Synthesis of Substituted Azaindenes: Synthesis of New Pyrazolo-[1,5-*a*]pyrimidine Derivatives

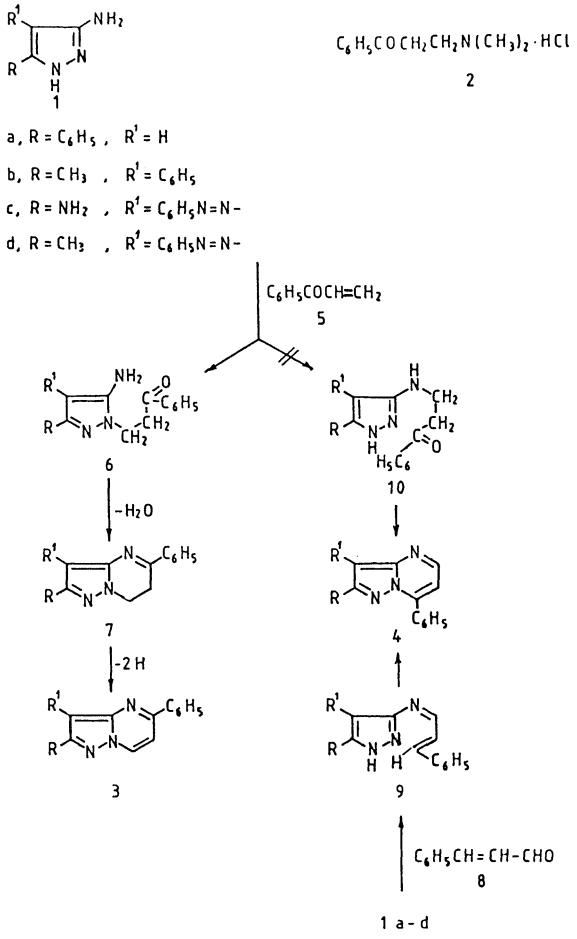
Mohamed Hilmy ELNAGDI* and Ayman Wahba ERIAN
Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt
(Received November 16, 1989)

Synopsis. Several new pyrazolo[1,5-*a*]pyrimidines were synthesized via the reaction of 4,5-disubstituted 3-aminopyrazoles **1a—d** with 3-dimethylaminopropiophenone, cinnamaldehyde, benzylideneacetophenone and tetracyanoethylene.

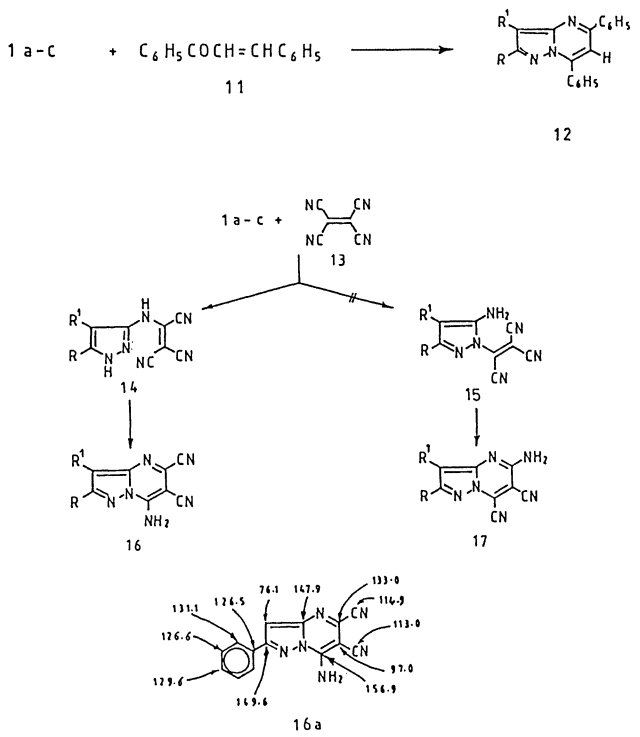
Interest in synthesis of condensed pyrazoles has recently been revived.[1-3] The considerable biological activities of pyrazolopyrimidines as CAMP-phosphodiasterase inhibitors,[4] xanthine oxidase inhibitors[5] and antischistosomal agents[6] are beyond this recent interest. As a part of a program at our laboratory directed for developing new antischistosomal agents, samples of certain substituted pyrazolo[1,5-*a*]pyrimidines were required. Certain substituted pyrazolo[1,5-*a*]pyrimidines were observed to act as inhibitors for snail metabolism.

One of the most utilized synthetic approaches to pyrazolo[1,5-*a*]pyrimidines is reaction of α,β-unsaturated reagents with 3-aminopyrazoles.[1] A limitation for utility of this approach is the difficulty of establishing structures of products resulting from reaction of non-symmetrical double bond systems with aminopyrazoles.

In the present paper we report synthesis of several new pyrazolo[1,5-*a*]pyrimidines via reaction of 3-aminopyrazoles with non-symmetrical double bond system and provide methods for establishing structure of reaction products. Thus, it has been found that the 3-aminopyrazoles **1a—d** react with 3-dimethylaminopropiophenone hydrochloride (**2**) in refluxing DMF to yield product of condensation via elimination of water, dimethylamine hydrochloride and hydrogen. These products can thus be formulated as **3** or isomeric **4**. Thus, addition of phenyl vinyl ketone (**5**), resulting from elimination of dimethylamine hydrochloride from **2**, to ring nitrogen would afford intermediate **6** which on cyclization via water elimination gives **7** which on aromatization would yield **3**. On the other hand, condensation with exocyclic amino function followed by cyclization can afford **4**. Although we have earlier shown[1] that ring nitrogen in aminopyrazoles is the most basic center, we have also reported that it is the most hindered site in the molecule. Thus, electrophilic attack at **1a—d** would be much governed by steric consideration and it is difficult to predict the reaction site with certain electrophile. Although in reaction under consideration one can assume that **5** is not a bulky reagent and that attack at ring nitrogen would take place, an independent proof for such prediction seemed mandatory. ^{1}H NMR indicated that the reaction products are **3**. Thus, ^{1}H NMR of **3d** revealed methyl group as a doublet at δ=2.50 and one proton multiplet at a δ=5.10 in addition to one proton doublet at δ=4.49, J=2 Hz, and aromatic protons at δ=7.20—7.75. The multiplicity of the one proton signal at δ=5.10 and the appearance of methyl group as a doublet can be only intelligibly interpreted in terms of long range coupling between CH_3 and a proton at C-7, providing evidence for structure **3**. Moreover, for this purpose, samples of **4a,b** were synthesized via condensation **1a,b** with cinnamaldehyde **8** and subsequent cyclization of resulting cinnamylidene derivatives **9**. These products proved different from products of reaction of **1a,b** and **2**. Thus, structure **3** could be established for the latter derivatives.



We have found that benzylideneacetophenone **11** reacts with **1a—c** to yield products of condensation via elimination of water and hydrogen molecule. These were formulated as **12**. Formation of **12** is assumed to proceed via intermediacy of acyclic adducts resulting from attack either by ring N-2 or exocyclic amino group and subsequent cyclization and aromatization via elimination of water and hydrogen molecule. Alternately one can assume condensation of carbonyl



function in **11** with exocyclic amino group and subsequent cyclization and oxidation. Since we could not isolate intermediates for this reaction, it is difficult to decide the reaction pathway.

Tetracyanoethylene (**13**) reacted with **1a—c** to yield products of condensation by the elimination of hydrogen cyanide. These may be formulated as acyclic **14** and **15** or cyclic **16** and **17**. Acyclic forms were ruled out based on the stability of the reaction products on refluxing in protic media, a condition that would effect cyclization of these products, structure **16** was preferred over isomeric **17** based on ^{1}H NMR which revealed NH_2 protons at δ=9.0. If these products were isomeric **17**, amino protons at much higher field should have appeared at δ=4.0. We have earlier[7] reported that 7-aminopyrazolo[1,5-*a*]pyrimidines having their protons deshielded by ring N anisotropy resonate at δ=8.0. Structure proposed for **16a** was further evidenced by ^{13}C NMR (see formula).

Experimental

All mps are uncorrected. IR spectra were recorded on a Pye-Unicam spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM-390 spectrometer. Microanalyses were performed by the Microanalytical Data Unit at Cairo University. Mass Spectra were recorded with a mass spectrometer MS 30 and MS 9 (AEI), 70 eV.

2,5-Diphenylpyrazolo[1.5-*a*]pyrimidine (3a). To a solution of **1a** (0.01 mol) in 10 ml DMF, 3-dimethylaminopropiophenone hydrochloride **2** (0.01 mol) was added. The reaction mixture was refluxed for 3 h, poured into ice-cold water. The solid product so formed was collected by filtration and crystallized from ethanol as white crystals; yield 64%; mp 165 °C. IR: 3050 cm^{-1} (olefinic C-H), 1600, 1590 (aromatic rings). ^{1}H NMR: δ=7.10—7.50 (m, 11H, aromatic protons and H-4 pyrazole); 7.80 (m, 1H, H-6), 8.80 (d, 1H, H-7). Found: C, 79.6; H, 4.9; N, 15.2%. Calcd for $C_{18}N_{13}N_3$: C, 79.70; H, 4.79; N, 15.49%.

6,7-Dihydro-2-methyl-3,5-diphenylpyrazolo[1,5-*a*]pyrimidine (7b). To a solution of **1b** (0.01 mol) in 10 ml DMF, 3-dimethylaminopropiophenone hydrochloride **2** (0.01 mol) was added. The reaction mixture was refluxed for 3 h, poured into ice-cold water. The solid product, so formed, was collected by filtration and crystallized from dilute ethanol as yellow crystals; yield 59%; mp 90 °C. IR: 2950, 2700 cm^{-1} (CH_3, CH_2); 1600 (aromatic rings). ^{1}H NMR: δ=2.35 (d, 3H, CH_3); 3.30 (m, 2H, H-6); 4.20 (m, 2H, H-7); 7.18—7.70 (m, 10 H, aromatic protons) MS: *m/z* 287 (M^+). Found: C, 79.5; N, 6.0; N, 14.6%. Calcd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.92; N, 14.63%.

3,5-Diphenyl-2-methylpyrazolo[1,5-*a*]pyrimidine (3b). **7b** was oxidized by refluxing in 10 ml acetic acid containing 0.01 g $KMnO_4$ for 30 min. The reaction product was diluted with water and the solid product so formed was filtered off and crystallized from ethanol as yellow crystals; yield 62%; mp 100 °C. IR: 2900, 2850 cm^{-1} (CH_3); 1600 (aromatic rings). ^{1}H NMR: δ=2.35 (d, 3H, CH_3); 4.70 (d, 1H, H-6), 5.06 (m, 1H, H-7), 7.17—7.70 (m, 10H, aromatic protons). Found: C, 79.8; N, 5.1; N, 14.7%. Calcd for $C_{19}H_{15}N_3$: C, 80.0; H, 5.26; N, 14.73%.

2,3-Disubstituted 5-Phenylpyrazolo[1,5-*a*]pyrimidines (3c, d). To a solution aminopyrazoles **1** (0.01 mol) in 10 ml DMF, 3-dimethylaminopropiophenone hydrochloride **2** (0.01 mol) was added. The reaction mixture was refluxed for **3** h, poured into ice-cold water. The solid product so formed was collected by filtration and crystallized from ethanol.

3c: Brown crystal, yield 71%; mp 104 °C. IR: 3500, 3300 cm^{-1} (NH_2); 1660, 1600 (aromatic rings). ^{1}H NMR: δ= 7.19—7.63 (m, 10 H, aromatic protons); 7.80 (d, 1H, H-6); 7.92 (in, 1H, H-7); 8.20 (br, 2H, NH_2). Found: C, 68.8; H, 4.5; N, 26.9%. Calcd for $C_{18}H_{14}N_6$: C, 68.78; N, 4.45; N, 26.75%.

3d: Orange crystals, yield 76%; mp 210 °C. IR: 2800, 2850 cm^{-1} (CH_3); 1600 (aromatic rings). ^{1}H NMR: δ=2.44 (d, 3H, CH_3); 4.90 (d, 1H, H-6); 5.06 (m, 1H, H-7), 7.19—7.78 (m, 10 H, aromatic protons). MS: *m/z* 313 (M^+). Found: C, 73.0; H, 4.8; N, 22.2%. Calcd for $C_{19}H_{15}N_5$: C, 72.84; N, 4.79; N, 22.36%.

3-Cinnamylideneaminopyrazole (9a,b). To a solution of 3-aminopyrazoles **1** (0.01 mol) in 10 ml pyridine, cinnamaldehyde **8** (0.01 mol) was added. The reaction mixture was refluxed for 2 h, poured into ice-cold water. The solid product so formed was collected by filtration and crystallized from DMF/ethanol mixture.

9a: Brown crystals, yield 80%; mp 197 °C. IR: 3400 cm^{-1} (NH); 1660, 1600 (C=C and aromatic rings). ^{1}H NMR: insoluble. MS: *m/z* 273 (M^+). Found: C, 79.3; H, 5.4; N, 15.3%. Calcd for $C_{18}H_{15}N_3$: C, 79.2; H, 5.49; N, 15.38%.

9b: Formed buff crystals, yield 78%; mp 165 °C. IR: 3300 cm^{-1} (NH), 2850 (CH_3), 1580 (aromatic rings). ^{1}H NMR: δ=2.50 (s, 3H, CH_3); 6.45 (br, 1H, NH), 7.20—7.55 (m, 13H, 2 Ph and propenyl protons). MS: *m/z* 287 (M^+). Found: C, 79.4; H, 6.0; N, 14.6%. Calcd for $C_{19}N_{17}N_3$: C, 79.44; H, 5.92; N, 14.63%.

2,3-Disubstituted 7-Phenylpyrazolo[1,5-*a*]pyrimidines (4a,b). A solution of **9** in 20 ml AcOH was refluxed for 1 h and then left to cool to room temperature. The solid product so formed was filtered off and crystallized from acetic acid.

4a: Formed buff crystals, yield 82%; mp 235 °C. IR: 3040 cm^{-1} (olefinic C-H)); 1610 (aromatic rings). ^{1}H NMR; insoluble. MS: *m/z* 271 (M^+). Found: C, 79.7; H, 4.7; N, 15.5%. Calcd for $C_{18}H_{13}N_3$: C, 79.70; H, 4.79; N, 15.49%.

4b: Formed buff crystals, yield 76%; mp 251 °C. IR: 2950, 2800 (CH_3), 1660 (aromatic rings). ^{1}H NMR: δ=2.48

(s, 3H, CH_3); 6.75—7.80 (m, 12H, 2 Ph; 1H, H-5 and 1H, H-6). Found: C, 79.9; H, 5.2; N, 14.7%. Calcd for $C_{19}H_{15}N_3$: C, 80.00; H, 5.26; N, 14.73%.

2,3-Disubstituted 5,7-Diphenyrazolo[1,5-*a*]pyrimidines (12a,b). To a solution of **1** (0.01 mol) in 20 ml acetic acid containing 2 g $AcONH_4$, 2-benzylideneacetophenone (**11**) was added. The reaction mixture was refluxed for 3 h. The reaction product was poured into ice-cold water, the solid product was filtered off and crystallized from acetic acid.

12a: Yellow crystals, yield 61%; mp 200 °C. IR: 1660, 1600, 1580 cm^{-1} (aromatic rings). ^1H NMR: δ=6.80—7.90 (m, aromatic protons). Found: C, 82.8; H, 4.8; N, 12.2%. Calcd for $C_{24}H_{17}N_3$: C, 82.99; H, 4.89; N, 12.10%.

12b: Yellow crystals, yield 2 g (57%); mp 292 °C. IR (KBr); 2850 cm^{-1} (CH_3); 1600 (aromatic rings). ^1H NMR: δ=2.5 (s, 3H, CH_3), 6.71—7.55 (m, 16H, 3 Ph and 1H, H-6) MS: *m/z* 361 (M^+). Found: C, 83.1; H, 5.2; N, 11.8%. Calcd for $C_{25}H_{19}N_3$: C, 83.10; H, 5.26; N, 11.63%.

2-Amino-5,7-diphenyl-3-phenylazopyrazolo[1,5-*a*]pyrimidine (12c). To a solution of **1c** (0.01 mol) in 10 ml pyridine, benzylidenacetophenone (**11**) (2.0 g, 0.01 mol) was added. The reaction mixture was refluxed for 2 h and then left to cool to room temperature, the solid product so formed was filtered off and crystallized from ethanol/DMF as red crystals; yield 61%; mp >300 °C. IR: 3450, 3320 cm^{-1} (NH_2); 1660, 1600 (aromatic rings). ^1H NMR: insoluble. Found: C, 73.8; H, 4.6; N, 21.4%. Calcd for $C_{24}H_{18}N_6$: C, 73.84; H, 4.61; N, 21.53%.

2,3-Disubstituted 7-Aminopyrazolo[1,5-*a*]pyrimidine-5,6-dicarbonitriles (16a—c). To a solution of **1** (0.01 mol) in 10 ml acetonitrile, tetracyanoethylene (0.01 mol) was added. The reaction mixture was refluxed for 15 min and then left to cool to room temperature. The solid product so formed was filtered off and crystallized from ethanol/DMF.

16a: Buff crystals, yield 69%; mp >300 °C. IR: 3400, 3200 cm^{-1} (NH_2); 2200 (CN); 1660 (aromatic ring). ^1H NMR: δ=6.43 (s, 1H, H-3); 6.91—7.40 (m, 5H, Ph); 8.37 (br, 2H, NH_2). ^{13}C NMR (see formula) MS: *m/z* 260 (M^+). Found: C, 64.6; H, 3.0; N, 32.3%. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.07; N, 32.30%.

16b: Yellow crystals, yield 64%; mp >300 °C. IR: 3450—3100 cm^{-1} (NH_2, CH_3); 2200 (CN), 1650 (aromatic ring). ^1H NMR: δ=2.50 (s, 3H, CH_3); 7.14—7.67 (m, 5H, Ph): 9.23 (br, 2H, NH_2). Found: C, 65.6; H, 3.6; N, 30.7%. Calcd for $C_{15}H_{10}N_6$: C, 65.69; H, 3.64; N, 30.65 %.

16c: Brown crystals, yield 60%, mp >300 °C. IR: 3445, 3200 (NH_2), 2200 (CN), 1650 (aromatic ring). ^1H NMR: δ=6.85—7.32 (m, 5H, Ph); 8.40 (br, 4H, $2NH_2$). Found: C, 55.4; H, 2.9; N, 41.5%. Calcd for $C_{14}H_9N_9$: C, 55.44; H, 2.97; N, 41.58%.

Spectroscopic measurements were performed at University of Missouri, Columbia, Missouri, U.S.A. by Prof. Dr. M. Tempesta, thanks to the support of International Organisation of Chemical Sciences in Development (IOCD).

References

1) M. N. Elnagdi, M. R. H. Elmoghayar, and G. E. H. Elgemeie, "Chemistry of Pyrazolopyrimidines," in "Advances in Heterocyclic Chemistry," ed by A. R. Katritzky, Academic Press, New York (1987), Vol. 41, p. 320.

2) M. N. Elnagdi, M. R. H. Elmoghayar, and K. U. Sadek, "Chemistry of Pyrazoles Condensed Heteroaromatic Five and Six Membered Rings," in "Advances in Heterocyclic Chemistry," ed by A. R. Katritzky, Academic press, New York (1990), Vol. 48, p. 219.

3) M. H. Elnagdi, N. H. Taha, F. M. Abd El All, R. M. Abdel-Motaleb, and F. F. Mahmoud, *Collections Czech. Chem. Commun.*, **53**, 1089 (1988).

4) T. Novinson, R. Hanson, M. K. Dimmitt, L. N. Simon, R. K. Robins, and D. E. O'Brien, *J. Med. Chem.*, **17**, 645 (1974).

5) K. Senga, T. Novinson, H. R. Wilson, and R. K. Robins, *J. Med. Chem.*, **24**, 610 (1981).

6) H. A. El-Fahham, F. M. Abdel-Galil, Y. R. Ibrahiem, and M. H. Elnagdi, *J. Heterocycl. Chem.*, **20**, 667 (1983).

7) E. M. Kandeel, V. B. Baghos, I. S. Mohareb, and M. H. Elnagdi, *Arch. Pharm. (Weinheim)*, **316**, 105 (1983).