

SUBSTITUENT INFLUENCED ALKYLATION OF 3-SUBSTITUTED 5-HYDROXYPYRAZOLES : CLAISEN REARRANGEMENT OF 5-ALLYLOXYPYRAZOLES ¹

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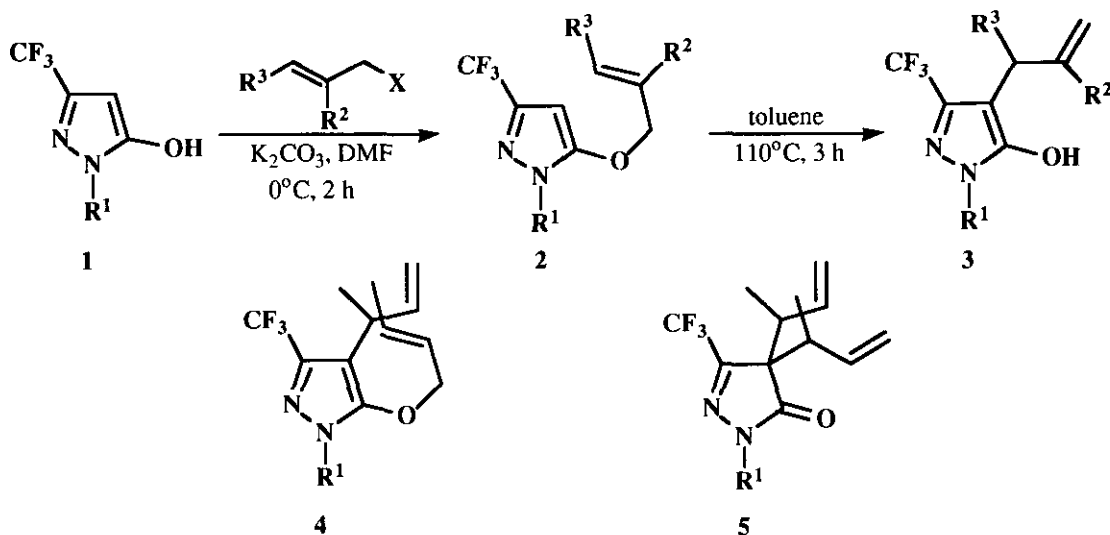
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Abstract - Conspicuous substituent effects of 3-substituted 5-hydroxypyrazoles in the process of alkylation and subsequent [3,3]-sigmatropic rearrangement of the resulting alkylated products are described.

Synthesis of highly functionalized pyrazoles has attracted many synthetic chemists not only due to the richness of pyrazole chemistry² but also the interesting biological activities exhibited by pyrazole containing compounds.³ Within the scope of our research toward functionalization of 5-hydroxypyrazoles, we considered 4-allyl-5-hydroxypyrazoles (3) as important intermediates for bicyclic pyrazolodihydrofurans in view of the close relationship to existing biologically active benzodihydrofurans.⁴

During the course of preparing 4-allyl-5-hydroxypyrazoles (3) by introducing the allylic moiety into C-4 position of 5-hydroxypyrazoles through [3,3]-sigmatropic rearrangement, we observed a dramatic substituent effect between CF₃ vs CH₃ at C-3 position of 5-hydroxypyrazoles. Thus, treatment of CF₃-substituted pyrazole (1a) with crotyl chloride in the presence of potassium carbonate at 0°C for 2 h afforded O-alkylated product (2a) along with trace amount (5%) of double Claisen reaction product (5). When the reaction mixture was further heated by refluxing in toluene for 3 h, the 5-crotyloxypyrazole (2a) was rearranged via [3,3]-sigmatropic mode to give 4-allyl-5-hydroxypyrazole (3a) in 73% overall yield from 1a (Scheme I). In order to clarify the origin of the double rearranged product (5), pyrazole (3a) was treated with crotyl chloride in DMF at 0°C for 2 h (the same conditions as the initial alkylation step) to give 5 without observing the expected precursor (4). From this result we believe that 5-crotyloxypyrazole (4) underwent [3,3]-sigmatropic rearrangement

much faster than **2a** mainly due to the steric interaction between vicinal substituents of pyrazole (**4**) so that **4** could not be detectable under the reaction conditions. Additional experiments with different substituents at *N*-1 position were carried out to afford 4-allyl-substituted 5-hydroxypyrazoles (**3a**) in good yield and the results are summarized in Table 1.



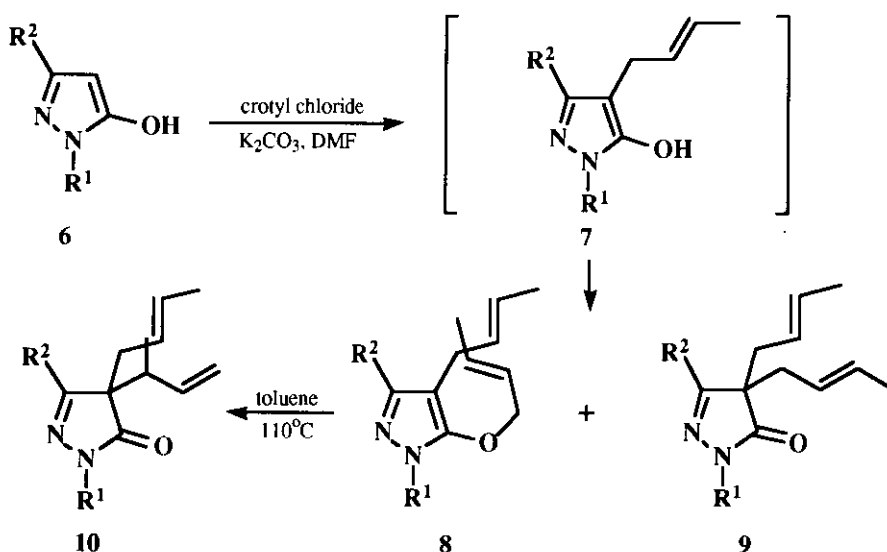
Scheme I

Table 1. Preparation of 4-allyl substituted 5-hydroxypyrazole (**3**)

Entry	Product	R ¹	R ²	R ³	X	Yield, % ^a
1	3a	CH ₃	H	CH ₃	Cl	73
2	3b	CH ₃	H	Ph	Br	70
3	3c	Ph	H	CH ₃	Cl	69
4	3d	Ph	H	Ph	Br	65
5	3e	CH ₃	CH ₃	H	Cl	72
6	3f	CH ₃	Br	H	Cl	71
7	3g	i-Pr	H	CH ₃	Cl	78
8	3h	Et	H	Ph	Br	53

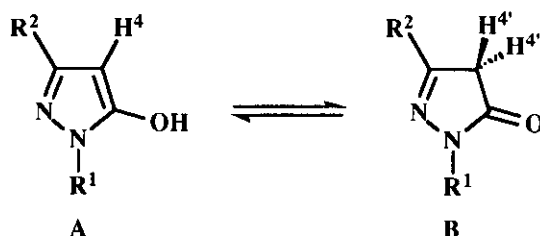
^a overall yield from **1**

On the other hand, the reaction proceeded in quite different manner when C-3 position of the 5-hydroxypyrazole (6) was substituted with alkyl instead of trifluoromethyl group. Reaction of 6a ($R^1=R^2=Me$) with crotyl chloride under the similar conditions for the preparation of 3 from 1 gave mixture of double C-alkylated product (9a) in 26% yield together with 10a in 13% yield. Analogously, the reaction of 6b ($R^1=Ph$, $R^2=t-Bu$) followed similar pattern as 6a to afford dialkylated compound (10b) in 12% yield along with trace amount of 10b.



Scheme II

To explain this remarkable difference in the reactivity between CF_3 vs CH_3 containing 5-hydroxypyrazoles, we turned our attention to tautomeric structures of the 5-hydroxypyrazoles. Reactivity and reaction mechanism in some heterocycles can be rationalized if tautomeric structures of the compounds are known and there are energy differences between those tautomers.^{5,6} These kind of tautomers between 5-hydroxypyrazole and 5-pyrazolone have been reported to exist in solution and even in crystals.⁷ In the 1H nmr spectrum of 5-hydroxypyrazole (1) containing CF_3 group, the appearance of C(4)-H at 5.9 ppm as a singlet clearly indicated 5-hydroxypyrazole form A (Table 2). In contrast, compounds (6) with alkyl substituent at C-3 position are believed to exist as pyrazolone form B as a sole or major component of tautomers judged from their chemical shifts of 1H nmr spectra as shown in Table 2. Judging from those 1H nmr analysis we reasoned that the reaction of 1 proceeded through O-alkylation exclusively due to the predominant 5-hydroxypyrazole form, whereas 6 resulted in mainly C-alkylated product due to the stability of 5-pyrazolone form.

Table 2. ^1H Nmr analysis of 5-hydroxypyrazole (5-pyrazolone) in CDCl_3 

Entry	R ¹	R ²	δH^4	$\delta \text{H}^{4'}$	Ratio of A : B
1	CH ₃	CF ₃	5.9	-	A only
2	Ph	CF ₃	6.2	-	A only
3	CH ₃	CH ₃	5.9	3.9	4 : 6
4	Ph	t-Bu	-	3.4	B only

It is further noteworthy that **3** and **5** showed quite strong fungicidal activities towards *Puccinia recondita*, *Erysiphe graminis*, and *Pyricularia oryzae*. In summary, we were able to prepare *N*(1)-substituted 4-allyl-5-hydroxy-3-trifluoromethylpyrazoles (**3**) from CF_3 -containing 5-hydroxypyrazoles (**1**) via [3,3]-sigmatropic rearrangement although alkyl-analogues underwent quite different reaction pathways with undesired results.

EXPERIMENTALS

General. Melting points are uncorrected. ^1H Nmr spectra were taken on a Jeol at 60 MHz and a Varian Gemini-200 at 200 MHz using TMS as an internal standard. The chemical shifts are being given in δ ppm down field. Ir spectra were recorded on a Shimadzu IR-534 spectrophotometer. Mass spectra were measured with a Shimadzu QP-1000 spectrometer. Merck Kieselgel 60 (230-400 mesh) was used for flash column chromatography.

5-Hydroxy-1-methyl-4-(1-methyl-2-propenyl)-3-trifluoromethylpyrazole (3a). General Procedure: To a mixture of 5-hydroxy-1-methyl-3-trifluoromethylpyrazole (**1a**) (2.4 g, 14.45 mmol) and anhydrous potassium carbonate (3.0 g, 21.7 mmol) in DMF (20 ml) was added dropwise crotyl chloride (1.5 ml, 1.62 g, 15.5 mmol) at 0°C . The resulting reaction mixture was allowed to proceed for 2 h at 0°C . The reaction mixture was poured into ice water and extracted with ether (3X). The combined organic layers were washed with water (2X), and

brine (1X), dried over anhydrous MgSO_4 and then concentrated in vacuo to afford crude mixture of **2a** and **5a** (2.91 g, 13.2 mmol) as a colorless liquid; ^1H nmr (CDCl_3) δ 1.82 (d, $J=5.2$ Hz, 3H), 3.69 (s, 3H), 4.62 (d, $J=5.2$ Hz, 2H), 5.62-5.95 (m, 2H), 5.70 (s, 1H). The crude product was dissolved in toluene (20 ml), and refluxed for 3 h. After concentration in vacuo, the residue was purified by column chromatography on silica gel (hexane : EtOAc = 9:1) to give the pyrazole (**3a**) (2.32 g, 73%) as a yellow solid and **5a** (0.11 g, 3%) as a colorless liquid: **3a**: mp 72°C ; ir (KBr) 3340, 2946, 1555, 1486, 1426, 1154, cm^{-1} ; ^1H nmr (CDCl_3) δ 1.30 (d, $J=6.5$ Hz, 3H), 3.55 (m, 1H), 3.65 (s, 3H), 5.01-5.41 (m, 2H), 5.90-6.45 (m, 1H), 7.35 (br. s, 1H); mass spectrum (EI) m/z 220 (M^+ , 100), 205 (91), 179 (45), 151 (5.1). **5a**: Ir (neat) 2997, 2913, 1698, 1590, 1515, 1233, 1107 cm^{-1} ; ^1H nmr (CDCl_3) δ 0.94 (d, $J=6.8$ Hz, 3H X 1/2, *dl*), 1.04 (d, $J=6.8$ Hz, 3H X 1/2, *dl*), 1.63 (d, $J=6.4$ Hz, 6H X 1/2, *meso*), 2.35-2.77 (m, 2H), 3.35 (s, 3H), 4.83-5.24 (m, 4H), 5.45-6.11 (m, 2H); mass spectrum (EI) m/z 274 (M^+ , 17), 247 (34), 205 (100).

5-Hydroxy-1-methyl-4-(1-phenyl-2-propenyl)-3-trifluoromethylpyrazole (3b). 70% yield: mp 90°C ; ir (film) 3335, 3009, 2920, 1552, 1485, 1420, 1159, 1126, 1060, 1034, 914 cm^{-1} ; ^1H nmr (CDCl_3) δ 3.60 (s, 3H), 4.85-5.45 (m, 3H), 6.01-6.65 (m, 1H), 7.33 (m, 5H); mass spectrum (EI) m/z 282 (M^+ , 100), 267 (15), 205 (6), 117 (24).

5-Hydroxy-1-phenyl-4-(1-methyl-2-propenyl)-3-trifluoromethylpyrazole (3c). 69% yield: mp 73°C ; ir (KBr) 3338, 3003, 2945, 1596, 1495, 1469, 1142, 1114, 1069, 1001, 914 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.33 (d, $J=6.7$ Hz, 3H), 3.60 (m, 1H), 5.20-5.51 (m, 2H), 6.01-6.52 (m, 1H), 7.49 (m, 5H); mass spectrum (EI) m/z 282 (M^+ , 100), 267 (13), 227 (32), 213 (9).

5-Hydroxy-1-phenyl-4-(1-phenyl-2-propenyl)-3-trifluoromethylpyrazole (3d). 65% yield: mp 85°C ; ir (KBr) 3340, 3008, 2987, 1587, 1463, 1140, 1104, 915 cm^{-1} ; ^1H nmr (CDCl_3) δ 4.90-5.55 (m, 3H), 6.10-6.61 (m, 1H), 7.35-7.70 (m, 10H); mass spectrum (EI) m/z 344 (M^+ , 100), 267 (6), 240 (9), 117 (88).

5-Hydroxy-1-methyl-4-(2-methyl-2-propenyl)-3-trifluoromethylpyrazole (3e). 72% yield: mp $144-145^\circ\text{C}$; ir (KBr) 3340, 2940, 1558, 1425, 1391, 1165, 1122, 1064, 942, 895 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.80 (s, 3H), 3.21 (s, 3H), 3.82 (s, 3H), 4.60-4.81 (m, 2H), 10.01 (br s, 1H); mass spectrum (EI) m/z 220 (M^+ , 71), 205 (50), 179 (100), 159 (31).

5-Hydroxy-1-methyl-4-(2-bromo-2-propenyl)-3-trifluoromethylpyrazole (3f). 71% yield: mp $164-165^\circ\text{C}$; ir (KBr) 3330, 2897, 1563, 1426, 1394, 1291, 1154, 1125, 1067, 891 cm^{-1} ; ^1H nmr (CDCl_3) δ 3.61-3.70 (m, 2H), 3.74 (s, 3H), 5.50-5.61 (m, 2H), 10.50 (br s, 1H); mass spectrum (EI) m/z 287 (M^++2 , 49), 286 (M^++1 , 34), 285 (M^+ , 49), 205 (100), 177 (24), 157 (26).

5-Hydroxy-1-isopropyl-4-(1-methyl-2-propenyl)-3-trifluoromethylpyrazole (3g). 78% yield: mp $82-83^\circ\text{C}$; ir (film) 3390, 2983, 1571, 1455, 1309, 1240, 1151, 1038 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.32 (d, $J=7.0$ Hz, 3H), 1.44 (d, $J=7.0$ Hz, 6H), 3.72 (m, 1H), 4.55 (m, 1H), 5.31-5.52 (m, 2H), 5.97-6.51 (m, 1H); mass spectrum (EI) m/z 248 (M^+ , 36), 233 (30), 209 (9), 205 (6).

5-Hydroxy-1-ethyl-4-(1-phenyl-2-propenyl)-3-trifluoromethylpyrazole (3h). 53% yield: mp 104°C ; ir (KBr) 3330, 3009, 2955, 1555, 1438, 1306, 1155, 1124, 1044, 991, 919 cm^{-1} ; ^1H nmr

(CDCl₃) δ 1.33 (t, $J=7.0$ Hz, 3H), 4.02 (q, $J=7.0$ Hz, 2H), 4.84-5.57 (m, 3H), 6.11-6.62 (m, 1H), 7.32 (m, 5H); mass spectrum (EI) m/z 296 (M^+ , 42), 217 (17), 164 (9), 91 (100).

1,3-Dimethyl-4-bis-(2-butenyl)-5-pyrazolone (9a) and 1,3-dimethyl-4-(2-butenyl)-4'-1-methyl-2-propenyl-5-pyrazolone (10a). To a mixture of 1,3-dimethyl-5-pyrazolone (6a) (1 g, 8.92 mmol) and anhydrous potassium carbonate (1.85 g, 13.4 mmol) in DMF (5 ml) was added dropwise crotyl chloride (0.81 g, 8.92 mmol) at 0°C. The resulting reaction mixture was allowed to proceed for 2 h at 0°C. The reaction mixture was poured into ice water and extracted with ether (3X). The combined organic layers were washed with water (2X), and brine (1X), dried over anhydrous MgSO₄, and then concentrated in vacuo to afford a crude product. The crude products were dissolved in toluene (10 ml), and refluxed for 3 h. After concentration in vacuo, the residue was purified by column chromatography on silica gel (hexane : EtOAc = 9:1) to give the pyrazole (9a) (0.51 g, 26%) and (10a) (0.26 g, 13%) as colorless liquids. **9a:** Ir (neat) 2991, 2837, 1696, 1597, 1417, 1369, 1226, 1034, 962 cm⁻¹; ¹H nmr (CDCl₃) δ 1.65 (d, $J=6.5$ Hz, 6H), 2.11 (s, 3H), 2.20-2.50 (m, 4H), 3.31 (s, 3H), 5.10-6.00 (m, 4H); ¹³C nmr (CDCl₃) δ 14.76, 18.25, 31.17, 37.80, 58.22, 123.98, 130.11, 162.05, 176.71; mass spectrum (EI) m/z 220 (M^+ , 26), 164 (55), 125 (100). **10a:** Ir (neat) 2994, 2912, 1695, 1590, 1482, 1305, 1249, 1211, 1116, 961 cm⁻¹; ¹H nmr (CDCl₃) δ 1.04 (d, $J=7.0$ Hz, 3H), 1.57 (d, $J=6.5$ Hz, 3H), 2.01 (s, 3H), 2.31-2.72 (m, 3H), 3.32 (s, 3H), 5.02-6.06 (m, 5H); mass spectrum (EI) m/z 220 (M^+ , 18), 205 (24), 164 (47), 125 (100).

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