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THE SELECTIVE SYNTHESIS OF 1,5-DISUBSTITUTED PYRAZOLES AND STRUCTURAL ELUCIDATION OF 1,3- AND 1,5-DISUBSTITUTED PYRAZOLES

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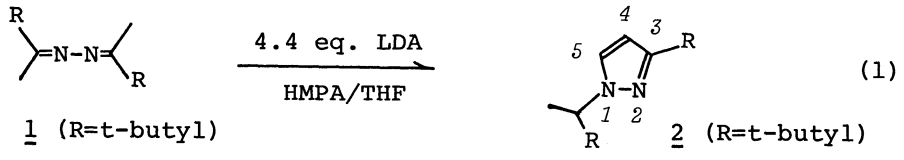
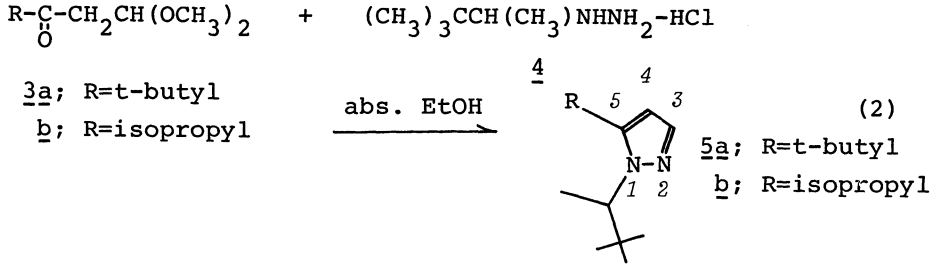
1,5-Disubstituted pyrazoles with a bulky group at 5-position is synthesized selectively from a monosubstituted hydrazine and a 1,3-dicarbonyl derivative. The structures of the positional isomers (1,3- and 1,5-disubstituted pyrazoles) are determined unambiguously by the C^{13}NMR study.

As an annoying problem for the synthesis of pyrazole has been recognized the formation of a mixture of the position isomers (i. e., 1,3- and 1,5-disubstituted pyrazoles), when an unsymmetrical 1,3-dicarbonyl compound or its derivative is reacted with a monosubstituted hydrazine.[1] Recently we have reported that 1,3-disubstituted pyrazoles can be synthesized selectively by treatment of methyl *sec*- or *tert*-alkyl ketazines with lithium diisopropylamide in a mixed medium of THF and hexamethylphosphoric triamide[2] (eq 1). In this communication we wish to report the selective synthesis of 1,5-disubstituted pyrazoles 5 (eq 2) and the structural



1 (R=t-butyl) — 4.4 eq. LDA, HMPA/THF → 2 (R=t-butyl) (1)



3a; R=t-butyl
b; R=isopropyl

abs. EtOH, 4 → 5a; R=t-butyl, b; R=isopropyl (2)

determination of these two positional isomers.

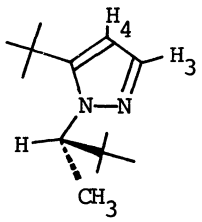
Interestingly, according to eq 2, only 1,5-disubstituted pyrazole 5, which had been expected to be the minor isomer of products,[3] was obtained exclusively.

Thus, (2,2-dimethoxy)ethyl t-butyl ketone[4] (3a, 522 mg, 3 mmol) and 1,2,2-trimethylpropylhydrazine[5] (4, 458 mg, 3 mmol) were refluxed for 2 hr in 3 ml of abs. ethanol. After evaporation of ethanol, the residue was extracted with ether and dried over sodium sulfate. Evaporation of the solvent and subsequent distillation (Kugelrohr 140-145°C/30 mmHg) gave 1-(1',2',2'-trimethyl)propyl-5-t-butylpyrazole 5a in 86% of isolated yield. Any contamination by 2 was not detectable by VPC. Similarly 1-(1',2',2'-trimethyl)propyl-5-isopropylpyrazole 5b (Kugelrohr 135-140°C/30 mmHg) was obtained selectively in 88% isolated yield by the reaction of 3b and 4. This selectivity may be the result of a retardation of the hydrazone formation due to the steric hindrance by a bulky group (R in 3).

While many spectroscopic (PMR and UV) studies have been reported on the structural determination of positional isomers of pyrazoles,[6] it is not straightforward to discriminate 2 and 5a by comparison with these spectra, e.g.,

2; $\delta^{TMS}_{CDCl_3}$ 0.87 (s, 9H), 1.29 (s, 9H), 1.44 (d, 7.0 Hz, 3H), 4.01 (q, 7.0 Hz, 1H), 6.00 (d, 2.2 Hz, 1H), and 7.15 (d, 2.2 Hz, 1H). ν^{max}_{neat} (cm^{-1}) 2970 (s), 1522 (m), 1370 (m), and 1240 (m). λ^{max}_{EtOH} 219 nm (log ε 3.74). m/e (%) 208 (M^+, 22), 193 (7), 151 (100), and 137 (25). VPC retention time 5.6 min (PEG, 1 m, 140°C, He).

5a; $\delta^{TMS}_{CDCl_3}$ 1.01 (s, 9H), 1.38 (s, 9H), 1.43 (d, 6.9 Hz, 3H), 4.26 (br. q, 6.9 Hz, 1H), 5.92 (d, 2.0 Hz, 1H), and 7.33 (d.d, 2.0 and 0.7 Hz, 1H). ν^{max}_{neat} (cm^{-1}) 2960 (m), 1520 (s), 1480 (m), and 1250 (m). λ^{max}_{EtOH} 217 nm (log ε 3.49). m/e (%) 208 (M^+, 5), 193 (5), 151 (100), and 137 (51). VPC retention time 3.3 min (PEG, 1 m, 140°C, He).



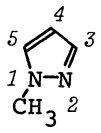
5a'

In the PMR spectra of those two isomers, none of the significant difference was observed except for the coupling patterns of the olefinic protons, i.e., H_3 proton of 5a appeared as a doublet of doublets (2.0 and 0.7 Hz) due to a coupling with H_4 and long-range coupling with a methine proton of substituent, though the other protons (H_4 of 5a and H_4 and H_5 of 2) appeared as a doublet. This seems to reflect that 1-(1',2',2'-trimethyl)propyl group of 5a is constrained to take a conformation by the steric replusion with t-butyl group at 5-position as depicted in 5a', which is favorable for a long-range coupling between H_3 and the mithine proton.[7] This assignment is consistent with that obtained by the C^{13}NMR studies (*vide infra*).

The C-13 magnetic resonance was found to be the effective and general method to discriminate the 1,3- and 1,5-positional isomers, since C_3 resonated at lower field by 10 ppm than C_5. The results obtained for 2, 5a, and 5b and the data of 1-methylpyrazole[8] were summarized in Table I. The assignment was confirmed by the partial decoupling and ^{13}C labeling experiments.[2]

By the examination of Table I, it becomes evident that the ring carbons substituted by t-butyl[9] and isopropyl group (C_3 of 2 and C_5 of 5a and 5b) appear at the lower field by ca. 20 ppm compared with the corresponding carbons of 1-methyl-

Table I. C^{13}NMR spectra of 2, 5a, 5b, and 1-methylpyrazole in $CDCl_3$ (TMS as an internal standard)

Compounds	C_3	C_4	C_5	t-Bu (tert. C, CH_3)		CH_3	N-C (tert)
2	159.8	100.3	127.7	31.9	28.2	17.5	63.0
				36.6	31.4		
5a	137.7	102.7	151.3	31.9	26.8	15.5	66.2
				35.6	30.7		
5b	137.5	100.3	149.5				
	139.2	105.7	128.7				

pyrazole,[8] while the other ring carbons of 2, 5a, and 5b appear at almost the same positions to those of the corresponding carbons of 1-methylpyrazole. On the bases of these observations, the structures of isomers 2 and 5 can be detemined unequivocally as the 1,3- and 1,5-disubstituted pyrazoles, respectively.

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