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A New Approach to Ethyl 1-Aroyl/Aroylmethyl-5-methyl-3-methylthiopyrazole-4-carboxylates: High Regioselectivity in Alkylation and Acylation Reactions between N-1 and N-2 of a Pyrazole Derivative

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Abstract: Two series, totalizing twelve, of new compounds, ethyl 1-aroyl/aroylmethyl-5-methyl-3-methylthiopyrazole-4-carboxylates **5**/**6**, have been synthesized *via* highly regioselective acylation and alkylation of ethyl 3-methyl-5-methylthio-1*H*- pyrazole-4-carboxylate **2a** with aroyl chloride **3** and alpha-tosyloxysubstitutedacetophenones **4**. Unexpected structures of the product have been unambiguously determined by both X-ray crystallographic analysis and 2D NMR.

Keywords: Pyrazole, regioselectivity, X-ray crystallographic analysis, 2D NMR.

It has been known that pyrazole ring has two main tautomeric isomers[1-3] as showed in **Scheme 1**. The proton could migrate at the two nitrogen atoms of the pyrazole ring. Taylor E. C. and Purdum W. R.[4] first reported the synthesis of **2** as an isomer of **2a**. And so far, only a few literatures[5-6] have reported that this pyrazole derivative was in form **2a**, rather than **2**, therefore both acylation or alkylation reaction occurred at N-1 of **2a**. But the regiochemistry of the N-substituted product of pyrazole has not been unambiguously proved because the spectral analytical data are unable to distinguish the alkylation or acylation position properly. To determine the structure of **2a** by 2D NMR spectroscopy also was unsuccessful. 2D NMR spectrum of **2a** exhibited a broad singlet at δ 11.60, for the proton of NH group. The broad singlet was caused by rapid migration of the proton of NH. **2a** existed as a mixture of two tautomeric isomers in deuteriochloroform.

Various substituents have been attached to pyrazole ring at 3-, 4-, or 5-position, however substitution at N-1 position mainly focused on alkyl and (substituted)phenyl groups. Zhao W. G.[5] and coworkers consequently reported the formylation at N-1 of **2a**. For searching lead compounds with good bioactivities, we have synthesized a series of

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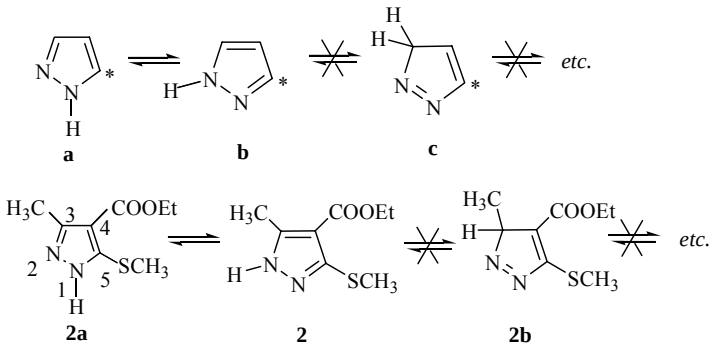
compounds by aloylation of pyrazole, which did not exhibit satisfactory fungicidal activities. The X-ray crystallographic analysis (**Figure 1** for **5c**) showed that the aroylation occurred at N-1 position of the form **2** rather than at N-1 in the form **2a**. No matter the R was electron-withdrawing group (such as R^3= *o*-NO_2-*p*-CF_3 for **5c**, **Table 1**) or electron-donating one (such as R^5= *p*-CH_3O for **5e**, **Table 1**). Subsequently we investigated the alkylation reaction of **2** with the alkylating reagents **4** or α-bromo-sustituted acetophenones **4'**. To our surprise, the alkylation also occurred at the N-1 in the form **2**, rather than at the N-1 in the form **2a**. The structure was unambiguously determined by X-ray crystallographic analysis (**Figure 2** for **6b**). The reason was proposed as follows: the repulsion effect between the negatively charge of nitrogen and

Scheme 1 Tautomerism occurring in the cases of pyrazole and **2a**



Scheme 2 The proposed mechanism for regioselective synthesis

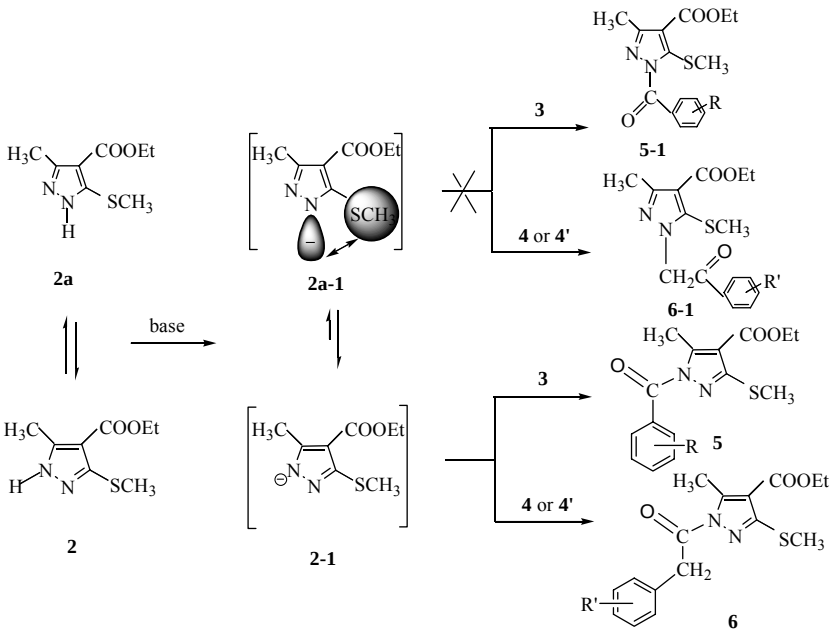


Table 1 The synthesized compounds

R	Compound	mp(ºC)	R	Compound	mp(ºC)
R^1= *p*-Cl	**5a**	101.5-102.5	R^7= *p*-C_2H_5O	**5g**	147-148
R^2= *p*-CF_3	**5b**	96.5-97	R^1= *p*-F	**6a**	157-158
R^3= *o*-NO_2-*p*-CF_3	**5c**	147.5-148.5	R^2= *p*-CH_3	**6b**	136-137
R^4-Ph= 2-Furyl	**5d**	130-131	R^3= 2,5-dichloro	**6c**	130-132
R^5= *p*-CH_3O	**5e**	123-124	R^4= H	**6d**	138-139
R^6= *m*-CH_3	**5f**	115-116	R^5= *p*-Cl	**6e**	145-146

Figure 1 The X-ray crystallographic structure of **5c**

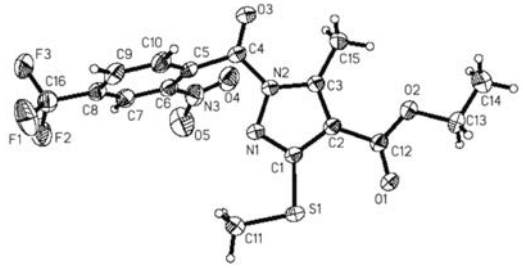
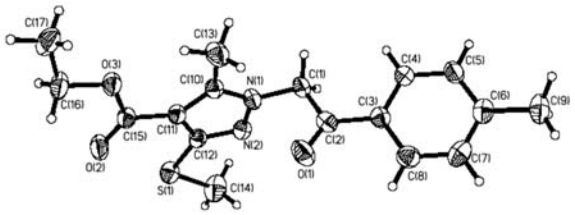


Figure 2 The X-ray crystallographic structure of **6b**



the negatively charged bulky methylthio group was strong in the form **2a-1**, while repulsion effect of the negative charge of nitrogen to methyl group was weak (**Scheme 2**). Consequently, the N atom near the methyl group was more nucleophilic than that near the methylthio group.

Experimental

The melting points were determined with a RY-1 apparatus in capillaries and the thermometer was uncorrected.All NMR spectra were recorded on a JEOL JNM-ECP 600M spectrometer, with TMS as internal standard and DMSO-d_6 as solvent. IR spectra were obtained on a Nicolet 501P FT-IR spectrophotometer. Elemental analysis was performed using a Elemento EL III analyzer. X-ray crystallographic analysis was performed on a Bruker SMART 1000 CCD diffractometer under conventional conditions.

The general procedure for preparation of **5**: *p*-Chlorobenzoic acid (0.783 g, 5 mmol) was dissolved in 10 mL of $SOCl_2$. The resulting solution was refluxed for 4 hours, and the excess $SOCl_2$ was evaporated *in vacuo* to afford crude **3a**.To **3a** were added 10 mL of $CHCl_3$, **2** (1.000 g, 5 mmol) and NaOH (0.200 g, 5 mmol), and the suspension was stirred at room temperature until the starting materials were completely consumed. After the removal of solid by filtration, the solvent was evaporated *in vacuo*, the residue was purified by recrystallization from absolute ethanol.**5a**, yield 89%. White needle, mp. 101.5-102.5ºC. ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm) 1.31 (t, 3H, J = 7.5 Hz), 4.27 (q, 2H, J = 7.5 Hz), 2.34 (s, 3H), 2.85 (s, 3H), 7.62, 7.95 (dd, 4H, J = 8.1, 8.1 Hz,). IR (KBr, cm^{-1}) 1723, 1689. Anal. Calcd. for $C_{15}H_{15}ClN_2O_3S$: C 53.25, H 4.47, N 8.28, S 9.46; Found: C 53.19, H 4.49, N 8.23, S 9.49. FAB-MS: 339.8 (M+1).

The general procedure for preparation of **6**: Into a 25 mL flask containing 15 mL of acetonitrile were introduced **2** (1.000 g, 5 mmol), **4** or **4'** (5 mmol) and potassium carbonate (1 g), and refluxed until the reaction completed. The resulting solution was filtered to remove the solid, and the solvent was evaporated *in vacuo*. The residue was purified by recrstallization from absolute ethanol. **6a**, yield 87%. White needle, mp157-158ºC. ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm) 1.29 (t, 3H, J = 7.1 Hz), 4.21 (q, 2H, J = 7.1 Hz), 2.37 (s, 3H), 2.37 (s, 3H), 5.92 (s, 2H), 7.45, 8.17 (t+q, 2H+2H, $^3J_{H\text{-}H}$= $^3J_{H\text{-}F}$ = 8.7 Hz, $^4J_{H\text{-}F}$ = 5.7 Hz). IR (KBr, cm^{-1}) 3066, 1702, 1688, 1507, 1544, 1596, 1495, 1270, 1230. Anal. Calcd. for $C_{16}H_{17}FN_2O_3S$: C 57.13%, H 5.10, N 8.33, S 9.51; Found: C 57.36, H 5.11, N 8.37, S 9.47. FAB-MS: 337.4 (M+1).

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