Transformations of Phenylhydrazones of Dialkyl 2-Oxo-propane-1,3-dicarboxylate and of Ethyl Acetoacetate in Concentrated Sulfuric Acid

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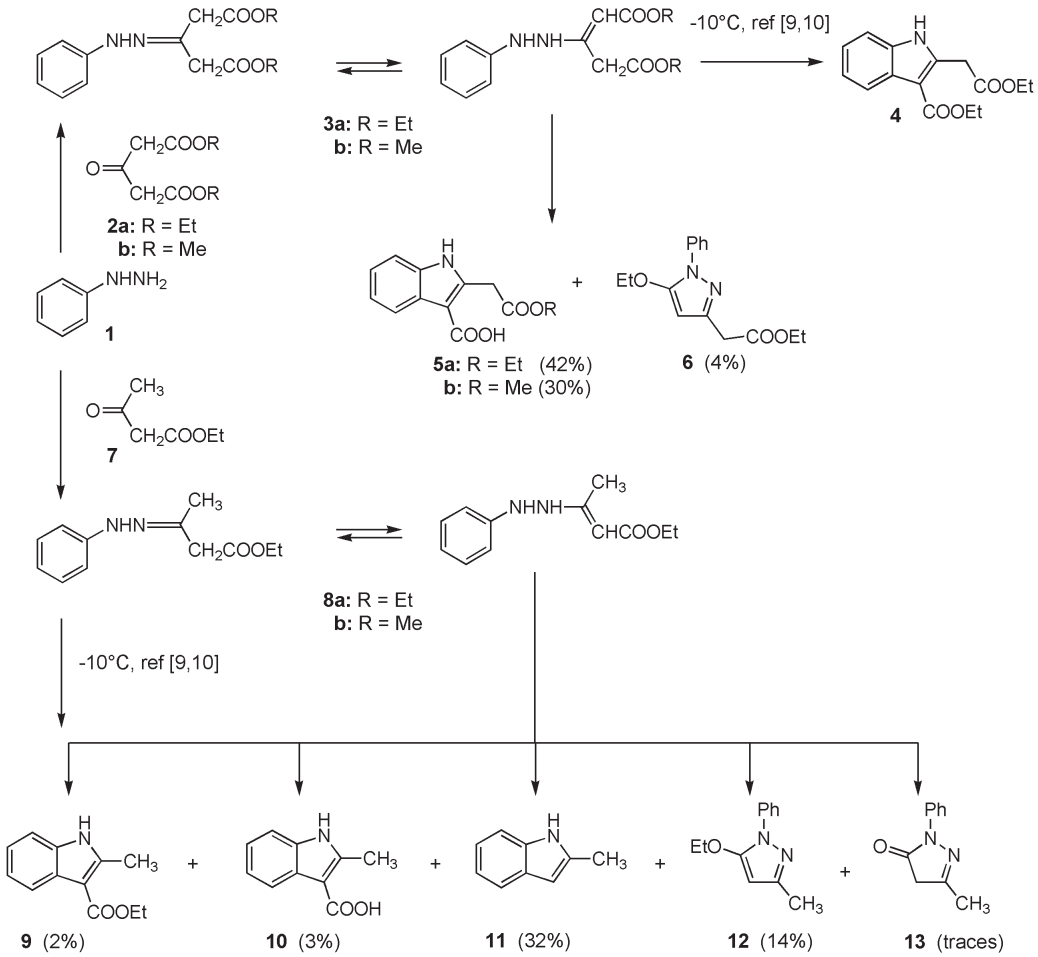
Received March 3, 2005

The hydrazones **3a,b**, prepared from phenylhydrazine (**1**) and dialkyl 2-oxopropane-1,3-dicarboxylate (**2a,b**) were converted in concentrated sulfuric acid at –5 °C into a mixture of alkyl (3-carboxyindol-2-yl)acetates (**5a,b**), and ethyl (5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)acetate **6**. The hydrazone **8**, prepared from **1** and ethyl acetoacetate (**7**) was transformed under the same conditions into a mixture of five compounds: ethyl 2-methylindol-3-carboxylate (**9**), 2-methylindol-3-carboxylic acid (**10**), 2-methylindol (**11**), 5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (**12**), and 3-methyl-1-phenyl-1*H*-pyrazol-5-one (**13**).

J. Heterocyclic Chem., **42**, 1413 (2005).

In connection with our research in the field of indole alkaloids, such as aplysinopsins, and their analogues [1–4] and meridianins and their analogues [5] on the basis of 3-dimethylaminopropenoates and related enaminones [6–8] we became interested in ethyl 3-ethoxycarbonylindol-2-acetate (**4**) and ethyl 2-methylindole-2-carboxylate (**9**). The preparations of both compounds have been described in the literature [9].

According to the literature [9] compound **4** has been prepared from phenylhydrazine (**1**) and diethyl 2-oxopropane-1,3-dicarboxylate (**2a**) to give the corresponding hydrazone or ne-hydrazine intermediate **3a** which has been then converted in concentrated sulfuric acid at –10 °C [10] into the indole derivative **4**. In an analogous manner, compound **9** has been obtained from hydrazone **8**, prepared from phenylhydrazine (**1**) and ethyl acetoacetate (**7**) in sulfuric acid [9,10].



When we carried out the transformation of phenylhydrazone **3a** in sulfuric acid at –5 °C two compounds were isolated ethyl 3-carboxyindol-2-yl acetate (**5a**) and ethyl (5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)acetate (**6**) in 42% and 4% yield, respectively, while from phenylhydrazone **3b** only methyl 3-carboxyindol-2-ylacetate **5b** was isolated in 30% yield. On the other hand, when hydrazone (**8**), prepared from phenylhydrazone (**1**) and ethyl acetoacetate (**7**), was added to concentrated sulfuric acid at –5 °C, four compounds were isolated: ethyl 2-methylindol-3-carboxylate (**9**), 2-methylindol-3-carboxylic acid (**10**), 2-methylindole (**11**), 5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (**12**) in 2%, 3%, 32% and 14% yield, while 3-methyl-1-phenyl-1*H*-pyrazol-5-one (**13**) was detected only in traces, on thin layer chromatography (Scheme 1).

The structures of new compounds were determined by ir, ^{1}H nmr, mass spectra, and elemental analyses for C, H, and N. The known compounds were identified by comparison with authentic samples, prepared according to procedures described in the literature.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR and 2D NMR HMBC, NOESY spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard (δ in ppm, *J* in Hz). IR spectra were recorded with Perkin–Elmer Spectrum BX FTIR and BIO RAD Excalibur Series FTS 3000 MX FTIR spectrophotometers (KBr discs, ν in cm^{-1}). MS spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin Elmer Series II CHN *Analyser* 2400. Medium pressure chromatography (MPLC) was performed with a Büchi isocratic system with detection on silica gel (Merck, silica gel 40, 0.015–0.035 mm); column dimensions (wet filled) 15x460 mm; backpressure 25–30 bar; detection: UV 254 nm; sample amount 200 mg of mixture.

Reaction of Phenylhydrazone of Dialkyl 2-Oxopropane-1,3-dicarboxylates in Sulfuric Acid. Preparation of **5a,b** and **6**.

Phenylhydrazine (**1**) (18 g) and diethyl 2-oxopropane-1,3-dicarboxylate (**2a**) (21 g) in ether (100 ml) with two drops of acetic acid at 0 °C for 1 h, followed by evaporation of solvent at room temperature, was added dropwise to concentrated sulfuric acid (70 ml) at –5 °C with vigorous stirring during 5 min. After 0.5 h at that temperature the mixture was poured into ice, and extracted with ether. Organic phase was dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Oily mixture of products was separated by chromatography. Fractions containing products were evaporated *in vacuo* to give **5a** and **6** in 42 and 4% yield, respectively.

2-(2-Ethoxy-2-oxoethyl)-1*H*-indole-3-carboxylic Acid (**5a**).

This compound was obtained as white solid (42%, 12 g) mp = 194–198 °C (ethanol/water) ^{1}H nmr ($CDCl_3$): δ 1.33 (t, 3H, *J* = 7.16, OCH_2CH_3); 4.27 (q, 2H, *J* = 7.16, OCH_2CH_3); 4.41 (s, 2H, CH_2); 7.21–7.26 (m, 2H, indole); 7.38–7.42 (m, 1H, indole); 8.18–8.21 (m, 1H, indole); 10.06 (broad s, 1H, NH). (DMSO): δ 1.19 (t, 3H, *J* = 6.97, OCH_2CH_3); 4.11 (q, 2H, *J* = 7.16, OCH_2CH_3); 4.18 (s, 2H, CH_2); 7.09–7.18 (m, 2H, indole); 7.40–7.43 (m, 1H, indole); 7.94–7.98 (m, 1H, indole); 11.82 (broad s, 1H, NH); 12.02 (broad s, 1H, COOH). ir: 3310, 1720, 1670, 1560, 1460, 1210, 740. ms: m/z (EI) 247 (M^+); hrms: m/z (EI) calcd. for $C_{13}H_{13}NO_4$: 247.084458. found: 247.084950.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.96; H, 5,51; N 5.42.

Ethyl (5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)acetate (**6**).

This compound was obtained as colorless oil, (4 %, 1060 mg) ^{1}H nmr ($CDCl_3$): δ 1.27 (t, 3H, *J* = 7.17, OCH_2CH_3); 1.42 (t, 3H, *J* = 6.96, OCH_2CH_3); 3.65 (s, 2H, CH_2); 4.11–4.22 (m, 4H, 2xOCH_2CH_3); 7.19–7.25 (m, 1H, phenyl); 7.35–7.42 (m, 2H, phenyl); 7.68–7.72 (m, 2H, phenyl) (The compound is identical with the compound reported in the literature [11]).

2-(2-Methoxy-2-oxoethyl)-1*H*-indole-3-carboxylic Acid (**5b**).

Phenylhydrazine (**1**) (18 g) and dimethyl 2-oxopropane-1,3-dicarboxylate (**2b**) (20 g) in ether (100 ml) with two drops of acetic acid at 0 °C for 1 h, followed by evaporation of solvent at room temperature, was added dropwise to concentrated sulfuric acid (70 ml) at –5 °C with vigorous stirring during 5 min. After 0.5 h at that temperature the mixture was poured into ice, and extracted with ether to give white solid 12.7 g (30%), mp = 176–180 °C (toluene) ^{1}H nmr ($CDCl_3$): δ 3.83 (s, 3H, OCH_3); 4.44 (s, 2H, CH_2); 7.25–7.29 (m, 2H, Ph); 7.39–7.43 (m, 1H, indole); 8.18–8.21 (m, 1H, indole); 9.92 (broad s, 1H, NH). (DMSO): δ 3.64 (s, 3H, OCH_3); 4.20 (s, 2H, CH_2); 7.10–7.19 (m, 2H, indole); 7.39–7.42 (m, 1H, indole); 7.94–7.97 (m, 1H, indole); 11.83 (broad s, 1H, NH); 12.05 (broad s, 1H, COOH). ir: 3380, 3120, 1730, 1650, 1460, 1210, 740.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.86; H, 4,73; N 6.31.

Reaction of Phenylhydrazone of Ethyl Acetotacetate in Sulfuric Acid. Preparation of compounds **9–13**.

Phenylhydrazine (**1**) (18 g) and ethyl acetotacetate (**7**) (15 g) in ether (100 ml) with two drops of acetic acid at 0 °C for 1 h, followed by evaporation of solvent at room temperature, was added dropwise to concentrated sulfuric acid (70 ml) at –5 °C with vigorous stirring during 5 min. After 0.5 h at that temperature the mixture was poured into ice, and extracted with ether. Organic phase was dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Oily mixture of products was separated by chromatography. Fractions containing product were evaporated *in vacuo* to give **9, 10**, **11**, and **12** in 2, 3, 32, and 14% yields, respectively. 3-Methyl-1-phenyl-1*H*-pyrazole-5-one (**13**) was present in traces, identified only by thin layer chromatography by comparison with an authentic sample.

Ethyl (2-Methylindol-3-yl)carboxylate (**9**).

This compound was obtained in 2 %, 480 mg; ^{1}H nmr ($CDCl_3$): δ 1.40 (t, 3H, *J* = 7.1, OCH_2CH_3); 2.28 (s, 3H, CH_3); 4.24 (q, 2H, *J* = 7.1, OCH_2CH_3); 7.25–7.32 (m, 2H, indole); 7.41–7.43 (m, 2H, indole), 7.84 (broad s, 1H, NH) (The compound is identical with the compound reported in the literature [9]).

2-Methyl-1*H*-indole-3-carboxylic acid (**10**).

This compound was obtained in 3 %, 640 mg; ^{1}H nmr ($CDCl_3$): δ 2.79 (s, 3H, CH_3); 7.21–7.26 (m, 2H, indole);

7.31–7.34 (m, 1H, indole); 8.16–8.19 (m, 1H, indole), 8.33 (broad s, 1H, NH) (The compound is identical with the compound reported in the literature [12]).

2-Methylindole (**11**).

This compound was obtained as white solid, which gradually darkened, (32 %, 4920 mg) ^{1}H nmr ($CDCl_3$): δ 2.33 (s, 3H, CH_3); 6.18 (s, 1H, 3-H); 7.02–7.12 (m, 2H, indole); 7.16–7.19 (m, 1H, indole); 7.48–7.51 (m, 1H, indole); 7.56 (broad s, 1H, NH) (The compound is identical with the compound reported in the literature [13]).

5-Ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (**12**).

This compound was obtained as colorless oil, (14 %, 3190 mg) ^{1}H nmr ($CDCl_3$): δ 1.42 (t, 3H, J = 7.1, OCH_2CH_3); 2.27 (s, 3H, CH_3); 4.11 (q, 2H, J = 7.1, OCH_2CH_3); 5.46 (s, 1H, 4-H); 7.18–7.23 (m, 1H, phenyl); 7.36–7.41 (m, 2H, phenyl); 7.69–7.72 (m, 2H, phenyl) (The compound is identical with the compound reported in the literature [14]).

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