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Reaction of 2-Nitroenamines and 2-Nitroalkenyl Sulfides with Ethyl Isocynoacetate: a Novel Synthesis of 1-Hydroxypyrazoles

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The reaction of 2-nitroalkenyl sulfides **2** and 2-nitroenamines **3** with ethyl isocynoacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gives ethyl 1-hydroxypyrazole-3-carboxylates **4** in moderate to good yields.

Pyrazoles have attracted much attention in agrochemical and pharmacological fields due to their bioactivity. Construction of the pyrazole ring is commonly accomplished by the condensation of the N(1)—N(2) and C(3)—C(4)—C(5) parts such as in the reaction of β -diketo compounds or α,β -unsaturated ketones with hydrazines.¹ Although combination of the N(1)—N(2)—C(3) and C(4)—C(5) units of the pyrazole ring is also established for this purpose by utilizing the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imides with alkynes,^{1,2} methods using the condensation of the N(2)—C(3)—C(4) and N(1)—C(5) units are very rare.² We now report the new preparation of 1-hydroxypyrazoles from 1-nitro-2-phenylsulfanyl alkenes and 2-nitroamines.

The nitro sulfide **2a** was reacted with ethyl isocynoacetate (1.1 equiv.) in THF by using DBU (1.1 equiv.) as a base. After 1 h the reaction was quenched with 2.5% aqueous HCl, extracted with EtOAc and concentrated to leave a brown solid. Chromatography of the mixture on silica gel (diethyl ether—CH₂Cl₂) gave *ca.* 1:1 mixture of **4a** and **5** in a very low yield probably due to irreversible adsorption of **4a** on the silica gel (Scheme). Benzylation of the reaction mixture with benzyl bromide and K₂CO₃ in dimethylformamide followed by chromatography (silica gel) afforded 1-benzyloxy pyraole **7a** in 47% yield. Structure determination was performed by comparison of the ¹³C NMR data with those calculated by using the values reported for hydroxypyrazole.⁵ Next, the nitroenamine **3a** was treated with ethyl isocynoacetate in the presence of DBU at room temperature. Trituration of the

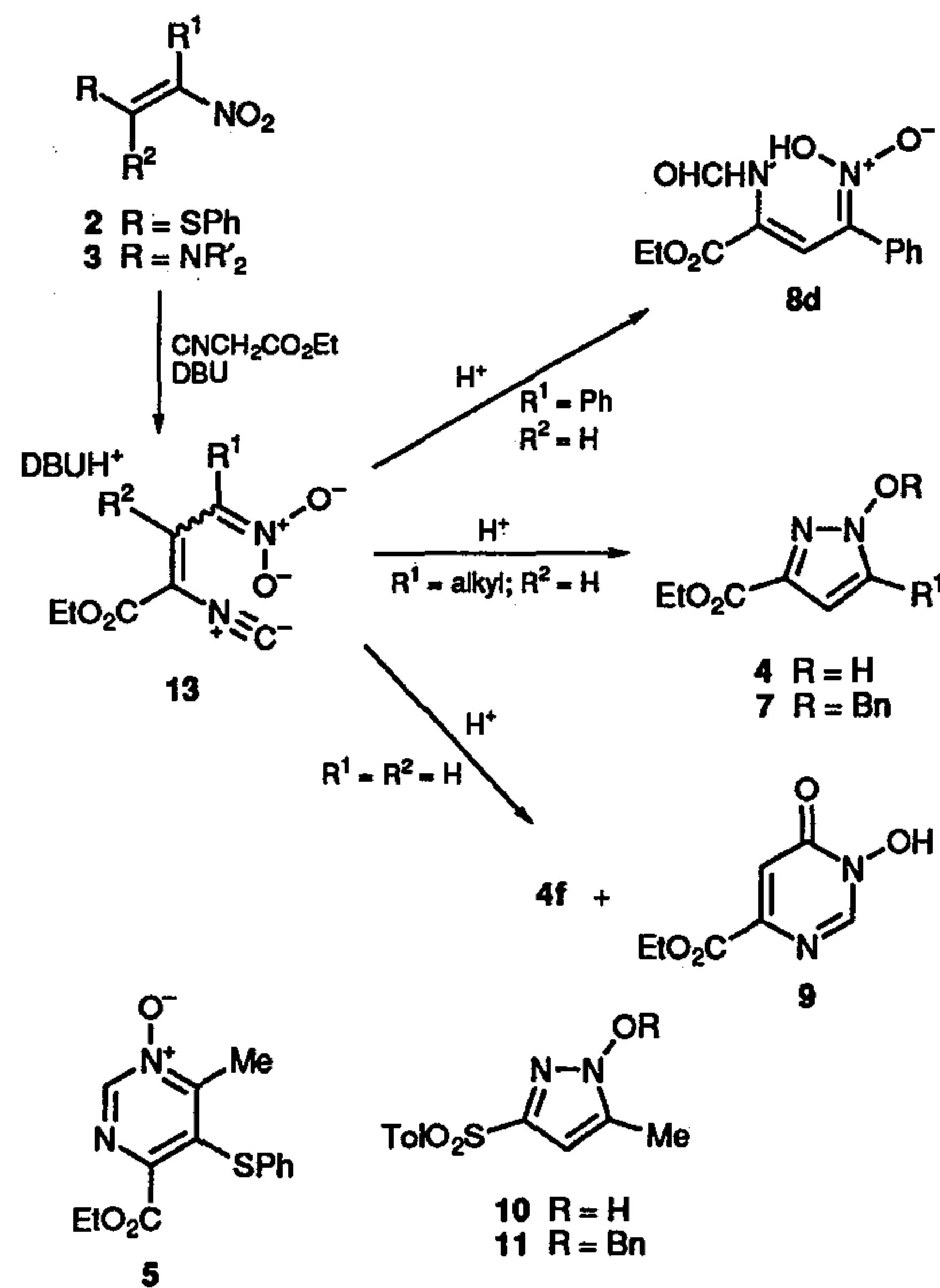


Table 2 Reaction of nitroolefins with ethyl isocynoacetate

Substrate				Yields (%)								
	R ¹	R ²	R	Quench ^a	Work-up ^b	4	5	7	8	9	11	13
2a	Me	H	PhS	A	C	Trace	Trace	—	—	—	—	—
2a	Me	H	PhS	B	C	—	—	47	—	—	—	—
2c	Et	H	PhS	B	C	—	—	47	—	—	—	—
3a	Me	H	Et ₂ N	A	T	79	—	—	—	—	—	—
3b	Et	H	Et ₂ N	A	T	55	—	—	—	—	—	—
3c	PhCH ₂	H	Et ₂ N	A	T	88	—	—	—	—	—	—
3d	Ph	H	Et ₂ N	A	R	—	—	—	15	—	—	—
3f	H	H	O(CH ₂ CH ₂)N	B	T+C ^c	—	—	28	—	24	—	—
3a^d	Me	H	Et ₂ N	B	C	—	—	—	—	—	4	—
3f	H	H	O(CH ₂ CH ₂)N	None	T	—	—	—	—	—	—	50

^aA: 2.5% HCl; B: 2.5% HCl, BnBr, K₂CO₃. ^bC: Chromatography on silica gel; T: Trituration with diethyl ether; R: Recrystallization from toluene. ^cThe reaction mixture was trituated with diethyl ether. The ether washings were benzylated and the resulting mixture was chromatographed on silica gel. ^dThe reaction was carried out using tosyl methyl isocyanide instead of ethyl isocynoacetate.

crude reaction mixture with diethyl ether—hexane gave **4a** as a pale-yellow powder in 79% yield. Other bases such as Et₃N, 4-dimethylaminopyridine and 1,4-diazabicyclo[2.2.2]octane were not effective for this reaction and the starting enamine

was not consumed at all. Various nitroalkenes, **2** and **3**, were treated under similar conditions and the results are listed in Table 2. The reaction of **3d** did not afford the expected pyrazole but instead the *aci*-nitro compound **8d**, while the reaction of **3f** gave the pyrimidine derivative **9** in addition to the expected hydroxypyrazole **4f**. The reaction of **3a** with

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p-tolylsulfonylmethyl isocyanide was carried out under similar conditions to give a complex mixture, benzylation of which afforded the benzyloxy pyrazole **11** in only 4% yield in addition to a large amount of benzyl *p*-tolylsulfone. In order to clarify the intermediates formed in the reaction, the reaction mixture was analysed without acidic quenching. The nitronate salt **13f** was obtained as an orange-yellow powder in 50% yield.

Techniques used: ¹H NMR, ¹³C NMR, CH COSY, COLOC, MS and high resolution MS

References: 8

Schemes: 3

Table 1: Yields of nitro compounds

Table 3: Analytical data for compounds **2-9** and **11**

Table 4: Spectroscopic data for nitroalkenyl sulfides **2**

Table 5: Spectroscopic data for 2-nitroenamines **3** and

1-hydroxypyrazoles **4**

Table 6: Spectroscopic data for compounds **5-9** and **11**

Table 7: Spectroscopic data for compound **13**

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