SUBSTITUENT INFLUENCED ALKYLATION OF 3-SUBSTITUTED 5-HYDROXYPYRAZOLES : CLAISEN REARRANGEMENT OF 5-ALLYOXYPYRAZOLES [1]

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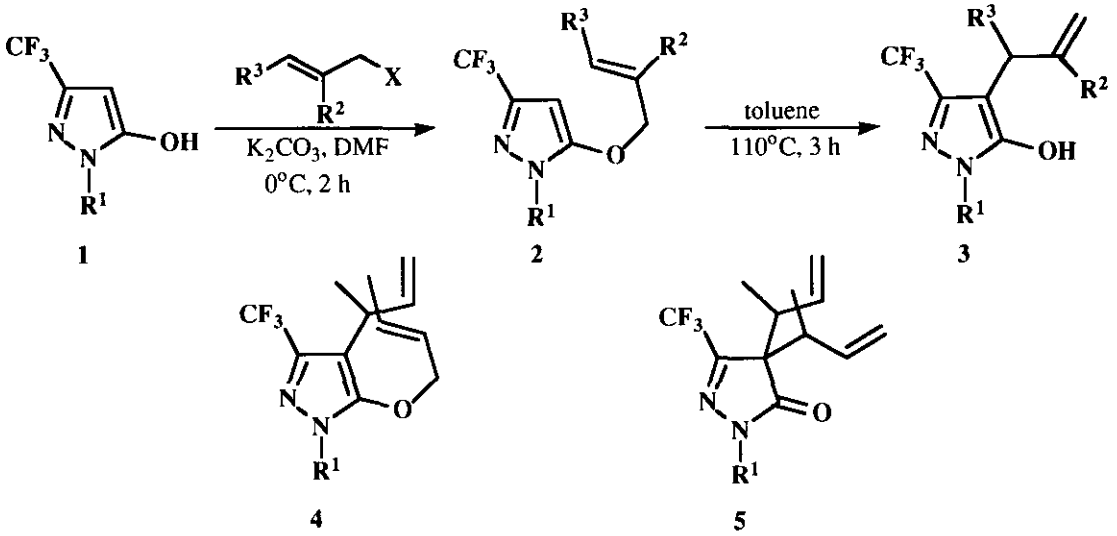
Abstract - Conspicuous substituent effects of 3-substituted 5-hydroxypyrazoles in the process of alkylation and subsequent [3,3]-sigmatropic rearrangement of the resulting alkylated products are described.

Synthesis of highly functionalized pyrazoles has attracted many synthetic chemists not only due to the richness of pyrazole chemistry[2] 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 CF_3 *vs* CH_3 at C-3 position of 5-hydroxypyrazoles. Thus, treatment of CF_3-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 precusor (**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.



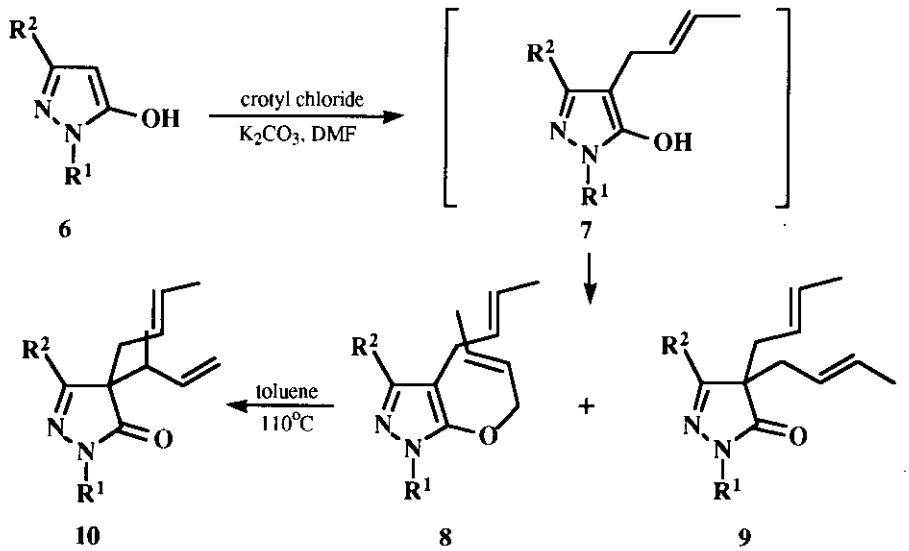
Scheme I

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**.

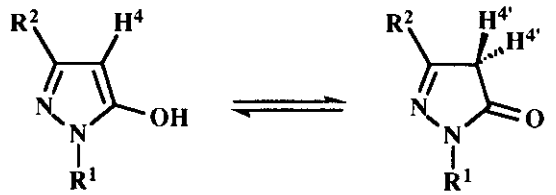


6 7 10 8 9

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 ^{1}H 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 ^{1}H nmr spectra as shown in Table 2. Judging from those ^{1}H 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. ^{1}H Nmr analysis of 5-hydroxypyrazole (5-pyrazolone) in $CDCl_3$



A B

Entry	R^1	R^2	δ H^4	δ $H^{4'}$	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. ^{1}H 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; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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°C; ir (KBr) 3340, 2940, 1558, 1425, 1391, 1165, 1122, 1064, 942, 895 cm^{-1}; ^{1}H 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°C; ir (KBr) 3330, 2897, 1563, 1426, 1394, 1291, 1154, 1125, 1067, 891 cm^{-1}; ^{1}H 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°C; ir (film) 3390, 2983, 1571, 1455, 1309, 1240, 1151, 1038 cm^{-1}; ^{1}H 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}; ^{1}H nmr

($CDCl_3$) 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 $MgSO_4$, 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 ($CDCl_3$) 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); ^{13}C nmr ($CDCl_3$) 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 ($CDCl_3$) 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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Received, 6th January, 1993