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.

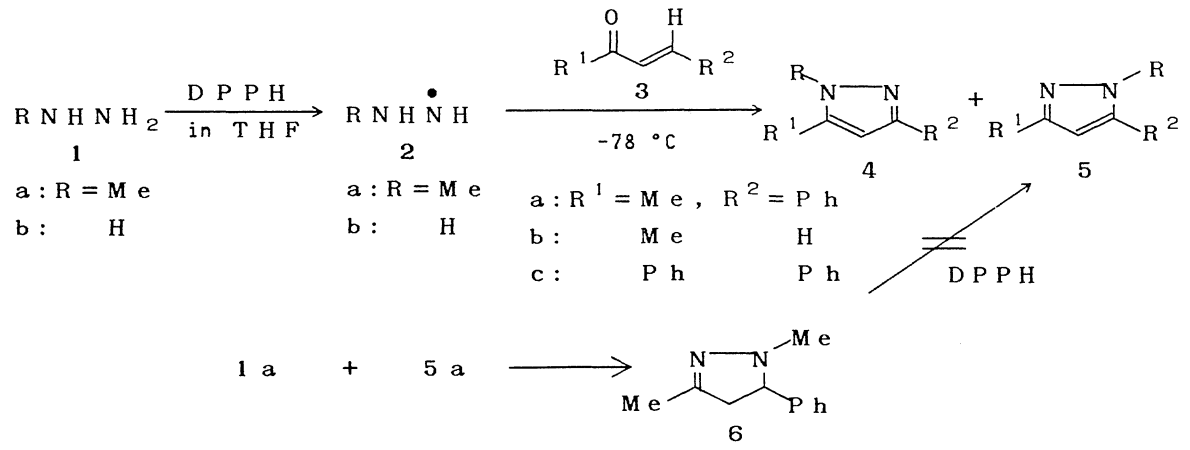
Recently, though free radicals have been actively used as intermediates in organic synthesis.[1] only a little is known about the application of such a reaction to the synthesis of heteroaromatics. The physical properties of these hydrazyl radicals have been well studied;[2,3] nevertheless, these radicals 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-diketones[5] 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 scarecely 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 resioselectively 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 resioselectivity 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 $DPPH_2$. This implies that DPPH abstracts hydrogen from **1a** to form $DPPH_2$ and the 2-methylhydrazyl radical. Both of the hydrogens on and N_1 and N_2 in 1-methylhydrazine (**1a**) may be abstractable by DPPH. However, sterically less hindered hydrogen on N_2 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 regioselectivlty in pyrazole formation from that in a normal Michael addition[10] 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 chromopher 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 cm^3 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 cm^3 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 benzene-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 cm^3 of benzene was refluxed overnight. The mixture was poured into water and extracted three times with 30 cm^3 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 °C/25 mmHg (lit,[9] 123—4 °C/20 mmHg) (1 mmHg=133.322 Pa). The structure of **6** was determined by a comparison with an authentic sample.[9]

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