A NEW ENAMINE-SALT FOR THE SYNTHESIS OF J-ALKYLATED ETHYL ACETOACETATE DERIVATIVES

Gábor Doleschall

Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences, Technical University, H-1111, Szt. Gellért-tér 4. Budapest, Hungary.

Summary: A convenient method for the preparation of **y**-alkylated ethyl acetoacetate from alkyl halides via a new isoxazole enamine-salts is reported.

Several methods have been reported for the synthesis of γ -alkylated β -keto--esters, among others the alkylation of the dianion of methyl acetoacetate¹. We wish to present here a new route to γ -alkylated β -keto-esters based on the C-alkylation of new enamine-salts (2) generated by treating ethyl (3-alkyl-2--methyl-2,5-dihydro-5-oxo-4-izoxazolecarboxylate) (1) with KOCMe₃. The structures of 2 were provided by ¹H-nmr³.

Hydrogenolysis of intermediates 3 in ethanol at $60-65^{\circ}$ C in the presence of Pd on carbon leads to derivatives of ethyl 3-methylamino-crotonate $(\underline{4})^4$, which were hydrolyzed to \boldsymbol{y} -alkylated ethyl acetoacetate $(\underline{5})$ in aq. acetic acid at $40-45^{\circ}$ C without the isolation of the intermediates (3 and 4).



A typical procedure is as follows: A mixture of $\underline{1a}$ (20 g, 0.108 mol) and KOCMe,(13 g, 0.115 mol) in dry DMF (80 mL) was stirred at 0°C for five minutes. To the solution 1-bromooctane (20.7 mL, 0.12 mol) was added and the mixture stirred at 0°C for one hour. After standing overnight in a refrigerator the reaction mixture was poured onto a mixture of water (200 mL), ice (100 g) and conc. HCl (10 mL) and extracted with CH₂Cl₂ (350 mL). The extract was washed with water (400 mL) and evaporated to dryness in vacuo (finally at 0.1-0.2 mmHg at 60-70°C). The residue, an oil (27 g) was hydrogenated in dry ethanol (300 mL) in the presence 10% Pd on carbon (6 g) at 60-65°C and atmospheric pressure for two hours. The catalyst was filtered off, washed with etanol(60 mL)

and evaporated to dryness in vacuo. The remaining oil (17 g) was stirred in AcOH (50 mL) and water (25 mL) at $40-45^{\circ}$ C for three hours. The mixture was poured onto a mixture of water (200 mL) and conc. HCl (10 mL) and extracted with CH₂Cl₂ (350 mL). The extract was washed with water (600 mL), evaporated to dryness in vacuo and the residue (15 g) was distilled under reduced pressure. After removal of a small amount of lambda battering material (40,42°C pressure. After removal of a small amount of low-boiling material (40-42°C at 0.2 mmHg, about 1 g of ethyl acetoacetate), the main fraction was 3-oxo--dodecanoate (5) (yield: 10.8 g, 41%, b.p.: 100-120°C at 0.15 mmHg).

R	R'-X			5	
		R	R '	Yield % ^a	b.p. ⁰ C/mmHg ^D
н	₽h-CH ₂ -Cl	н	Benzyl ^C	35	110-112/0.15 (170-171/13) ⁵
н	(CH ₃) ₂ CH-I	н	2-propyl	44	93-94/12 (108-113/18) ⁶
Me	(CH ₃) ₂ CH-I	Me	2-propyl	21	153-155/0.1
н	$CH_3(CH_2)_7 - Br$	н	l-octyl	41	100-102/0.15 (138-145/1)7
н	EtOOC-CH2-C1	н	EtOOC-CH ₂ -	24	122-126/0.3 (122-126/0.3) ⁸
н	AcO-(CH ₂) ₄ -Br	н	Ac0-(CH ₂) ₄ -	28	118-120/0.1
				1	1

a) All compounds had correct elemental analyses and gave $^{
m I}$ H-nmr and IR spectra consistant with the structures listed and were identical with authantic products.

b) Values in paratheses are from literature.

c) Intermediates 3 were isolated: R=H,R'=Ph-CH. (yield 63%, m.p.: 83-84^oC from 2-propanol) and R=H,R'=EtOOC-CH₂ (yield 61%, m.p.: 93-94^oC from 2-propanol).

References and Notes

- 1, S.N.Huckin, L.Weiler: J.Am.Chem.Soc.<u>96</u> 1082 (1974), J.Zimmermann, D.Seebach:
- Helv.Chim.Ácta 70 1104 (1987). 2, <u>1a</u> was obtained in 55% yield (m.p.: 131-132⁰C from 2-propanol) from the sodium salt of the ethyl (3-methyl-5-hydroxy-4-isoxazolecarboxylate) with dimethylsulfate in dry DMF at 110-120°C. G.Doleschall: Tetrahedron Letters 28 2993 (1987), L.Claisen: Ber. <u>30</u> 1480 (1897). The alternative method for preparation of <u>la</u> was the reaction of diethyl acetylmalonate with N-methylhydroxylamine hydrochloride in ethanol. H.Ulrich, J.N.Tilley, A.A. Sayight: J.Org.Chem.27 2160 (1962). <u>1b</u> was obtained from diethyl propi-onylmalonate refluxing in ethanol with a 20% excess of NH₂OH.HCl and the ethyl (3-ethyl-5-hydroxy-4-isoxazolecarboxilate) obtained was converted into sodium salt in ethanol with sodium ethoxyde and evaporated to dryness
- into socium sait in ethanoi with socium ethoxyde and evaporated to oryne; in vacuo. This sodium salt was converted to <u>1b</u> with dimethyl sulfate in dry DMF at 110-120°C in yield 73% (m.p.:58-59°C from ether). 3, ¹H-nmr spectra: 2a(DMSO-d₂) **d**: 1.15 (3H,t,OEt), 2.75 (3H,s,N-Me), 3.90 (2H,s,=CH₂) 3.95 (2H,q,OEt). 2b(DMSO-d₂) **d**: 1.10 (3H,t,OEt), 1.35 (3H,d₂, =CH-CH₃, J:7Hz), 2.55 (3H,s,N-Me), 3.90 (2H,q,OEt), 4.40 (1H,g,=CH-Me, =CH-CH₃, J:7Hz).
- 4, <u>4</u> (R=R'=H) was isolated in yield 83% (m.p.: 1-2⁰C, b.p.: 55-56⁰C/0.2 mmHg)
- and was identical with an authentic product: O.Kuckert:Ber. <u>18</u>, 618 (1885). 5, N.Borsche, H.Lewinsohn: Ber. <u>66</u> 1796 (1933). 6, H.B.Kagan, Y.Heng Suen: Bl <u>1966</u> 1819. 7, H.Breusch, A.Keskin: Rev.Fac.Sci.Istanbul(A) <u>11</u> 28 (1946), O. B. Stanbul (A) <u>11</u> 28 (1946), CA 1946 5400. 8, B.Riegel, W.M.Lilienfeld: J.Am.Chem.Soc. 67 1274 (1945).

(Received in UK 3 October 1988)