An Unexpected and Green Synthetic Protocol for 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 Ring

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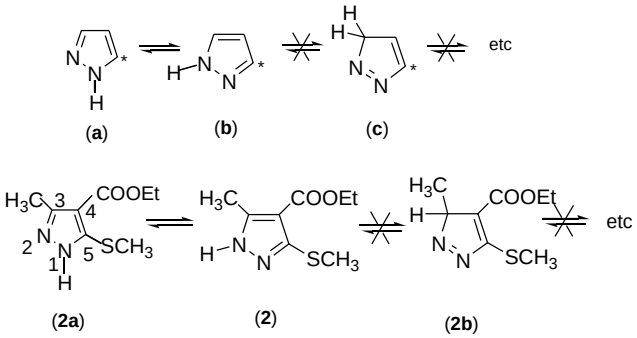
Two series, totaling twelve, of new compounds, ethyl 1-aroyl/(aroylmethyl)-5-methyl-3-methylthiopyrazole-4-carboxylates (**5**/**6**), have been synthesized via highly regioselectively acylation and alkylation reactions of ethyl 3-methyl-5-methylthio-1*H*-pyrazole-4-carboxylate (**2a**) with aroyl chloride (**3**) and eco-friendly reagents alpha-tosyloxysubstituted acetophenones (**4**), respectively, and a green protocol has been developed. The acylation reactions were carried out under ultrasound irradiation, and the alkylation reactions were under microwave irradiation and ultrasound irradiation, respectively. Conventional reaction conditions, as well as the use of alpha-bromosubstituted acetophenone (**4′**) have also been applied in the synthesis of some randomly selected compounds in both series and have generated identical compounds correspondingly. Unexpected structures of compounds were unambiguously determined by X-ray crystallographic analysis.

Keywords: Pyrazole; Regioselectivity; X-ray crystallographic analysis; 2D NMR.

INTRODUCTION

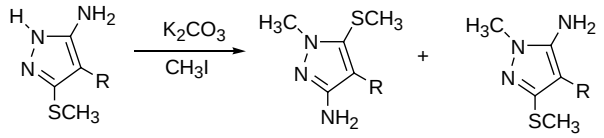
It is known that a pyrazole ring has two main tautomeric isomers[1-3] (as shown in Scheme I; one carbon atom has been labeled by an asterisk in order to make the tautomerism easier to understand) due to the migration of the proton at the unsubstituted N-position between the two nitrogen atoms of the pyrazole ring. Both (**a**) and (**b**) are the main isomers; however, (**c**), and the others are not, since they are highly unstable due to the absence of a conjugate system which exists in both (**a**) and (**b**). It still holds true in the case of the intermediate **2a** as also shown in Scheme I. Consequently, the acylation or alkylation of the N-position of intermediate **2a** has the possibility to take place at the nitrogen atom near the methylthio group or the one near the methyl group, or both. Taylor and Purdum[4] are the first to report the synthesis of **2** as a form of the other isomer **2a**. And so far, only Zhao,[5] Fan,[6] and their coworkers have used this pyrazole derivative in their works as a form of **2a** rather than **2**, both consequently reporting acylated or alkylated products at the N-1 of **2a**. The regiochemistry of the reported products by the above authors, nonetheless, has never been unambiguously proved, and as we all know the one-dimensional ^{1}H NMR, even plus IR, MS and elemental analysis is unable to distinguish between either of the two isomers of starting material **2** and the two potential products generated from the alkylation or acylation at N-1 or N-2 in each case. An attempt to determine the structure of **2a** by two-dimensional nuclear magnetic resonance (2D NMR) spectroscopy was unsuccessful. 2D NMR spectrum of **2a** exhibited a broad singlet at δ 11.60, which has been safely as-

Scheme I Tautomerism occurring in the case of pyrazole and **2a**



signed to the proton in NH group. The broad singlet is caused by the rapid migration of the proton in NH between the two nitrogen atoms and has no coupling with any carbon atom in the molecule, revealing that compound **2a** exists as a mixture of rapid tautomeric equilibrium in deuteriochloroform which is basically the same solvent as the one in the synthesis of **5** (see experimental section). A plausible reaction mechanism was herein proposed (Scheme III; see Results and Discussion). Recently, Ren[7] and coworkers have reported two regioselective reactions between ethyl 5-amino-3-methylthio-1*H*-pyrazole-4-carboxylate and 5-amino-3-methylthio-1*H*-pyrazole-4-carbonitrile with iodomethane in acetone in the presence of potassium carbonate, respectively (Scheme II), but the result was less representative (with only one alkylating reagent, no acylating reagents and only one reaction condition), and the reaction generated large amounts of isomer when using 5-amino-3-methylthio-1*H*-pyrazole-4-carbonitrile. Herein we would like to report our systematic research result with excellent regioselectivity, more representative alkylating reagents and acylating reagents with substituents from electron-withdrawing groups to electron-donating ones, various reaction conditions (microwave irradiation, ultrasound irradiation, and conventional stirring at room temperature or refluxing), and unambiguous characterization of the structures.

Scheme II A previously reported regioselective example



R= CN, COOEt

The ultrasound-assisted[8] and microwave-promoted[9-11] reactions have long been the focus of research interests and have showed such advantages as enhanced reaction rates, higher yields, milder reaction conditions, and higher selectivities.

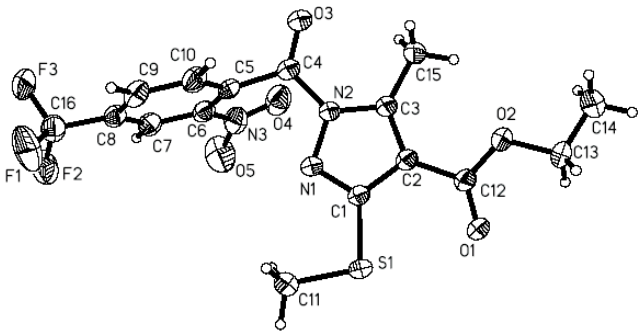
The alpha-haloketones are a class of versatile reagents in organic synthesis; they are, however, difficult to obtain and highly lachrymatory, toxic, and not readily available and which have been replaced in this work by eco-friendly alpha-tosyloxyketones prepared from [hydroxy(tosyloxy)-iodo]benzene (HTIB)[12-14] and corresponding ketones in the refluxing acetonitrile.

RESULTS AND DISCUSSION

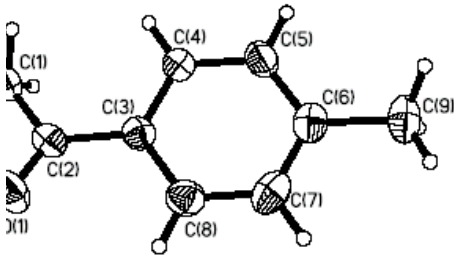
Various substituents have been attached to the pyrazole ring at 3-, 4-, or 5-position, but the functional groups at N-1 position have been mainly focused on alkyl and substituted-phenyl groups. Zhao[5] and coworkers consequently reported the substituted formylation at N-1 of **2a** with an attempt to search lead compounds with good bioactivities, yet unfortunately the compounds produced by acylation at "N-1 of **2**a" exhibited not very satisfactory fungicidal activities. Inspired by all these facts, we hoped to synthesize a series of N-aroylated **2a** with an attempt to improve the fungicidal activities of these compounds and explore other biological activities through the modification of the substituents attached to the benzene ring (Scheme III and Table 1). Unexpectedly, X-ray crystallographic analysis (Fig. 1 for **5c**) showed that the N-position aroylation had occurred at N-1 in **2** rather than N-1 in **2a**, and more surprisingly, the aroylation occurred at this position in the manner of high regioselectivity, with a result that the aroylation occurred almost regiospecifically at this position by the assay of High-Performance Liquid Chromatography (HPLC), and less than one percent of the other isomer was detected in all cases, that is, with R being from electron-withdrawing groups (such as R^3 = *o*-NO_2-*p*-CF_3 for **5c)** to

Table 1. The compounds which have been synthesized

R	Compound	R	Compound
R^1 = *p*-Cl	**5a**	R^1 = *p*-F	**6a**
R^2 = *p*-CF_3	**5b**	R^2 = *p*-CH_3	**6b**
R^3 = *o*-NO_2-*p*-CF_3	**5c**	R^3 = 2,5-dichloro	**6c**
R^4-Ph = 2-Furyl	**5d**	R^4 = H	**6d**
R^5 = *p*-CH_3O	**5e**	R^5 = *p*-Cl	**6e**
R^6 = *m*-CH_3	**5f**		
R^7 = *p*-C_2H_5O	**5g**		



electron-donating groups (such as R^5 = *p*-CH_3O for **5e**), and the reactions proceeding either under ultrasound irradiation or under the conventional stirring at room temperature. Encouraged by all these observations, we subsequently investigated the application of this procedure to alkylation of N-1 of **2**, with the alkylating reagents being alpha-tosyloxysubstituted acetophenones (**4**) or alpha-bromosustituted acetophenones (**4′**). And, to our surprise, the alkylation also occurred at the N-1 in **2**, rather than the previously reported N-1 in **2a**, which has also been unambiguously determined by X-ray



crystallographic analysis (Fig. 2 for **6b**). And the alkylation reactions were more regioselective with the other isomer in each case undetectable even by HPLC, regardless of the reaction condition, and the substituent. A plausible reaction mechanism was proposed (Scheme III) based on the facts that **2a** exists as a mixture of rapid equilibrium in solution but its N-alkylation of or N-acylation showed high regioselectivity. The anion generated by the removal of the proton at N-1 in **2a** might well exist as a form of **2-1** rather than **2a-1**, which is presumably caused by (i) the repelling effect between the negative charge of the anion **2a-1** and the more bulky methylthio group than the methyl group; (ii) by the repelling effect between the negative charge of the anion **2a-1** and the more negative charge of the sulfur atom in methylthio group than the methyl group (Scheme III); and (iii) the repelling effect between the bulky acylating or alkylating reagents and the more bulky methylthio group occurring when the remarkably bulky acylating or alkylating reagents approach the negative charge of the substrate (Fig. 3). Great care has been taken to determine the proposed regiochemistry of the reported compounds (**5a-g** and **6a-e**). Up to now, all attempts to obtain single crystals of the other compounds (in addition to the aforementioned **5c** and **6b**) have been unsuccessful, and unfortunately, our attempt to employ the 2D NMR technique to distinguish between the two possible regioisomers in each case has also failed. The long-range ^{1}H-^{13}C couplings useful for this purpose in 2D NMR technique (^{1}H-^{1}H NMR, HMQC and HMBC) have not been detected (Fig. 4; exemplified by **5a** and **6d**). Therefore, the structures of the other reported compounds are based on the plausible reaction mechanism as described above, and the involved steric and electronic repelling effects have been strongly supported by similar earlier reports.[15-18]

In addition to the synthesis of all the **5** under ultrasound irradiation at room temperature and **6** under ultrasound microwave irradiation, some randomly selected compounds, **5a** and **5b**, were also obtained by conventional reaction conditions (stirring at room temperature), and **6a** and **6c** by conventional refluxing in acetonitrile from **2** and corresponding **4** or under ultrasound irradiation at reflux temperature of acetonitrile. In the case of the synthesis of **5**, as summarized in Table 2, utilizing ultrasound irradiation to replace the conventional stirring significantly enhanced the reaction rates and slightly improved the yields, while generating identical compounds correspondingly, which have been substantiated by m.p., mixed m.p., IR, and ^{1}H NMR. In the case of the synthesis of **6** by microwave irradiation and ultrasound irradiation, respectively; the qualitative relationship of the reaction time and reaction temperature was preliminarily studied. As summarized in Table 3, under the ultrasound irradiation, the reaction seemed to proceed more rapidly than it did under microwave irradiation, and the reason might well be that the reaction temperature could go up to the reflux temperature of acetonitrile (b.p. 81.6 °C; hot-water-bath temperature was kept at 85-90 °C) in the case of ultrasound irradiation, while it could only reach 60-70 °C in the case of microwave irradiation. The above explanation was supported by a further study (as shown in Table 3): when irradiated by microwave at 1200W (instead of 500W), the reaction could come to an end in 10 minutes with basically unchanged isolated yield, in which situation the reaction temperature also went up to the

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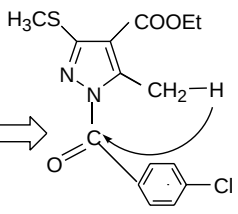

(**5a**)

reflux temperature of acetonitrile. It is worth noting that in the case of microwave irradiation, the reacting system was poorly mixed, that is, the solution and the solid proton-acceptor were not fully stirred; rather, the solid proton-acceptor precipitated in the bottom of the solution. In reality, the microwave-assisted reactions were carried out discontinuously (5 minutes each) with vigorous shaking at each end of a period.

Also, some randomly selected compounds (**6a** and **6b**) were obtained from alpha-bromoacetophenones (**4′**), in comparison with the alpha-tosyloxyacetophenones (**4**), in refluxing acetonitrile with a result that the refluxing procedures also generated the same compounds correspondingly in slightly lower isolated yields but were overwhelmingly time-consuming (a period of around 10 hours was often necessary in both cases).

Pyrazole derivatives have been reported to possess various and potent bioactivities.[19-22] And, we have determined the fungicidal activity of the two series, totaling twelve, of new compounds bearing pyrazole rings, and preliminary studies showed that some of the title compounds exihibited satisfactory antifungal activities (at 50 ppm) against *Phoma asparagi* (**5c**, **5e** and **6a**) and *Alternaria solani* (**5c**, **5d**, **6c** and **6d**), and further studies in herbicidal and other bioactivities are underway.

CONCLUSION

In summary, we have developed an efficient and facile protocol for the synthesis of ethyl 1-aroyl/(aroylmethyl)-5-methyl-3-methylthiopyrazole-4-carboxylates (**5**/**6**) via a highly regioselective nucleophilic substitution reaction of ethyl 3-methyl-5-methylthio-1*H*-pyrazole-4-carboxylate (**2a**) with aroyl chloride (**3**) and eco-friendly reagents alpha-tosyloxysubstituted acetophenones (**4**), respectively. This protocol might well have the potential to be extensively applied to the acylation and alkylation at the N-position of N-unsubstituted pyrazole derivatives regioselectively. Microwave and ultrasound irradiations were also applied in both reactions.

EXPERIMENTAL

Melting points were measured with a RY-1 apparatus in capillaries and were uncorrected. IR spectra were obtained on a Nicolet 501P FT-IR instrument as KBr pellets. NMR (^{1}H NMR ^{13}C NMR and 2D NMR, including HMQC and HMBC) spectra were recorded on a Jeol JNM-ECP 600M spectrometer (600 MHz) in DMSO-d_6 (unless otherwise stated), and the chemical shifts were expressed in ppm with reference to TMS as internal standard. Coupling constants are reported in Hertz (Hz). Elemental analyses were performed with a Perkin-Elmer 2400 instrument. High-Performance Liquid Chromatographic assays were carried out employing a Waters 1525 instrument under conventional conditions. Thin layer chromatography was used to monitor the course of reactions and ascertain the purity of compounds, and detection of the components was made by exposure to ultraviolet light. Ultrasound irradiations were carried out in a hot-water-bath (85-90 °C) at 25 W using a CX-250 apparatus with the frequency being 33 KHz. Microwave irradiations were performed using a Galanz WP750L23-6 instrument at 2450 MHz, which has been modified with a hole in the top of the oven equipped with a refluxing condenser.

The intermediate **1** and synthon **2** were prepared according to the literature procedures.[4,23] **4′** was also prepared by reported procedures.[12-14]

All the physical properties of **5** reported in this paper were from the reactions under ultrasound irradiation. And all physical properties of **6** were from the reactions under microwave irradiation using alpha-tosyloxysubstituted acetophen-

ones (**4**) as starting materials.

General procedure for the synthesis of ethyl 1-aroyl-5-methyl-3-methylthiopyrazole-4-carboxylates (5)

Substituted benzoic acid or furoic acid (5 mmol) was dissolved in 10 mL of freshly distilled $SOCl_2$. The resulting solution was refluxed for around 4 hours, and the excessive $SOCl_2$ was evaporated *in vacuo* to afford crude compounds **3**. To the crude **3** were added 10 mL of $CHCl_3$, **2** (1.000 g, 5 mmol) and NaOH (0.2 g, 5 mmol), and the suspended solution was stirred at room temperature or irradiated with ultrasound until the starting materials were completely consumed. After the removal of solids in the reacting system by filtration through a Hirsch funnel, the solvent was evaporated *in vacuo* to give a residue, which was purified by recrystallization from absolute ethanol.

Ethyl 1-(*p*-chlorobenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5a)

Yield 89%. White needle-like crystals, m.p. 101.5-102.5 °C. IR (KBr) ν: 1723, 1689; ^{1}H NMR ($CDCl_3$) δ: 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 Hz); Anal. Calcd for $C_{15}H_{15}ClN_2O_3S$: C, 53.25%, H, 4.47%, N, 8.28%. Found: C, 53.19%, H, 4.49%, N, 8.23%.

Ethyl 1-(*p*-trifluromethylbenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5b)

Yield 85%. White needle-like crystals, m.p. 96.5-97 °C. IR (KBr) ν: 1715, 1699; ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, 3H, *J* = 7.8 Hz), 4.39 (q, 2H, *J* = 7.8 Hz), 2.41 (s, 3H), 2.99 (s, 3H), 7.75, 8.12 (dd, 4H, *J* = 8.6 Hz); Anal. Calcd for $C_{16}H_{15}F_3N_2O_3S$: C, 51.60%, H, 4.60%, N, 7.53%. Found: C, 51.55%, H, 4.63%, N, 7.55%.

Ethyl 1-(*o*-nitro-*p*-trifluromethylbenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5c)

Yield 87%. White prism-like crystals, m.p. 147.5-148.5 °C. IR (KBr) ν: 1736, 1709; ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.8 Hz), 4.28 (q, 2H, *J* = 7.8 Hz), 2.06 (s, 3H), 2.51 (s, 3H), 8.10, 8.60 (m, 3H); Anal. Calcd for $C_{16}H_{14}F_3N_3O_5S$: C, 46.04%, H, 3.38%, N, 10.07%. Found: C, 46.11%, H, 3.35%, N, 10.04%.

Ethyl 1-(2-furoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5d)

Yield 85%. White needle-like crystals, m.p. 130-131 °C. IR (KBr) ν: 1718, 1693; ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.8 Hz), 4.28 (q, 2H, *J* = 7.8 Hz), 2.50 (s, 3H), 2.85 (s, 3H), 6.80-8.20 (m, 3H); Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05%, H, 4.80%, N, 9.52%. Found: C, 53.09%, H, 4.78%, N, 9.55%.

Ethyl 1-(*p*-methoxybenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5e)

Yield 72%. White needle-like crystals, m.p. 123-124 °C. IR (KBr) ν: 1701, 1696; ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.8 Hz), 4.28 (q, 2H, *J* = 7.8 Hz), 2.38 (s, 3H), 2.81 (s, 3H), 7.10, 7.99 (dd, 4H, *J* = 7.8 Hz), 3.87 (s, 3H); Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47%, H, 5.43%, N, 8.38%. Found: C, 57.49%, H, 5.45%, N, 8.39%.

Ethyl 1-(*m*-methylbenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5f)

Yield 68%. White prism-like crystals, m.p. 115-116 °C. IR (KBr) ν: 1716, 1696; ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.8 Hz), 4.30 (q, 2H, *J* = 7.8 Hz), 2.38 (s, 3H), 2.84 (s, 3H), 7.40-7.74 (m, 3H), 2.34 (s, 3H); Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36%, H, 5.70%, N, 8.80%. Found: C, 60.34%, H, 5.72%, N, 8.82%.

Ethyl 1-(*p*-ethoxybenzoyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (5g)

Yield 74%. White needle-like crystals, m.p. 147-148 °C. IR (KBr) ν: 1703, 1687; ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.8 Hz), 4.28 (q, 2H, *J* = 7.8 Hz), 1.40 (t, 3H, *J* = 8 Hz), 4.28 (q, 2H, *J* = 8 Hz), 2.38 (s, 3H), 2.82 (s, 3H), 7.32, 8.36 (dd, 4H, *J* = 7.8 Hz); Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60%, H, 5.79%, N, 8.05%. Found: C, 58.56%, H, 5.76%, N, 8.01%.

General procedure for the synthesis of ethyl 1-aroylmethyl-5-methyl-3-methylthiopyrazole-4-carboxylates (6)

Into a 25 mL three-necked round-bottomed flask containing 15 mL of acetonitrile, were introduced compound **2** (1.000 g, 5 mmol), **4** or **4′** (5 mmol) and potassium carbonate (1 g), followed by:

(i) the microwave irradiation at 500W or 1200W for a specified period discontinuously (5 minutes each; vigorous shaking at the end of each period) until the reaction was completed as indicated by TLC.

(ii) irradiation by ultrasound at 25W using a CX-250 apparatus for a specified period in a hot-water-bath (85-90 °C) until the reaction was completed.

(iii) the conventional refluxing in acetonitrile until the reaction was completed.

The resulting solution was filtered through a Hirsch funnel to remove the solids existing in solution, and the solvent was evaporated *in vacuo* to give a residue, which was purified by recrstallization from absolute ethanol.

Ethyl 1-[(*p*-fluorobenzoyl)methyl]-5-methyl-3-methylthiopyrazole-4-carboxylate (6a)

Yield 87%. White needle-like crystals, m.p. 157-158

°C. IR (KBr) ν: 3066, 1702, 1688, 1507, 1544, 1596, 1495, 1270, 1230; ^{1}H NMR ($CDCl_3$) δ: 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); Anal. Calcd for $C_{16}H_{17}FN_2O_3S$: C, 57.13%, H, 5.10%, N, 8.33%. Found: C, 57.36%, H, 5.11%, N, 8.37%.

Ethyl 1-[(*p*-methylbenzoyl)methyl]-5-methyl-3-methylthiopyrazole-4-carboxylate (6b)

Yield 85%. White prism-like crystals, m.p. 136-137 °C. IR (KBr) ν: 3064, 1696, 1680, 1606, 1539, 1493, 1268, 1233; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.1 Hz), 4.21(q, 2H, *J* = 7.1 Hz), 2.36 (s, 3H), 2.37 (s, 3H), 5.88 (s, 2H), 2.51 (s, 3H), 7.41, 7.98 (dd, 2H+2H, *J* = 8.1 Hz); Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42%, H, 6.07%, N, 8.43%. Found: C, 61.39%, H, 6.04%, N, 8.46%.

Ethyl 1-[(2,5-dichlorobenzoyl)methyl]-5-methyl-3-methylthiopyrazole-4-carboxylate (6c)

Yield 90%. White needle-like crystals, m.p. 130-132 °C. IR (KBr) ν: 3072, 1733, 1691, 1462, 1492, 1535, 1269, 1202; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 2.38 (s, 3H), 2.41 (s, 3H), 5.79 (s, 2H), 7.67, 8.11 (d+m, H+2H); Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_3S$: C, 49.74%, H, 4.81%, N, 7.25%. Found: C, 49.88%, H, 4.79%, N, 7.31%.

Ethyl 1-(benzoylmethyl)-5-methyl-3-methylthiopyrazole-4-carboxylate (6d)

Yield 69%. White needle-like crystals, m.p. 138-139 °C. IR (KBr) ν: 3060, 1702, 1700, 1598, 1546, 1491, 1449, 1272, 1227; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 2.37 (s, 3H), 2.41 (s, 3H), 5.77 (s, 2H), 7.29, 7.83 (t+m, H+4H); Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36%, H, 5.71%, N, 8.80%. Found: C, 60.30%, H, 5.73%, N, 8.83%.

Ethyl 1-[(*p*-chlorobenzoyl)methyl]-5-methyl-3-methylthiopyrazole-4-carboxylate (6e)

Yield 87%. White needle-like crystals, m.p. 145-146 °C. IR (KBr) ν: 3087, 1679, 1699, 1590, 1535, 1491, 1268, 1227; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 2.37 (s, 3H), 2.37 (s, 3H), 5.93 (s, 2H), 7.69, 8.09 (dd, 2H+2H, *J* = 8.1 Hz); Anal. Calcd for $C_{16}H_{17}ClN_2O_3S$: C, 54.54%, H, 4.87%, N, 7.95%. Found: C, 54.59%, H, 4.89%, N, 7.99%.

Crystal structure determination of 5c

A colorless crystal of the compound **5c** with a dimension of 0.28 mm × 0.36 mm × 0.38 mm was mounted on a glass fiber in a random orientation. X-ray diffraction was performed on a BRUKER SMART 1000 CCD diffractometer equipped with a graphite monochromated Mo*Kalpha* radiation (λ = 0.71073 Å) with an ω scan mode in the range of 2.50 ≤ θ ≤ 26.40° at 293(2) K. A total of 5352 reflections were collected with 3739 unique ones (R_{int} = 0.021), of which 2273 reflections with $I > 2\sigma(I)$ were considered to be observed and used in the succeeding refinements. Intensity data were corrected for *Lp* factors and empirical absorption. The structure was solved by direct methods and expanded by using Fourier differential techniques with SHELXL-97. All non-hydrogen atoms were located with successive difference Fourier syntheses. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added according to the theoretical models. Full matrix least-squares refinement gave the final wR_2 = 0.1273 and wR = 0.0467, $W = 1/[\sigma^2(F_0^2) + (0.1014P)^2 + 0.29P]$, where $P = (Fo^2+2Fc^2)/3$, S = 1.000, $(\Delta/\sigma)_{max}$ = 0.000 e/Å^3 $(\Delta\rho)_{max}$ = 0.180 e/Å^3, $(\Delta\rho)_{min}$ = -0.230 e/Å^3. The crystal belongs to a Triclinic, space group *P-1* with a = 8.450(3), b = 8.798(3), c = 13.604(4) Å, α = 98.903(6), β = 98.903(6)°, γ = 109.126(5), V = 922.4(5) Å^3, Z = 2, D_c = 1.503 g/cm^3, μ = 0.239 mm^{-1}, F(000) = 428.

Crystal structure determination of 6b

A colorless crystal of the compound **6b** with a dimension of 0.22 mm × 0.18 mm × 0.12 mm was mounted on a glass fiber in a random orientation. X-ray diffraction was performed on a BRUKER SMART 1000 CCD diffractometer equipped with a graphite monochromated Mo*Kalpha* radiation (λ = 0.71073 Å) with an ω scan mode in the range of 3.03 ≤ θ ≤ 22.60° at 293(2) K. A total of 8715 reflections were collected with 3064 unique ones (R_{int} = 0.0351), of which 1982 reflections with $I > 2\sigma(I)$ were considered to be observed and used in the succeeding refinements. Intensity data were corrected for *Lp* factors and empirical absorption. The structure was solved by direct methods and expanded by using Fourier differential techniques with SHELXL-97. All non-hydrogen atoms were located with successive difference Fourier syntheses. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added according to the theoretical models. Full matrix least-squares refinement gave the final wR_2 = 0.1399 and wR = 0.0351, $W = 1/[\sigma^2(F_0^2) + (0.1014P)^2 + 0.29P]$, where $P = (Fo^2+2Fc^2)/3$, S = 1.004, $(\Delta/\sigma)_{max}$ = 0.000 e/Å^3 $(\Delta\rho)_{max}$ = 0.213 e/Å^3, $(\Delta\rho)_{min}$ = -0.159 e/Å^3. The crystal belongs to a monoclinic, space group $P2_1/c$ with a = 16.690(6), b = 7.771(3), c = 13.720(4) Å, α = 90.00, β = 101.969(6), γ = 90.00, V = 1740.8(10) Å^3, Z = 4, D_c = 1.268 g/cm^3, μ = 0.201 mm^{-1}, F(000) = 704.

Crystallographic data (excluding structure factor) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 240135 for **5c** and CCDC 240136 for **6b**.

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