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

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The reaction of 2-nitroalkenyl sulfides **2** and 2-nitroenamines **3** with ethyl isocyanoacetate 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 isocyanoacetate (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–CH_2Cl_2) 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 K_2CO_3 in dimethylformamide followed by chromatography (silica gel) afforded 1-benzyloxypyraole **7a** in 47% yield. Structure determination was performed by comparison of the ^{13}C NMR data with those calculated by using the values reported for hydroxypyrazole.[5] Next, the nitroenamine **3a** was treated with ethyl isocyanoacetate in the presence of DBU at room temperature. Trituration of the crude reaction mixture with diethyl ether–hexane gave **4a** as a pale-yellow powder in 79% yield. Other bases such as Et_3N, 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

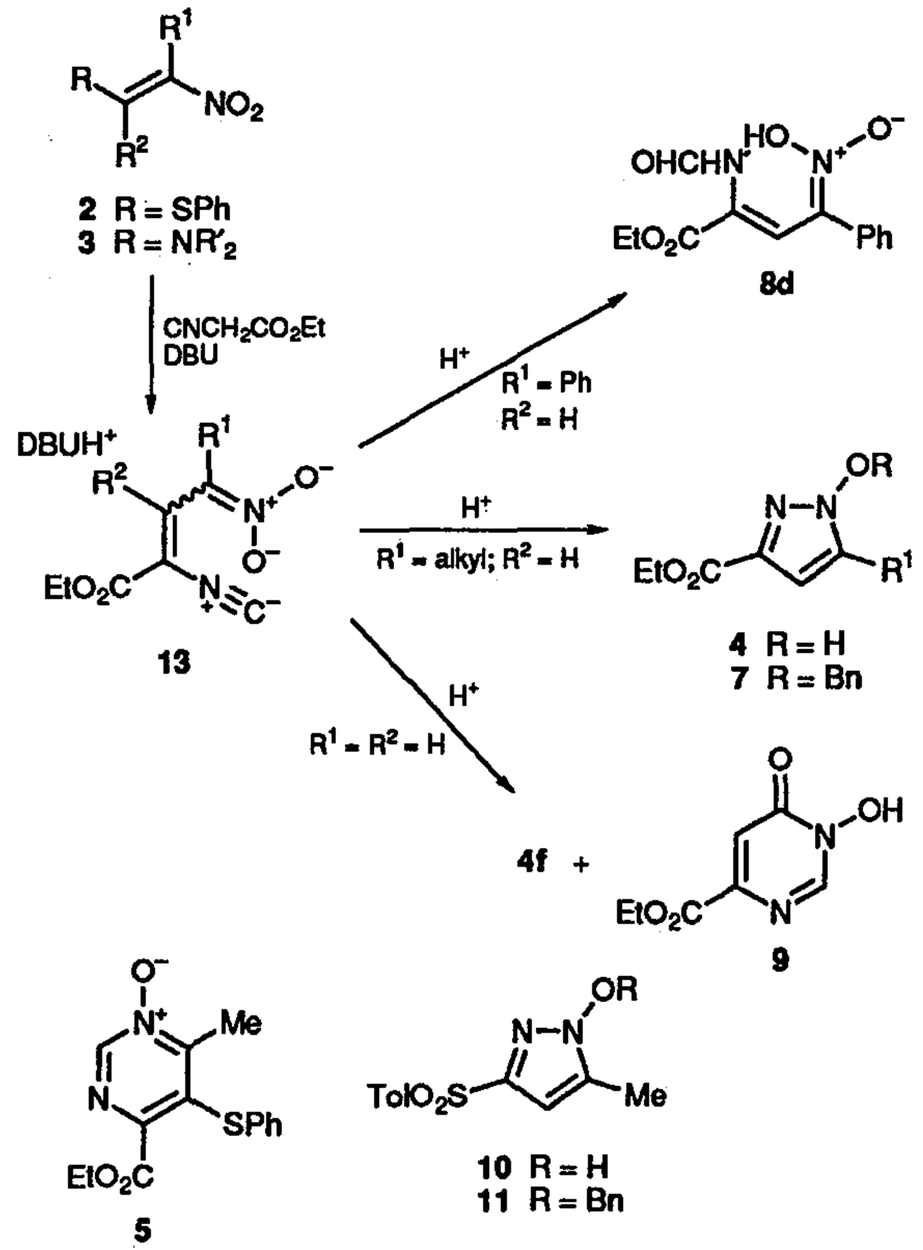

Table 2 Reaction of nitroolefins with ethyl isocyanoacetate

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_2N	A	T	79	—	—	—	—	—	—
3b	Et	H	Et_2N	A	T	55	—	—	—	—	—	—
3c	$PhCH_2$	H	Et_2N	A	T	88	—	—	—	—	—	—
3d	Ph	H	Et_2N	A	R	—	—	—	15	—	—	—
3f	H	H	$O(CH_2CH_2)N$	B	T+C[c]	—	—	28	—	24	—	—
3a[d]	Me	H	Et_2N	B	C	—	—	—	—	—	4	—
3f	H	H	$O(CH_2CH_2)N$	None	T	—	—	—	—	—	—	50

[a]A: 2.5% HCl; B: 2.5% HCl, BnBr, K_2CO_3. [b]C: Chromatography on silica gel; T: Trituration with diethyl ether; R: Recrystallization from toluene. [c]The reaction mixture was triturated with diethyl ether. The ether washings were benzylated and the resulting mixture was chromatographed on silica gel. [d]The reaction was carried out using tosyl methyl isocyanide instead of ethyl isocyanoacetate.

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p-tolylsulfonylmethyl isocyanide was carried out under similar conditions to give a complex mixture, benzylation of which afforded the benzyloxypyrazole **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: ^{1}H NMR, ^{13}C 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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