Synthesis of Pyrazole Derivatives Using 1-Benzoyl-1-phenylhydrazine

Abdou Ahmed EL-SAYED and Masaki OHTA

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

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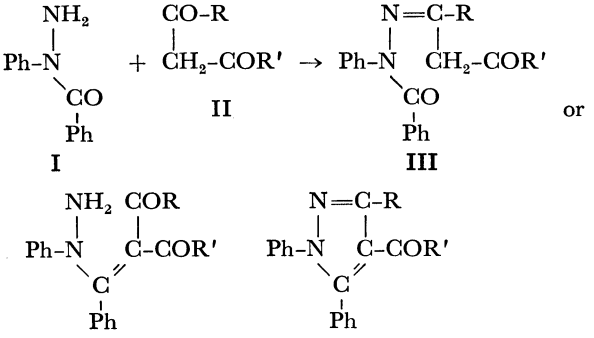
Condensation of 1-benzoyl-1-phenylhydrazine (I) with β-ketoesters and β-diketones was investigated. Reaction of I with ethyl acetoacetate, ethyl benzoylacetate and diethyl acetonedicarboxylate in the presence of phosphorus pentoxide afforded the corresponding hydrazones which were easily cyclized by sodium hydroxide to give pyrazole derivatives. Reaction of I with acetylacetone proceeded to give hydrazone without condensing agent. 4-Carboxy-1,5-diphenylpyrazol-3-ylacetic acid and its mono- and diester were also prepared.

The most general and widely applicable method for the preparation of pyrazoles consists of the condensation of hydrazines or monosubstituted hydrazines with 1,3-dicarbonyl compound or a precursor of such a species. Another well-known scheme of pyrazole synthesis consists of a combination of N–N–C and C–C units, aliphatic diazo compounds being mostly employed as compounds containing the former.

1-Acyl-1-substituted hydrazine which has a H_2N–N–CO– grouping is expected to condense with 1,3-dicarbonyl compound, but only one example of such condensation is found in literature.[1] We would like to report on the reaction of 1-benzoyl-1-phenylhydrazine (I) with 1,3-dicarbonyl compounds (II) to give pyrazole derivatives.

The reaction of I with 1,3-dicarbonyl compound may proceed *via* intermediate (III or IV) to give pyrazole derivatives (V).



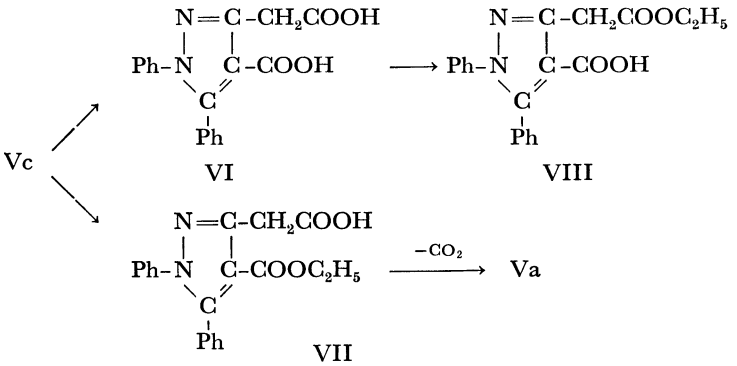
III and V, a: $R=CH_3$, $R'=OC_2H_5$
b: $R=Ph$, $R'=OC_2H_5$
c: $R=CH_2COOC_2H_5$, $R'=OC_2H_5$
d: $R=R'=CH_3$

We found that the reaction of I with β-ketoesters was difficult in the absence of a condensing agent even by heating the reaction mixture at 140°C. However, when the reaction components were heated in benzene in the presence of phosphorus pentoxide, condensation occurred easily and intermediate hydrazone (III) was formed by elimination of 1 mol of water. An alternative isomeric structure (IV) for the intermediate can be excluded by the fact that the product showed no characteristic absorption of amino group in its IR spectrum.

The ring closure of III to produce pyrazole (V) through dehydration between carbonyl and active methylene group was accomplished by using alkaline reagent, as usually employed for a similar mode of cyclization.[1,2] The most satisfactory procedure of cyclization consists of the treatment of an alcoholic solution of III with sodium hydroxide solution at room temperature. Compounds Va and Vb, obtained by the condensation of I with ethyl acetoacetate and benzoylacetoacetate, respectively, were found to be the same as reported in literature.[3,4]

When I and diethyl acetonedicarboxylate were subjected to react under the same conditions, hydrazone (IIIc) was obtained. Cyclization of IIIc with sodium hydroxide afforded ethyl 4-carbethoxy-1, 5-diphenylpyrazol-3-ylacetate (Vc) which is a new compound. The structure of Vc is consistent with the following results.

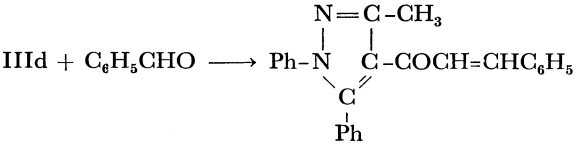
Hydrolysis of diethyl ester (Vc) with concentrated aqueous-alcoholic potassium hydroxide solution gave an alcohol-insoluble potassium salt, from which dicarboxylic acid(VI) was obtained. When the hydrolysis was carried out in the cold, the half ester (VII) was obtained.



1) K. v. Auwers and H. Mauss, *J. Prakt. Chem.*, **117**, 311 (1927).
2) A. Alemagna, R. Bacchtti, and S. Rossi, *Gazz. Chim. Ital.*, **93**, 748 (1963).
3) L. Knorr and A. Blank, *Ber.*, **18**, 312 (1885).
4) G. Minunni and S. Urso, *Gazz. Chim. Ital.*, **58**, 691 (1928).

When VII was subjected to thermal decarboxylation, it gave a compound which was found to be identical with Va. Esterification of dicarboxylic acid with ethanol and hydrogen chloride afforded half ester (VIII), which is isomeric with VII. When the esterification of VI was carried out by refluxing ethanol–benzene solution of VI in the presence of *p*-toluenesulfonic acid with continuous removal of water, a mixture of both esters (Va and VIII) was obtained.

Condensation of I with acetylacetone could be accomplished by heating the reaction mixture at 120°C in the absence of condensing agent, an intermediate hydrazone (IIId) being obtained. The hydrazone, when treated with alcoholic sodium hydroxide, gave a new compound, 4-acetyl-3-methyl-1,5-diphenylpyrazole (Vd). Compound Vd readily condensed with benzaldehyde in the presence of sodium hydroxide to give 4-cinnamoyl-3-methyl-1,5-diphenylpyrazole (IX).



IX

The procedures for preparation of 4-carboxyl-1,5-diphenylpyrazol-3-ylacetic acid and all its possible esters were found to be satisfactory and compounds with interesting synthetical possibilities are now available.

Experimental

Preparation of Hydrazone (IIIa). To a solution of 4.25 g (0.02 mol) of I in 100 ml of benzene was added 2.6 g (0.02 mol) of ethyl acetoacetate and 2 g of phosphorus pentoxide. The mixture was refluxed on a water bath for 5 hr. The hot benzene solution was separated by decantation and the solvent was removed under reduced pressure. The residual oily product was triturated with a small amount of ethanol and the resulting solid was recrystallized from ethanol to afford colorless crystals, mp 142°C. 5.8 g (90%).

Found: C, 70.20; H, 5.98; N, 8.55%. Calcd for $C_{19}H_{20}O_3N_2$: C, 70.53; H, 6.09; N, 8.64%.

Cyclization of IIIa to Pyrazole (Va). Two milliliters of 2M sodium hydroxide was added dropwise at room temperature with vigorous stirring to a solution of IIIa (1 g) in 50 ml of ethanol. Stirring was continued until the yellow color disappeared completely. Fifty milliliters of water was then added. The precipitate was collected by filtration and recrystallized from ethanol to give colorless crystals, mp 121°C (lit. mp 122°C). Yield 95%.

Found: C, 74.35; H, 5.77; N, 9.28%. Calcd for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.15%.

4-Carbethoxy-1,3,5-triphenylpyrazole (Vb). Hydrazone (IIIb) was prepared from 1-benzoyl-1-phenylhydrazine (4.2 g) and ethyl benzoylacetate (3.8 g) by the same method as for the preparation of IIIa. The hydrazone (6.2 g), obtained as an oily product, was dissolved in 100 ml of ethanol, to which 5 ml of 2 M sodium hydroxide solution was gradually added. The solution was then stirred for 10 min, diluted with water and the precipitate formed was collected to give 4.8 g of Vb which was recrystallized from ethanol to give colorless crystals, mp 143—144°C (lit. mp 145—146.5°C).

Found: C, 77.97; H, 5.60; N, 7.58%. Calcd for $C_{24}H_{20}O_2N_2$: C, 78.24; H, 5.42; N, 7.60%.

Ethyl 4-Carbethoxy-1,5-diphenylpyrazol-3-ylacetate (Vc). To a solution of 1-benzoyl-1-phenylhydrazine (4.2 g) and diethyl acetonedicarboxylate (4.1 g) in 100 ml of benzene was added 2 g of phosphorus pentoxide and the mixture was refluxed on a water bath for 5 hr. The hot benzene solution was separated by decantation and concentrated *in vacuo*. The residual oil (6.8 g) was dissolved in 100 ml of ethanol and to the resulting solution was added gradually 5 ml of 2 M sodium hydroxide solution at 10—15°C with stirring. Stirring was continued for 30 min at room temperature, after which water was added to precipitate Vc which was recrystallized from dilute ethanol to give colorless crystals (4.5 g), mp 67.5—68°C.

Found: C, 69.50; H, 5.65; N, 7.51%. Calcd for $C_{22}H_{22}O_4N_2$: C, 69.82; H, 5.86; N, 7.40%. IR: 1743, 1693 cm^{-1}.

Preparation of Hydrazone (IIId). A mixture of acetylacetone (1 g) and 1-benzoyl-1-phenylhydrazine (2.1 g) was heated in an oil bath at 120°C for about 30 min. After cooling, the solid product was recrystallized from ethanol to afford IIId as colorless crystals, mp 147—148°C.

Found: C, 73.35; H, 5.91; N, 9.70%. Calcd for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52%.

4-Acetyl-3-methyl-1,5-diphenylpyrazole (Vd). To a solution of 2 g of the hydrazone (IIId) in 50 ml of ethanol was added 5 ml of 2 M sodium hydroxide solution. This was left to stand at room temperature for 1 hr and then diluted with water. The precipitates were collected, washed with water, and recrystallized from dilute ethanol to give Vd, colorless crystals, mp 93—95°C.

Found: C, 77.94; H, 5.98; N, 10.21%. Calcd for $C_{18}H_{16}ON_2$: C, 78.23; H, 5.84; N, 10.14%, IR: 1660 cm^{-1}.

4-Cinnamoyl-3-methyl-1,5-diphenylpyrazole (IX). To a solution of 2.8 g of Vd and 1.1 g of benzaldehyde in 50 ml of ethanol was added gradually with stirring 10 ml of aqueous sodium hydroxide solution (40%). The reaction mixture was left to stand for 2 hr at room temperature and then diluted with water. Precipitates were collected, washed thoroughly with water and recrystallized from ethanol to give IX, pale yellow crystals, mp 157—158°C. 3.2 g.

Found: C, 82.10; H, 5.65; N, 7.73%. Calcd for $C_{25}H_{20}ON_2$: C, 82.39; H, 5.53; N, 7.68%. IR: 1650 cm^{-1}.

4-Carboxy-1,5-diphenylpyrazol-3-ylacetic Acid (VI). A solution of the diethyl ester (Vc, 3 g) in ethanol (25 ml) containing potassium hydroxide (2.5 g) and water (5 ml) was refluxed at 100°C for 30 min and concentrated, cooled, and acidified with dilute hydrochloric acid. The product was collected and washed with water, and then crystallized from dilute acetic acid (80%) to give dicarboxylic acid (VI) in colorless prisms, mp 251—252°C with decomposition.

Found: C, 66.85; H, 4.37; N, 8.57%. Calcd for $C_{18}H_{14}O_4N_2$: C, 67.07; H, 4.38; N, 8.69%. IR: 3500—2500, 1710, 1665 cm^{-1}.

4-Carbethoxy-1,5-diphenylpyrazol-3-ylacetic Acid (VII). Ethyl 4-carbethoxy-1,5-diphenylpyrazol-3-ylacetat (4 g) was dissolved at room temperature in ethanol (30 ml) containing potassium hydroxide (3.5 g) and water (2 ml). After 30 min dipotassium salt of the dicarboxylic acid (0.5 g) was separated by filtration and the filtrate was diluted with water and acidified with dilute hydrochloric acid to precipitate VII which was recrystallized from ethanol to give 2.6 g of colorless plates, mp 195—196°C.

Found: C, 68.65; H, 5.04; N, 8.16%. Calcd for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.18; N, 8.00%. IR: 3300—

2500, 1743, 1715 cm^{-1}.

The above half ester (2 g) was heated at 190—200°C in an oil bath until evolution of carbon dioxide was over. The residue solidified on treating with ethanol, and by recrystallization from ethanol, the compound Va (1 g) was obtained in colorless crystals, mp 120—121°C.

Ethyl 4-Carboxy-1,5-diphenylpyrazol-3-ylacetate (VIII). (i) Dry hydrogen chloride was passed into a suspension of 2 g of VI in 20 ml of absolute ethanol until VI dissolved completely (15 min). The reaction mixture was allowed to stand at room temperature for 2 hr. Crystals separated out were collected and washed to give 1.2 g of the crude half ester VIII. Recrystallization from benzene gave colorless prisms, mp 185—186°C.

Found: C, 68.30; H, 4.93; N, 7.97%. Calcd for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.18; N, 8.00%. IR: 3200—2500, 1740, 1665 cm^{-1}.

(ii) To a suspension of 2 g of VI in anhydrous benzene (50 ml) and absolute ethanol (1 ml) was added 0.5 g of *p*-toluenesulfonic acid. The mixture was refluxed for 5 hr using a water separator. Benzene was removed and the oily residue was boiled in petroleum ether (bp 40—60°C) and cooled, and the precipitates were collected and recrystallized from benzene to give 0.7 g of VIII. Mixed melting point measurement with an authentic sample showed no depression.

Evaporation of the petroleum ether filtrate and recrystallization of the residue from dilute ethanol gave 0.6 g of diester (Vc), mp 67—68°C.

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