Rearrangement of 1-Amino- and 1-Alkylamino-pyrazoles to 5-Aminopyrazoles

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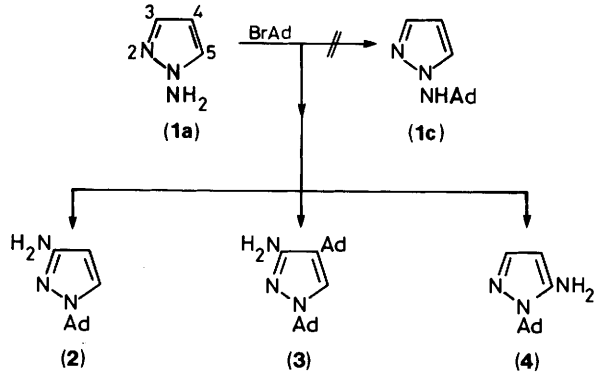
Rearrangement of 1-aminopyrazole and 1-alkylaminopyrazoles into the corresponding 5-aminopyrazoles has been achieved in 48% aqueous hydrobromic acid. The reaction, occurring through a ring opening–ring closure mechanism, constitutes a new and unambiguous procedure for the preparation of 1-substituted 5-aminopyrazoles. The products have been identified on the basis of ^1H and ^{13}C n.m.r. spectroscopic results and comparison with authentic samples.

Because of our interest in the biological properties of heterocyclic derivatives containing an 1-adamantyl group, we attempted to synthesize 1-(1-adamantylamino)pyrazole (**1c**; R = Ad) starting from 1-aminopyrazole (**1a**; R = H) and 1-bromoadamantane, according to the experimental conditions previously used.[1] Instead of derivative (**1c**) we obtained a complex mixture† of compounds from which the following were isolated and identified: 1-(1-adamantyl)-3-aminopyrazole (**2**) (15%), 1,4-bis(1-adamantyl)-3-aminopyrazole (**3**) (30%), and 1-(1-adamantyl)-5-aminopyrazole (**4**) (25%) (Scheme 1).

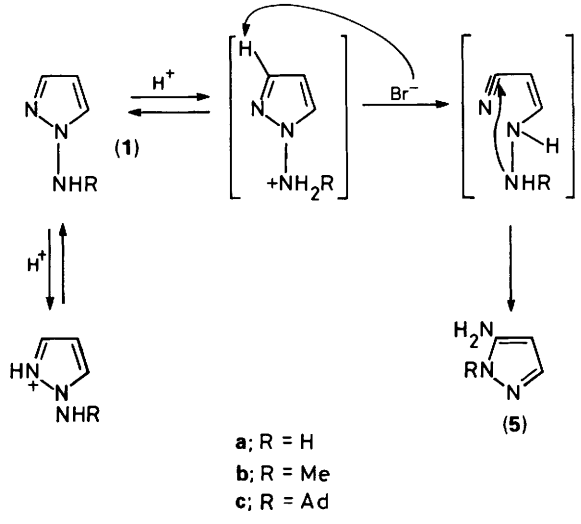
The structures of these new derivatives were confirmed by ^1H (200 MHz) and ^{13}C (50 MHz) n.m.r. spectra, all compounds showing chemical shifts in accordance with the calculated ones from 1-(1-adamantyl)pyrazole[2] considering the substituent chemical shifts effects of amino[3] and 1-adamantyl groups[4] (Table).

To explain these results, we assumed that owing to protonation of 1-aminopyrazole (**1a**) by traces of hydrobromic acid, this compound rearranges to the 3(5)-amino derivative (**5a**) (Scheme 2); subsequent adamantylation on both nitrogens and on the 4-carbon atom then gave (**2**), (**3**), and (**4**).

In order to check this explanation, 1-aminopyrazole (**1a**) and 1-methylaminopyrazole (**1b**) were heated with 48% aqueous hydrogen bromide at 140 °C for 14 h to afford 3(5)-aminopyrazole (**5a**)[3] (33%) and 1-methyl-5-aminopyrazole (**5b**)[3] (70%), respectively. Compound (**1a**) was prepared from



Scheme 1.



Scheme 2.

pyrazole and hydroxylamine-*O*-sulphonic acid.[5] A two-step procedure involving formylation of (**1a**) with 98% formic acid to give (**1d**; R = CHO) and reduction of this last compound with $LiAlH_4$ gave 1-methylaminopyrazole (**1b**) in 50% overall yield.

The mechanism proposed in Scheme 2 accounts for a reaction without precedent in pyrazole chemistry and involves a β-hydrazinoacrylonitrile intermediate. This kind of compound

† *Typical Procedure.*—A mixture of 1-aminopyrazole (0.83 g, 10 mmol) and 1-bromoadamantane (2.15 g, 10 mmol) was heated at 160–170 °C for 2 h. After cooling, the crude reaction mixture was chromatographed on a silica gel column (70–230 mesh, ASTM) with chloroform–ethanol (9:1, v/v) to give in the following elution order: compound (**3**), m.p.; 204–206 °C (Found: C, 78.45; H, 9.2; N, 11.95. $C_{23}H_{33}N_3$ requires C, 78.58; H, 9.46; N, 11.95%); compound (**2**)·HBr, m.p. 225—226 °C (Found: C, 52.05; H, 6.7; N, 14.1. $C_{13}H_{20}BrN_3$ requires C, 52.35; H, 6.71; N, 14.09%); and compound (**4**)·HBr, m.p. 244–245 °C (Found: C, 52.65; H, 6.95; N, 13.95. $C_{13}H_{20}BrN_3$ requires C, 52.35; H, 6.71; N, 14.09%).

Table. ^1H and ^{13}C N.m.r. data (chemical shifts, δ in p.p.m. and couplings constants, J in Hz)

Compound	1-position	3-position	4-position	5-position	1-position	C-3	C-4	C-5
(**1b**)[a]	NH, 5.20 CH_3, 2.90 (J_{NHCH_3} 5.9)	7.38 ($J_{3,4}$ 2.1)	6.09 ($J_{4,5}$ 2.3)	7.34 ($J_{3,5}$ 0.9)	CH_3, 39.7 (^1J 136.7)	137.2 (^1J 185.9)	103.7 (^1J 177.4)	127.8 (^1J 186.0)
(**2**)·HBr[b]	Ad[c]	NH_2, 4.62	5.80 ($J_{4,5}$ 3.0)	7.85	Ad[c]	150.0	93.7 (^1J 184.6)	134.6 (^1J 193.4)
(**3**)[a]	Ad[c]	NH_2, 3.30	Ad[c]	6.97	Ad[c]	150.0	116.3	122.0 (^1J 180.6)
(**4**)·HBr[b]	Ad[c]	7.92 ($J_{3,4}$ 2.4)	6.35	NH_2, 3.42	Ad[c]	130.5 (^1J 190.5)	100.6 (^1J 181.5)	139.8

[a] In deuteriochloroform ($CDCl_3$). [b] In [$^2H_6$]dimethyl sulphoxide. [c] Data for 1-adamantyl groups are similar to the ones described in refs. 1, 2, and 4.

has been isolated in the synthesis of *C*-aminopyrazoles from β-keto nitriles.[6,7]

All known methods[6,7] of preparation of 1-alkyl-5-aminopyrazoles yield mixtures with isomeric 3-aminopyrazoles. The rearrangement of 1-amino into 5-amino-pyrazoles is a selective way to obtain these last compounds. Other heterocycles, such as 1-aminoindazoles, are possible substrates for similar reactions.

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