Synthesis of 1-Benzoylpyrroline Derivative and Related Compounds

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Pyrroline Derivatives

Several new pyrroline derivatives were prepared from 4-amino-1-benzoyl-3-benzylidene-4-pyrroline-2-one (**4**).

Enamines have been extensively used for the synthesis of heterocycles and fused heterocycles [1–3]. The use of 5-amino-3-methylisoxazole as starting compound for the synthesis of isoxazolo[4,3-b]-pyridine derivatives was reported by us [4]. Recently we have reported an efficient procedure for the synthesis of the 4-aminopyrroline derivative (**4**) [5]. In continuation of this work we report here a new synthesis of **4** by the reaction of benzylidenemalononitrile (**1**) with hippuric acid (**2**). We assume that **4** is formed through addition of the active methylene of **2** to one of the cyano functions of **1** and subsequent cyclization to form the nonisolable derivative **3.** The addition of active methylene to the cyano function of **1** has been previously observed [6]. The decarboxylation of pyrrole derivatives under acidic conditions are a known phenomenon [7]. **4** is identical with the product obtained by us recently [5] (*cf.* Experimental).

On refluxing **1** and **2** in acetic anhydride for a longer time the acetyl derivative **5** are formed, together with **4.**

4 reacts with acrylonitrile in aqueous pyridine to form the pyrrolo[3,2-b]pyridine (**6**). The behaviour of **4** towards acrylonitrile finds a precedent in the reaction of the same reagent with 4-arylazo-3,5-diaminoisoxazole [8].

5-Amino-3-phenylisoxazole has been reported to react with cyanochalcones to afford isoxazolo-[4,3-b]pyridines [9]. In a similar manner **4** reacts with benzalethylcyanoacetate to give the pyrrolo[3,2-b]pyridine (**7**). The IR spectrum of the compound reveals the presence of an OH group.

Compound **4** reacts with benzoylisothiocyanate and thiourea to give the pyrrolo[3,4-d]pyrimidines **8** and **9,** respectively. Hydrolysis of the C=S group and aromatization occurred under the reaction conditions. A ready aromatization was previously observed in hydropyridines [6, 10].

Compound **8** was easily coupled with benzenediazonium chloride to give the corresponding azo derivative **10.**

4 reacts with phenylhydrazine to yield the pyrrolo[3,4-c]pyrazole (**11**). Structure **11** was proposed based on analytical and spectral data (*cf.* Experimental part).

On the other hand, aniline reacts with **4** to give compound **12** *via* condensation with the carbonyl group.

The dipyrroline urea derivative **13** was isolated upon reaction of **4** with carbon disulphide. The behaviour of **4** towards carbon disulphide was found to be analogous to the behaviour of 4-aminopyrazolone derivative towards the same reagent [11].

The procedures described above were found satisfactory for the synthesis of new pyrrolo[3,2-b]pyridine, pyrrolo[3,4-d]pyrimidine and pyrrolo[3,4-c]-pyrazole derivatives.

Experimental

Melting points are uncorrected. IR spectra were measured (KBr) on a Pye-Unicam SP 1000. ^{1}H NMR were measured in DMSO on a Varian A 60 MHz using TMS as internal standard and chemical shifts are expressed as ppm. The microanalyses were performed by the microanalytical unit at Cairo University.

4-Amino-1-benzoyl-3-benzylidene-4-pyrroline-2-one (**4**)

To a mixture of 1.5 g (0.01 mol) of benzylidenemalononitrile (**1**) and 1.8 g (0.01 mol) of hippuric acid (**2**) was added 30 ml acetic anhydride. The reaction mixture was refluxed for 2 h and then poured on crushed ice and was left overnight. The

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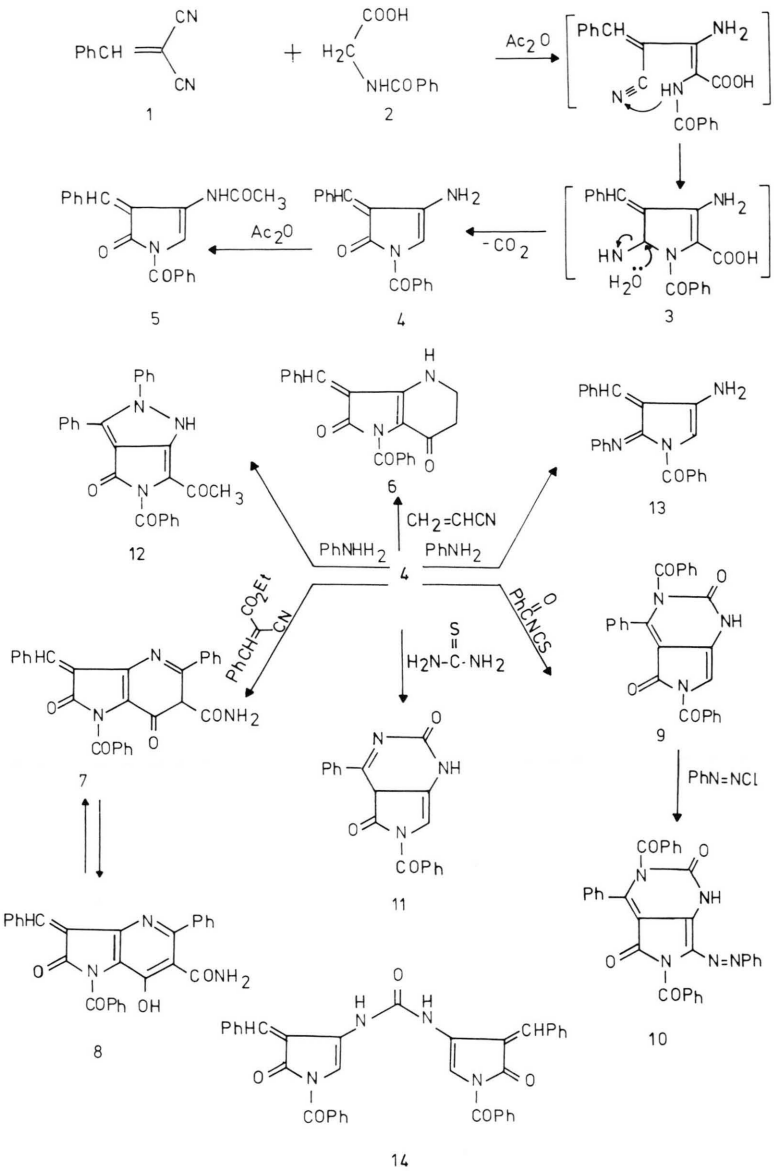

solid product so precipitated was collected by filtration, washed well with water and recrystallized from ethanol. Yellow crystals, m.p. 165 °C, yield 2.3 g (80%). IR: 3200, 3100 (NH_2), 1800 (ring CO) and 1770 cm^{-1} (benzoyl CO). ^1H NMR: $\delta = 4.55$ (s, 2H, NH_2), 5.3 (s, 1H pyrrole H-5), 7.16–8.1 (m, 11H, 2 C_6H_5 and ylidene CH).

$C_{18}H_{14}N_2O_2$ (290.3)

Calcd	C 74.5	H 4.9	N 9.6,
Found	C 74.3	H 4.8	N 9.8.

Preparation of **4** *and the acetyl derivative* (**5**)

The procedure as described above was followed but the reaction mixture was refluxed for 4 h. The solid product separated after decomposition of the acetic anhydride with water was filtered off and was treated with hot ethanol which on cooling gives **4,** 0.6 g (20%) (m. p. and mixed m. p. 165 °C/165 °C). The remaining undissolved product was recrystallized from acetic acid and was identified as **5** (m.p. and mixed m.p. 222 °C/222 °C) [5]. Yellow crystals,

yield 1.9 g (60%). IR: 3330 (NH), 1750 (ring CO), 1670 (benzoyl CO) and 1640 cm^{-1} (amide CO).

$C_{20}H_{16}N_2O_3$ (332.3)

Calcd	C 72.3	H 4.9	N 8.4,
Found	C 72.6	H 4.7	N 8.6.

1-Benzoyl-3-benzylidene-5,6-dihydropyrrolo-[3,2-b]pyrimidine-2,7-dione (**6**)

A solution of 2.9 g (0.01 mol) of **4** in pyridine (30 ml) was treated with 0.5 g (0.01 mol) of acrylonitrile and the reaction mixture was refluxed for 4 h then evaporated *in vacuo*. The resulting solid product was collected by filtration and recrystallized from ethanol. Yellow crystals, m.p. 149 °C, yield 2.4 g (70%). IR: 3200 (NH), 1760 (ring CO), 1670 cm^{-1} (benzoyl CO).

$C_{21}H_{16}N_2O_3$ (344.3)

Calcd	C 73.2	H 4.7	N 8.1,
Found	C 73.2	H 4.8	N 8.0.

6-Amido-1-benzoyl-3-benzylidene-7-hydroxy-5-phenylpyrrolo[3,2-b]pyridine-2-one (**7**)

To a solution of 2.9 g (0.01 mol) of **4** in ethanol (40 ml) was added 2.0 g (0.01 mol) of benzylidenethylcyanoacetate and triethylamine (1 ml). The reaction mixture was refluxed for 5 h, then evaporated *in vacuo*. The solid product formed was collected by filtration and recrystallized from ethanol. Pale yellow crystals, m.p. 96 °C, yield 3.2 (70%). IR: 3500 (OH), 3100, 3000 (NH_2), 1745 (ring CO), 1675 (benzoyl CO) and 1630 cm^{-1} (amide CO).

$C_{28}H_{19}N_3O_4$ (461.4)

Calcd	C 72.9	H 4.2	N 9.1,
Found	C 72.9	H 3.9	N 9.3.

1,4-Dibenzoyl-3-phenylpyrrolo[3,4-d]pyrimidine-2,5-dione (**8**)

A solution of 2.9 g (0.01 mol) of **4** in 30 ml dioxane was added to a solution of the benzoylisothiocyanate (prepared from 0.8 g (0.01 mol) of NH_4SCN and 1.4 g (0.01 mol) of benzoyl chloride as has been described [8]) and the reaction mixture was refluxed for 5 h. The solvent was then evaporated *in vacuo*. The remaining solid product was then triturated with water, collected by filtration, and recrystallized from ethanol. Colourless crystals, m.p. 260 °C, yield 2.8 g (65%). IR: 3385 (NH), 1755 (ring CO) and 1660 cm^{-1} (benzoyl CO).

$C_{26}H_{17}N_3O_4$ (435.4)

Calcd	C 71.7	H 3.9	N 9.7,
Found	C 71.8	H 4.0	N 9.9.

1-Benzoyl-3-phenylpyrrolo[3,4-d]pyrimidine-2,5-dione (**9**)

To a solution of 2.9 g (0.01 mol) of **4** in ethanol (40 ml) was added 0.8 g (0.01 mol) of thiourea and triethylamine (1 ml). The reaction mixture was heated under reflux for 5 h, then evaporated *in vacuo*. The solid product formed was filtered off and recrystallized from ethanol. Colourless crystals, m.p. 235 °C, yield 2.3 g (69%). IR: 3385 (NH), 1760 (ring CO) and 1665 cm^{-1} (benzoyl CO).

$C_{19}H_{12}N_3O_3$ (330.3)

Calcd	C 69.1	H 3.7	N 12.7,
Found	C 69.0	H 3.4	N 12.8.

Coupling of **8** *with benzenediazonium chloride* (**10**)

A solution of 0.01 mol benzenediazonium chloride (prepared by adding 0.7 g (0.01 mol) of $NaNO_2$ to 0.9 g (0.01 mol) of aniline in 10 cc HCl) was added gradually while stirring to a cold solution (0–5 °C) of 4.4 g (0.01 mol) of **8** in ethanol (30 ml) and sodium acetate (1 g). The reaction mixture was then left in the ice bath for 30 min and the precipitate formed was collected by filtration and recrystallized from ethanol. Yellow crystals, m.p. 84 °C, yield 3.5 g (67%). IR: 3400 (NH), 1750 (ring CO) and 1660 cm^{-1} (benzoyl CO).

$C_{32}H_{21}N_5O_4$ (539.5)

Calcd	C 71.2	H 3.9	N 13.0,
Found	C 71.5	H 3.8	N 12.8.

6-Acetyl-1-benzoyl-3,4-diphenylpyrrolo-[3,4-c]pyrazole-2-one (**11**)

A solution of 2.9 g (0.01 mol) of **4** in glacial acetic acid (30 ml) was treated with 1.1 g (0.01 mol) of phenylhydrazine. The reaction mixture was refluxed for 5 h and the solvent was then evaporated *in vacuo*. The remaining oily product was triturated with ethanol, the solid so formed was filtered off and recrystallized from acetic acid. Pale yellow crystals, m.p. 150 °C, yield 2.5 g (60%). IR: 3100 (NH), 1800 (ring CO), 1770 (benzoyl CO) and 1660 cm^{-1} (acetyl CO).

$C_{26}H_{19}N_3O_3$ (421.4)

Calcd	C 74.1	H 4.5	N 10.0,
Found	C 74.1	H 4.7	N 10.0.

Reaction of **4** *with aniline* (**12**)

A mixture of 2.9 g (0.01 mol) of **4** and 0.9 g (0.01 mol) of aniline was heated at 100 °C (bath temperature) for 3 h then the reaction mixture was cooled and triturated with ethanol. The solid product so formed was collected by filtration and recrystallized from ethanol. Colourless crystals, m.p. 238 °C,

yield 2.3 g (63%). IR: 3400, 3200 (NH_2) and 1670 cm^{-1} (benzoyl CO).

$C_{24}H_{19}N_3O$ (365.4)

Calcd	C 78.9	H 5.2	N 11.5,
Found	C 79.1	H 5.0	N 11.5.

Reaction of **4** *with carbon disulphide* (**13**)

To a solution of 2.9 g (0.01 mol) of **4** in pyridine (30 ml) was added 0.8 g (0.01 mol) of carbon disulphide. The mixture was heated on a water bath for 5 h, then evaporated *in vacuo*. The oily product was triturated with methanol, filtered off and recrystallized from ethanol. Yellow crystals, m.p. 126 °C, yield 4.2 g (69%). IR: 3300 (NH), 1800 (ring CO), 1715 (benzoyl CO) and 1650 cm^{-1} (amide CO).

$C_{37}H_{26}N_4O_5$ (606.6)

Calcd	C 73.3	H 4.3	N 9.2,
Found	C 73.6	H 4.4	N 9.0.

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