

Preparation of Pyrazoles Using Hydrazyl Radicals Initiated by DPPH

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Synopsis. Hydrazyl radicals, initiated by DPPH, reacted with α,β -unsaturated ketones without any good leaving group on their β -positions to yield pyrazoles regioselectively.

Recently, though free radicals have been actively used as intermediates in organic synthesis,¹⁾ only a little is known about the application of such a reaction to the synthesis of heteroaromatics. The physical properties of these hydrazyl radicals have been well studied;^{2,3)} nevertheless, these radicals have not been used in any successful organic synthesis. The hydrazyl radicals can be expected to be useful as synthetic intermediates for introducing a nitrogen-nitrogen chromophore in the synthesis of such heteroaromatics as pyrazoles, which are important and useful compounds in organic and drug synthesis.⁴⁾ The widely accepted methods for the synthesis of pyrazoles involve the reaction of hydrazines with bifunctional compounds, such as 1,3-diketones⁵⁾ or α,β -unsaturated ketones with good leaving groups on their β -positions.⁵⁾ Unsaturated ketones without any good leaving group on their β -positions have been scarcely used in the synthesis of pyrazoles. We report here on a novel, convenient method for the synthesis of pyrazoles using hydrazyl radicals, initiated by 2,2-diphenyl-1-picrylhydrazyl (DPPH), and simple α,β -unsaturated ketones without any good leaving groups on the β -positions.

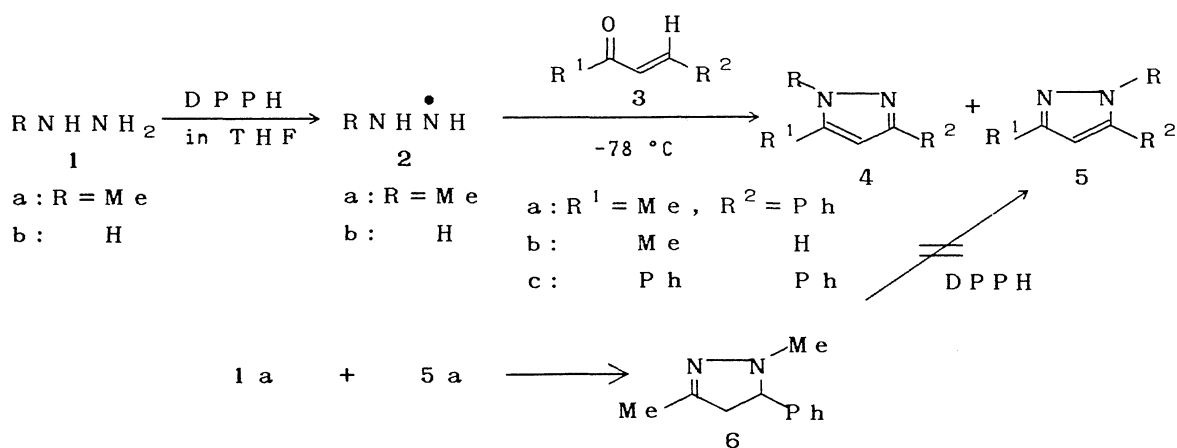
The reaction of methylhydrazine (**1a**) with 4-phenyl-3-buten-2-one (**3a**) in the presence of DPPH at -78°C proceeded regioselectively to give 1,5-dimethyl-3-phenyl-1*H*-pyrazole (**4a**) in 12% yield. Only a trace amount of an isomeric pyrazole, 1,3-dimethyl-5-phenyl-1*H*-pyrazole (**5a**), was detected. Similarly, the reaction of **1a** with 3-buten-2-one (**3b**) under the same conditions gave dimethylpyrazoles **4b** and **5b** in

50 and 7% yields, respectively. The reaction of **1a** with 1,3-diphenyl-2-propen-1-one (**3c**) under the same conditions also gave 1-methyl-3,5-diphenyl-1*H*-pyrazole (**4c**) in 30% yield. The structures of the pyrazoles, **4a–c** and **5a–b**, were determined by a comparison with authentic samples.^{6–8)}

In these pyrazole formations, the role of DPPH is quite important. No pyrazoles were produced when DPPH was absent. Methylhydrazine did not react with **5a** at -78°C . When a mixture of **1a** and **3a** was refluxed in benzene, 1,3-dimethyl-5-phenyl-2-pyrazoline (**6**) was obtained in 92% yield. The structure of the pyrazoline **6** was determined by a comparison with an authentic sample.⁹⁾ The pyrazoline **6** may be considered to be a precursor of the pyrazoles. However, this idea can be excluded for the following reasons: 1) The regioselectivity of pyrazoline formation is completely reversed to that in the pyrazole formation. The dehydrogenation of the pyrazoline **6** should give a minor isomer of the pyrazoles **5a**. 2) When **6** was stirred with DPPH, no pyrazoles were formed. Pyrazoline formation can be explained in terms of the 1,2-addition of the hydrazine **1a** to the α,β -unsaturated ketones **3** followed by cyclization and dehydration.

Table 1. Yields of the Reaction of **1** with **3** in the Presence of DPPH

	R	R ¹	R ²	Yield/%	
				4	5
a	Me	Me	Ph	12	Trace
b	Me	Me	H	50	7
c	Me	Ph	Ph	30	
d	H	Me	Ph	27	
e	H	Me	H	24	
f	H	Ph	Ph	23	



Scheme 1.

The behavior of **1a** in the pyrazole formation should be quite different from that in pyrazoline formation. When **1a** was added to a THF solution of DPPH, a purple color characteristic of the DPPH radical in THF changed to the brown characteristic of DPPH₂. This implies that DPPH abstracts hydrogen from **1a** to form DPPH₂ and the 2-methylhydrazyl radical. Both of the hydrogens on and N₁ and N₂ in 1-methylhydrazine (**1a**) may be abstractable by DPPH. However, sterically less hindered hydrogen on N₂ seems to be predominantly abstracted by the sterically hindered DPPH radical. The 2-methylhydrazyl radical (**2a**) is probably an intermediate in pyrazole formation. The quite different regioselectivity in pyrazole formation from that in a normal Michael addition¹⁰ can be reasonably explained in terms of the addition of radical **2a** to the β -position of enones.

Hydrazine itself (**1b**) could also be used as a radical precursor. The hydrazyl radical (**2b**) was easily prepared by the addition of DPPH to a THF solution of **1b** at -78°C . The reactions of **2b** with the enones **3a**, **3b**, and **3c** gave the corresponding pyrazoles **4d**, **4e**, and **4f** in 27, 24, and 23% yields, respectively. The structures of **4d**–**f** were determined by a comparison with authentic samples.¹⁾

The hydrazyl radicals, initiated easily and rapidly by DPPH, reacted with simple α,β -unsaturated ketones without any good leaving group on their β -positions. The hydrazyl radicals can be used as reagents for introducing a nitrogen-nitrogen chromophore in the synthesis of heteroaromatics.

Experimental

General Procedure for Preparation of Pyrazoles. To the solution of a hydrazine (0.75–1.5 mmol) dissolved in 30 cm³ of THF and cooled to -78°C , was added DPPH (0.75–1.5 mmol) with stirring. The mixture was cooled to -78°C and added dropwise to a solution of enones (0.5–1 mmol) in 50 cm³ of THF at -78°C . The mixture was stirred for 2 h at the same temperature. After concentration in vacuo, the residue was chromatographed on a silica-gel column (Merck Kieselgel 60). Elution with benzene or a mixture of ben-

zene-ethyl acetate gave **4** and/or **5**. The structures of **4a**–**f** and **5a**–**b** were determined by a comparison with direct comparisons with authentic samples.^{6,7,8,11)}

Preparation of 1,3-Dimethyl-5-phenyl-2-pyrazoline (6). A solution of benzalacetone (0.50 g, 3.4 mmol) and methylhydrazine (0.51 g, 4.7 mmol) in 50 cm³ of benzene was refluxed overnight. The mixture was poured into water and extracted three times with 30 cm³ of dichloromethane. The dichloromethane solution was washed with water and then dried over magnesium sulfate. After filtration and removal of the solvent, the residue was chromatographed on a silica-gel column (Merck Kieselgel 60). Elution with benzene gave **6** (0.54 g, 3.1 mmol, 92%): $131^\circ\text{C}/25\text{ mmHg}$ (lit.⁹⁾ $123\text{--}4^\circ\text{C}/20\text{ mmHg}$ (1 mmHg=133.322 Pa). The structure of **6** was determined by a comparison with an authentic sample.⁹⁾

References

- 1) B. Giese, "Radicals in Organic Synthesis; Formation of Carbon-Carbon Bonds," Pergamon Press, New York (1986).
- 2) E. Hayon and M. Simic, *J. Am. Chem. Soc.*, **94**, 42 (1972).
- 3) a) D. E. Wood, C. A. Wood, and W. A. Lathan, *J. Am. Chem. Soc.*, **94**, 9278 (1972); b) S. F. Nelsen and R. T. Landis, II, *ibid.*, **95**, 2719 (1973); *ibid.*, **95**, 6451 (1973); *ibid.*, **96**, 1788 (1974); c) R. A. Kaba, L. Lunazzi, D. Lindsay, and K. U. Ingold, *ibid.*, **97**, 6762 (1975).
- 4) J. Elguero, "Comprehensive Heterocyclic Chemistry," ed by A. R. Katritzky and C. W. Rees, Pergamon Press, New York (1984), Vol. 5, p. 167.
- 5) a) F. G. Badder, F. H. Al-Hajjar, and N. R. El-Rayyes, *J. Heterocycl. Chem.*, **13**, 257 (1976); b) H. Dorn, *Chem. Heterocycl. Compd.*, **16**, 1 (1980).
- 6) J.-L. Aubagnac, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, **1969**, 3306.
- 7) G. Coispeau and J. Elguero, *Bull. Soc. Chim. Fr.*, **1970**, 2717.
- 8) J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.*, **1966**, 2832.
- 9) J. L. Aubagnac, P. Bouchet, J. Elguero, R. Jacquier, and C. Marzin, *J. Chim. Phys. Phys.-Chim. Biol.*, **64**, 1649 (1967).
- 10) E. Benary and W. Kerckhoff, *Ber.*, **59**, 2548 (1926).
- 11) K. van Auwers and Th. Breyhan, *J. Prakt. Chem.*, **143**, 259 (1935).