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البحث هذا لم يدخل ضمن البحوث التي حكمت
في مرحلة ترقيتي لأستاذ مساعد

Synthesis and Rearrangement of Pyrazolylamino Alcohols†

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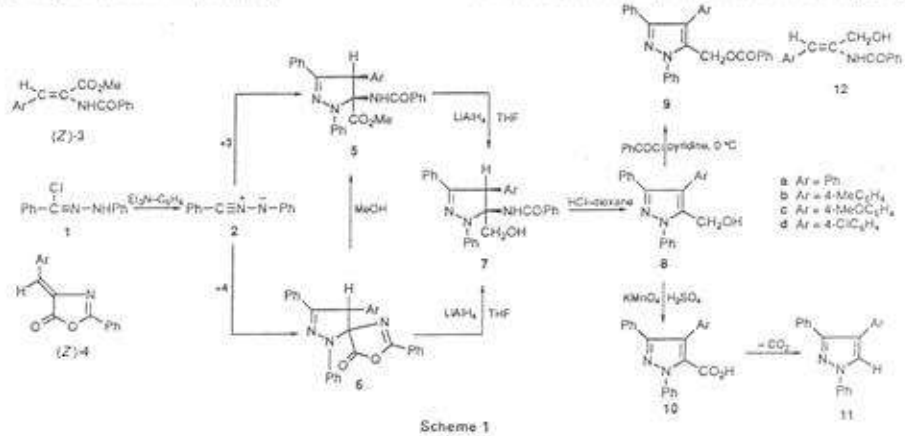
4-Aryl-5-benzoylamino-5-hydroxymethyl-1,3-diphenyl-2-pyrazolines **7** were prepared by $LiAlH_4$ reduction of either the spiropyrazolines **6** or the corresponding pyrazoline esters **5**; treatment of **7** with hydrochloric acid in dioxane at room temperature, gave 4-aryl-5-hydroxymethyl-1,3-diphenylpyrazoles **8**.

In a recent paper,[1] we reported the synthesis of pyrazolylamino acid esters **5** *via* 1,3-dipolar cycloaddition of benzonitrilium *N*-phenylimide **2** to esters of (*Z*)-α,β-didehydroamino acids **3** or methanolysis of the spiropyrazolines **6** obtained by the cycloaddition of **2** to (*Z*)-oxazolones **4**. In continuation of such a study, we report herein the synthesis and acid-catalysed rearrangement of the corresponding pyrazolylamino alcohols **7** (Scheme 1).



Scheme 1

The title compounds **7** were prepared by lithium aluminium hydride reduction of **6** or **5**. Attempts to prepare **7** by the cycloaddition of **2** to the corresponding α-benzoylaminocinnamyl alcohols **12**, obtained from reduction of **4** by lithium aluminium hydride,[2] failed, however. The structures of the products **7** were supported by microanalysis and by IR and ^1H NMR spectral data (see Experimental section).

Treatment of **7** with hydrochloric acid in dioxane at room temperature afforded 4-aryl-5-hydroxymethyl-1,3-diphenylpyrazoles **8** in 50–75% yield (Scheme 1). The latter products **8** were also characterized by microanalysis and spectral data (IR and ^1H NMR) together with their chemical transformations. For example, the IR spectra of the products **8** isolated revealed the absence of the characteristic absorption bands of the CONH group which are present in the spectra of **7**. The spectra of **8** showed, however, the OH band in the region 3362–3389 cm^{-1}. The ^1H NMR spectra of **8** revealed two characteristic signals in the region δ 4.4–4.6 (2 H) and δ 3.6–3.7 (1 H), assignable to the CH_2OH protons. The latter OH proton signal disappeared upon exchange with deuterium oxide. Furthermore, treatment of **8a** with benzoyl chloride in pyridine afforded the benzoate ester **9a**. Oxidation of **8a** with potassium permanganate in acid medium yielded 1,3,4-triphenylpyrazole **11a**, which was identical in all respects with an authentic sample.[3]

To account for the formation of **8**, it is suggested that the benzoyl group undergoes N → O migration to give the benzoate ester **9** together with the concurrent elimination of ammonia. The resulting benzoate ester **9** undergoes acid

Scheme 2

hydrolysis to give **8** (Scheme 2). Such a mechanism is analogous to the one found in the chemistry of ephedrine[4,5] and α-benzoylaminocinnamyl alcohol.[2] The involvement of **9** as an intermediate is supported by the observation that similar

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treatment of an authentic sample of **9a** with hydrochloric acid in dioxane at room temperature afforded the alcohol **8a**. The other mechanism involving direct elimination of benzamide from **7** was excluded on the basis that no benzamide was detected in the isolated crude reaction. This exclusion is further supported by the observation that benzamide was recovered unchanged when it was similarly treated with hydrochloric acid in dioxane at room temperature.

Experimental

Mps were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr discs using a Perkin Elmer model 1430 ratio recording spectrophotometer. ^{1}H NMR spectra were obtained in [^{2}H]chloroform on a Varian Gemini 200 mHz spectrophotometer. Elemental analyses were carried out by the Microanalytical Centre at the University of Cairo. The substrates **5a–d** and **6a–d** were prepared as previously reported.[1] The previously unreported spiropyrazoline **6d** was obtained in 70% yield, mp 120 °C, ν_{max}/cm^{-1} (KBr) 1830 (C=O); δ_H ($CDCl_3$) 5.25 (1 H, s), 6.90–8.00 (19 H, m) (Found: C, 72.5; H, 4.2; N, 8.9. $C_{27}H_{21}ClN_2O_2$ requires C, 72.88; H, 4.19; N, 8.80%).

1,3-Diphenyl-5-benzoylamino-5-hydroxymethyl-4-aryl-2-pyrazolines **7a–d**.—To a stirred mixture of lithium aluminium hydride (1.5 g, 0.04 mol) in dry tetrahydrofuran (150 ml) was added the appropriate spiropyrazoline **6** (0.02 mol) during 30 min. The reaction mixture was stirred for 5–12 h at room temperature, then a solution of ethyl acetate in tetrahydrofuran (10 ml 1:9) was added. The resulting mixture was cooled to 0–5 °C, treated with aqueous hydrochloric acid (10%, 25 ml) and filtered. The filtrate was extracted with benzene and washed with water and the extract was dried over anhydrous sodium sulfate then filtered. The solvent in the filtrate was evaporated and the residue was kept overnight in a refrigerator. The solid product was collected and recrystallized from ethyl acetate–diethyl ether mixture to give **7**. **7a** (65% yield): mp 200 °C, ν_{max}/cm^{-1} (KBr) 1663 (C=O), 3264 (NH), 3346 (OH); δ_H ($CDCl_3$) 4.51 (2 H, d), 4.65 (1 H, br s), 6.36 (1 H, s), 7.00–7.90 (20 H, m), 8.70 (1 H,s) (Found: C, 77.9; H, 6.1; N, 9.2. $C_{29}H_{25}N_3O_2$ requires C, 77.85; H, 5.59; N, 9.40%). **7b** (60% yield): mp 157 °C, ν_{max}/cm^{-1} (KBr) 1663 (C=O), 3262 (NH), 3372 (OH); δ_H ($CDCl_3$) 2.33 (3 H, s), 4.5 (2 H, d), 4.80 (1 H, br s), 6.30 (1 H, s), 7.00–7.80 (19 H, m), 8.30 (1 H, s) (Found: C, 78.2; H, 6.0; N, 8.9. $C_{30}H_{27}N_3O_2$ requires C, 78.09; H, 5.86; N, 9.11%). **7c** (60% yield): mp 120 °C, ν_{max}/cm^{-1} (KBr) 1663 (C=O), 3264 (NH), 3313 (OH); δ_H ($CDCl_3$) 3.85 (3 H, s), 4.47 (2 H, s), 4.75 (1 H, br s), 6.02 (1 H, s), 6.97–7.75 (19 H, m), 8.20 (1 H, s) (Found: C, 74.8; H, 5.8; N, 8.7. $C_{30}H_{27}N_3O_3$ requires C, 75.47; H, 5.66; N, 8.81%). **7d** (70% yield): mp 179 °C, ν_{max}/cm^{-1} (KBr) 1664 (C=O), 3264 (NH), 3368 (OH); δ_H ($CDCl_3$) 4.50 (2 H, d), 4.60 (1 H, br s), 6.30 (1 H, s), 6.90–7.80 (19 H, m), 8.23 (1 H, s) (Found: C, 72.1; H, 4.7; N, 8.8. $C_{29}H_{24}ClN_3O_2$ requires C, 72.27; H, 4.98; N, 8.72%).

Similar treatment of **5** with lithium aluminium hydride under the same conditions gave, after work-up as above, the corresponding products **7**, identical in all respects with those obtained above.

Rearrangement of **7**. *General Method*.—A solution of the appropriate **7** (0.004 mol) in dioxane (40 ml) was mixed with 10 M hydrochloric acid (2 ml) and the reaction mixture was stirred at room temperature for 10–12 h. The excess of solvent was evaporated and the residue was extracted with ether. The ether layer was washed twice with water followed by aqueous sodium hydrogen carbonate (2%) then with water, dried over sodium sulfate and then filtered. The solvent in the filtrate was evaporated and the oily residue left was triturated with a light petroleum–ether mixture where it solidified. The white solid formed was collected by filtration and recrystallized from light petroleum (b.p. 60–80 °C) to give **8** in 40–75% yield. **8a** (50% yield): mp 133 °C, ν_{max}/cm^{-1} (KBr) 3362 (OH); δ_H ($CDCl_3$) 3.60 (1 H, s), 4.50 (2 H, s), 7.30–7.80 (15 H, m) (Found: C, 80.5; H, 5.8; N, 8.5. $C_{22}H_{18}N_2O$ requires C, 80.98; H, 5.52; N, 8.59%). **8b** (55% yield): mp 110 °C, ν_{max}/cm^{-1} (KBr) 3323 (OH); δ_H ($CDCl_3$) 2.4 (3 H, s), 3.6 (1 H, s), 4.5 (2 H, s), 7.10–7.90 (14 H, m) (Found: C, 79.9; H, 5.8; N, 8.0. $C_{23}H_{20}N_2O$ requires C, 81.18; H, 5.88; N, 8.24%). **8c** (40% yield): mp 170 °C, ν_{max}/cm^{-1} (KBr) 3325 (OH); δ_H ($CDCl_3$) 3.75 (1 H, s), 3.80 (3 H, s), 4.60 (2 H, s), 6.70–7.70 (14 H, m) (Found: C, 77.3; H, 5.5; N, 7.8. $C_{23}H_{20}N_2O_2$ requires C, 77.53; H, 5.62; N, 7.87%). **8d** (75% yield): mp 107 °C, ν_{max}/cm^{-1} (KBr) 3389 (OH); δ_H ($CDCl_3$) 3.63 (1 H, s), 4.41 (2 H, s), 7.19–7.77 (14 H, m) (Found: C, 73.0; H, 4.5; N, 7.3. $C_{22}H_{17}ClN_2O$ requires C, 73.23; H, 4.72; N, 7.77%).

Oxidation of **8a**.—To a solution of **8a** (0.5 g, 0.001 mol) in ethanol (5 ml) was added a solution of potassium permanganate in aqueous sulfuric acid (18 M, 2 ml). The reaction mixture was refluxed for 2 h, then filtered. The solid product was crystallized from dioxane–water mixture to give **11a**, mp 180 °C not depressed when mixed with an authentic sample of 1,3,4-triphenylpyrazole.[2]

Benzoylation of **8**.—To a cold solution of **8** (0.003 mol) in pyridine (10 ml) was added benzoyl chloride (0.35 ml, 0.003 mol) dropwise with stirring. The reaction mixture was stirred for 2 h then treated with cold dilute hydrochloric acid. The solid formed was filtered off and recrystallized from ethanol to give the corresponding benzoate ester **9**. **9a** (60% yield): mp 110 °C, ν_{max}/cm^{-1} (KBr) 1737 (C=O); δ_H ($CDCl_3$) 4.70 (2 H, s), 7.30–8.00 (20 H, m) (Found: C, 80.1; H, 4.8; N, 6.2. $C_{29}H_{22}N_2O_2$ requires C, 80.93; H, 5.12; N, 6.51%). **9b** (65% yield): mp 158–160 °C, ν_{max}/cm^{-1} (KBr) 1716 (C=O); δ_H ($CDCl_3$) 2.30 (3 H, s), 4.75 (2 H, s), 7.30–8.40 (19 H, m) (Found: C, 80.3; H, 5.5; N, 6.5. $C_{30}H_{24}N_2O_2$ requires C, 81.08; H, 5.40; N, 6.30%).

Treatment of **9a** with hydrochloric acid in dioxane following the same procedure described above for **7** gave, after work-up, **8a** and benzoic acid.

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