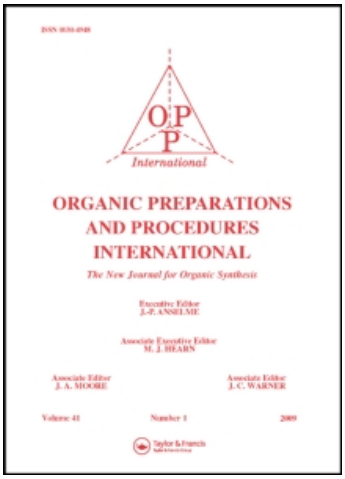


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF DIMETHYL DIACETOXYFUMARATE AND ITS CONDENSATION WITH HETEROCYCLIC AMINES

M. Tisler[a]; R. Zupet[a]
[a] Department of Chemistry, University of Ljubljana, Ljubljana, YUGOSLAVIA

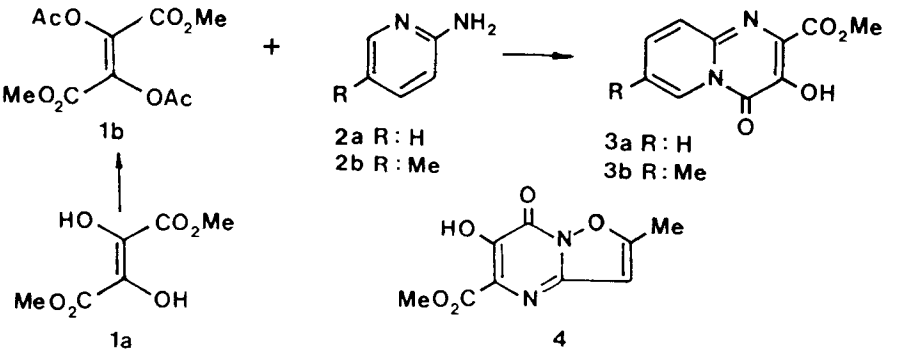
To cite this Article Tisler, M. and Zupet, R.(1990) 'AN IMPROVED SYNTHESIS OF DIMETHYL DIACETOXYFUMARATE AND ITS CONDENSATION WITH HETEROCYCLIC AMINES', Organic Preparations and Procedures International, 22: 4, 532 — 534
To link to this Article: DOI: 10.1080/00304949009356320
URL: http://dx.doi.org/10.1080/00304949009356320

AN IMPROVED SYNTHESIS OF DIMETHYL DIACETOXYFUMARATE AND ITS CONDENSATION WITH HETEROCYCLIC AMINES

Submitted by (08/14/89) M. Tisler* and R. Zupet

Department of Chemistry
University of Ljubljana
61000 Ljubljana, YUGOSLAVIA

The synthetic routes to 4-oxo-4H-pyrido[1,2-a]pyrimidines have been reviewed.[1] For the most part, condensation between 2-aminopyridines and 1,3-ketoesters, malonates, alkoxymethylene malonates, cyanoacetates or lactones are employed. So far, the only attempt to use a fumarate for the preparation of the aforementioned bicyclic system is the reaction between tetrazolo[5,1-a]pyridine and dimethyl maleate or fumarate at elevated temperatures.[2] A similar rearrangement of a tetrazolylpyridine to the same bicyclic system was described by us.[3]



It appears that the acid-catalyzed condensation of dimethyl diacetoxyfumarate (1b) is limited to a few heterocyclic amines. With 2-aminopyridine (2a) or its 5-methyl analog (2b), 2-carbomethoxy-3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine (3a) or its 7-methyl analog (3b) were formed. While condensation of 1b with various aminopyrimidines failed, 3-amino-5-methylisoxazole reacted with 1b to afford 5-carbomethoxy-6-hydroxy-2-methyl-7-oxo-isoxazolo[2,3-a]pyrimidine (4). The chemistry of several isomeric isoxazolopyrimidine systems was investigated in detail, but there is only one report on a 7-oxo-isoxazolo[2,3-a]pyrimidine. A derivative of this system was prepared by condensation of 3-aminoisoxazole with ethyl acetoacetate.[4] Some mesoionic isoxazolo[2,3-a]pyrimidinediones were obtained by cycloaddition of C_3O_2 to 3-aminoisoxazoles.[5]

In all cases, the second acetoxy group of 1b is transformed into a hydroxy group (see 3 and 4). The advantage of the present method lies in the simultaneous introduction of a carbalkoxy and hydroxy group in the pyrimidine part of the bicyclic system. The reported

synthesis[6] of dimethyl diacetoxyfumarate (1b) by acetylation of dimethyl dihydroxyfumarate (1a, prepared from dihydroxyfumaric acid[7] by reaction with diazomethane[6] or acid-catalyzed esterification with methanol[8]) is unreliable (considerable amounts of material were lost during purification) and thus is inadequate for the preparation of large quantities of 1b. We have developed a more efficient approach by using isopropenyl acetate for the acetylation which provides 1b in 86% yield.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian EM 360 L instrument using TMS as the internal reference.

Dimethyl diacetoxyfumarate (1b).- Dimethyl dihydroxyfumarate (1a) (3 g), isopropenyl acetate (15 ml) and 0.1 g of p-toluenesulfonic acid were heated under reflux for 8 hrs. The mixture was left standing overnight; the precipitated solid was collected and the filtrate was evaporated to dryness. Upon crystallization of the residue from methanol, 1.12 g (86%) of 1b, mp. 103-108°, lit. [6] mp. 105-108°, was obtained.

Anal. Calcd for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65. Found: C, 46.14; H, 4.72

2-Carbomethoxy-3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine (3a).- A mixture of (1b) (1.54 g), 2a (0.188 g), methanol (10 ml) and a small amount of p-toluenesulfonic acid was heated under reflux for 3 hrs. After standing overnight at room temperature, some semisolid material separated. The solvent was evaporated and the residue treated with a small quantity of ethyl acetate to separate the solid material from the oil. Upon crystallization of the solid from ethanol, the product (75 mg, 17%), mp. 210-212°, was obtained.

Mass spectrum: $M^+ = 220$. ^1H NMR ($CDCl_3$): δ 4.12 (s, 3H, COOMe), 7.05 (ddd, 1H, $J_{6,7}$ = 7.3, $J_{7,8}$ = 6.1 and $J_{7,9}$ = 1.9 Hz, H-7), 7.53 (ddd, 1H, $J_{8,9}$ = 9.0 Hz, H-8), 7.7 (dd, 1H, H_9), 8.86 (dd, 1H, H_6), 10.74 (bs, 1H, OH).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72

Found: C, 54.51; H, 3.85; N, 12.50

2-Carbomethoxy-3-hydroxy-7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine (3b).- A mixture of 1b (520 mg), 2b (216 mg), methanol (5 ml) and few drops of glacial acetic acid was heated under reflux for 3 hrs. Chromatographic analysis (Merck DC-Fertigplatten Kieselgel 60 F_{245}, 0.25 mm, chloroform and methanol, 10:1) revealed that the reaction was completed. The oily residue obtained upon evaporation was treated with ethyl acetate and the crystalline material obtained was crystallized from ethanol (248 mg, 53% yield) to give the product with mp. 186-188°.

^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, Me-7), 4.1 (s, 3H, COOMe), 7.4 (d, 1H, J = 10Hz, H-9), 7.65 (d, 1H, H-8), 8.7 (s, 1H, H-6), 10.1-10.5 (bs, 1H, OH).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96

Found: C, 56.52; H, 4.60; N, 12.04

5-Carbomethoxy-6-hydroxy-2-methyl-7-oxo-isoxazolo[2,3-a]pyrimidine (4).- A mixture of 3-amino-5-methylisoxazole (98 mg), 1b (260 mg) and methanol (4 ml) was heated under reflux for 4 hrs. The solvent was evaporated and the oily residue crystallized upon cooling. Crystallization from 1-propanol yielded the product (85 mg, 40% yield), mp. 164-166°.

^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, Me), 3.85 (s, 3H, COOMe), 5.65 (s, 1H, H-3), 6.80 (bs, 1H, OH).

Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.21

Found : C, 45.42; H, 4.02; N, 13.48

REFERENCES

1. I. Hermecz and Z. Meszaros; "Advances in Heterocyclic Chem." A. R. Katritzky, Ed., Academic Press, New York, NY, 1983, Vol. 33, p 241.

2. R. Huisgen, K. Fraunberg and H. H. Sturm, Tetrahedron Lett., 2589 (1969).

3. M. Kovacic, S. Polanc, B. Stanovnik and M. Tisler, J. Heterocyclic Chem., 11, 949 (1975).

4. M. H. Elnagdi, E. M. Kandeel and K. V. Sadek, Z. Naturforsch., 32B, 311 (1977).

5. I. A. Shehata and R. A. Glennon, J. Heterocyclic Chem., 24, 1291 (1987).

6. S. Goodwin and B. Witkop, J. Am. Chem. Soc., 76, 5599 (1954).

7. E. F. Hartree, "Biochemical Preparations", Vol. 3, p. 56, J. Wiley & Sons, New York, NY, 1953.

8. E. E. Jaffe and H. Matrick, J. Org. Chem., 33, 4004 (1968).

****

DEOXYGENATION OF EPOXIDES WITH ALUMINUM

Submitted by (08/24/89) Peter W. D. Mitchell

Union Camp Technology Center
Box 3301, Princeton, NJ 08543

Amalgamated aluminum dissolves readily in isopropanol to give aluminum isopropylate and hydrogen. It was thought that this economical and easy-to-handle system might be capable of reducing epoxides to alcohols and provide a useful alternate to expensive reagents