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 benzoylisothiocyanate to afford isoxazolo[4,3-b]pyridines [9]. In a similar manner 4 reacts with benzylethycyanocetate 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 hydropryridines [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]pyrimidines and pyrrolo[3,4-c]-pyrazole derivatives.

Experimental

Melting points are uncorrected. IR spectra were measured (KBr) on a Pye-Unicam SP 1000. 1H 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
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). $^1$H NMR; $\delta$ = 4.55 (s, 2H, NH$_2$), 5.3 (s, 1H pyrrole H-5), 7.16—8.1 (m, 11H, 2 C$_6$H$_5$ and ylidene CH).

C$_{18}$H$_{14}$N$_2$O$_2$ (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).

\[ C_{20}H_{16}N_2O_3 \text{ (332.3)} \]
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 (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).

\[ C_{19}H_{16}N_3O_3 \text{ (330.3)} \]
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 NaNO₂ 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).

\[ C_{23}H_{24}N_3O_4 \text{ (539.5)} \]
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-d]pyrimidine-2,5-dione (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 form was filtered off and
recrystallized from acetic acid. Pale yellow crystals,
m.p. 150 °C, yield 2.5 g (60%). IR: 3100 (NH), 1780
(ring CO), 1770 (benzoyl CO) and 1660 cm⁻¹ (acetyl
CO).

\[ C_{26}H_{18}N_3O_3 \text{ (421.4)} \]
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 recrystal-
lized from ethanol. Colourless crystals, m.p. 238 °C,
yield 2.3 g (63%). IR: 3400, 3200 (NH\textsubscript{2}) and 1670 cm\textsuperscript{-1} (benzoyl CO).

C\textsubscript{24}H\textsubscript{19}N\textsubscript{3}O (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 \textit{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\textsubscript{2}), 1800 (ring CO), 1715 (benzoyl CO) and 1650 cm\textsuperscript{-1} (amide CO).

C\textsubscript{37}H\textsubscript{26}N\textsubscript{4}O (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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