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A CONVENIENT SYNTHESIS OF ALKYL HETEROARYLPYRUVATES

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ABSTRACT: Several ethyl heteroarylpyruvates were obtained by condensation of the corresponding methyl substituted azines or azoles with diethyl oxalate and in the presence of potassium tert-butoxide. The obtained compounds exist exclusively or predominantly in the enol form.

Alkyl substituted azines undergo base-catalyzed deprotonation at the alpha-position of the side chain with aqueous or alcoholic bases [1]. The reaction has been used for the preparation of heteroarylpyruvates and some alkaloids [2]. When methylazines or methylazoles were condensed with diethyl oxalate and in the presence of sodium or potassium ethoxide [3-5] the yields were usually low [6]. These can be improved if adjacent elec-

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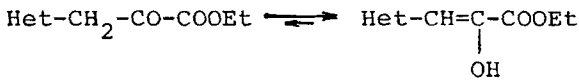
[*]Dedicated to Prof.E.Ziegler at the occasion of his 80th birthday

tron-withdrawing substituents are present [7,8]. 2- or 4-methylpyridine did not react [9] unless their N-oxides were used [10]. Similarly, some methylpyrimidines were unreactive [12,13]. In some cases the use of alkali amides caused the formation of an unsaturated acid (9)[14].

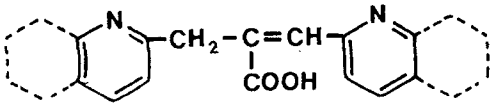
We have found that potassium tert-butoxide is advantageous for the synthesis of ethyl heteroarylpyruvates (1-8) even for the otherwise unreactive 4-methylpyridine [9]. From the ^{1}H NMR spectra it is evident that the products exist in solution entirely in the enol form (1b,3b-8b), except for 2 where the enol and keto form are present in a ratio of 2:1 (2b:2a). Strong enolization may be ascribed partly to a hydrogen bonded structure as in the case of 10.



a b

Het:

1: 2′-pyridyl-
2: 4′-pyridyl-
3: 4′-pyrimidinyl-
4: 6′-methyl-4′-pyrimidinyl
5: 2′-pyrazinyl-
6: 2′-quinolyl-
7: 2′-benzothiazolyl-
8: 2′-pyridyl 1′-oxide



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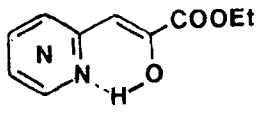

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Table I: Results of preparation of ethyl heteroarylpyruvates

Compound No.	Yield (%)	Crystallized from	Mp (°C)	Molecular formula	Analytical data (%) Calcd. C	H	N	Found C	H	N
1	41	ethyl acetate	123-125	$C_{10}H_{11}NO_3$	62.16	5.74	7.25	62.30	5.67	7.29
2	38[a]	propyl ether	121-122	$C_{10}H_{11}NO_3$	62.16	5.74	7.25	62.66	5.76	7.42
3	65[b]	ethanol	134-135	$C_9H_{10}N_2O_3$	55.66	5.19	14.43	55.90	5.22	14.66
4	60	ethanol	145-146	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46	57.47	5.69	13.08
5	65[b]	ethanol	73-74	$C_9H_{10}N_2O_3$	55.66	5.19	14.43	55.92	5.23	14.07
6	82[b]	ethanol	128-130	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	69.24	5.82	5.58
7	73[b]	propanol	161-162	$C_{12}H_{11}NO_3S$	57.81	4.44	5.62	57.93	4.52	5.81
8	72[c]	ethanol	82-84	$C_{10}H_{11}NO_4$	57.41	5.22	6.70	57.74	5.22	7.07

a) Ref. [6] gives 12% yield of the oxime by using potassium ethoxide as base. The keto ester was not isolated and characterized.

b) Ref. [5] gives no yield.

c) Ref. [10] gives 34.6% yield. With NaH in benzene yield was 6.5%.

EXPERIMENTAL

General procedure:

To a stirred solution of diethyl oxalate (100 mmol) and the corresponding methyl heterocycle (100 mmol) in dry diethyl ether (250 ml) potassium tert-butoxide (100 mmol) was added in small portions with such a rate t the solution is kept at moderate temperature. After some time from the reaction mixture a yellowish--brown precipitate is separated. The mixture was stirred at room temperature for 2-5 hours and the product was filtered and washed with dry diethyl ether.

The obtained potassium salt was dissolved in water (100 ml) and the solution was acidified with dilute hydrochloric acid (1:1) to pH 4-5. In most cases the solid product was filtered, whereas the oily product formed when preparing compounds 3 and 9 was extracted with chloroform. The extracts were dried over anhydrous sodium sulfate, the solvent was evaporated to dryness and the residue left for crystallization.
The obtained products are presented in Table I [16].

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15. ^{1}H NMR spectra were recorded on a Varian M 360 L spectrometer with TMS as internal standard. All melting points are uncorrected and were taken on a Kofler micro hot stage. Microanalyses were obtained on a Perkin-Elmer Analyzer 240 C.

16. The ^{1}H NMR data for the compounds in this work are:
2 (DMSO-d_6) keto form: δ 1.35 (t, 3H, $CH_2\underline{CH}_3$), 4.30 (q, 2H, $C\underline{H}_2Me$), 4.15 (s, 2H, $C\underline{H}_2CO$), 7.25 (d, 2H, $H_{3'}$, $H_{5'}$), 8.65 (d, 2H, $H_{2'}$, $H_{6'}$), J_{H_2,H_3}, = J_{H_5,H_6}, = 5.0 Hz. Enol form: δ 1.40 (t, 3H, $CH_2\underline{CH}_3$), 4.35 (q, 2H, $C\underline{H}_2Me$), 6.45 (s, 1H, $C\underline{H}$=), 6.90-7.10 (broad s, 1H, OH), 7.70 (d, 2H, H_3, $H_{5'}$), 8.65 (d, 2H, H_2,$H_{6'}$), J_{H_2,H_3}, = J_{H_5,H_6}, = 5.0 Hz.
3: ($CDCl_3$) δ 1.40 (t, 3H, $CH_2\underline{CH}_3$), 4.50 (q, 2H, $C\underline{H}_2Me$), 6.50 (s, 1H, -CH=), 7.20 (d, 1H, $H_{5'}$), 8.80 (d, 1H, $H_{6'}$), 9.20 (s, 1H, $H_{2'}$), 13.2-15.2 (broad s, 1H, OH), $J_{5',6'}$ = 5.0 Hz.
4: ($CDCl_3$) δ 1.40 (t, 3H, $CH_2\underline{CH}_3$), 2.60 (s, 3H, 6'-Me), 4.40 (q, 2H, $C\underline{H}_2Me$), 6.40 (s, 1H, -CH=), 7.00 (s, 1H, $H_{5'}$), 9.00 (s, 1H, $H_{2'}$).
5: ($CDCl_3$) δ 1.4 (t, 3H, $CH_3\underline{CH}_3$), 4.4 (q, 2H, $C\underline{H}_2CH_3$), 6.65 (s, 1H, -CH=), 8.4-8.8 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$),

10.8-12.5 (broad s, 1H, OH), $J_{5',6'}$ = 2.0 Hz.

6: ($CDCl_3$) δ 1.40 (t, 3H, $CH_2C\underline{H}_3$), 4.40 (q, $C\underline{H}_2CH_3$), 6.40 (s, 1H, -CH=), 7.10 (d, 1H, $H_{3'}$), 7.3-7.8 (m, 5H, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$, OH), 8.00 (d, 1H, $H_{4'}$), $J_{H_{3'}, H_{4'}}$ = 8.0 Hz.

7: ($CDCl_3$) δ 1.40 (t, 3H, $CH_2C\underline{H}_3$), 4.45 (q, 2H, $C\underline{H}_2CH_3$), 6.85 (s, 1H, -CH=), 7.3-7.8 (m, 2H, $H_{5'}$, $H_{6'}$), 7.8-8.3 (m, 2H, $H_{4'}$, $H_{7'}$), 10.7-11.3 (broad s, 1H, OH).

8: ($CDCl_3$) δ 1.40 (t, 3H, $CH_2C\underline{H}_3$), 4.35 (q, 2H, $C\underline{H}_2CH_3$), 4.35 (q, 2H, $C\underline{H}_2H_3$), 6.60 (s, 1H, -CH=), 7.1-7.8 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 8.30 (d, 1H, $H_{6'}$), 14.2-14.4 (broad s, 1H, OH). $J_{5',6'}$ = 5.0 Hz.

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