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# REACTIONS WITH NITRILES: A NOVEL SYNTHESIS OF FURO[2,3-c]PYRAZOLES AND PYRANO[2,3-c]PYRAZOLES

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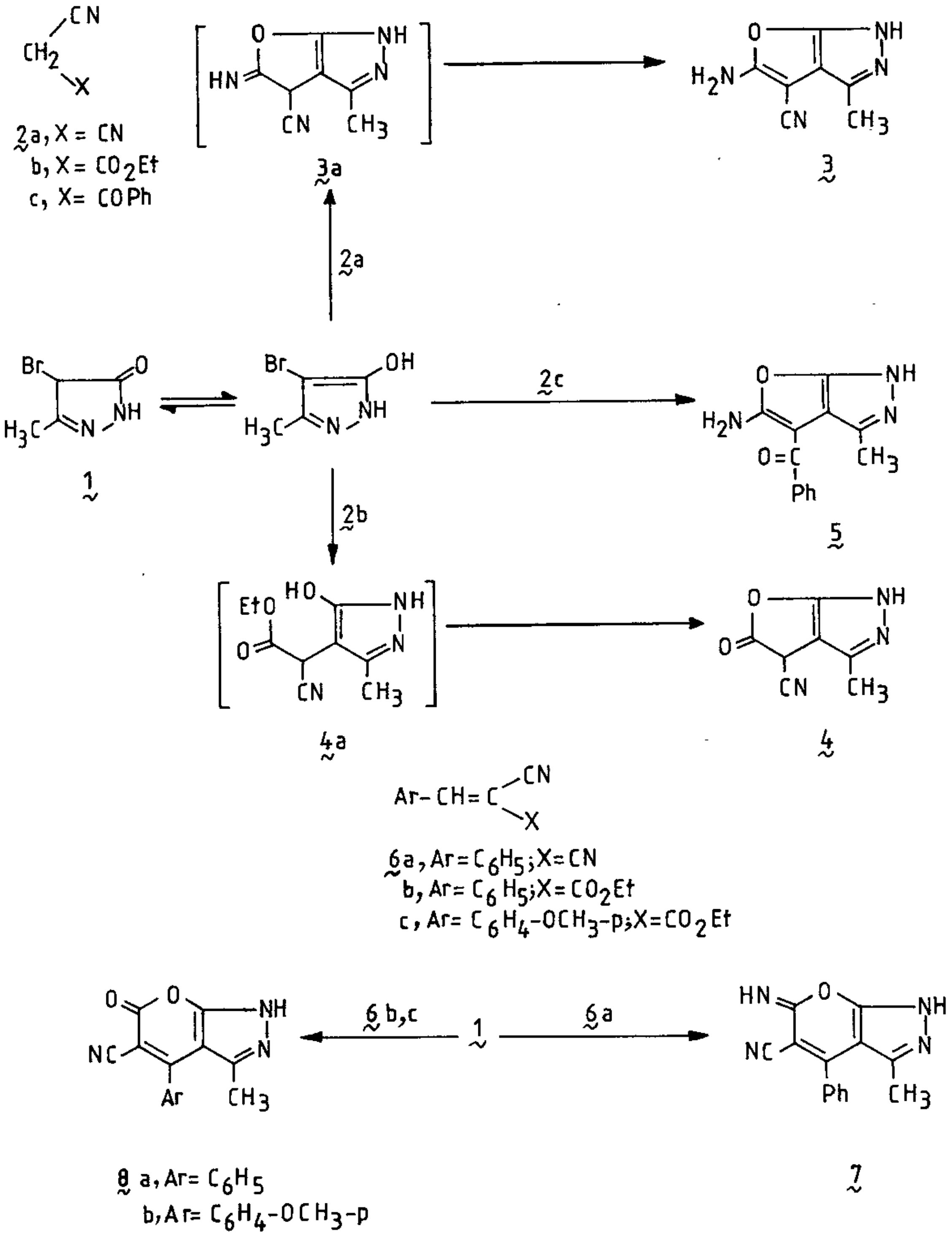
Abstract - Several new furo[2,3-c]pyrazole and pyrano[2,3-c]-pyrazole derivatives were synthesised via the reaction of the 4-bromo-2-pyrazolin-5-one derivative 1 with activated nitriles and their ylidene derivatives. The synthesised products were established based on elemental analyses, IR and $^1$H NMR spectral data.

In the last few years we have been interested in the synthesis of heterocyclic derivatives of potential biological and medicinal activities[1,2]. We have recently reported a novel synthesis of pyranoazoles via the reaction of 4-arylideneazolones with α-functional nitriles[3]. Continuing this effort we report here on the reaction of α-functional nitriles and their ylidene derivatives with the readily available 3-methyl-4-bromo-2-pyrazolin-5-one (1). Compound 1 was prepared by heating under reflux for 2 h a solution of 3-methyl-2-pyrazolin-5-one in chloroform with N-bromosuccinimidide then removal of the solvent, trituration with water and crystallisation from ethanol. The synthesised compounds bear latent functional substituents and appear promising for biological activity studies as well as for further chemical transformations.

Thus, it has been found that equimolecular amounts (20 mmol) of 1 and malononitrile (2a) reacted in absolute ethanol (30 ml) in the presence of piperidine (0.5 ml) under reflux for 3 h to give the condensation product 3. The structure of furo[2,3-c]pyrazole 3 was established based on elemental analysis and spectral studies. The IR spectrum of the product revealed absorption peaks belong to CN and $NH_2$ functions thus supporting the amino-tautomer 3 rather than the imino


2a, X = CN
b, X = CO2Et
c, X = COPh
3a
3
2a
1
2c
5
2b
4a
4
6a, Ar = C6H5; X = CN
b, Ar = C6H5; X = CO2Et
c, Ar = C6H4-OCH3-p; X = CO2Et
6 b,c
6a
8 a, Ar = C6H5
b, Ar = C6H4-OCH3-p
7

one 3a. Moreover,, compound 3 was found stable toward the reagents capable of hydrolysis of the imino into carbonyl groups[4]. The $^{1}$H NMR spectrum of 3 revealed also one methyl, $NH_2$ and NH signals. These data can only be intelligibly interpreted in terms of structure 3.

Similar to the behaviour of 1 toward 2a, compound 1 reacted with ethyl cyanoacetate (2b) to give the furo[2,3-c]pyrazole derivative 4. The formation of 4 in the reaction of 1 and 2b is assumed to proceed via elimination of HBr to give the acyclic intermediate ester 4a which then cyclises by ethanol elimination to yield the final isolable 4. The structure of 4 was assigned based on both elemental and spectral data (cf. Tables 1 and 2).

In a similar manner 1 and benzoylacetonitrile (2c) reacted to afford 5 whose structure was confirmed by spectral data.

The reactivity of the bromopyrazolone 1 was further demonstrated by the reaction with the cinnamonitrile derivatives 6a-c. Thus, it has been found that the reaction of equimolecular amounts (20 mmol) of 1 and 6a (reflux for 2 h in absolute ethanol, 30 ml and in the presence of piperidine, 0.5 ml) afforded a product of molecular formula $C_{14}H_{10}N_4O$. The IR spectrum of the product revealed absorption peaks corresponding to CN and NH groups. The $^{1}$H NMR spectrum revealed one methyl and two NH signals only. Based on the above data the product was assigned the pyrano[2,3-c]pyrazole structure 7.

Similarly, compounds 6b,c reacted with 1 to afford the pyrano[2,3-c]pyrazole derivatives 8a,b repectively. The structure of 8a was established by synthesis via another route by hydrolysis of 7 using conc. HCl (reflux for 2 h in glacial acetic acid, removal of the solvent in vacuo, trituration with water and crystallisation from ethanol).

Now the behaviour of 1 toward other activated nitriles is under investigation. Work in progress will be the subject of another communication.

Table 1: List of the bromopyrazolone derivative 1, the furo[2,3-c]pyrazole derivatives 3-5 and the pyrano[2,3-c]pyrazole derivatives 7 and 8a,b.

| Compound* | Solvent of cryst. | Colour | M.p. (°C) | Yield (%) | Mol. Formula |
|---|---|---|---|---|---|
| 1 | Ethanol | yellow | 180 | 95 | $C_4H_5N_2OBr$ |
| 3 | Ethanol | violet | 204 | 85 | $C_7H_6N_4O$ |
| 4 | Acetic acid | colourless | 192 | 80 | $C_7H_5N_3O_2$ |
| 5 | Acetic acid | colourless | 195 | 83 | $C_{13}H_{11}N_3O_2$ |
| 7 | Ethanol | colourless | 255 | 90 | $C_{14}H_{10}N_4O$ |
| 8a | Ethanol | colourless | 190 | 80 | $C_{14}H_9N_3O_2$ |
| 8b | Acetic acid | yellow | 182 | 85 | $C_{15}H_{11}N_3O_3$ |

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

Table 2: IR and $^{1}$H NMR data.

| Comp. | IR(Unicam SP-1100, KBr, cm$^{-1}$) | $^{1}$H NMR(DMSO, EM-360 60 MHz, δ ppm) |
|---|---|---|
| 1 | 3200(NH); 2990(saturated CH); 1680(C=O) and 1640(C=N). | 2.2(s, 3H, $CH_3$); 5.1(s, 1H, pyrazole H-4) and 10.2 (s,br, 1H, NH). |
| 3 | 3340, 3300, 3200($NH_2$ and NH); 2220(CN); 1650( NH) and 1630 (C=N). | 2.1(s, 3H, $CH_3$); 10.1(s, br, 2H, $NH_2$) and 10.8(s, br, 1H, NH). |
| 4 | 3220(NH); 2980(saturated CH); 2220(CN); 1690(C=O) and 1640 (C=N). | 2.3(s, 3H, $CH_3$); 6.78(s, 1H, furan H-4) and 9.8(s, br, 1H, NH). |
| 5 | 3350, 3300, 3250($NH_2$ and NH) and *1730(benzoyl C=O).* | 2.1(s, 3H, $CH_3$); 7.1-7.5(m, 5H, aromatic *protons); 8.2(s, br, 2H, $NH_2$) and 10.8* s, br, 1H, NH). |

Table 2: Contd.

| Comp. | IR(Unicam SP-1100, KBr, $cm^{-1}$) | $^1H$ NMR(DMSO, EM-360 60 MHz, δ ppm) |
|---|---|---|
| **7** | 3250, 3200(two NH) and 2220 (CN). | 2.3(s, 3H, $CH_3$); 7.2-7.8(m, 5H, aromatic protons); 9.6(s, br, 1H, NH) and 10.3 (s, br, 1H, NH). |
| **8a** | 3200(NH); 2220(CN); 1690(C=O) and 1630(C=N). | 2.0(s, 3H, $CH_3$); 7.2-7.8(m, 5H, aromatic protons) and 10.4(s, br, 1H, NH). |
| **8b** | 3220(NH); 2220(CN); 1680(C=O) and 1630(C=N). | 2.2(s, 3H, $CH_3$); 2.4(s, 3H, $OCH_3$); 6.8-7.3(m, 4H, aromatic protons) and 10.1 (s, br, 1H, NH). |

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