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REGIOSELECTIVE NUCLEOPHILIC SUBSTITUTION IN ACTIVATED 1-AMINOPYRAZOLIUM CATIONS: A FACILE SYNTHESIS OF 5-SUBSTITUTED 1-METHYLPYRAZOLES[1]

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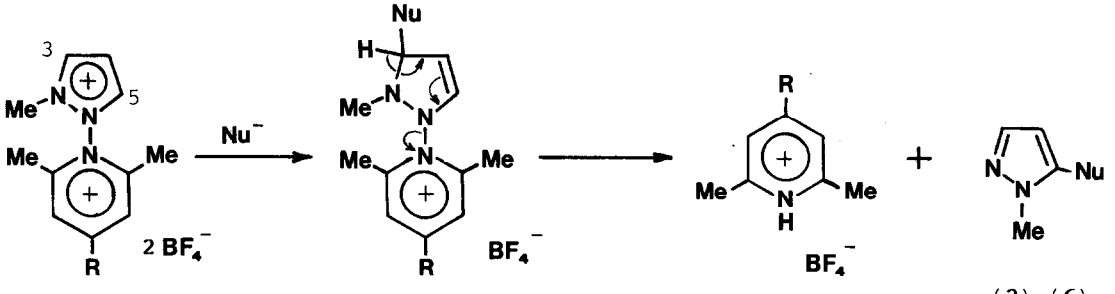
5-Substituted 1-methylpyrazoles were easily obtained in good yields by the attack of nucleophiles (NaCN, H_2O, EtSH, pyrazole, imidazole) to 2,6-dimethyl-1-(2-methylpyrazol-1-io)-4-phenylpyridinium bistetrafluoroborate (**1b**), without significant formation of any 3-substituted isomer.

Despite the great number of methods described for the preparation of substituted pyrazoles, a wide-scope reaction for the selective introduction of groups at the 3- or 5-position of the pyrazole nucleus is still lacking.[2] We have recently reported[3] that cyanide ion reacts smoothly at room temperature with the dication (**1a**), yielding a 1:1 mixture of 5-cyano-1-methylpyrazole (**2**) and collidine, without traces of the 3-cyano isomer. The reaction was an extension to azoles of the well-known Katritzky's activation of primary amines towards S_N reactions by means of their transformation into pyridinium cations,[4] and probably involves an addition-elimination mechanism,[3,5] according to the following Scheme:

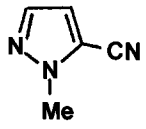


(**1a**) R = **Me**
(**1b**) R = **Ph**

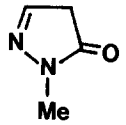
We report herein the straightforward synthesis of pyrazoles (**2**)-(**6**) from (**1b**), a dication which practically eliminates the concurrent attack of nucleophiles on the pyridinium moiety, a serious side-reaction found during the previous studies with (**1a**).[3] Compounds (**2**)-(**6**) are representative examples of novel or tediously multi-step accessible pyrazoles, and their synthesis illustrates the use of either C-, O-, S-, or N-nucleophiles in the reaction.

For the synthesis of (**1b**), 1-aminopyrazole (1.33 g, 0.016 mol)[8] and 2,6-dimethyl-4-phenylpyrylium tetrafluoroborate[9] were refluxed in dry ethanol (50 cm^3) for 1 h. Crystals of 2,6-dimethyl-4-phenyl-1-(1-pyrazolyl)pyridinium tetrafluoroborate

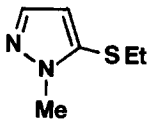
(**7**) mp 201-203°C[10,11] (3.30 g, 98%) separated on cooling. The salt (3.44 g, 0.01 mol) was heated (100°C, 4h) in freshly distilled dimethyl sulphate (15 cm^3). The solution was cooled, and the crystalline product filtered, washed with dry ethanol, and dissolved in the minimum amount of hot 50% aq. HBF_4. Crystals of the bisfluoroborate of (**1b**), mp 221-222°C[10,11] developed upon dropwise addition of diethyl ether. The yield was 3.78 g (75%).



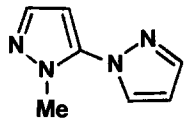
(**2**)



(**3**)



(**4**)



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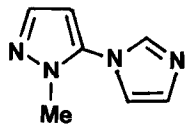


(**6**)

The reactions of (**1b**) with nucleophiles were typically performed in water at room temperature, and monitored by ^1H nmr for disappearence of the starting compound. Final products were obtained by direct extraction or evaporation of the resulting solutions, and purified as indicated in Table 1.

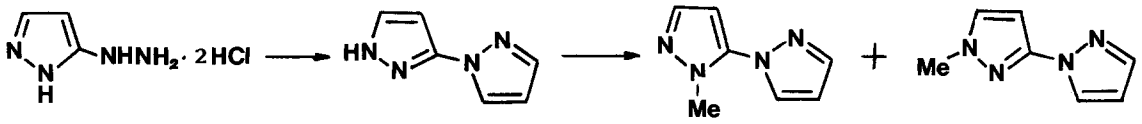
Table 1. Reactions of (**1b**)(1.0 mmol) with nucleophiles in H_2O at 25°C.

Product	Reaction conditions	Physical data	Isolated yield
(**2**)	0.2M NaCN (6 cm^3,1.2 mmol) 1 h[a]	Mp 23-27°C Bp 90°C/8 torr	ca. 100%[b]
(**3**)	H_2O (25 cm^3) 30 days[c,d]	Mp 105.5-110.5°C[e]	70%[f]
(**4**)	EtSH (2.5 mmol) + H_2O (10 cm^3) 7 days[c,g]	Bp 45°C/0.01 torr	80%[f]
(**5**)	0.04M pyrazole (25 cm^3,1.0 mmol) 15 days[a]	Bp 85°C/2 torr	73%[f]
(**6**)	0.04M imidazole (25 cm^3,1.0 mmol) 12 h[c]	Mp 54.5-55°C Bp 80°C/0.002 torr	85%[f]

[a]Purified by bulb-to-bulb distillation; [b]A GC-MS analysis of the crude extract showed also traces (<1%) of 2-hydroxymethyl-6-methyl-4-phenylpyridine and 2-cyanomethyl-6-methyl-4-phenylpyridine, but no 3-cyano-1-methylpyrazole (ref.3); [c]Purified by column chromatography; [d]Use of DMSO/H_2O enhanced rate, but yielded also significant amounts of 3-hydroxy-1-methylpyrazole; [e]Lit. (ref.12) 112.5-119.5°C; [f]Isomeric 3-substituted 1-methylpyrazole was not detected by ^1H nmr in the crude reaction mixture; [g]Use of NaSEt/DMSO afforded also 15-20% of 2-ethylthiomethyl-6-methyl-4-phenylpyridine.

Structures (**2**)[3] and (**3**)[12] were identified by comparison with authentic samples, prepared by unambiguous routes. For the rest of pyrazoles (**4**)-(**6**), ^1H and ^{13}C nmr assignment criteria were used. Both the relatively small solvent effects on the ^1H chemical shift of the H_3 signal[13] and the long-range ^2J coupling constants[14] for C_3 and C_4 (Table 2) demonstrated the 1,5-disubstituted pattern of the pyrazole nucleus. Moreover, in the case of (**5**), the 1,3-disubstituted isomer (**9**) was also accessible by methylation of 1,3(5)-bipyrazole (**8**).[15] The nmr data for (**9**) [^1H nmr chemical shift for H_5: 7.33 ($CDCl_3$), 7.74 (DMSO-d_6), 6.65 (C_6D_6)], showing

large solvent shifts, and the ^{13}C long-range coupling constants for C_4 and C_5 (^2J=8.8; ^2J=8.1) are in full accord and complementary to the assignments of Table 2.



(8) (5) (9)

Table 2. Spectroscopic assignment of pyrazoles (**4**)-(**6**).

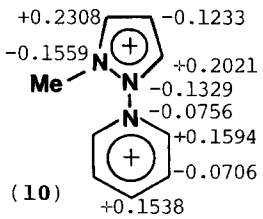
	^1H Nmr chemical shifts for H_3			^{13}C Nmr chemical shifts and C-H coupling constants (Hz) in $CDCl_3$[b]		
	$CDCl_3$[a]	DMSO-d_6	C_6D_6	C_3	C_4	
4	7.47	7.43	7.49	138.7 ^1J=185.7; ^2J=5.7	111.2 ^1J=178.1; ^2J=10.5	133.6[c]
5	7.43	7.52	7.38	138.1 ^1J=187.3; ^2J=4.2	100.1 ^1J=178.9; ^2J=10.9	139.0[c]
6	7.55	7.53	7.31	138.8 ^1J=188.3; ^2J=4.6	102.5 ^1J=179.6; ^2J=10.4	135.7[c]

[a] Other signals: (**4**) 1.25 and 2.76 (J=7.4Hz)(SEt), 3.91(NMe), and 6.33(J=1.9)(H_4); (**5**) 3.80(NMe), 6.21(J=2.0)(H_4), 6.41($H_{4'}$), 7.58(J=2.5)($H_{5'}$), and 7.71 (J=1.8Hz)(H_3); (**6**) 3.72(NMe), 6.32(J=2.0)(H_4), 7.10[c]($H_{5'}$), 7.27($H_{4'}$), and 7.68($H_{2'}$).

[b] Other signals: (**4**) 14.7 and 30.2 (SEt), 36.5(^1J=139.9)(NMe); (**5**) 30.7(^1J=127.0)(NMe), 107.2(^1J=178.4;^2J=10.5;^2J=8.6)($C_{4'}$), 131.3(^1J=189.1;^2J=9.2;^3J=4.5)($C_{5'}$), and 141.9(^1J=186.8;^2J=6.1;^3J=8,6)($C_{3'}$); (**6**) 35.7(^1J=140.8)(NMe), 120.5(^1J=192.1;J=15.2)($C_{5'}$), 130.5(^1J=191.8;J=10.5)($C_{4'}$), and 138.0(^1J=218.4)($C_{2'}$).

[c] Complex multiplet.

We believe that both steric and electronic factors govern the high selectivity found in the reactions of (**1b**) with nucleophiles. The steric hindrance caused by methyl substituents at positions 2 and 6 of the pyridinium cation is expected to favor the attack of the reagent at position 3 of the pyrazolium ring.[17] Furthermore, a theoretical MNDO calculation[18] carried out on the model compound 1-(2-methylpyrazol-1-io)pyridinium dication (**10**), showed a higher charge density (net atomic charge) at position 3 than at position 5. Although from a molecular orbital point of view position 3 was also anticipated to be more reactive (Σc^2 for positions 3 and 5, taking into account the whole set of unoccupied orbitals, were estimated as 0.00692 and 0.00123, respectively), the small magnitude of the values strongly suggests electrostatic rather than molecular orbital control for these reactions.



(**10**)

ACKNOWLEDGMENT

We are grateful to Dr. José Elguero, C.S.I.C., Madrid, for his encouragement and fruitful discussions throughout this work.

REFERENCES AND NOTES

[1] Presented in part at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada.

[2] See, for example, K. Schofield, M.R. Grimmett, and B.R.T. Keene, 'The Azoles', Cambridge UP, New York, 1976, or J. Elguero, 'Pyrazoles and their Benzo Derivatives', in 'Comprehensive Heterocyclic Chemistry', A.R. Katritzky and C.W. Rees, Eds., Pergamon Press, Oxford, Vol. 5, p. 167, 1984.

[3] M.L. Castellanos, M. Llinàs, M. Bruix, J. de Mendoza, and M. Rosario Martín, J. Chem. Soc., Perkin Trans. 1, 1985, 1209.

[4] A.R. Katritzky, Tetrahedron, 1980, **36**, 679; A.R. Katritzky and G. Musumarra, Chem. Soc. Rev., 1984, **13**, 47.

[5] Although not dealing with pyridinium cations as leaving groups, two additional examples of such 'cine' substitution reactions have been described in the azole series. Thus, 1-methoxy-3-methylbenzimidazolium iodide has been shown to react with nucleophiles at the very active position 2, yielding 2-substituted 1-methylbenzimidazoles.[6] More recently, Habraken et al.,[7] have described an elegant reaction of 1-nitropyrazoles with nitrogen nucleophiles (secondary amines and pyrazoles), to give the corresponding C-substituted aminopyrazoles or bipyrazoles. The activation of the ring with a second nitro group was, however, necessary for the reaction to take place. Moreover, concurrent attack of the nucleophile to the $N\text{-}NO_2$ substituent was found in some cases.

[6] S. Takahashi and H. Kano, Tetrahedron Lett., 1965, 3789.

[7] (a) C.L. Habraken and E.K. Poels, J. Org. Chem., 1977, **42**, 2893; (b) P. Cohen-Fernandes, C. Erkelens, C.G.M. Van Eendenburg, J.J. Verhoeven, and C.L. Habraken, J. Org. Chem., 1979, **44**, 4156.

[8] H. Koga, M. Hirobi, and T. Okamoto, Tetrahedron Lett., 1978, 1291; the compound was best obtained by aminating pyrazole (5.4 g, 0.08 mol) with H_2NOSO_3H (11.5 g, 0.10 mol) in 5% aq. KOH (225 cm^3) at 70°C. Continuous extraction with diethyl ether afforded a 1:1 mixture of pyrazole and 1-aminopyrazole (100% from transformed pyrazole) which was directly used in the next step, without further purification.

[9] Obtained as for the ClO_4^- salt: P.F.G. Praill and A.L. Whitear, J. Chem. Soc., 1961, 3573.

[10] Satisfactory CHN analyses, as well as ir and ms spectra were obtained for all new compounds.

[11] ^1H Nmr data (200 MHz, DMSO-d_6): (**7**), 2.43(6H, s, C-Me), 6.85(1H, dd, $H_{4'}$), 7.68-7.74(3H, m, Ph), 8.06(1H, d, J=2.1Hz, $H_{3'}$), 8.14-8.19(2H, m, Ph), 8.49(1H, d, J=2.6Hz, $H_{5'}$), and 8.63 (2H, s, $H_{3(5)}$) ppm. (**1b**), 2.59(6H, s, C-Me), 4.09(3H, s, N-Me), 7.50(1H, dd, $H_{4'}$), 7.74-7.80 (3H, m, Ph), 8.20-8.25(2H, m, Ph), 8.82(2H, s, $H_{3(5)}$), 9.16(1H, d, J=3.4Hz, $H_{5'}$), and 9.23 (1H, d, J=3.1Hz, $H_{3'}$) ppm.

[12] W. Sucrow and K.P. Grosz, Chem. Ber., 1976, **109**, 261.

[13] J. Elguero, R. Jacquier, and H.C.N. Tien Duc, Bull. Soc. Chim. Fr., 1966, 3727.

[14] M. Bruix, R.M. Claramunt, J. Elguero, J. de Mendoza, and C. Pascual, Spectrosc. Lett., 1984, **17**, 757.

[15] 3(5)-Hydrazinopyrazole dihydrochloride[16] (1.11 g, 6.52 mmol) and 1,1,3,3-tetramethoxypropane (0.96 g, 5.84 mmol) were kept for 24 h at room temp. in a mixture of H_2O (15 cm^3) and ethanol (10 cm^3). The solution was neutralized, evaporated, and the solid residue extracted with anhydrous ethanol. Evaporation of the solvent gave 1,3(5)-bipyrazole (**8**)(0.63 g, 80%), mp 91-92°C (lit.[7b] mp 90°C). A solution of (**8**)(0.56 g, 4.18 mmol) and sodium methoxide (from 0.11 g of sodium) in methanol (18 cm^3) was refluxed for 4 h with an excess of iodomethane (2 cm^3). Standard work-up gave a mixture of the methylated isomers (**5**) and (**9**)(0.56 g, 91%) in a 1:3 ratio. Distillation (2 torr) afforded pure (**5**) and (**9**)(bp 95-100°C/2 torr).[10]

[16] Despite a recent statement by M.A. Khan and A.C. Carreira Freitas, J. Heterocycl. Chem., 1983, **20**, 277, this compound was easily prepared from 3(5)-aminopyrazole, following the general method described for other analogues: J. de Mendoza and J.M. García-Marquina, An. Quím., 1970, **66**, 911; E. Alcalde, J.M. García-Marquina, and J. de Mendoza, ibid., 1974, **70**, 959. Mp (2HCl salt) 192°C[10], ^1H nmr (200 MHz, DMSO-d_6), 5.90 and 7.70 (J=2.3Hz) ppm.

[17] The more hindered derivative 2,4,6-triphenyl-1-(1-pyrazolyl)pyridinium cation cannot be methylated on the pyrazole nucleus, even under forcing conditions, M.L. Castellanos and J. de Mendoza, not published results.

[18] For details of the calculations, see M.L. Castellanos, S. Olivella, N. Roca, J. de Mendoza, and J. Elguero, Can. J. Chem., 1984, **62**, 687.

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