrazonoester 3, even in boiling DMF.

Michael adducts formed by the addition of morpholine to β-acyl acrylic acids are in general thermally reversible.[8] In our case, heating adduct 6 led to a mixture of three compounds. The two major substances were identified as ethyl-2 morpholino-3-cyanopropionate 7 (40 % of the mixture) and as ethyl-3-cyanopropenoate 8 (about 40 % of the mixture). Compound 8 could also be prepared in a nearly quantitative yield by means of a potassium carbonate treatment of the methiodate 4. The third product (20 %) was identified as the ethyl-3 morpholino propenoate 9 identical to a sample obtained by Michaël addition of morpholine onto ethyl propiolate. The obtention of the enaminoester 9 starting from 4 results from an addition of morpholine onto the intermediate 3-cyanopropenoate 8 in the less hindered position, followed by elimination of HCN. In a similar manner the addition of thiophenol to the quaternary ammonium salt 4 followed by alkalinization led to the expected cyanoester 11. It is noteworthy that the replacement of sodium thiophenate by thiophenol led to the other regioisomer 12. We can assume that in presence of a base the methiodate 4 is converted into the nitrile 8, which then adds the thiophenate anion in the less hindered position as previously observed with morpholine. Also, ethyl 3-cyanopropenoate in presence of thiophenol (scheme 2) led to the same regioisomer 12.



SCHEME 2

a : EtOH , HN O , rt , 12h , 80% ; b : K_2CO_3 , ETHER - H_2O , 8h , 75% ; c : EtOH , HN O, rt , 3 days , 95%
d : EtOH , rflx ,36h , 100% ; e : EtOH, PhSH , KOH , rt , 4h , 40% ; f : EtOH ,PhSNa , 5h , 0° C, 68% ; g : EtOH , NEt_3 , PhSH , 4h , 98 %

Finally, methiodide 4 constitutes a very convenient starting material for the preparation of ethyl β-formylacrylate 1. A 6 h reflux in a biphasic system, followed by a bulb-to-bulb distillation of the crude oil yielded pure ethyl β-formylacrylate 1. However, for many reactions methiodide 4 can be directly used ; Thus, treatment of the salt 4 with phenylhydrazine afforded the corresponding N-phenylhydrazone, which is easily converted into the N-phenylpyridazone 13 (m.p. 107-108°C[9]) in a buffered medium[10] (Scheme 1).

The methiodide of ethyl (E) β-formyl acrylate dimethylhydrazone can also be considered as a stable masked form of (or starting material) for trans-ethyl β-formylacrylate. The easy transformation of the hydrazonium salt moiety of 1 into either a formyl or a cyano group led to a series of 1,4 adducts with regiocontrol of the addition in presence of various nucleophiles.

REFERENCES

1. S.R. LANDOR, P.D. LANDOR, M. KALLI, J. Chem. Soc., Perkin Trans I, 2921 (1983).
2. H.D. SCHARF, J. JANUS, Chem. Ber., 111, 2741 (1978).
3. I. BANGA, M. GERENDAS, K. LAKI, G. PAPP, E. PORGES, F.B. STRAUB, SZENT-GYORGYI, Z. Physiol. Chem., 254, 147 (1938).
4. G.S. BATES, S. RAMASWAMY, J. Chem. Soc., Chem. Commun., 904 (1980).
5. A.I. MEYERS, R.L. NOLEN, E.W. COLLINGTON, T.A. NARWID, R. STRICKLAND, J. Org. Chem., 38, 1974 (1973).
6. A. STAMBOULI, R. AMOUROUX, M. CHASTRETTE, Tetrahedron Lett., 28, 5301 (1987).
7. Th. SEVERIN, H. POEHLMANN, Chem. Ber., 111, 1564 (1978).
8. N.H. CROMWELL, K.E. COOK, J. Org. Chem., 23, 1237 (1958).
9. H. McNAB, I. STOBIE, J. Chem. Soc., Perkin Trans I, 1845 (1982).
10. N.H. CROMWELL, K.E. COOK, P.L. GREGER, J. Am. Chem. Soc., 78, 4416 (1978).

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