Synthesis of new heterocycles containing pyrazole

B Djerrari,a J Fifani,a N H Ahabchane,a E M Essassi,a,* B Garrigues,b,* & M Pierrotc

a Laboratoire de chimie Organique Hétérocyclique, Faculté des Sciences, Université Mohammed V, avenue Ibn Battouta, Rabat, Maroc.

b Hétérochimie Fondamentale et Appliquée, Université Paul Sabatier 118,Route de Narbonne 31062 Toulouse Cedex -France.

c Laboratoire de Bioinorganique Structurale Université d’Aix - Marseille 1et 3 Faculté des Sciences et Techniques de Saint Jérome 13397 Marseille Cedex 20 France.

Received 5 August 2002; accepted (revised) 26 May 2003

New heterocyclic systems derived from pyrazole associating different nuclei such as pyrimidobenzimidazole, pyrimidopyrimidine, thiazolopyrimidine and pyrazolylpyridone have been synthesized by the treatment of some bisnucleophiles with acetoacetylpyrazole resulting from dehydroacetic acid.

In previous studies we have shown that dehydroacetic acid constitutes an interesting 1,3-difunctional synthon, liable to react with various nucleophilic reagents leading to different heterocyclic systems derived from 1,5-benzodiazepine1,2 pyrazole3, benzimidazole1 and pyridone4.

In the same way, phenylhydrazine reacted with dehydroacetic acid to give acetoacetylpyrazole5.1. These results prompted us to study the reaction of some ambident nucleophiles such as o-phenylenediamine, o-aminophenol, aminobenzimidazole, aminopyridine, aminothiazole and cyanoacetamide with acetoacetylpyrazole as route to pyrazole linked to different heterocyclic systems susceptible to possess important biological properties.

Results and Discussion

Action of o-phenylenediamine and o-aminophenol on 1

Used in stoichiometric amounts or in excess under ethanol reflux, o-phenylenediamine 2 or o-aminophenol 3 reacted with β-diketone 1 to give, via deacetylation 6 of 1, a product which had spectral data consistent with its formulation 4-o-methyliminoaminophenyl(hydroxyphenyl)-pyrazole 4/5 (Scheme I).

It has been noticed that the heating of 4 in xylene leads to compounds 6 and 7 (Scheme II) whose structures were identified by comparing their physical characteristics with those given in the literature 7,8.

In contrast, compound 5 remained unchanged, when it was heated under the similar conditions, as compound 4.

Action of 2-aminobenzimidazole 8 on 1

The reaction of acetoacetylpyrazole 1 with 2-aminobenzimidazole 8 in refluxing butanol, after
work-up and purification gave 4-pyrazolyppyrimido­
benzimidazole \( 9 \) as shown in Scheme III.

The structure of \( 9 \) was supported by \(^1\)H, \(^13\)C NMR, and mass spectral data.

\(^1\)H NMR spectra of \( 9 \), showed in addition to the signals relative to pyrimidine and pyrazole methyls, the signal at 6.74 ppm due to pyrimidine proton.

Further, \(^13\)C NMR spectrum of \( 9 \) provided additional evidence for this assigned structure. In particular, it exhibited the signals at 92.62 and 161.57 ppm, respectively attributable to \( C_4 \) and \( C_5 \) carbons of the pyrazole ring.

The reaction pathway that accounts for the formation of \( 9 \) from \( 8 \) and \( 1 \) is outlined in Scheme IV.

**Action of 2-amino-3-hydroxypyridine 10 on 1**

Treatment of compound 10 with \( \beta \)-diketone 1 in refluxing ethanol afforded a mixture of three products; pyrazolone \( 7 \) initially isolated, pyrazolylidenepyrimido­pyrimidine \( 11 \) and pyridopyrimidine \( 12 \) (Scheme V). The structures of compounds \( 11 \) and \( 12 \) were fully characterised by \(^1\)H NMR, \(^13\)C NMR and mass spectroscopy.

The \(^1\)H NMR spectrum of compound \( 11 \) showed, in particular, signals at 2.30 and 2.71 ppm assigned respectively to the methyl groups of the pyrimidine and pyrazole rings. The signal at 8.08 ppm corresponds to the proton at \( C_3 \) of the pyrimidine nucleus.

\(^1\)H NMR spectra of compound \( 12 \) revealed, in particular, signals at 2.38 and 6.25 ppm assignable respectively to the methyl and vinyl protons of the pyrimidine ring.

The formation of \( 11 \) and \( 12 \) can be explained by following mechanism: the first step corresponds to the attacks of the amino group of \( 10 \) on the acetyl group at position 3 of 1. Intermediate [A] formed, undergoes intramolecular cyclization by dehydration leading to intermediate [B]. Latter undergoes the attack of the endocyclic NH of \( 10 \) and affords pyrimidine \( 11 \) < pathway a >, and pyridopyrimidine \( 12 \) and \( 7 \) < pathway b > as shown in Scheme VI.

Thus, the condensation of 1 with 10 constitutes a new route to pyrazole associated to pyridopyrimidine.

**Action of 2-aminothiazole on 1**

Treatment of 1 with 2-aminothiazole 13 in butanol under reflux for 1 hr gave exclusively pyrazoly­lidenethiazolopyrimidine 14 (Scheme VII) whose structure was established on the basis of its spectral
data ($^1$H NMR, $^{13}$C, IR) as well as X-ray structural data\textsuperscript{10} (\textbf{Figure 1}).

The thiazolopyrimidine bicycle is completely plane and forms an angle of 41.8° with the pyrazolylidene ring. This latter forms an angle of 24.35° with the phenyl borne by N atom.

The compound 14 crystallises with two molecules of water which are linked by hydrogen bonds.

\textbf{Condensation of cyanoacetamide with 1}

The reaction was performed with equimolar amounts of the reagents in refluxing ethanol and piperidine according to Guarreschi reaction.

The pyrazolylpyridone 16 is obtained in good yield, as shown in Scheme VIII. Its structure was deduced from IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopy.

$^1$H NMR spectra revealed, in particular, signals at 1.58 and 2.31 ppm corresponding respectively to pyridine and pyrazole methyls, whereas the signal due to the pyridine proton appeared at 6.03 ppm.

The $^{13}$C NMR spectra exhibited, in particular, signals at 90.29 and 160.77 ppm respectively due to C$_4$ and C$_3$ of pyrazole ring. A signal relative to the tertiary carbon of the pyridine nucleus, was observed at 98.57 ppm.

IR spectra showed characteristic absorption at 2200 cm$^{-1}$ corresponding to a nitrile group.

In this paper we have shown that acetooacetylpyrazole 1 resulting from dehydroacetic acid is a useful
djerrari et al.: synthesis of new heterocycles containing pyrazole

00

1 CN CH3 +

CH2

CH3

HO /C'::::::- O

H2N

EtOH

15

Ph,

N-N

HO CH3

N

CH

16

Scheme VIII

synthon for the preparation of new heterocyclic systems associating nuclei such as benzimidazole, pyrimidopyrimidine, thiazolopyrimidine and pyridone11,12 to a pyrazolic ring.

Experimental Section

General. Melting points were determined on a Buchi Tottoli apparatus and are uncorrected. Spectra were recorded using the following instruments: IR, Perkin-Elmer 577 spectrometer (KBr disks); NMR, Bruker (AC 250 spectrometer 250 MHz for 1H and 62.89 MHz for 13C), chemical shifts are given in δ, ppm downfield from TMS internal standard; and mass spectra were recorded on a Varian MAT 311 A (electron impact) spectrophotometer.

Action of o-phenylenediamine 2 or o-aminophenol 3 on 1. To a solution of acetoacetylpyrazole 1 (0.001 mole) in 40 mL ethanol, 0.002 mole of 2/3 was added. The reaction mixture was refluxed 2 hr and the solvent was removed under reduced pressure. The residue was purified by recrystallization from ethanol to give 4/5.

Compound 4. It was obtained in 80% yield; m.p. 212-14 °C; 1H NMR (CDCl3): δ 2.20 (s, 3H, CH3), 2.37 (s, 3H, CH3), 6.73-8.08 (m, 9H, CH arom.), 12.55 (s, 1H, OH); 13C NMR (CDCl3) δ 16.63 (CH3), 17.56 (CH3), 100.50 (Cq), 116.33 (CH), 118.52 (CH), 119.17 (CH), 122.13 (Cq), 124.38 (CH), 127.66 (CH), 128.10 (CH), 129.31 (CH), 139.08 (Cq), 142.74 (Cq), 147.49 (Cq), 165.59 (Cq), 165.85 (Cq); Mass (IE): m/z (%) 306 (31), 292 (21), 291 (100).

Compound 5. It was obtained in 85% yield, m.p. 246-48°C; 1H NMR (DMSO-d6): δ 2.36 (s, 3H, CH3), 2.40 (s, 3H, CH3), 6.90-8.05 (m, 9H, CH arom.), 10.26 (s,1H, OH); 13C NMR (DMSO-d6):δ 16.70 (CH3), 17.04 (CH3), 99.26 (Cq), 116.23 (CH), 117.93 (CH), 119.22 (CH), 123.50 (CH), 123.65 (CH), 126.65 (CH), 128.62 (CH), 139.05 (Cq), 147.39 (Cq), 151.51 (Cq), 164.86 (Cq), 165.05 (Cq); Mass (IE): m/z (%). 307 (6), 199 (15), 134 (22), 77 (100), 65 (43).

Synthesis of 4-pyrazolyltrimidobenzimidazole 9. A solution of aminobenzimidazole 8 (0.001 mole) and acetoacetylpyrazole 1 (0.005 mole was refluxed for 1 hr in butanol (40 mL). The solvent was removed under reduced pressure. The residue on crystalization from ethanol gave compound 9 in 65% yield; m.p. 196-98 °C; 1H NMR (DMSO-d6): δ 2.11 (s, 3H, CH3), 2.51 (s, 3H, CH3), 6.74 (s, 1H, CH), 7.01- 8.15 (m,1OH, CH arom.), 10.26 (s,1H, OH); 13C NMR (DMSO-d6): δ 14.48 (CH3), 24.48 (CH3), 92.62 (Cq), 107.93-127.93 (=CH), 212.3-153.50 (Cq); Mass (IE): mlz 355.

Action of 2-amino-3-hydroxypyridine on 1. To acetoacetyLPyrazole 1 (0.005 mole) in 40 mL ethanol, a solution of 2-amino-3-hydroxypyridine 10 (0.005 mole) in ethanol (20 mL) was added. The reaction mixture was heated under reflux for 18 hr and the solvent was removed in vacuo. The resulting crude material was chromatographed on a silica gel column using a 60:40 mixture of hexane and ethyl acetate as eluant to give the compounds 11, 12 and 7.

4-pyrazolylidenepyridopyrimidine 11. This compound was obtained in 35% yield; m.p. 210-12°C; 1H NMR (DMSO-d6): δ 2.30 (s, 3H, CH3), 2.71 (s, 3H, CH3), 7.33 (s, 1H, CH pyrimidine), 7.52-7.67 (m,5H, CH arom.), 8.08 (dd, 1H, J = 7,4 Hz, J = 2,4 Hz, CH pyridine), 8.24 (dd, 1H, J = 7,4 Hz, J = 2,4 Hz, CH pyridine), 8.36 (t, 1H, J = 7,4 Hz), 13C NMR (DMSO-d6): δ 15.00 (CH3), 24.20 (CH3), 93.10 (Cq), 98.50 (=CH), 115.90 (=CH), 117.60 (=CH), 118.70 (=CH), 122.40 (=CH), 128.20 (=CH), 128.50 (=CH), 140.40 (Cq), 142.50 (Cq), 146.30 (Cq), 149.70 (Cq), 150.30 (Cq), 161.90 (Cq), 162.90 (Cq); Mass (IE): mlz (%) 332 (100), 315 (31), 199 (64), 135 (5), 77 (51).

2-Methylpyrido[1,2-a]pyrimidin-4-one 12. It was obtained in 25% yield; m.p. 146-48 °C; 1H NMR (CDCl3): δ 2.38 (s, 3H, CH3), 6.25 (s, 1H, CH pyrimidine), 7.03-7.09 (m, 2H, pyridine), 8.46 (d, 1H, J = 2,3 Hz); 13C NMR (CDCl3): δ 24.20 (CH3),...
103.60 (=CH), 113.10 (=CH), 115.10 (=CH), 117.80 (=CH), 144.10 (Cq), 148.30 (Cq), 157.80 (Cq), 163.10 Cq); Mass (I.E): m/z(%) 176 (69), 148 (34), 147 (15), 120 (32).

**Synthesis of pyrazolylidenethiazolo-pyrimidine 14.** To a solution of 1 (0.005 mole) in 30 mL of butanol, 0.005 mole of 2-aminothiazole 13 was added. The reaction mixture was refluxed for 1 hr and the solvent was removed in vacuo. The product obtained was purified by recrystallization from ethanol to give 14 in 85% yield; m.p. 267-69 °C; 

1H NMR (CDCl₃): δ 2.40 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 7.06 (s, 1H, =CH pyrimidine), 7.24-7.35 (m, 5H arom.), 8.05 (s, 1H, =CH), 8.80 (d, 1H, J =4.9 Hz, =CH); 13C NMR (CDCl₃): 16.25 (CH₃), 24.60 (CH₃), 95.37 (Cq), 111.90 (=CH), 119.60 (=CH), 112.60 (=CH), 124.00 (=CH), 128.60 (=CH), 130.30 (=CH), 139.76 (Cq), 146.50 (Cq), 150.10 (Cq), 162.60 (Cq), 163.70 (Cq); Mass (I.E): m/z (%): 322 (58), 189 (100), 161 (5), 125 (27), 77 (54).

**Synthesis of pyrazolylpyridone 16.** Acetoacetylpyrazole 1 (4.85.10⁻³ mole) was added to a solution of cyanoacetamide 15 (0.005 mole) in ethanol (90%). Piperidine (0.023 mole) was added to the resulting solution and the mixture was refluxed for 8 hr. After evaporation of solvent the residue was recrystallized from ethanol to give 16 in 85% yield; m.p. 233-34 °C; IR (KBr): 2200 (CN), 1740 (CO); 1H NMR (DMSO-d₆): δ 1.58 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 6.03 (s, 1H, CH), 7.34-8.10 (m, 5H, CH arom.); 13C NMR (DMSO-d₆): δ 16.80 (CH₃), 20.90 (CH₃), 90.29 (Cq), 98.50 (=CH), 117.70 (=CH), 118.30 (Cq), 122.60 (=CH), 128.30 (=CH), 145.60 (Cq), 149.40 (Cq), 156.60 (Cq), 160.70 (Cq), 164.40 (Cq); Mass (I.E): m/z (%): 306 (100), 173 (19), 91 (12), 84 (71), 77 (38), 56 (47).

**References**
12 Yale H L, U S Pat 3 929 787; Chem Abstr, 84 1976 105645.