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SYNTHESIS OF PYRROLE, PYRROLO[3,4-b]PYRIDINE AND PYRROLO[3,2-b]PYRIDINE DERIVATIVES

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Abstract - The reaction of ethyl benzylidenecyanoacetate (1) with hippuric acid (2) in acetic anhydride leads to pyrrole derivative 5 together with the acetyl derivative 6. Treatment of 5 with ethyl acetoacetate, acetylacetone and malononitrile give the pyrrolo[3,4-b]pyridines 7, 10 and 11 respectively. Coupling of 5 and 7 with benzenediazonium chloride yield the phenylazo derivatives 8 and 9 respectively. On the other hand, ethyl cyanoacetate reacts with 5 to give the pyrrolo[3,2-b]pyridine derivative 13.

Activated nitriles have been extensively utilized for the synthesis of polyfunctionally substituted heterocycles[1-3]. This paper deals with the synthesis of the pyrrole derivative 5 which was subsequently utilized for the synthesis of pyrrolo[3,4-b]pyridine and pyrrolo[3,2-b]pyridine derivatives. Compound 5 was obtained in good yield on refluxing 0.01 mole of ethyl benzylidenecyanoacetate (1) and 0.01 mole of hippuric acid (2) in 30 ml of acetic anhydride for 1 h. When the reaction mixture was refluxed for 3 h compound 5 was isolated together with the N-acetyl derivative 6 resulting from acetylation of 5 which takes place in the reaction medium. Compound 5 was assumed to be formed through addition of active methylene of hippuric acid to the cyano function of ethyl benzylidenecyanoacetate to form the 1:1 adduct 3. The intermediate 3 was readily cyclizes via loss of ethanol to form 4. The addition of active methylene reagents to the cyano function of the cinnamonitrile derivatives and not to the activated double bond have been recently observed[4]. The elimination of carboxyl group of 4 takes place under the reaction conditions to form the final isolable product 5. A common concomitant was the elimination of carboxyl, acetyl, alkyl and other groups from pyrroles under acidic conditions[5]. Structure 5 was established based on elemental analysis and spectral data. ^{1}H Nmr revealed a singlet at δ 5.3 for pyrrole H-2.

Reaction of 5 with ethyl acetoacetate in refluxing ethanol solution brings about a conjugate addition followed by a cyclization step involving the amino and the carbonyl group of 5 to form the dihydropyridine derivative which was spontaneously oxidized to form pyrrolo[3,4-b]pyridine derivative 7. Dihydropyridine forms seemed unlikely as one would expect that the product was readily oxidized under the reaction conditions in a way similar to that reported for their oxocounter analogues[6]. Structure 7 was elucidated on the basis of elemental and spectroscopic data. The ^{1}H Nmr of 7 (DMSO) showed the following signals: 1.3 (t, 3H, CH_3); 3.3 (s, 3H, CH_3); 3.8 (s, 1H, pyrrole H-2); 4.21 (q, 2H, CH_2); 7.41-8.19 (m, 10H, $2C_6H_5$); 10.21 (s, 1H, NH).

Similarly 5 reacted with acetylacetone under the same reaction conditions to yield the pyrrolo[3,4-b]-pyridine derivative 10. The ^{1}H Nmr of 10 (DMSO) showed signals at 1.25 (s, 3H, CH_3); 3.3 (s, 3H, CH_3); 3.76 (s, 1H, pyrrole H-2); 7.45-8.2 (m, 10H, $2C_6H_5$); 10.2 (s, 1H, NH).

Compounds 5 and 7 were coupled with benzenediazonium chloride in ethanolic solution and in the presence of sodium acetate to yield the phenylazo derivatives 8 and 9 respectively.

Malononitrile reacts with 5 in refluxing ethanol and in the presence of triethylamine for 3 h to *yield the pyrrolo[3,4-b]pyridine derivative* 11. The formation of 11 was assumed to proceed via addition of the active methylene of malononitrile to the double bond of arylidene of 5 to form 1:1 adduct followed by cyclization via addition of the amino function to one of the cyano groups and spontaneous aromatization. The cyano group was hydrolyzed under the reaction conditions to give the amide derivative 11. The formation of pyridine derivatives via addition to the double bond of the arylidenes and subsequent addition to the cyano functions was previously observed[6].

On the other hand, ethyl cyanoacetate reacted with 5 under the same conditions of reaction with malononitrile to yield the pyrrolo[3,2-b]pyridine derivative 13. The reaction implies the formation of the intermediate 12 followed by cyclization step involving the hydroxyl group and the pyrrole H-2 to form 13. The ^{1}H Nmr of the product revealed the absence of a resonance for pyrrole H-2 and revealed a pattern that can be reasonably interpreted in terms of structure 13. Thus, the ^{1}H Nmr of 13 (DMSO) showed the following signals: 1.2 (t, 3H, CH_3); 4.1 (q, 2H, CH_2); 7.15 (s, 1H, pyridine H-3); 7.23-8.3 (m, 13H, $2C_6H_5$, NH_2 and benzylidene-H).

The yield, physical and the corresponding IR data are collected in Table 1.

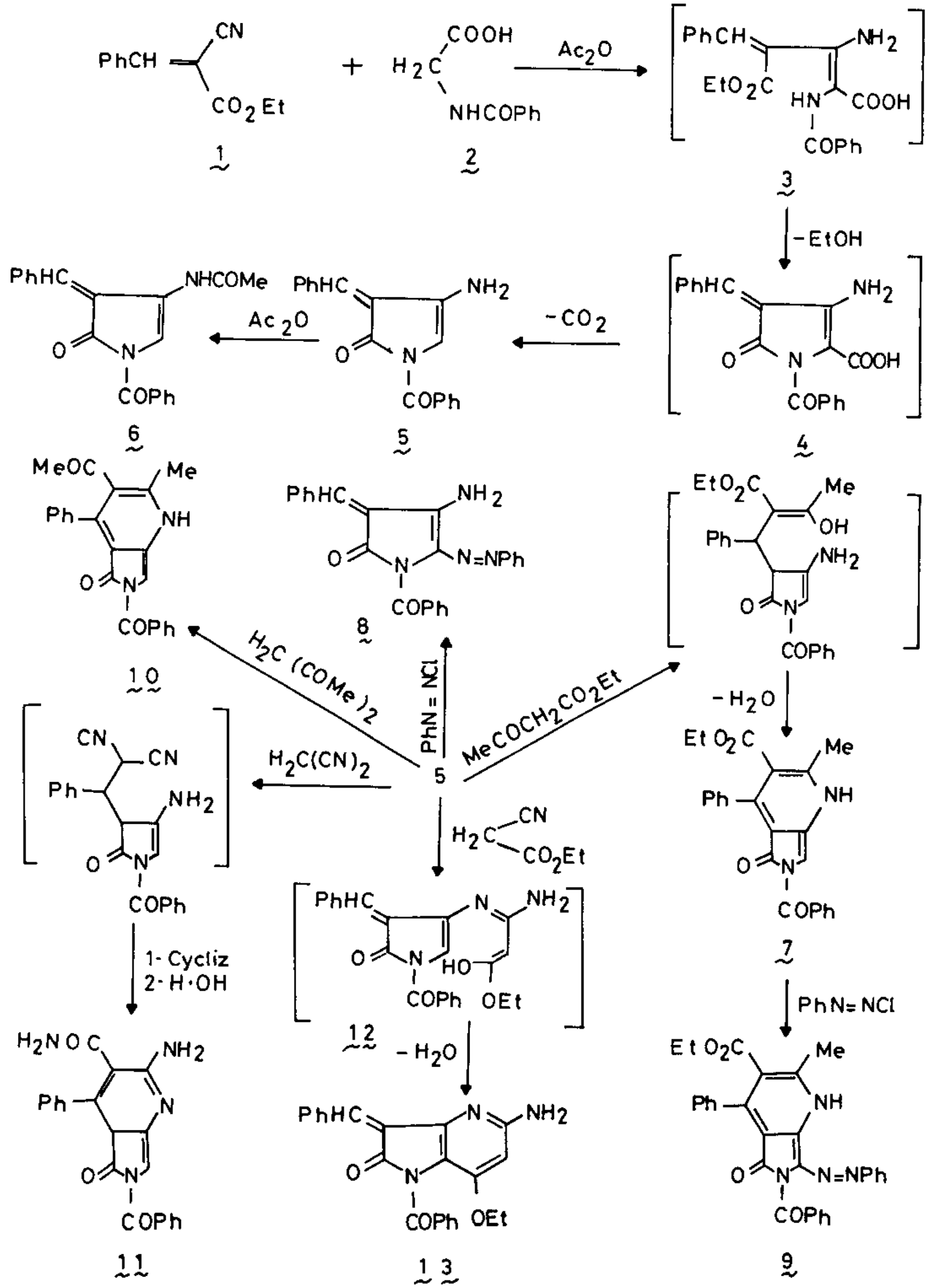
1
2
Ac₂O
3
-EtOH
4
-CO₂
5
Ac₂O
6
8
PhN=NCl
10
H₂C(COMe)₂
MeCOCH₂CO₂Et
-H₂O
7
H₂C(CN)₂
H₂C(CN)CO₂Et
1- Cycliz
2- H·OH
11
12
-H₂O
13
PhN=NCl
9

Table 1: Physical and IR data of the newly prepared compounds.

Compound* colour	Mp (^{o}C)	Cryst. Solvent	Yield %	IR (KBr) cm^{-1} (selected bands)
5 yellow	165	Ethanol	80	3200~3100 (NH_2), 1800 (ring CO), and 1670 (benzoyl CO)
6 pale yellow	222	acetic acid	60	3330 (NH), 1750 (ring CO), 1670 (benzoyl CO), and 1640 (amide CO).
7 colourless	120	Ethanol	70	3300 (NH), 1740 (ring CO), 1650 (benzoyl CO), and 1640 (ester CO).
8 brownish yellow	97	Ethanol	85	3200~3100 (NH_2), 1750 (ring CO), and 1660 (benzoyl CO).
9 yellow	95	Ethanol	75	3300 (NH), 1750 (ring CO), 1660 (benzoyl CO), and 1640 (ester CO).
10 colourless	105	Ethanol	75	3290 (NH), 1720 (ring CO), 1650 (benzoyl CO).
11 colourless	262	Dioxan	60	3340~3500 (NH_2), 1750 (ring CO), 1660 (benzoyl CO), and 1640 (amide CO).
13 colourless	138	Ethanol	75	3300~3280 (NH_2), 1740 (ring CO), and 1670 (benzoyl CO).

* Satisfactory elemental analyses for all the newly prepared compounds were obtained.

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