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CHEMOSELECTIVE SYNTHESIS OF PYRAZOLE DERIVATIVES *VIA* β-ENAMINO KETO ESTERS

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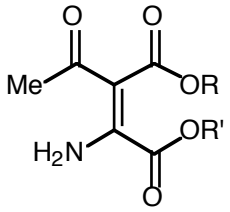
Abstract - β-Enamino keto ester (**2a**) reacts with hydroxylamine to give an isoxazole derivative (**3**). Compound (**2a**) reacts with hydrazine, alkyl- and arylhydrazines to give pyrazole derivatives (**4a-e**) as only reaction products. Methylation of compound (**4a**) afforded the two isomeric pyrazole derivatives (**4b**) and (**5**)

The metal promoted reactions of β-dicarbonyl compounds with nitriles afford β-enamino diones derived from a new carbon-carbon bond formation between the intercarbonylic methylene group of dicarbonyl and the cyano group of nitriles.[1] The compounds obtained in these reactions can be useful intermediates in the synthesis of heterocycles and we have reported on the syntheses of 4-amino quinolines and pyridines[2] and tetronic acid derivatives.[3]

β-Alkoxycarbonyl-β-enamino keto esters (**1**) obtained in the reactions of β-keto esters with alkyl cyanoformates[4] react with hydrazines and hydroxylamine to give pyrazole and isoxazole derivatives in good yields under very mild experimental conditions. In the reactions of compounds (**1**) with substituted hydrazines two pyrazole derivatives have been obtained corresponding to the two possible isomeric pyrazoles. The high reactivity of compounds (**1**) with nucleophiles was related to the presence of an ester group in the *beta* position, and this favors a Michael addition of nucleophiles to the unsaturated C=C double bond, followed by cyclisation to heterocycles.[5]

In the course of our studies on the reactivity of β-keto esters with nitriles we have obtained a series of β-enamino keto esters bearing an alkyl or aryl group linked to the *beta* carbon atom, corresponding to the general structure (**2**) (R'=alkyl or aryl).[6]

In order to compare the reactivity of compounds (**2**) with that of compounds (**1**), we studied the reactions of compound (**2a**) with hydroxylamine, hydrazine, alkyl- and arylhydrazines and in this paper we report on the results obtained.



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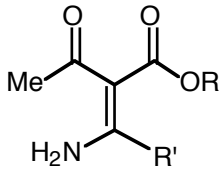

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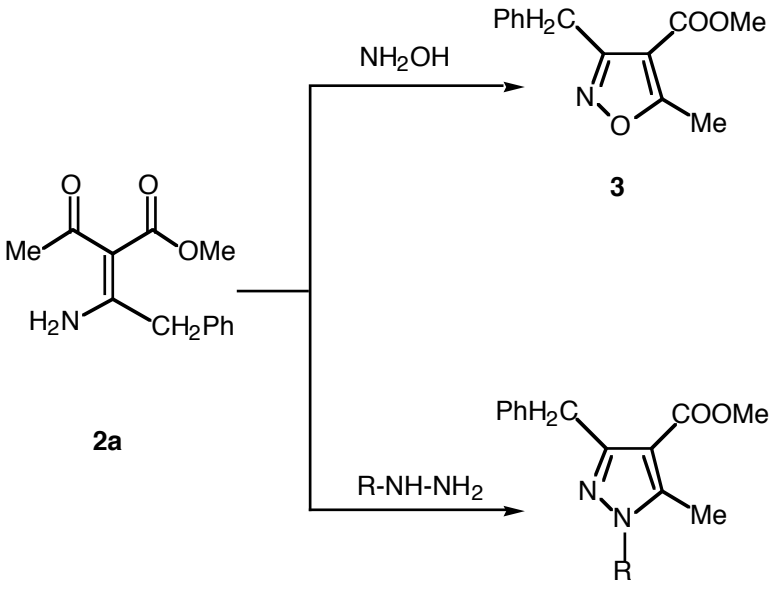
Compound (**2a**) was easily prepared from the reaction of methyl acetoacetate with benzyl cyanide in the precence of stoichiometric amount of tin(IV) chloride.[6]

Attempts to react compound (**2a**) with hydroxylamine and hydrazines at room temperature in experimental conditions similar to that used in the reactions of compounds (**1**) did not afford any reaction product. Compound (**2a**) reacted instead with hydroxylamine, hydrazine, alkyl- and arylhydrazines when the reactions were carried out heating at reflux in ethanol for 3-4 h. In these reactions isoxazole (**3**) and pyrazole derivatives (**4a-e**) were obtained in good yields. Noteworthy the reactions of compound (**2a**) with substituted hydrazines afford only one of the two possible isomeric pyrazole derivatives.



2a

3

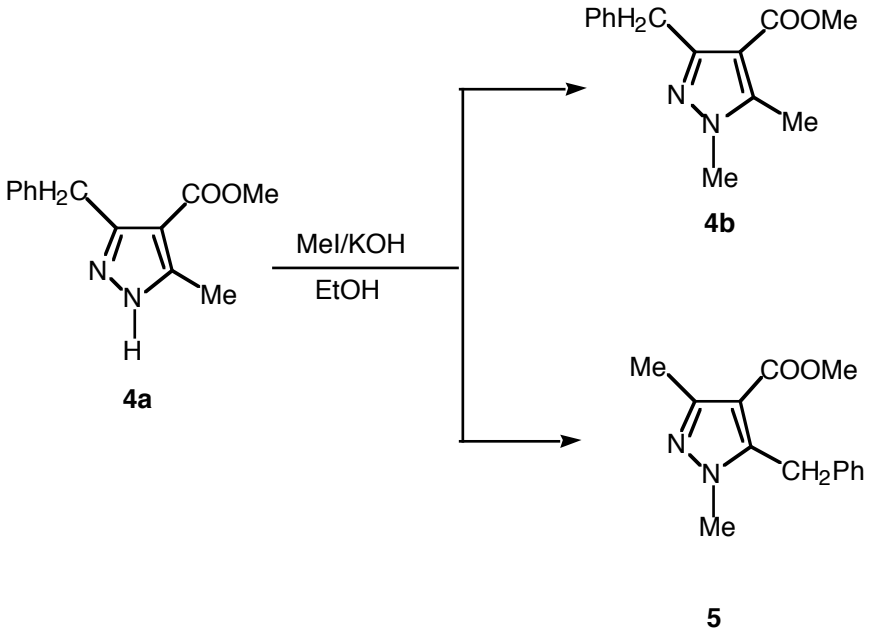
4 **a**: R=H
b: R=Me
c: R=Ph
d: R=*p*-ClC$_6$H$_4$
e: R=CH$_2$Ph

The structure of isoxazole derivative (**3**) was assigned on the basis of its NMR spectra. The ^{13}C-NMR spectrum shows two resonances at 165.11 and 175.71 ppm attributable to C-3 and C-5 carbon atoms of the ring. In the coupled ^{13}C-NMR spectrum the resonance at 162.11 is detected as a triplet (^2J=7.5 Hz) while the absorption at 175.71 is detected as a quartet (^2J=7.0 Hz). These multiplicities can be explained by a long range coupling of C-3 carbon atom with the hydrogens of benzylic methylene and of C-5 carbon atom with

the hydrogens of methyl group thus comfirming the assigned structure.

The structure of pyrazole derivatives (**4**) could also be assigned on the basis of NMR spectra but a definitive assignement can be achieved only comparing the spectra of the two isomeric 3-benzyl-5-methyl- and 5-benzyl-3-methyl-pyrazole isomers.

With the aim of obtaining both these isomers the pyrazole (**4a**) was reacted with methyl iodide in the presence of KOH in ethanol. In this reaction the two isomeric pyrazole derivatives (**4b**) and (**5**) were isolated in 53% and 32% yields respectively.



The ^{1}H-NMR spectra of all pyrazole derivatives are similar and did not allow us to attribute the relative structure. The ^{13}C-NMR spectra show instead interesting differences. Compounds (**4b-e**) and (**5**) show resonances in the range 144.23-145.56 ppm and 150.25-153.90 ppm attributable respectively to the C-5 and C-3 carbon atom of pyrazole ring.[7,8] The coupled ^{13}C-NMR spectra of these compounds show long range coupling costants (^{2}J in the range 5.8-7.1 Hz) between the C-3 and C-5 carbon atoms of the ring and the hydrogens of the methyl or benzylic methylene groups linked to these atoms. In compound (**4b**) obtained in higher yield in the reaction of **4a** with methyl iodide and in compounds (**4b-e**) obtained in the reaction of **2a** with substituted hydrazines the C-3 resonance at *ca.* 152 ppm is detected as a triplet while the C-5 resonance at *ca*. 145 ppm is detected as a quartet. These multiplicities can be explained by a long range coupling of C-3 carbon atom with the benzylic methylene group and of C-5 carbon atom with the hydrogens of methyl group and these data allow us to assign to these compounds the structure (**4**).

This assignement is confirmed by the coupled ^{13}C-NMR spectrum of the compound (**5**) obtained in lower yield in the reaction of **4a** with methyl iodide. In this compound the resonance at 150.25 ppm attributable to C-3 carbon atom is detected as a quartet while the resonance at 145.56 ppm attributable to C-5 carbon atom is detected as a triplet and this confirms the structure of 5-benzyl-3-methylpyrazole assigned to this isomer.

The results obtained demonstrate that compound (**2a**) is less reactive than compounds (**1**) towards ambident nucleophiles but these reactions are highly chemoselective.

The reactions of compound (**2a**) with hydroxylamine and hydrazines afford in good yield isoxazole and pyrazole derivatives giving only one of the two possible isomers. The formation of obtained compounds can be explained by a Michael addition of more nucleophilic NH_2 group of ambident nucleophile onto the C=C double bond followed by elimination of ammonia and cyclisation to the heterocycle.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer Paragon 500 FT-IR spectrophotometer (values in cm^{-1}). NMR spectra were recorded on Bruker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hertz. Column chromatogrhy was performed using Merck silica gel (230-400 mesh).

4-Amino-3-methoxycarbonyl-5-phenyl-3-penten-2-one (2a)[6]

To a stirred solution of methyl acetoacetate (3.24 mL, 30 mmol) and benzyl cyanide (3.46 mL, 30 mmol) in dry toluene (40 mL) $SnCl_4$ (3.5 mL, 30 mmol) was added. The reaction mixture was stirred at rt for 30 min and heated under reflux for 1.5 h. The obtained solid was filtered off, washed with light petroleum, treated with a saturated aqueous solution of $NaHCO_3$ (20 mL) and the suspension was stirred at rt for 30 min. The suspension was extracted with ethyl acetate (3 x 20 mL) and the organic layer was dried over Na_2SO_4, concentrated under reduced pressure to give an oil which was treated with light petroleum to give colorless crystals, mp 44-46°C, 5.3 g (76%). IR (KBr): 3350, 1700, 1600, 1250, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: δ: 2.29 (s, 3H, Me), 3.76 (s, 3H, OMe), 3.95 (s, 2H, CH_2Ph), 5.54 (br, 1H, NH), 7.10-7.40 (m, 5 H, Ph), 11.44 (br, 1H, NH).

Methyl 3-benzyl-5-methylisoxazole-4-carboxylate (3)

To a solution of hydroxylamine hydrochloride (125 mg, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) in ethanol (5 mL), stirred for 15 min, compound (**2a**) (350 mg, 1.5 mmol) was added and the reaction mixture was heated under reflux for 5 h. The solution was concentrated under reduced pressure to give an oil which was dissolved in ethyl acetate (10 mL). The solution was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil which was purified by flash chromatography (eluent: ethyl acetate/light petroleum 1:5): colorless crystals, mp 57-59°C (light petroleum), 252 mg (73%). IR (KBr): 1720, 1459, 1114 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (s, 3H, Me), 3.77 (s, 3H, OMe), 4.20 (s, 2H, CH_2), 7.27 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.42 (q, J=130.3 Hz, Me), 31.69 (t, J=129.3 Hz, CH_2Ph), 51.47 (q, J=146.5 Hz, OMe,), 108.09 (s, C-4), 126.65 (d, Ph), 128.41 (d, Ph), 128.91 (d, Ph), 136.69 (s, Ph), 162.11 (t, ^{2}J=7.5 Hz, C-3), 162.45 (s, COO), 175.71 (q, ^{2}J=7.0, C-5). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52 ; H, 5.67 ; N, 6.06 . Found : C, 67.30 ; H, 5.90 ; N, 6.00 .

Methyl 3-benzyl-5-methylpyrazole-4-carboxylate (4a)

A solution of compound (**2a**) (466 mg, 2 mmol) and hydrazine hydrate (0.107 mg, 2.2 mmol) in ethanol (5 mL) was heated under reflux for 5 h and concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (10 mL). The obtained solution was washed with 1N HCl and water, dried (Na_2SO_4) and concentrated under reduced pressure to give colorless crystals, mp 92-93°C (light petroleum), 414 mg (90%). IR (KBr): 3279, 1681, 1578, 1133 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (s, 3H, Me), 3.75 (s, 3 H , OMe) , 4.17 (s , 2H , CH_2 P h) , 7.11 - 7.18 (m, 5H, Ph) , 11.28 (br , 1H , NH) .

^{13}C-NMR ($CDCl_3$) δ: 12.76 (q, J=128.4 Hz, Me), 33.10 (t, J=128.0 Hz, CH_2Ph), 50.87 (q, J=145.5, OMe), 108.48 (s, C-4), 126.31 (d, J=159.4 Hz, Ph), 128.37 (d, J=162.0 Hz, Ph), 128.63 (d, J=162.4 Hz, Ph), 138.34 (s, Ph), 148.02 (s, C-3), 151.24 (s, C-5), 164.74 (s, COO). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13 ; N, 12.17 . Found : C, 67.55 ; H, 6.25 ; N, 12.05 .

According to this procedure the following compounds have been obtained:

Methyl 3-benzyl-1,5-dimethylpyrazole-4-carboxylate (4b)

This compound was obtained from **2a** and methylhydrazine: colorless crystals, mp 54-56°C (light petroleum), 90% yield. IR (KBr) 1700, 1540, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H, Me), 3.71 (s, 3H, NMe), 3.73 (s, 3H, OMe), 4.16 (s, 2H, CH_2Ph), 7.16-7.25 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) δ: 11.22 (q, J=128.8 Hz, Me), 33.89 (t, J=128.1 Hz, CH_2Ph), 36.04 (q, J=139.3 Hz, NMe), 50.65 (q, J=145.7 Hz, OMe), 108.92 (s, C-4), 125.85 (d, J=122.3 Hz, Ph), 128.10 (d, J=135.8 Hz, Ph), 128.64 (d, J=135.5 Hz, Ph), 139.81 (s, Ph), 144.23 (q, ^{2}J=5.8 Hz, C-5), 152.38 (t, ^{2}J=7.0 Hz, C-3), 164.53 (s, COO). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found : C , 68.60 ; H, 6.30 ; N , 11.60 .

Methyl 3-benzyl-5-methyl-1-phenylpyrazole-4-carboxylate (4c)

This compound was obtained from **2a** and phenylhydrazine: yellow crystals, mp 94-96°C (light petroleum), 84% yield. IR: (KBr): 1709, 1495, 1126 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (s, 3H, Me), 3.79 (s, 3H, OMe), 4.11 (s, 2H, CH_2Ph), 7.13-7.16 (m, 10 H, Ph). ^{13}C-NMR ($CDCl_3$) δ: 12.62 (q, J=129.0 Hz, Me), 33.97 (t, J=128.0 Hz, CH_2Ph), 50.79 (q, J=145.2 Hz, OMe), 110.19 (s, C-4), 125.62 (d, Ph), 125.90 (d, Ph), 128.08 (d, Ph), 128.45 (d, Ph), 128.75 (d, Ph), 129.16 (d, Ph), 138.68 (s, Ph), 139.56 (s, Ph), 144.79 (q, ^{2}J=6.2 Hz, C-5), 153.54 (t, ^{2}J=6.8 Hz, C-3), 164.48 (s, COO). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92 ; N, 9.14 . Found : C, 74. 65 ; H, 5.80 ; N, 9.25.

Methyl 3-benzyl-1-*p*-chlorophenyl-5-methylpyrazole-4-carboxylate (4d)

To a solution of *p*-chlorophenylhydrazine hydrochloride (268 mg, 1.5 mmol) and triethylamine (0.25 mL, 1.8 mmol) in ethanol (5 mL), stirred for 15 min at rt, compound (**2a**) (233 mg, 1 mmol) was added and the reaction mixture was heated under reflux for 5 h. The solution was concentrated under reduced pressure to give an oil which was dissolved in ethyl acetate (10 mL). The solution was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was crystallized from ethyl ether-light petroleum: yellow crystals, mp 64-68°C (light petroleum), 290 mg (85% yield). IR (KBr): 1710, 1503, 1092 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (s, 3H, Me), 3.79 (s, 3H, OMe), 4.27 (s, 2H, CH_2), 7.27-7.46 (m, 9H, Ph). ^{13}C-NMR ($CDCl_3$) δ:12.67 (q, J=129.5 Hz, Me), 33.99 (t, J=128.4 Hz, CH_2), 50.91 (q, J=145.7 Hz, OCH_3), 110.62 (s, C-4), 126.02 (d, Ph), 126.64 (d, Ph), 127.75 (d, Ph), 128.17 (d, Ph), 128.79 (d, Ph), 134.33 (s, Ph), 137.27 (s, Ph), 139.44 (s, Ph), 144.85 (q, ^{2}J=7.6 Hz, C-5), 153.90 (t, ^{2}J=7.3 Hz, C-3), 164.38 (s, COO). *Anal.* Calcd for $C_{19}H_{17}N_2O_2Cl$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.82; H, 5.20; N, 8.12.

According to this procedure the following compound has been obtained:

Methyl 1,3-dibenzyl-5-methylpyrazole-4-carboxylate (4e)

This compound was obtained from **2a** and benzylhydrazine hydrochloride: colorless crystals, mp 117-120°C (light petroleum), 78% yield . IR (KBr): 1702, 1493, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (s, 3H, Me), 3.76 (s, 3H, Me), 4.28 (s, 2H, CH_2Ph), 5.31 (s, 2H, NCH_2Ph), 7.31 (m, 10H, Ph). ^{13}C-NMR ($CDCl_3$) δ: 11.35 (q, J=129.2 Hz, Me), 34.04 (t, J=128.1 Hz, CH_2), 50.72 (q, J=138.7 Hz, OCH_3), 53.00

(t, J=138.3 Hz, CH_2N), 109.64 (s, C-4), 125.89 (d, Ph), 126.63 (d, Ph), 127.83 (d, Ph), 128.14 (d, Ph), 128.70 (d, Ph), 128.84 (d, Ph), 136.10 (s, Ph), 139.86 (s, Ph), 144.5 (q, ^{2}J=6.3 Hz, C-5), 152.9 (t, ^{2}J=6.7 Hz, C-3), 164.51 (s, COO). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.72; H, 6.20; N, 8.65.

Reaction of compound (4a) with methyl iodide

Methyl 3-benzyl-1,5-dimethylpyrazole-4-carboxylate (4b)

Methyl 5-benzyl-1,3-dimethylpyrazole-4-carboxylate (5)

To a solution of KOH (70 mg, 1.25 mmol) in absolute ethanol (3 mL) compound (**4a**) (230 mg, 1 mmol) was added. The solution was stirred at rt for 10 min and then CH_3I (0.125 mL, 2 mmol) was added. The reaction mixture was stirred at rt for 15 min, heated under reflux for 2 h, and concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate (10 mL). The solution was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which was purified by flash chromatography (eluent: ethyl acetate/light petroleum 1:3) to give two compounds :

(**4b**): 129 mg (53%) mp, IR and ^{1}H-NMR were identical to thoose of compound (**4b**) previously described.

(**5**) **:** 79 mg (32.5%) mp 63-66°C (light petroleum). IR (KBr): 1703, 1545, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H, Me), 3.59 (s, 3H, NMe), 3.77 (s, 3H, OMe), 4.35 (s, 2H, CH_2-Ph), 7.11-7.21 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) δ: 14.20 (q, J=128.9 Hz, Me), 30.46 (t, J=128.0 Hz, CH_2Ph,), 36.18 (q, J=139.6 Hz, NMe), 50.72 (q, J=146.7 Hz, OMe), 109.72 (s, C-4), 126.47 (d, Ph), 127.91 (d, Ph), 128.58 (d, Ph), 136.68 (s, Ph), 145.56 (q, ^{2}J=6.7 Hz, C-3), 150.25 (t, ^{2}J=7.1, C-5), 165.5 (s, COO). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83 ; H, 6.60; N, 11.47. Found : C, 68.68 ; H, 6.80 ; N, 11.35.

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