Regioselective Acetylation of some N-Methylpyrrole Derivatives with Isopropenyl Acetate and Different Acetic Anhydrides

Tibor Gizur* and Kálmán Harsányi

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We studied the reactions of some N-methylpyrrole derivatives with isopropenyl acetate and different acetic anhydrides. We have found that the reaction with isopropenyl acetate afforded 5-acetylpyrrole derivatives while with acetic anhydrides acetylation occurred on the α-carbon atom of the side-chain of pyrrole-2-acetic acid derivatives.

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Previously we described the reaction of some 1,4-dimethyl-1*H*-pyrrol-2-acetic acid derivatives 1 [1] with isopropenyl acetate, which resulted in the corresponding 5-acetyl derivatives [2] (Scheme 1). We continued studying this reaction and obtained similar results with pyrano[4,3-b]pyrrole derivative 2. The preparation of 2 was performed as shown in Scheme 2, starting from the known pyrrol-2-acetic acid 4.

Scheme 1

Y=H; COOEt

The reaction of **7a** [1] with isopropenyl acetate yielded the cyclic anhydride **8a** instead of the 5-acetyl derivative. Anhydride **8a** did not react further even with excess isopropenyl acetate. A similar cyclic anhydride **8b** was obtained when the reaction was performed with **7b** (Scheme 3). In order to study the formation of cyclic anhydrides the reactions of **7a-c** were studied with acetic anhydride, chloroacetic anhydride and trifluoroacetic anhydride. Reacting **7a** with any of these acetic anhydrides gave **8a**. However, if **8a** was reacted with acetic anhydride in the presence of a small amount of pyridine, a cyclic anhydride \rightarrow **9a** lactone transformation (Scheme **3**) occurred similarly as that described by the Japanese authors in the case of the corresponding *N*-methylindole derivative [5].

When 7b was reacted with acetic anhydride at 40° the anhydride 8b was obtained, which reacted further to give 9b at higher temperature even without pyridine. The formation of 9a and b respectively can be explained by the acylation of 8a or b with acetic anhydride on the methylene carbon then by the splitting off carbon dioxide out of the β -ketocarboxylic acid derivative and recyclization. In

Scheme 2

A: 1,1'-carbonyldiimidazole, (EtOOCCH₂COO)₂Mg; B: NaOH; C: NaBH₄; D: isopropenyl a cetate

Scheme 3

order to prove this reaction sequence we succeeded in the preparation of 9a enol-lactone compound from 6 by ester hydrolysis and the cyclization of the intermediate 13, which could be performed even by proton catalysis or by the reaction with acetic anhydride. We were able to find further evidence of the acylation of α -methylene group of the pyrrole side-chain. We could transfer 7a or b respectively to 10 by trifluoroacetic anhydride in dioxane which

*F in the case of 8a

contained the trifluoromethyl group as evidence of the reaction sequence described above. Further evidence originated by acylation of 7c with chloroacetic anhydride. In this reaction the primarily built-in chloroacetyl group was able to react with the enol generated out of the carbonyl on the position 6. Compound 16 was the first number of a new condensed 7H-furano[3',2':5,6]pyrano[4,3-b]pyrrole ring system.

Scheme 4

A: trifluo roacetic arhydride/pyridine B: aq. s odium hydroxide

The acetylation of 9a with trifluoroacetic anhydride resulted in 14a, and the same compound could be obtained under the same condition starting from 13 (R = H). The possibility of the formation of the alternative structure 15 could be excluded on the basic of the 'H-nmr spectrum of 14 (Scheme 3). Monoester 4 and 11 [1] reacted similarly affording compounds 12 when trifluoroacetic anhydride was used. In the case of 11a-11b the reaction most probably started with the parallel formation of a mixed anhydride and the trifluoroacetylation with an other molecule of trifluoroacetic anhydride on the α-methylene group. Following the enolisation of the β -ketocarboxylic ester moiety the enol-lactone formation occurred with the elimination of one molecule trifluoroacetic acid. On the other hand when 4a-4b were the substrates, the trifluoroacetylation of the \alpha-methylene group and the mixed anhydride formation was followed by a double intramolecular transesterification (Scheme 4). The hydrolysis of 12a afforded 7a.

EXPERIMENTAL

Proton nmr spectra were recorded on Varian EM-360 (60 MHz) instrument and proton chemical shifts are reported in parts per million (ppm) downfield from TMS as the internal reference. Infrared spectra were recorded on a Perkin Elmer 257 spectrophotometer. All melting point are uncorrected. Melting points were determined on a Büchi 510 apparatus.

2-Acetyl-1,3,6-trimethyl-6,7-dihydro-1H-pyrano[4,3-b]pyrrol-4-one (3).

A mixture of 10.2 g (0.055 mole) of 2 37.92 (42 ml, 0.38 mole) of isopropenyl acetate and 1 ml of methanesulfonic acid in 200 ml of dichloromethane was refluxed for 8 hours. Then a further 18.9 g (21 ml, 0.19 mole) of isopropenyl acetate was added and the reaction mixture was refluxed for 12 hours. After cooling, the solution was washed with 50 ml 1 N sodium hydroxide solution and 50 ml water. The organic layer was dried and evaporated under reduced pressure. The oily residue solidified under ether and recrystallized from 10 ml ethanol, yield 4.13 g (34%), mp 141-143°; ir (potassium bromide): 1703, 1640 cm⁻¹ (C=0); ¹H-nmr (deuteriochloroform): 1.6 (d, 3H, CH₃), 2.5 (s, 3H, CH₃),

2.7 (s, 3H, CH_3), 2.9 (d, 2H, CH_2), 3.9 (s, 3H, $N-CH_3$), 4.7 (m, H, CH_3).

Anal. Calcd. for $C_{12}H_{15}NO_3$ (221.24): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.86; N, 6.55.

Ethyl 4-(1,4-Dimethyl-3-ethoxycarbonyl-1*H*-pyrrol-2-yl)acetoacetate (5).

A solution of 11.26 g (0.05 mole) of 4 in 250 ml of dry THF was stirred for 1 hour with 8.91 g (0.055 mole) of 1,1'-carbonyldiimid-azole at room temperature. Diethyl magnesiumdimalonate (7.15 g, 0.055 mole) was added and the mixture was stirred for 18 hours and evaporated to dryness under reduced pressure. The residue was solved in 200 ml of dichloromethane and extracted with 80 ml of 1 N hydrochloric acid solution and 50 ml of water. The organic layer was dried and evaporated under reduced pressure. The oily residue solidified under 15 ml of diisopropyl ether, yield 12.53 g (85%), mp 87-88°; ir (potassium bromide): 1727, 1712, 1662 cm⁻¹ (C=0); 'H-nmr (deuteriochloroform): 1.2 (t, 3H, CH₃), 1.3 (t, 3H, CH₃), 2.2 (s, 3H, CH₃), 3.4 (s, 3H, N-CH₃), 3.5 (s, 2H, CH₂), 4.2 (q, 2H, CH₂), 4.25 (s, 2H, CH₂), 4.3 (q, 2H, CH₂), 6.3 (s, H, CH).

Anal. Calcd. for C₁₅H₂₁NO₅ (295.33); C, 61.00; H, 7.16; N, 4.74. Found: C, 61.14; H, 7.06; N, 4.60.

1-(1,4-Dimethyl-3-ethoxycarbonyl-1*H*-pyrrol-2-yl)-2-propanone (6).

To a mixture of 6.38 g (0.02 mole) of 5 in 20 ml of ethanol, 20 ml of 5% aqueous sodium hydroxide solution was added and the reaction mixture was refluxed for 1 hour. After cooling 24.5 ml of 1 N hydrochloric acid was added. The ethanol was removed under reduced pressure. The crystalline product was filtered and washed with water, yield 3.79 g (79%), mp 77-79°; ir (potassium bromide): 1720, 1670 cm⁻¹ (C=0); ¹H-nmr (deuteriochloroform): 1.3 (t, 3H, CH₃), 2.3 (s, 6H, 2CH₃), 3.5 (s, 3H, N-CH₃), 4.2 (s, 2H, CH₂), 4.3 (q, 2H, CH₂), 6.4 (s, H, CH).

Anal. Calcd. for C₁₂H₁₇NO₃ (223.71): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.62; H, 7.80; N, 6.31.

1,3,6-Trimethyl-6,7-dihydro-1 *H*-pyrano[4,3-b]pyrrol-4-one (2).

Sodium borohydride (2.6 g, 0.0687 mole) was added slowly to a solution of 15.63 g (0.0687 mole) of $\bf 6$ in 200 ml of methanol with stirring and external ice-cooling. Then mixture was stirred for 1 hour at ambient temperature and 3 ml of 1:1 aqueous hydrochloric acid solution was added. The mixture was evaporated under reduced presure. The residue was dissolved in 200 ml of dichloromethane and extracted with 100 ml of 1 N hydrochloric acid and 50 ml water. The organic layer was dried and evaporated. The oily residue solidified under petroleum ether, yield 10.1 g (66%), mp 162-164°; ir (potassium bromide): 1685 cm⁻¹ (C = 0); 'H-nmr (deuteriochloroform): 1.5 (d, 3H, CH₃), 2.3 (s, 3H, CH₃), 2.8 (m, 2H, CH₂), 3.6 (s, 3H, N-CH₃), 4.7 (m, H, CH), 6.4 (s, H, CH).

Anal. Calcd. for $C_{10}H_{13}NO_2$ (179.21): C, 67.02; H, 7.31; N, 7.81. Found: C, 67.12; H, 7.46; N, 7.91.

1,3-Dimethyl-1,7-dihydropyrano[4,3-b]pyrrole-4,6-dione (8a).

A mixture of 5.32 g (0.027 mole) of 7a, 10.83 g (12 ml, 0.109 mole) of isopropenyl acetate and 0.25 ml of methanesulfonic acid in 25 ml of dichloromethane was refluxed for 3 hours. After cooling the precipitated crystalline product was filtered, yield 2.74 g (57%), mp 181-182°, identical to a sample prepared by a known procedure [6].

1,3,6-Trimethyl-1H-pyrano[4,3-b]pyrrol-4-one (9a).

a.

A mixture of 0.7 g (4 mmoles) of **8a**, 0.2 ml of pyridine in 20 ml of acetic anhydride was refluxed for 3 hours. Then the mixture was poured into 50 ml of water and 10 ml 40% aqueous sodium hydroxide solution was added. The solution was extracted with 2 x 30 ml of dichloromethane. The organic layer was dried and evaporated. The oily residue solidified under ether, yield 0.2 g (28%), mp 148-150°; ir (potassium bromide): 1710 cm⁻¹ (C=O); ¹H-nmr (deuteriochloroform): 2.27 (s, 3H, CH₃), 2.33 (2, 3H, CH₃), 3.6 (s, 3H, N-CH₃), 6.1 (s, H, CH), 6.64 (s, H, CH).

Anal. Calcd. for C₁₀H₁₁NO₂ (177.20): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.62; H, 6.16; N, 7.75.

b.

Compound 13 (1.95 g, 0.01 mole) was refluxed in 20 ml of acetic anhydride for 4 hours. After cooling 30 ml of ether was added. The crystalline product was filtered off and washed with 30 ml of ether, yield 1.4 g (79%), mp 148-150°, identical to a sample prepared by the previous procedure.

5-Acetyl-3-carboxy-1,4-dimethyl-1H-pyrrole-2-acetic Acid (71).

Ethyl (5-acetyl-1,4-dimethyl-3-ethoxycarbonyl-1*H*-pyrrol-2-yl)-acetate (12 g, 0.0406 mole) [2] in 100 ml of 25% aqueous sodium hydroxide solution was refluxed for 3 hours. After cooling the mixture was acidified with 50 ml of concentrated hydrochloric acid. The precipitated crystalline product was filtered off and washed with 2 x 30 ml of water, yield 8.5 g (88%), mp 225-226°; IR(KBr): 1730, 1630 cm⁻¹ (C=O); ¹H-nmr (DMSO-d₆): 2.5 (2, 3H, CH₃), 2.6 (s, 3H, CH₃), 3.7 (s, 3H, N-CH₃), 4.2 (s, 2H, CH₂).

Anal. Calcd. for C₁₁H₁₈NO₅ (239.29): C, 55.21; H, 5.48; N, 5.85. Found: C, 55.12; H, 5.30; N, 5.94.

2-Acetyl-1,3-dimethyl-1,7-dihydropyrano[4,3-b]pyrrole-4,6-dione (8b).

Compound 7b (8.7 g, 0.036 mole) in 90 ml of acetic anhydride was stirred for 2 hours at 40°. The mixture was cooled under 10°. The crystalline product was filtered off and washed with 2 x 50 ml of ether, yield 4.3 g (54%), mp 185-188°; ir (potassium bromide): 1790, 1750, 1650 cm⁻¹ (C=0); 'H-nmr (DMSO-d₆): 2.5 (s, 3H, CH₃), 2.6 (s, 3H, CH₃), 3.7 (s, 3H, N-CH₃), 4.3 (s, 2H, CH₂).

Anal. Calcd. for $C_{11}H_{11}NO_4$ (221.22): C, 59.72; H, 5.01; N, 6.33. Found: C, 59.61; H, 4.95; N, 6.28.

2-Acetyl-1,3,6-trimethyl-1*H*-pyrano[4,3-*b*]pyrrol-4-one (9b).

Compound 7b (12.9 g, 0.054 mole) in 20 ml of acetic anhydride was stirred and refluxed for 2 hours. The mixture was cooled under 10° and 100 ml of ether was added. The crystalline product was filtered off and washed with 50 ml of ether. The crude product was stirred in 150 ml of boiling methanol for 15 minutes. The mixture was cooled and the product was filterd off, yield 7.9 g (67%), mp 210-212°; ir (potassium bromide): 1720, 1640 cm⁻¹ (C=0); 'H-nmr (deuteriochloroform): 2.28 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 2.75 (s, 3H, CH₃), 3.87 (s, 3H, N-CH₃), 6.18 (s, H, CH). Anal. Calcd. for C₁₂H₁₃NO₃ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.65; H, 5.81; N, 6.48.

2-Acetyl-1,3-dimethyl-6-trifluoromethyl-1*H*-pyrano[4,3-*b*]pyrrol-4-one (10b).

A mixture of 2.39 g (0.01 mole) of 7b and 6 ml of trifluoroacetic anhydride in 30 ml of dioxane was refluxed for 3 hours. After cooling, the solution was evaporated under reduced pressure.

The oily residue solidified under ether, yield 2.1 g (77%) mp 200-203°; ir (potassium bromide): 1760, 1640 cm⁻¹ (C=0); 1 H-nmr (deuteriochloroform-DMSO-d₆): 2.6 (s, 3H, CH₃), 2.7 (s, 3H, CH₃), 4.0 (s, 3H, CH₃), 10.7 (s, H, CH).

Anal. Calcd. for $C_{12}H_{10}F_3NO_3$ (273.20): C, 52.76; H, 3.69; N, 5.13. Found: C, 52.66; H, 3.71; N, 5.02.

2-(4-Chlorobenzoyl)-1,3-dimethyl-6-trifluoromethyl-1*H*-pyrano-[4,3-*b*]pyrrol-4-one (**10c**).

A mixture of 5.1 g (0.017 mole) of 7c and 20 ml of trifluoroacetic anhydride was refluxed for 4 hours. After cooling, the solution was evaporated under reduced pressure. The residue was stirred in 40 ml of dichloromethane for 10 minutes. The crystalline product was filtered off and recrystallized from ethanol, yield 4.71 g (75%), mp 248-250°; ir (potassium bromide): 1750, 1660 cm⁻¹ (C = 0); 'H-nmr (DMSO-d₆): 2.1 (s, 3H, CH₃), 3.8 (s, 3H, N-CH₃), 5.6 (s, H, CH), 7.6 (q, 4H, Ar-H).

Anal. Calcd. for $C_{17}H_{11}CIF_3NO_3$ (369.73): C, 55.22; H, 3.0; N, 3.78; Cl, 9.59; F, 15.41. Found: C, 55.31; H, 2.89; N, 3.71; Cl, 9.38; F. 15.28.

1,3-Dimethyl-7-ethoxycarbonyl-6-trifluoromethyl-1*H*-pyrano[4,3-*b*]pyrrol-4-one (**12a**).

2-Acetyl-1,3-dimethyl 7-ethoxycarbonyl-6-trifluoromethyl-1*H*-pyrano[4,3-*b*]pyrrol-4-one (**12b**).

Typical Procedure.

A solution of 11 or 4 (0.01 mole) and 10 ml of trifluoroacetic anhydride in 25 ml of dioxane was refluxed 3 hours. After cooling, the solution was evaporated under reduced pressure. The oily residue solidified under ether.

The yield of **12a** was 2.16 g (71%) from **4a** [1], 2.08 g (69%) from **11a** [1], mp 140-144°; ir (potassium bromide): 1740, 1730 cm⁻¹ (C = O); 'H-nmr (deuteriochloroform): 1.4 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.7 (s, 3H, $N-CH_3$), 4.4 (q, 2H, CH_2), 6.7 (s, H, CH_3).

Anal. Calcd. for C₁₃H₁₂F₃NO₄ (303.24): C, 51.49; H, 3.99; N, 4.60; F, 18.78. Found: C, 51.37; H, 3.81; N, 4.57; F, 18.65.

The yield of **12b** was 1.19 g (35%) from **4b**, 1.81 g (52%) from **11b**, mp 131-132° ir (potassium bromide): 1750, 1720, 1670 cm⁻¹ (C = 0); 'H-nmr (deuteriochloroform): 1.4 (t, 3H, CH₃), 2.5 (s, 3H, CH₃), 2.7 (2, 3H, CH₃), 3.8 (s, 3H, N-CH₃), 4.4 (q, 2H, CH₂).

Anal. Calcd. for $C_{15}H_{14}F_3NO_5$ (345.28): C, 52.18; H, 4.09; N, 4.05; F, 16.50. Found: C, 52.08; H, 4.19; N, 4.19; F, 16.20.

Compounds **4b** and **11b** were prepared similarly to **4a** and **11a** [cf. reference 1]. 5-Acetyl-1,4-dimethyl-3-ethoxycarbonyl-1H-pyrrol-2-acetic Acid (**4b**). The yield was 59%, mp 130-132°; ir (potassium bromide): 1720, 1640 cm⁻¹ (C = O); ¹H-nmr (deuteriochloroform): 1.3 (t, 3H, CH₃), 2.5 (s, 3H, CH₃), 2.6 (s, 3H, CH₃), 3.8 (s, 3H, N-CH₃), 4.2 (s, 2H, CH₂), 4.4 (q, 2H, CH₂), 9.8 (s, H, COOH). Anal. Calcd. for $C_{13}H_{17}NO_5$ (267.29): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.53; H, 6.50; N, 5.17.

Ethyl 5-Acetyl-3-carboxy-1,4-dimethyl-1 H-pyrrol-2-acetate (11b).

This compound was obtained in 75% yield, 158-160°; ir (potas-

sium bromide): 1725, 1650 cm⁻¹ (C=O); 'H-nmr (DMSO-d₆): 1.3 (t, 3H, CH₃), 2.5 (s, 3H, CH₃), 2.6 (s, 3H, CH₃), 3.8 (s, 3H, N-CH₃), 4.1 (s, 2H, CH₂), 4.2 (q, 2H, CH₂).

Anal. Calcd. for $C_{13}H_{17}NO_5$ (267.29): C, 58.42; H, 6.41; N, 5.26. Found: C, 58.68; H, 6.48; N, 5.31.

1-(1,4-Dimethyl-3-carboxy-1H-pyrrol-2-yl)-2-propanone (13).

Compound **6a** (1.7 g, 7 mmoles) was refluxed in 50 ml of 1 N sodium hydroxide solution for 2 hours. The mixture was cooled under 10° and 50 ml of 1 N hydrochloric acid solution was added. The crystalline product was filtered off and washed with 10 ml of water, yield 1.0 g (73%), mp 168-169°; ir (potassium bromide): 1710, 1660 cm⁻¹ (C = 0); ¹H-nmr (deuteriochloroform): 2.3 (s, 6H, 2 CH₃), 2.4 (s, 2H, CH₂), 4.1 (s, 3H, N-CH₃), 6.3 (s, H, CH), 7.6* (s, H, COOH).

Anal. Calcd. for C₁₀H₁₃NO₃ (195.27): C, 61.52; H, 6.71; N, 7.17. Found: C, 61.40; H, 6.65; N, 7.28.

1,3,6-Trimethyl-7-trifluoroacetyl-1H-pyrano[4,3-b]pyrrol-4-one (14a).

Compound 13 (4.77 g, 0.024 mole) was refluxed in 40 ml of trifluoroacetic anhydride for 5 hours. After cooling, the solution was evaporated under reduced pressure. The oily residue solidified under ether, yield 5.27 g (80%), mp 149-150°; ir (potassium bromide): 1750, 1730 cm⁻¹ (C=O); 'H-nmr (deuteriochloroform): 2.3 (s, 3H, CH₃), 2.7 (s, 3H, CH₃), 3.8 (s, 3H, N-CH₃), 6.2 (s, H, CH). Anal. Calcd. for C₁₂H₁₀F₃NO₃ (273.21): C, 52.75; H, 3.68; N, 5.12. Found: C, 52.86; H, 3.71; N, 5.06.

5-(4-Chlorobenzoyl)-4,6-dimethyl-7H-furano[3',2':5,6]pyrano-[4,3-b]pyrrole-3,7-dione (16).

A mixture of 1.58 g (5 mmoles) of 7c [1], 0.25 ml of pyridine and 10 g of chloroacetic anhydride was stirred at 100° for 2 hours. Then 80 ml of water was added and the solution was extracted with 2 x 40 ml of dichloromethane. The organic layer was dried and evaporated. The oily residue solidified under ether. The product was recrystallized from acetonitrile, yield 0.7 g (39%), mp 183-185°; ir (potassium bromide): 1750, 1650 cm⁻¹ (C=0); 'H-nmr (deuteriochloroform): 2.1 (s, 2H, CH₃), 4.3 (s, 3H, N-CH₃), 5.1 (s, 2H, CH₂), 7.5 (q, 4H, Ar-H).

Anal. Calcd. for $C_{18}H_{12}CINO_5$ (357.75): C, 60.43; H, 3.38; Cl, 9.91; N, 3.91. Found: C, 60.53; H, 3.40; Cl, 10.02; N, 3.85.

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