

### Synthesis of aminopyrazolecarboxylic acid derivatives

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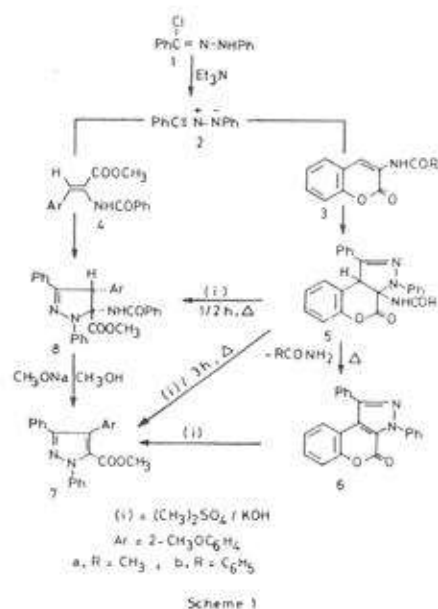
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Diphenylnitrilimine (2) adds regioselectively to 3-acylamino coumarins (3a, b) and methyl  $\alpha$ -acylamino-*o*-methoxycinnamate (4) to yield exclusively the cycloadducts (5a, b) and (8) respectively. Compounds 5 were converted into 8 by their treatment with KOH and dimethyl sulfate in methanol. The regiochemistry of the cycloadducts have been confirmed by their conversion to the known 1,3-diphenylchromeno[3,4-*c*]pyrazol-4-(3*H*)-one and methyl 1,3-diphenyl-4-(*o*-methoxyphenyl)pyrazole-5-carboxylate (6) and (7) respectively.

Our interest in the applications of 1,3-dipolar cycloaddition reactions to the synthesis of heterocyclic amino acid esters prompted us to study the reaction of diphenylnitrilimine (2) with 3-acylamino coumarins (3a, b) and methyl  $\alpha$ -benzoylamino-*o*-methoxycinnamate (4) (Scheme 1). To our knowledge such reactions have not yet been explored although the cycloaddition reactions of 2 with coumarin<sup>1-3</sup>, thiocoumarin<sup>4</sup> and methyl cinnamate<sup>5</sup> had been reported. In the present work, we found that the reactions in question provide access to aminopyrazolecarboxylic acid derivatives (Scheme 1).

Reaction between 2, generated *in situ* by the action of triethylamine on *N*-phenylbenzohydrazonyl chloride 1, and 3-acylamino coumarins (3a, b) in chloroform or benzene at reflux yielded the corresponding cycloadducts (5a, b) respectively as the only isolable products as evidenced by <sup>1</sup>H NMR analysis of the crude reaction product in each case. The structure assignments of the cycloadducts (5a, b) were made on the basis of analytical and spectroscopic data. Thus, the IR spectra revealed, in each case, two carbonyl absorption bands near 1719 and 1671 cm<sup>-1</sup> and an amide NH band near 3373 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra showed two characteristic singlets near  $\delta$  5.90 and 8.65 ppm assignable to 9b-H and NH protons respectively.



The assigned regiochemistry of the cycloadducts (5a, b) was evidenced by their chemical transformations outlined in scheme 1. Thus, when 5a or 5 was refluxed in xylene for 24 hr, a single product was obtained, identical in all respects (IR, m.p. and m.m.p.) with an authentic sample of 1,3-diphenylchromeno[3,4-*c*]pyrazol-4-(3*H*)-one (6)<sup>6</sup>. When the cycloadduct (5) was warmed with KOH and dimethyl sulfate in methanol for 30 min, methyl 1,3-diphenyl-4-(*o*-methoxyphenyl)-5-benzoylamino-2-pyrazoline-5-carboxylate (8) was obtained. However, prolonged heating of this reaction mixture for 3 hr did afford methyl 1,3-diphenyl-4-(*o*-methoxyphenyl)pyrazole-5-carboxylate (7). It seems that under the latter conditions compound 5 underwent ring opening to give 8 which in alkaline medium eliminated benzamide to afford 7. This was supported by an independent preparation of 8 and its conversion into 7. Thus, treatment of 1 with methyl  $\alpha$ -benzoylamino-*o*-methoxycinnamate (4) in chloro-

as the only isolable product. Heating of the latter with sodium methoxide in methanol gave 7 (Scheme 1).

#### Experimental

Melting points are uncorrected. IR (KBr) spectra were recorded on Pye Unicam SP3-300 infrared spectrophotometer, PMR spectra on Varian T-60A NMR spectrometer using TMS as internal standard in deuterated chloroform (chemical shifts in  $\delta$ , ppm). Elemental analyses were carried out at the Micro-analytical Laboratory of the University of Cairo, Giza, Egypt. The coumarin derivatives (3a, b)<sup>6</sup>, (Z)-methyl 2-benzoylamino-*o*-methoxycinnamate (4)<sup>7</sup> and N-phenylbenzohydrazonoyl chloride (1)<sup>8</sup> were prepared by previously described methods.

#### Reactions of 2 with 3 and 4: General procedure

Equimolar quantities of the appropriate dipolarophile 3 (or 4) and the hydrazonoyl chloride 1 (5 mmole each) were dissolved in hot chloroform or benzene (30 ml). To the resulting solution was added triethylamine (0.7 ml, 5 mmole). The mixture was refluxed for 18 hr and the solvent distilled under reduced pressure. The oily residue left was triturated with methanol and the solid produced was collected and crystallized from ethanol.

Compound 5a, m.p. 205°C (m.m.p. with 3a, 185-89°C); yield 70%; IR (KBr): 3336 (NH), 1744, 1685 (CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ): 2.2 (s, 3H,  $\text{CH}_3\text{CO}$ ), 5.9 (s, 1H, 9b-H), 6.7-7.6 (m, 14H, ArH), 8.6 (s, 1H, CONH) (Found: C, 72.3; H, 4.8; N, 10.5.  $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3$  requires C, 72.5; H, 4.8; N, 10.6%).

Compound 5, m.p. 175°C (m.m.p. with 3, 155-60°C); yield 66%; IR (KBr): 3373 (NH), 1719, 1671 (CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ): 5.85 (s, 1H, 9b-H), 7.0-8.0 (m, 19H, ArH), 8.8 (s, 1H, CONH) (Found: C, 75.5; H, 4.5; N, 9.1.  $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_3$  requires C, 75.80; H, 4.6; N, 9.1%).

Compound 8, m.p. 190°C; yield 66%; IR (KBr): 1725, 1680 (CO), 3412 (NH)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ): 3.75 (s, 3H,  $\text{CH}_3\text{OAr}$ ), 3.9 (s, 3H,  $\text{CH}_2\text{OCO}$ ), 5.58 (s, 1H, 4-CH), 6.75-7.75 (m, 20H, ArH and CONH) (Found: C, 73.7; H, 5.2; N, 8.2%.  $\text{C}_{31}\text{H}_{27}\text{N}_3\text{O}_4$  requires C, 73.6; H, 5.4; N, 8.3%).

#### Conversion of 5 into 6

A solution of 5a (or 5) (10 mmole) in xylene (30 ml) was refluxed for 24 hr and cooled. The solid that

precipitated was collected and crystallized from ethanol to give in both cases 6 in 85% yield, m.p. 245°C (Lit.<sup>3</sup> m.p. 248°C).

The solvent in the filtrate left after separation of crude 6 from thermolysis of 5 was distilled under reduced pressure. Trituration of the oily residue with methanol precipitated white solid. It was collected and crystallized from ethanol to give pure benzamide, m.p. 130°C (not depressed when mixed with authentic sample of benzamide Lit.<sup>9</sup> m.p. 129-30°C).

#### Conversion of 5 into 7 and 8

To a mixture of equimolar quantities of 5 and KOH (10 mmole each) in methanol (20 ml) was added dimethyl sulfate (5 g, 40 mmole) dropwise with stirring. The mixture was then refluxed for 30 min and cooled. The solid that separated was collected and crystallized from ethanol to give a product that was found identical in all respects (m.p., m.m.p. and IR) with 8 obtained above.

When the above reaction mixture was refluxed for 3 hr, it yielded a solid upon cooling. The latter was collected and crystallized from acetic acid to give 7 in 92% yield, m.p. 170°C (Lit.<sup>3</sup> m.p. 170°C).

#### Conversion of 8 into 7

To a sodium methoxide solution, prepared from sodium metal (0.1 g, 50 mg atom) and methanol (40 ml), compound 8 (2.5 g, 5 mmole) was added. The mixture was refluxed for 3 hr and cooled. The solid that separated was collected and crystallized from acetic acid. The product obtained was found to be identical in all respects (m.p., m.m.p. and IR) with the compound 7 obtained above.

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