4-Alkoxycarbonyl, 4-Alkylthiocarbonyl and 5-Alkoxycarbonyloxy Derivatives of 1-Substituted-3-methylpyrazol-5-ones

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The reaction of 1-substituted-3-methylpyrazol-5-ones **1** with alkyl chloroformates and calcium hydroxide in dioxane have been studied. With 1-phenyl-3-methylpyrazol-5-one, the isolated product was alkyl 3-methyl-5-oxo-1-phenylpyrazole-4-carboxylate **2** but with 1-alkyl-3-methylpyrazol-5-one formation of 1-alkyl-5-alkoxycarbonyloxy-3-methylpyrazole **3** was observed. Replacement of alkyl chloroformate by bis(alkoxythiocarbonyl) sulfide results in the formation of 4-alkoxythiocarbonyl derivatives **4** in low yield with both 1-substituted-3-methylpyrazol-5-ones.

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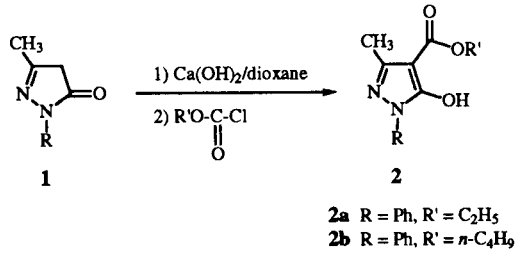
It is known that 4-acyl derivatives of 3-methylpyrazol-5-ones are effective chelating and extracting reagents of a wide variety of metal ions [1-5]. These compounds are prepared with acyl chlorides or anhydrides as acylating agents, in the presence of bases like calcium hydroxide or pyridine [6-8]. We have found a similar behavior with 4-alkyldithiocarbonyl derivatives of 3-methylpyrazol-5-ones, where the alkyldithiocarbonylation is achieved with carbon disulfide and alkyl halides [9-11]. 4-Alkyldithiocarbonyl-3-methylpyrazol-5-ones form square planar complexes with Cu(II) and Ni(II), and they can be used for efficient extraction of Cu(II), Ni(II), Co(II) and Cd(II) [12,13]. As a part of a program on the synthesis of heterocycle substituted molecules with chelating, extractive or biological properties we report here the synthesis of 4-alkoxycarbonyl, 5-alkoxycarbonyloxy and 4-alkoxythiocarbonyl derivatives of 1-substituted-3-methylpyrazol-5-ones.

Deprotonation of 1-substituted-3-methylpyrazol-5-one **1** with calcium hydroxide in dioxane, followed by the addition of alkyl chloroformate affords a derivative whose structure depends on the nature of the 1-substituent group.

With 1-phenyl-3-methylpyrazol-5-one, the isolated compounds correspond to alkyl 5-hydroxy-3-methyl-1-phenylpyrazole-4-carboxylates **2** as indicated in Scheme 1.

Scheme 1



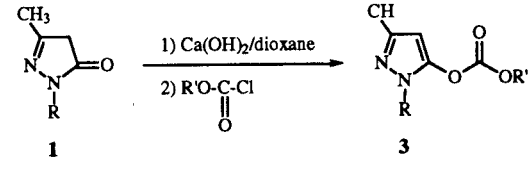
1 **2**

2a R = Ph, R' = C_2H_5
2b R = Ph, R' = *n*-C_4H_9

The enolic structure of **2** was assigned from ^1H and ^{13}C nmr information. The ^1H nmr spectra shows a broad downfield signal at 10.06-10.08 ppm for the hydroxylic proton and in the ^{13}C nmr the C-5 bonded to the OH is observed at 157.4-157.5 ppm, in agreement with other reported values [8-11].

With 1-alkyl-3-methylpyrazol-5-one and under the same reaction conditions, we have observed the formation of 1-alkyl-3-methyl-5-alkoxycarbonyloxypyrazole **3** (Scheme 2).

Scheme 2



1 **3**

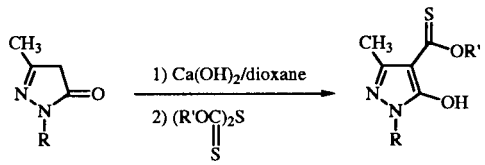
3a R = *n*-C_8H_{17}, R' = C_2H_5
3b R = *n*-C_8H_{17}, R' = *n*-C_4H_9
3c R = *n*-$C_{12}H_{25}$, R' = C_2H_5
3d R = *n*-$C_{12}H_{25}$, R' = *n*-C_4H_9

The most important feature from ^{13}C nmr spectra of compounds **3** is a signal at 92.0 ppm assigned to C-4. When this C-4 is bonded to a carbonyl or dithiocarboxyl group this signal is observed at 100-110 ppm [8-11].

Replacement of the alkyl chloroformate by the thioacylating reagent bis(alkoxythiocarbonyl) sulfide result in the formation of the 4-alkoxythiocarbonyl derivative **4** in low yield, as shown in Scheme 3.

In the ^1H nmr spectra of **4**, the hydroxylic proton is observed at 12.40-12.60 ppm, a value very closly related

Scheme 3



1 4

4a R = Ph, R' = C_2H_5
4b R = Ph, R' = *n*-C_4H_9
4c R = *n*-C_8H_{17}, R' = C_2H_5
4d R = *n*-$C_{10}H_{21}$, R' = *n*-C_4H_9

to those reported in 4-alkyldithiocarbonyl derivatives of **1** [9-11]. The ^{13}C nmr spectra shows the enolic C-5 carbon at 159.1 ppm and the thiocarbonyl carbon at 204.4 ppm [9-11]. The low yield of the reaction can be attributed to the acid work-up used in the isolation of **4**. It has been reported that *O*-ethylthiobenzoate is hydrolyzed to ethyl benzoate and/or thiobenzoic acid under different acidic and alkaline conditions [14,15].

EXPERIMENTAL

Microanalyses were obtained at Laboratorio de Microanálisis del Departamento de Química de la Universidad de Concepción. The ^1H nmr spectra were measured on a Varian EM 360A spectrometer using tetramethylsilane as the internal standard. The ^{13}C nmr spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The ir spectra were measured with a Perkin Elmer 599 spectrometer. Absorption frequencies are quoted in reciprocal centimeters.

General Procedure for the Reaction of 1-Substituted-3-methylpyrazol-5-ones **1** with Alkyl Chloroformates.

A mixture of 1-substituted-3-methylpyrazol-5-ones **1** (10 mmoles) and calcium hydroxide (1.11 g, 15 mmoles), in dioxane (50 ml) was stirred one hour at 40-50°. After cooling to room temperature, the alkyl chloroformate (11 mmoles) was added followed by a reflux of two hours. The cooled reaction mixture was poured in aqueous 3 *M* hydrochloric acid (100 ml) mixed with crushed ice (100 g) and after stirring over a period of 30 minutes was extracted with chloroform (4 x 25 ml). The organic layer was washed with aqueous 0.06 *M* hydrochloric acid, dried (sodium sulfate) and evaporated to yield an oil or a solid which was crystallized or recrystallized from methyl alcohol-water.

Ethyl 5-Hydroxy-3-methyl-1-phenylpyrazole-4-carboxylate (**2a**).

This compound was obtained in a 50% yield, as a crystalline solid, mp 114-115° (methyl alcohol-water); ir (potassium bromide): ν C=O 1780, associated OH-carbonyl 3300-2490, pyrazole ring 1560; pmr (deuteriochloroform): δ 1.34 (t, 3H, J = 6.5 Hz, CH_3), 2.25 (s, 3H, CH_3), 4.1 (q, 2H, J = 6.5 Hz, OCH_2), 7.1-7.4 (m, 5H, Ph), 10.06 (s, 1H, OH); cmr (deuteriochloroform): δ 13.9 (CH_3), 14.4 (CH_3), 60.6 (OCH_2), 93.7 (*C*=C-OH), 121.1, 126.7, 129.1, 137.5 (6C, Ph), 148.5 (C=N), 157.5 (C=*C*-OH), 167.3 (C=O).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.34; H, 5.69. Found: C, 63.10; H, 5.91.

n-Butyl 5-Hydroxy-3-methyl-1-phenylpyrazole-4-carboxylate (**2b**).

This compound was obtained in a 65% yield, as a crystalline solid, mp 83-84°, ir (potassium bromide): ν C=O 1780, associated OH-carbonyl 3300-2500, pyrazole ring 1540; pmr (deuteriochloroform): δ 0.80 (t, 3H, J = 7.0 Hz, CH_3), 1.20-1.60 (m, 4H, CH_2), 2.25 (s, 3H, CH_3), 4.10 (t, 2H, J = 7.3 Hz, OCH_2), 7.00-7.50 (m, 5H, Ph), 10.08 (s, H, OH); cmr (deuteriochloroform): δ 13.7 (CH_3), 14.4 (CH_3), 19.2 (CH_2CH_3), 30.8 (*C*H_2), 64.4 (OCH_2), 93.7 (*C*=C-OH), 121.1, 126.7, 129.1, 137.5 (6C, Ph), 148.4 (C=N), 157.5 (C=*C*-OH), 167.3 (C=O).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.69; H, 6.57. Found: C, 65.65, H, 6.78.

1-(*n*-Octyl)-3-methyl-5-ethoxycarbonyloxypyrazole (**3a**).

This compound was obtained as a yellow oil, 50% yield; ir (liquid film): ν C=O 1750; pmr (deuteriochloroform): δ 0.80 (t, 3H, J = 6.8 Hz, CH_3), 1.20 (m, 12H, CH_2), 1.40 (t, 3H, J = 7.0 Hz, CH_3), 2.20 (s, 3H, CH_3), 3.80 (t, 2H, J = 7.1 Hz, NCH_2), 4.30 (q, 2H, J = 7.0 Hz, OCH_2), 5.80 (s, 1H, CH=); cmr (deuteriochloroform): δ 13.5 (CH_3), 14.0 ($(CH_2)_6CH_3$), 14.3 (CH_3), 18.8-31.7 ($(CH_2)_6CH_3$), 47.3 (NCH_2), 65.5 (OCH_2), 92.6 (*C*=C-O), 144.7 (C=*C*-O), 148.8 (C=N), 150.8 (C=O).

Anal. Calcd. for $C_{15}H_{26}N_2O_3$: C, 63.88; H, 9.28. Found: C, 63.75; H, 9.31.

1-(*n*-Octyl)-3-methyl-5-(*n*-butoxycarbonyloxy)pyrazole (**3b**).

This compound was obtained as a red oil, 51% yield: ir (liquid film): ν C=O 1770; pmr (deuteriochloroform): δ 0.80 (t, 3H, J = 6.8 Hz, CH_3), 1.25 (m, 16H, CH_2), 1.5-1.9 (m, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.80 (t, 2H, J = 7.0 Hz, NCH_2), 4.20 (t, 2H, J = 7.0 Hz, OCH_2), 5.8 (s, 1H, CH=); cmr (deuteriochloroform): δ 13.5 (CH_3), 14.0 ($(CH_2)_6CH_3$), 14.3 (CH_3), 18.8-31.7 (CH_2), 47.4 (NCH_2), 69.5 (OCH_2), 92.7 (*C*=C-O), 144.8 (C=*C*-O), 146.9 (C=N), 151.0 (C=O).

Anal. Calcd. for $C_{17}H_{30}N_2O_3$: C, 65.77; H, 9.74. Found: C, 65.67; H, 9.68.

1-(*n*-Dodecyl)-3-methyl-5-ethoxycarbonyloxypyrazole (**3c**).

This compound was obtained as a yellow oil, 52% yield; ir (liquid film): ν C=O 1770; pmr (deuteriochloroform): δ 0.95 (t, 3H, J = 6.6 Hz, CH_3), 1.20 (m, 20H, CH_2), 1.30 (t, 3H, J = 7.0 Hz, CH_3), 2.15 (s, 3H, CH_3), 3.80 (t, 2H, J = 7.1 Hz, NCH_2), 4.20 (q, 2H, J = 7.0 Hz, OCH_2), 5.80 (s, 1H, CH=); cmr (deuteriochloroform): δ 14.0 (CH_3), 14.2 ($(CH_2)_{10}CH_3$), 22.5-31.4 (CH_2), 47.2 (NCH_2), 65.4 (OCH_2), 92.5 (*C*=C-O), 144.5 (C=*C*-O), 145.7 (C=N), 150.6 (C=O).

Anal. Calcd. for $C_{19}H_{34}N_2O_3$: C, 67.42; H, 10.12. Found: C, 67.38; H, 10.10.

1-(*n*-Dodecyl)-3-methyl-5-(*n*-butyloxycarbonyloxy)pyrazole (**3d**).

This product was obtained as a yellow oil, 52% yield; ir (liquid film): ν C=O 1780; pmr (deuteriochloroform): δ 0.85 (t, 6H, J = 7.1 Hz, CH_3), 1.20-1.40 (m, 24H, CH_2), 2.15 (s, 3H, CH_3), 3.90 (t, 2H, J = 7.1 Hz, NCH_2), 4.20 (t, 2H, J = 7.0 Hz, CH_3),

5.80 (s, 1H, CH=); cmr (deuteriochloroform): δ 13.5 (CH_3), 14.0 ($(CH_2)_{10}CH_3$), 18.8 (CH_3), 22.6-31.8 (CH_2), 47.3 (NCH_2), 69.5 (OCH_2), 92.7 (*C*=C-O), 144.7 (C=*C*-O), 150.9 (C=O).

Anal. Calcd. for $C_{21}H_{38}N_2O_3$: C, 68.81; H, 10.45. Found: C, 68.75; H, 10.39.

General Procedure for Reaction of 1-Substituted-3-methylpyrazol-5-ones **1** with bis(Alkoxythiocarbonyl) Sulfide.

A mixture of 1-substituted-3-methylpyrazol-5-one (**1**) (10 mmoles), calcium hydroxide (1.11 g, 15 mmoles), bis(alkoxythiocarbonyl) sulfide (11 mmoles) in dioxane (50 ml) is refluxed until the pyrazolone **1** is completely consumed, monitoring the progress of the reaction by tlc. The cooled reaction mixture is poured in aqueous 3 *M* hydrochloric acid (100 ml) mixed with crushed ice (100 g) and after stirring 30 minutes, it was extracted with ethyl acetate (4 x 25 ml). The organic layer was dried (sodium sulfate) and evaporated to yield a red oil or solid, which is recrystallized from methyl alcohol-water.

4-Ethoxythiocarbonyl-5-hydroxy-3-methyl-1-phenylpyrazole (**4a**).

This compound was obtained in 38% yield as red needles (methyl alcohol-water), mp 39-40°; ir (potassium bromide): ν associated OH-thiocarbonyl 3300-2500, pyrazole ring 1570; pmr (deuteriochloroform): δ 1.44 (t, 3H, J = 6.5 Hz, CH_3), 2.40 (s, 3H, CH_3), 4.60 (q, 2H, 6.5 Hz, OCH_2), 7.46-7.86 (m, 5H, Ph), 12.40 (s, 1H, OH); cmr (deuteriochloroform): δ 13.8 (CH_3), 15.9 (OCH_2CH_3), 66.3 (OCH_2CH_3), 104.1 (C-COH), 121.5, 126.9, 129.0, 137.5, (Ph), 147.0 (C=N), 159.1 (C-OH), 204.4 (C=S).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 58.99; H, 5.69.

4-(*n*-Butoxycarbonyl)-5-hydroxy-3-methyl-1-phenylpyrazole (**4b**).

This compound was obtained in 22% yield as a red oil; ir (liquid film): ν associated OH-thiocarbonyl 3300-2500, pyrazole ring 1570; pmr (deuteriochloroform): δ 0.80 (t, 3H, J = 6.8, CH_3), 1.30-1.90 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 4.60 (t, 2H, 7.0 Hz, OCH_2), 7.30-7.90 (m, 5H, Ph), 12.60 (s, 1H, OH); cmr (deuteriochloroform): δ 13.6 (CH_3), 15.5 (CH_2CH_3), 19.6 (CH_2), 30.6 (CH_2), 64.4 (OCH_2), 104.2 (C-4), 122.0, 127.0, 129.2 and 137.0 (6C, Ph), 142.2 (C-3), 159.3 (C-5), 204.6 (C=S).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25. Found: C, 61.86; H, 6.02.

4-Ethoxythiocarbonyl-5-hydroxy-3-methyl-1-(*n*-octyl)pyrazole (**4c**).

This compound was obtained in 20% yield as a red oil; ir (liquid film): ν associated OH-thiocarbonyl 3320-2480, pyrazole ring 1565; pmr (deuteriochloroform): δ 0.80 (t, 3H, J = 6.5 Hz, CH_3), 1.20-1.30 (m, 12H, CH_2), 1.60 (t, 3H, OCH_2CH_3), 2.20 (s, 3H, CH_3), 3.80 (t, 2H, NCH_2), 4.50 (t, 2H, 6.5 Hz, OCH_2), 12.50 (s, 1H, OH); cmr (deuteriochloroform): δ 13.5 (CH_3), 15.1 (CH_3), 18.8-31.9 (CH_2), 48.2 (NCH_2), 62.5 (OCH_2), 103.9 (C-4), 145.4 (C-3), 157.6 (C-5), 206.4 (C=S).

Anal. Calcd. for $C_{15}H_{26}N_2O_2S$: C, 60.37; H, 8.78. Found: C, 60.43; H, 8.69.

4-Butoxythiocarbonyl-1-(*n*-decyl)-5-hydroxy-3-methylpyrazole (**4d**).

This compound was obtained in 16% yield; ir (liquid film): ν associated OH-thiocarbonyl 3300-2500, pyrazole ring 1540; pmr (deuteriochloroform): δ 0.90 (t, 6H, CH_3), 1.10-1.30 (m, 20H, CH_2), 2.30 (s, 3H, CH_3), 3.70 (t, 2H, NCH_2), 4.50 (t, 2H, OCH_2), 12.50 (s, 1H, OH); cmr (deuteriochloroform): δ 13.6 (CH_3), 16.2 (CH_3), 31.7-19.0 (CH_2), 47.3 (NCH_2), 63.2 (OCH_2), 144.8 (C-3), 158.0 (C-5), 205.3 (C=S).

Anal. Calcd. for $C_{19}H_{34}N_2O_2S$: C, 64.36; H, 9.76. Found: C, 64.54; H, 9.80.

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