Efficient Synthesis of 1-Aryl-4-[(ethoxycarbonyl)oxy]-1*H*-pyrazole-3-carboxylates

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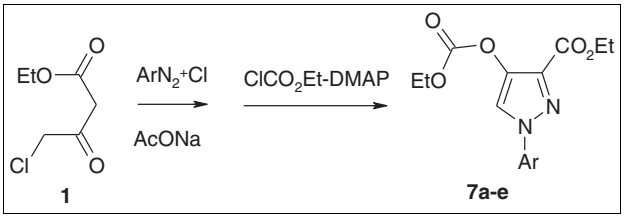

Two-step synthesis of *N*-aryl 4-[(ethoxycarbonyl) oxy]-1*H*-pyrazole-3-carboxylates is achieved starting from the commercially available ethyl 4-chloroacetoacetate and aromatic amines. Azo coupling followed by cyclization with ethyl chloroformate–DMAP pair resulted in the formation of new 4-oxy-1*H*-pyrazole derivatives in high yields.

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INTRODUCTION

The first 1-aryl-4-oxypyrazoles **A** (Fig. 1) were synthesized at the very beginning of the 20th century by cyclization of the corresponding hydrazones of 4-bromo-**B** [1a–c], 4-chloro-**C** [1d,e], or 4-iodoacetoacetates **D** [1f] under the action of various bases (KOAc [1a,e,f], NaOH [1d], or NaOEt [1c,g]). Nevertheless, potassium acetate [2] in boiling EtOH same as sodium acetate [3] in water became the most popular reagent among others and has been repeatedly used for the cyclization. Strong alkaline conditions (KOH_{aq} or $NaOH_{aq}$) cause hydrolysis of the ester after the cyclization to give the corresponding acid [2e]. Several alternative approaches for the synthesis of pyrazoles **A** have been also reported [2e,4].

As hydroxy compounds [5], the 4-oxypyrazoles **A** yield the corresponding 4-(chlorobenzenesulfonates) [6a], 4-benzoates [1b], and 4-acetates [1b,3c,6b] when appropriate acid chloride or anhydride is added to their alkaline solutions. Further, 4-*O* derivatives were synthesized using chlorodifluoromethane and analogs [2f], benzyl chloride [2g], ethyl chloroacetate [6b], allyl bromide [7a], and 3-bromopropanol derivatives [7b].

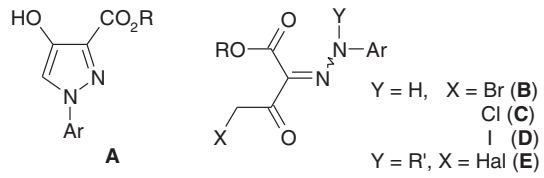


Figure 1. Oxypyrazoles **A** and hydrazones of acetoacetates **B–C**.

The practical application of pyrazoles **A** began in color photography, where they were used as color-forming agents [2c]. Later, several derivatives of **A** were tested as active ingredients for the treatment of various diseases related to neuropeptide Y [2g], as plant growth regulators or pesticides [7b,8a,b], and as bactericides, disinfectants, and antiseptics [8c]; and were found to possess arthropodicidal, nematocidal, anthelminthic, and anti-protozoal activities [2b,9] and also to have a potential antitumor and anti-HCV effect [10].

Associated with our interest in the expansion of a range of hydrazone derivatives **E**, new potent substituents in the hydrazone =N–NH– moiety are highly desirable. Several analogs of such derivatives are already known. Thus, the imino-hydrogen atom of the hydrazones was replaced with the acetyl group (Ac_2O-Et_3N) [1f,11a,b], chlorine (Cl_2 in AcOH–AcONa) [1e], methyl group ($(MeO)_2SO_2$, K_2CO_3) [11c], and dithiocarboxy group (CS_2, Na) [11d], or involved in intramolecular cyclization to form pyridazine carboxylates ($POCl_3$-DMF, DMF dimethyl acetal, or formaldehyde–DMAP) [11e–i] and intramolecular arylation to form cinnoline carboxylates (NaH or K_2CO_3–TBAB or K_2CO_3-DB-18-c-6) [12a–d] and other heterocycles [12e,f].

Bearing this information in mind, ethyl chloroformate, as a source of the ethoxycarbonyl moiety that should possess a number of useful properties [13], was suggested. However, it has become apparent in the course of this study that

desirable hydrazone derivatives **E** could not be obtained. Instead, pyrazoles **A** were identified as products, which became the subject of the present work.

RESULTS AND DISCUSSION

The starting hydrazones **3a–e** were prepared from commercially available chloroacetoacetate **1** and aromatic amines **2a–e** by azo coupling in AcONa buffer in high yields, according to the experimental procedure A adopted for this study (Scheme 1 and Table 1). However, careful inspection of reaction mixtures showed that the azo coupling was followed in several cases by intramolecular cyclization, giving notable amounts of 4-oxypyrazoles **4b–d**. Thus, the highest yield was observed for the NO_2 derivative **4d**, in contrast to NMe_2 derivative **4a** and thiophene derivative **4e**, which were not observed at all. The yield of cyclization product increased in the substituent series $NMe_2 < Me < I < NO_2$, which is consistent with their electronic properties and matches the changing acidity of the hydrazone =N–NH– moiety. In general terms, the formation of 4-oxypyrazoles **4** in the course of the azo coupling reaction in basic conditions is predictable, as they are formed from azo compounds in a similar way [1–3]. However, the formation of these products in the azo coupling reaction was not previously reported.

An attempt to obtain derivatives of hydrazones **3a–e** with ethyl chloroformate under basic conditions (DMAP) resulted in the formation of pyrazoles **6a–e** in high yields (47–96%, Table 1) instead of desirable hydrazones **5a–e**. The structure of the products was elucidated by spectroscopy. Thus, neither a two-proton signal of the CH_2Cl group at approximately 4.8 ppm in ^{1}H NMR nor a signal at approximately 45 ppm in ^{13}C NMR, expected for **5a–e**, was observed. Instead, one-proton singlet at approximately 8.1 ppm in the proton spectra and the signal at approximately 120 ppm (^{13}C NMR) supported the presence of the =C–H moiety of a pyrazole ring [14a]. Lack of a chlorine atom was established by ESI MS. The pyrazole

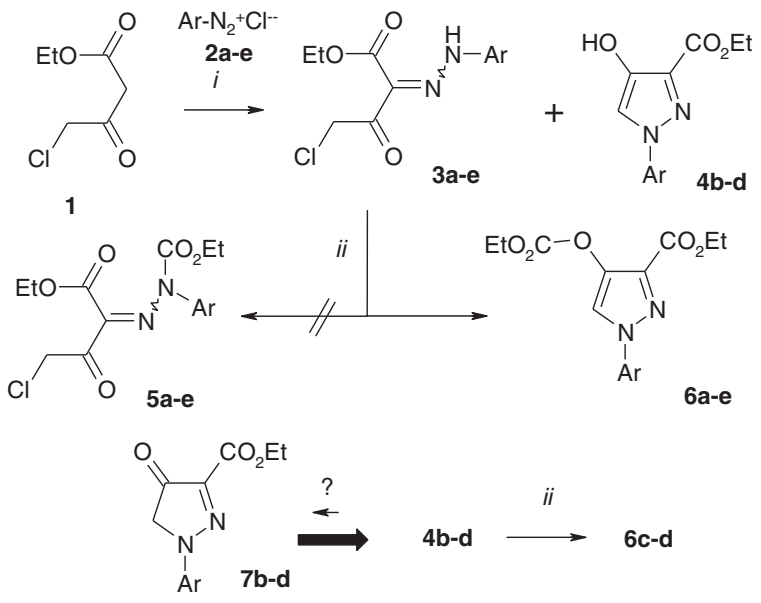
Table 1

Yields of the reaction products **3** and **4** (procedure A) and **6** (procedure B).

		Yields of reaction products (%) by procedures		
		A		B
Entry	Structure features	**3**	**4**[a]	**6**
a	NMe_2	91	0	92
b	Me	92	3	96
c	I	72	20	95 (97)[b]
d	NO_2	32	52	94 (96)[b]
e	Thiophene	94	0	13[c] (47[d])[c]

[a]By-product of the synthesis of **3**.
[b]Yields in the reaction of **4c** or **4d** with DMAP–$ClCO_2Et$ according to procedure B.
[c]The balance is the initial hydrazone **3e**.
[d]The reaction was carried out at 60°C.

Scheme 1



Ar = 4-Me_2N-C_6H_4 (**a**), 4-Me-C_6H_4 (**b**), 4-I-C_6H_4 (**c**), , 4-O_2N-C_6H_4 (**d**), 2-(EtO_2C)thien-3-yl (**e**).
Reaction conditions: *i.* 0 °C, AcONa, H_2O-acetone; *ii.* DMAP-EtO_2CCl, 0 °C,

structure of **6d** was confirmed by X-ray analysis (Fig. 2 and Supporting Information 2) [14b].

One can assume that DMAP, being first coordinated in a complex with ethyl chloroformate, nevertheless promotes the intramolecular cyclization of the hydrazone N–NH– fragment with the chloroketone moiety but not its acylation with the rest of the ethoxycarbonyl. Surprisingly, the acylation step still occurs in the course of the cyclization, and the corresponding carbonates **6a–e** arise. It is probable that these two processes proceed very fast or even simultaneously, as no 4-oxypyrazole **4c** was detected as an intermediate in the corresponding reaction on testing (TLC). Indeed, 4-oxypyrazoles **4c,d** themselves also give acylation products **6c,d** under the action of the EtO_2CCl–DMAP complex within a short time and in excellent yields even in the cold (Table 1 and experimental procedure B).

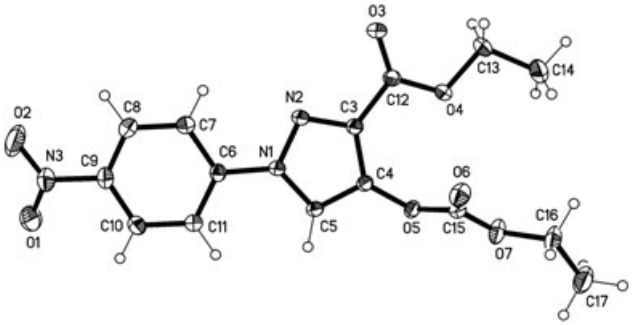


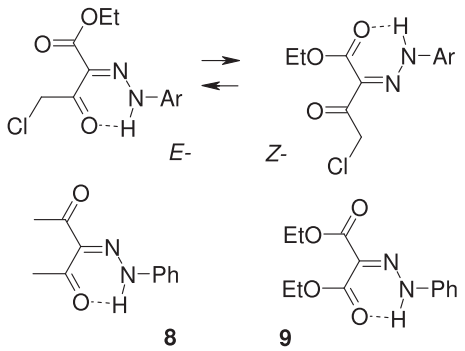
Figure 2. X-ray molecular structure of pyrazole **6d**. Ellipsoids correspond to 50% probability levels.

Several comments concerning spectral characteristics of both hydrazones **3a–e** and 4-oxypyrazoles **4b–d** should be given as these facts are still modesty covered.

The ^1H and ^{13}C NMR spectra of hydrazones **3a–e** imply the presence of two geometric isomers *E* and *Z* but correspond neither to enol nor to azo structures [16]. The shift of the NH protons can be used for the determination of the isomeric composition (Table 2 and Supporting Information 1). Thus, derivatives of symmetric ketones and esters of types **8** and **9** demonstrate the considerable difference in chemical shifts of the NH protons that makes the classification of β-ketoester derivatives rather certain [15]. Usually, those of the *E*-isomers resonate at approximately 14 ppm, downfield from the NH protons of the corresponding *Z*-isomers at approximately 12 ppm [4e].

Table 2

Chemical shifts of NH protons and *E*-/*Z*-isomers ratio in ^1H NMR spectra of hydrazones **3a–e**.



		Solvents, chemical shifts (in ppm), and *E*-/*Z*-isomers ratio [a]					
		DMSO-d_6			$CDCl_3$		
Entry	Structural feature	*E*	*Z*	*E*/*Z*	*E*	*Z*	*E*/*Z*
a	NMe_2	14.72	12.53	0.21	15.33	13.37	1.62
b	Me	14.14	12.21	0.20	14.83	13.13	0.11
c	I	13.96	12.03	0.06	14.61	13.02	0.38
d	NO_2	13.67	12.07	0.05	14.44	13.06	0.09
e	Thiophene	14.84	13.52	0.03	15.20	14.05	0.01
8	Ph				14.74 [15a]		
9	Ph				12.80 [15b]		

[a]Determined from ^1H NMR spectra of raw reaction products.

There is a dependence of shifts on the solvent used: the proton resonance of *E*-isomers decreases by almost 0.6 ppm and for *Z*-isomers by almost 0.9 ppm when DMSO-d_6 is replaced with $CDCl_3$. In the series of substituents NMe_2–Me –I–NO_2, the shift of their NH protons for both *E*- and *Z*-isomers increases from the lower to higher field, corresponding to the electronic effect of the substituents [17a]. In fact, the *Z*-isomer is the main one for the majority of hydrazones **3b–e** (except **3a** in $CDCl_3$), and the isomer ratio (*E*/*Z*) changes in its favor in the aforementioned order, both in DMSO and $CDCl_3$. Variability in the *E*-/*Z*-isomers ratio for each of **3a–e** in different solvents indicates the interconversion between isomers in solutions.

Over the temperature range from 22 to 65/70°C, the NH resonance of *E*- (at ca. 15 ppm) and *Z*-isomers (at ca. 13 ppm) same as $ClCH_2$ resonance (at ca. 4.8 ppm) in **3a,e** both in $CDCl_3$ and DMSO revealed a systematic insignificant upfield shift on heating (in the range between 0.07 and 0.26 ppm) but returns to its original value after cooling (Fig. 3 and Tables 3–7 in the Supporting Information 1). Thus, the *E*-isomers shift is always less than that of the *Z*-isomers. Interestingly, *E*-/*Z*-isomers ratio for **3a** in $CDCl_3$ and for **3e** in DMSO-d_6 significantly changed within these studies, namely, from 77:23 (at 22°C) to 44:56 (at 65°C) for **3a** and from 7:93 (at 22°C) to 18:82 (at 74°C) for **3e**. Moreover, altered isomers ratio remained unchanged after cooling to initial temperature. We can say that a rise in the temperature removes the solvent molecules, on average, further from the solute molecules, and therefore, their mutual influence will decrease. Then, the observable changes of *E*-/*Z*-isomers ratio should be a result of internal effects in molecules of hydrazones **3a,e** or between them.

No enol tautomers of hydrazones **3a–e** could be visualized with $FeCl_3$ solution [17b]. On the contrary, ethyl chloroacetoacetate **1** itself quickly develops a cherry-red color with $FeCl_3$, indicating the presence of an enol.

Isolated 4-oxypyrazoles **4b–d** exist as HO derivatives only, and no keto tautomers **7b–d** (Scheme 1) were detected in their NMR spectra. Thus, ^{1}H NMR spectra of **4b–d** in $CDCl_3$ contains strong singlets of the =C–H fragment at approximately 7.65 ppm and broader singlets of the HO group at approximately7.35 ppm. The spectrum of **4d** in DMSO-d_6 showed for this fragment two singlets at 9.47 (HO–) and 8.24 (=C–H) ppm only [18]. No signals that one would expect for the O=CCH_2 fragment of the corresponding 4-oxo-4,5-dihydro-1*H*-pyrazole were observed to any detectable extent, neither in the ^{1}H NMR (at 5.0–4.0 ppm) nor in the ^{13}C NMR (at ca. 187 and ca. 64 ppm) [19].

The enol compound 4-oxypyrazole **4c** forms a chelate complex of gray-violet color with aqueous $FeCl_3$, as do salicylates [17b].

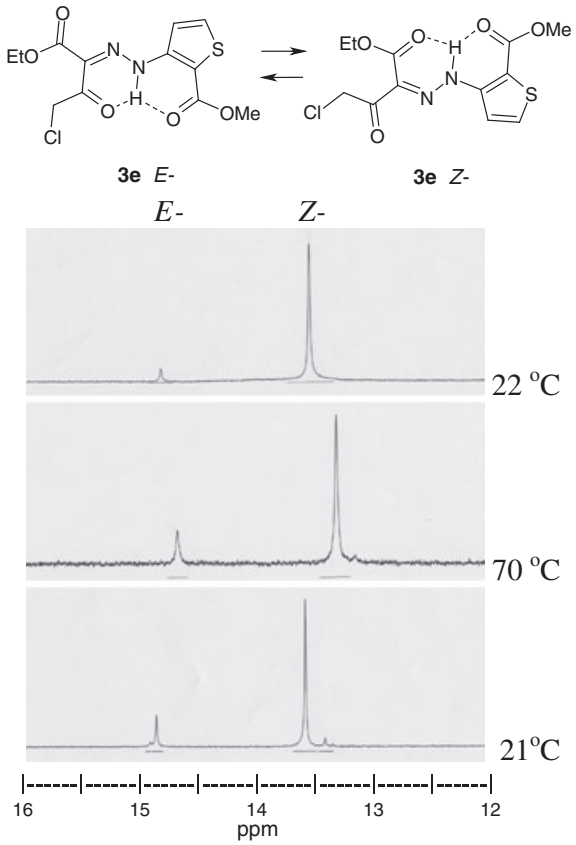


Figure 3. Partial ^{1}H NMR spectra (16–12 ppm) of hydrazone **3e** in DMSO-d_6 showing the NH proton resonance as a function of temperature from 22 to 70°C followed by cooling to 21°C.

CONCLUSIONS

In summary, we have synthesized a new series of 4-EtO_2CO-pyrazole derivatives via a two-step procedure, starting from commercially available educts. Azo coupling of diazonium salts with ethyl 4-chloroacetoacetate, followed by intramolecular cyclization of the product mediated by DMAP in the presence of ethyl chloroformate, gave a novel family of pyrazoles, which has a convenient protection for HO function [13a], a potent functionality for further heterocyclizations [13b], or may alternatively act as an important building block for construction of bioactive molecules [13c–e]. The structural features of intermediates and new pyrazoles have been investigated by NMR spectroscopy.

EXPERIMENTAL

Typical experimental procedure A

Synthesis of hydrazone 3a. A precooled (ice-bath) solution of $NaNO_2$ (159 mg, 2.3 mmol) in H_2O (2 mL) was added dropwise to a precooled solution (ice-bath) of *p*-toluidine **2a** (246 mg, 2.3 mmol) and conc. HCl (2.2 mL) in H_2O (3 mL). The pale yellow solution of the diazonium salt thus obtained was neutralized with a solution of

AcONa (1.64 g, 20 mmol) in H_2O (4 mL), and the resulting mixture was added dropwise to a precooled (ice-bath) stirred suspension of ethyl chloroacetoacetate **1** (328 mg, 2 mmol), AcONa (2.5 g, 30.5 mmol), and acetone (15 mL) in H_2O (20 mL). After stirring for 2 h, the red reaction mixture was treated with water (20 mL), and the voluminous precipitate thus formed was filtered off, washed with H_2O (4 × 5 mL), and dried in the air to give a red-brown mass (^{1}H NMR analysis of the crude product showed in fact two components with insignificant amounts of impurities). Purification was achieved by chromatography over silica gel (eluted with a mixture hexane–CH_2Cl_2, 1:1) to give 518 mg (92%) of the mixture of *E-*/*Z*-hydrazones, as a yellow powder.

Compound (3a, mixture of E- and Z-isomers). mp: 147–148°C, R_f (C_6H_{14}–Et_2O, 1:1): 0.55. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 15.33 (s, 0.81H, NH), 13.37 (s, 0.19H, NH), 7.40–7.38 (m, 2H), 6.75–6.74 (m, 2H), 4.87 (s, 1.6H, CH_2Cl), 4.72 (s, 0.4H, CH_2Cl), 4.38 (q, *J* = 7.1 Hz, 0.4H, OCH_2), 4.34 (q, *J* = 7.1 Hz, 1.6H, OCH_2), 3.02 (s, 6H, $N(CH_3)_2$), 1.43–1.40 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.04, 186.05, 165.14, 164.29, 149.70, 149.08, 131.46, 131.06, 122.83, 122.08, 121.14, 118.46, 117.39, 113.06, 112.82, 61.16, 60.79, 49.38, 46.68, 40.62, 40.48, 14.34, 14.11. ESI MS (positive mode) *m/z*: 312.0 $[M + 1, Cl = 35]^+$, 314.0 $[M^* + 1, Cl = 37]^+$. *Anal*. Calcd for $C_{14}H_{18}ClN_3O_3$: C, 53.94; H, 5.82; N, 13.48. Found: C, 53.78; H, 5.80; N, 13.33.

Compound (3b, mixture of E- and Z-isomers). mp: 94–95°C, (Lit mp 95°C[20]), R_f (CH_2Cl_2): 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 14.83 (br s, 0.33H, NH), 13.13 (br s, 0.67H, NH), 7.37–7.35 (m, 0.7H), 7.26–7.21 (m, 3.3H), 4.87 (s, 0.65H, CH_2Cl), 4.72 (s, 1.35H, CH_2Cl), 4.39 (q, *J* = 7.1 Hz, 1.33H), 4.36 (q, *J* = 7.1 Hz, 0.67H), 2.38 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.00, 186.20, 164.70, 163.71, 138.91, 136.75, 135.73, 130.24, 124.18, 123.13, 116.76, 115.83, 61.46, 61.08, 49.56, 46.71, 21.02, 20.92, 14.29, 14.05. ESI MS (positive mode) *m/z*: 282.7 $[M + 1, Cl = 35]^+$, 284.7 $[M^* + 1, Cl = 37]^+$, 304.9 $[M + 23, Cl = 35]^+$, 306.9 $[M^* + 1, Cl = 37]^+$.

Compound (3c, mixture of E- and Z-isomers). mp: 122–123°C, R_f (CH_2Cl_2): 0.43. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 14.60 (s, 0.24H, NH), 13.01 (s, 0.76H, NH), 7.74–7.72 (m, 0.48H), 7.73–7.71 (m, 1.52H), 7.22–7.20 (m, 0.48H), 7.12–7.10 (m, 1.52H), 4.85 (s, 0.50H, CH_2Cl), 4.69 (s, 1.50H, CH_2Cl), 4.39 (q, *J* = 7.1 Hz, 1.50H, OCH_2), 4.36 (q, *J* = 7.1 Hz, 0.50H, OCH_2), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.61, 186.26, 164.34, 163.46, 140.96, 140.91, 138.66, 125.37, 124.10, 118.43, 117.58, 90.37, 89.05, 61.84, 61.39, 49.54, 46.54, 14.29, 14.04. ESI MS (positive mode) *m/z*: 395.0 $[M + 1, Cl = 35]^+$, 397.0 $[M^* + 1, Cl = 37]^+$, 417.0 $[M + 23, Cl = 35]^+$, 419.0 $[M^* + 1, Cl = 37]^+$. *Anal*. Calcd for $C_{12}H_{12}ClIN_2O_3$: C, 36.53; H, 3.07; N, 7.10. Found: C, 36.32; H, 3.00; N, 7.01.

Compound (3d, mixture of E- and Z-isomers). mp: 136–138°C (Lit mp 146°C[16]), R_f (CH_2Cl_2): 0.43. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 14.41 (s, 0.22H, NH), 13.03 (s, 0.78H, NH), 8.32–8.30 (m, 2H), 7.56–7.54 (m, 0.27H), 7.45–7.43 (m, 0.73H), 4.86 (s, 0.24H, CH_2Cl), 4.70 (s, 0.76H, CH_2Cl), 4.42 (q, *J* = 7.1 Hz, 0.74H, OCH_2), 4.39 (q, *J* = 7.1 Hz, 0.26H, OCH_2), 1.44–1.41 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.26, 186.36, 163.81, 162.89, 146.22, 146.04, 145.09, 144.49, 127.84, 125.86, 125.70, 125.43, 116.41, 115.45, 62.34, 61.80, 49.31, 46.22, 14.21, 13.95.

Compound (3e, mixture of E- and Z-isomers). mp: 222–223°C, R_f (CH_2Cl_2): 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 15.20 (s, 0.1H, NH), 14.05 (s, 0.9H, NH), 7.58–7.51 (m, 0.2H), 7.55–7.52 (m, 0.9H), 7.43–7.41 (m, 0.9H), 4.82 (s, 0.2H, CH_2Cl), 4.70 (s, 1.8H, CH_2Cl), 4.48 (q, *J* = 7.1 Hz, 1.8H), 4.37 (q, *J* = 7.1 Hz, 0.2H), 4.01 (s, 0.3H), 3.98 (s, 2.7H), 1.44 (t, *J* = 7.1 Hz, 2.7H), 1.43 (t, *J* = 7.1 Hz, 0.3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.44, 186.42, 164.27, 163.40, 162.88, 162.05, 147.77, 147.68, 132.40, 132.07, 126.71, 125.00, 119.25, 118.32, 112.35, 110.76, 61.98, 61.45, 52.51, 52.46, 49.13, 46.51, 14.22, 14.09. ESI MS (positive mode) *m/z*: 333.1 $[M + 1, Cl = 35]^+$, 335.1 $[M^* + 1, Cl = 37]^+$, 355.1 $[M^* + 23, Cl = 35]^+$, 337.1 $[M^* + 1, Cl = 37]^+$, 501.1 $[3M + 2, Cl = 35]^+$, 503.1 $[3M^* + 2, Cl = 37]^+$. *Anal*. Calcd for $C_{12}H_{14}ClN_2O_5S$: C, 43.18; H, 4.23; N, 8.39. Found: C, 42.97; H, 4.20; N, 8.18.

Compound (4b). mp: 107–109°C (Lit mp 98°C [3a]), R_f (CH_2Cl_2): 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2H), 7.58 (s, 1H, NCH=), 7.34 (br s, 1H, OH), 7.28–7.26 (m, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.00, 147.48, 137.64, 137.57, 130.07, 129.93, 119.65, 113.01, 61.39, 20.94, 14.36. ESI MS (positive mode) *m/z*: 199.8, 246.3 $[M + 1]^+$, 269.3 $[M + 23]^+$, 278.6, 398.2, 515.2 $[2M + 23]^+$.

Compound (4c). mp: 121–122°C, R_f (CH_2Cl_2): 0.21. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80–7.77 (m, 2H), 7.58 (s, 1H, NCH=), 7.48–7.44 (m, 2H), 7.34 (br s, 1H, OH), 4.51 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.75, 147.63, 139.50, 138.47, 130.86, 121.19, 112.67, 92.06, 61.63, 14.36. ESI MS (positive mode) *m/z*: 359.0 $[M + 1]^+$, 381.0 $[M + 23]^+$, 738.9 $[2M + 23]^+$. *Anal*. Calcd for $C_{12}H_{11}IN_2O_3$: C, 40.25; H, 3.10; N, 7.82. Found: C, 40.03; H, 3.04; N, 7.58.

Compound (4d). mp: 208–210°C (Lit mp 220°C[4d]), R_f (CH_2Cl_2): 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 9.1 Hz, 2H), 7.90 (d, *J* = 9.1 Hz, 2H), 7.71 (s, 1H), 7.38 (s, 1H, OH), 4.53 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.47, 147.93, 146.31, 143.95, 132.43, 125.27, 119.28, 112.76, 61.90, 14.29. ESI MS (positive mode) *m/z*: 278.1 $[M + 1]^+$, 300.1 $[M + 23]^+$, 577.2 $[2M + 23]^+$.

Typical experimental procedure B

Synthesis of pyrazole 6a. A fine powder of DMAP (27 mg, 0.22 mmol) was added in one portion to a precooled (ice-bath) solution of ethyl chloroformate (19 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) followed by 5-min stirring. A solution of hydrazone **3a** (19 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to this colorless mixture at the same temperature. The yellow reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (5 mL), and washed with HCl (5% aq soln, 2 × 1 mL) to remove DMAP (in the case of **3c**, no washing with the acid was performed). The organic solution was dried (Na_2SO_4) and concentrated, and the product **6a** was isolated from the residue by flash chromatography over silica gel (eluted with the mixture hexane–diethyl ether, 1:1) as a colorless solid (20 mg, 94%).

Compound (6a). mp: 109–110°C, R_f (C_6H_{14}–Et_2O, 1:1): 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.01, 152.68, 150.14, 137.48, 134.01, 129.61, 121.31, 120.18, 112.30, 65.37, 60.95, 40.47, 14.26, 14.16. ESI MS (positive mode) *m/z*: 348.1 $[M + 1]^+$, 370.1 $[M + 23]^+$, 695.2 $[2M + 1]^+$, 717.3 $[2M + 23]^+$. *Anal*. Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.68; H, 6.06; N, 12.10.

Compound (6b). mp: 75–76°C, R_f (CH_2Cl_2): 0.26. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.26

(d, $J = 7.7$ Hz, 2H), 4.44 (q, $J = 6.9$ Hz, 2H), 4.37 (q, $J = 6.9$ Hz, 2H), 2.40 (s, 3H), 1.42 (t, $J = 6.9$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.84, 152.59, 137.90, 137.68, 137.26, 134.80, 129.99, 120.22, 119.75, 65.46, 61.10, 20.95, 14.24, 14.15. ESI MS (positive mode) *m/z*: 319.1 $[M + 1]^+$, 341.1 $[M + 23]^+$. *Anal*. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.37; H, 5.74; N, 8.79.

Compound (6c). mp: 112–113°C, R_f (CH_2Cl_2): 0.31. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 4.45 (q, $J = 7.0$ Hz, 2H), 4.38 (q, $J = 7.0$ Hz, 2H), 1.42 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.60, 152.48, 139.16, 138.57, 137.95, 135.53, 121.31, 119.97, 92.47, 65.57, 61.27, 14.22, 14.14. ESI MS (positive mode) *m/z*: 431.1 $[M + 1]^+$, 453.1 $[M + 23]^+$, 861.0 $[2M + 1]^+$, 883.0 $[2M + 23]^+$. *Anal*. Calcd for $C_{15}H_{15}IN_2O_5$: C, 41.88; H, 3.51; N, 6.51. Found: C, 41.58; H, 3.50; N, 6.30.

Compound (6d). mp: 133–134°C, R_f (CH_2Cl_2): 0.20. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, $J = 9.1$ Hz, 2H), 8.23 (s, 1H), 7.95 (d, $J = 9.1$ Hz, 2H), 4.46 (q, $J = 7.1$ Hz, 2H), 4.39 (q, $J = 7.1$ Hz, 2H), 1.43 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.28, 152.33, 146.59, 143.54, 138.45, 136.87, 125.32, 120.20, 119.50, 65.76, 61.54, 14.18, 14.12. ESI MS (positive mode) *m/z*: 350.1 $[M + 1]^+$, 372.1 $[M + 23]^+$, 699.2 $[2M + 1]^+$, 721.2 $[2M + 23]^+$. *Anal*. Calcd for $C_{15}H_{15}N_3O_7$: C, 51.58; H, 4.33; N, 12.03. Found: C, 51.39; H, 4.36; N, 11.99.

Compound (6e). mp: 102–103°C, R_f (CH_2Cl_2–Et_2O, 1:1): 0.65. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 7.56 (d, $J = 5.4$ Hz, 1H), 7.50 (d, $J = 5.4$ Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 3H), 1.42 (t, $J = 7.1$ Hz, 3H), 1.41 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.74, 160.61, 152.60, 141.49, 136.33, 135.39, 130.56, 130.53, 127.05, 125.89, 125.87, 121.74, 65.43, 61.21, 61.19, 52.50, 52.48, 14.21, 14.16. ESI MS (positive mode) *m/z*: 369.1 $[M + 1]^+$, 391.1 $[M + 23]^+$, 737.2 $[2M + 1]^+$, 759.2 $[2M + 23]^+$. *Anal*. Calcd for $C_{15}H_{16}N_2O_7S$: C, 48.91; H, 4.38; N, 7.60. Found: C, 48.78; H, 4.35; N, 7.51.

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[14] (a) In the carbon spectra of pyrazoles **6a**,**e** a doubling of several signals was observed, namely, N=CH, $COO\underline{CH_3}$, $COO\underline{CH_2}$, thienyl C_4. These effects could be rationalized as hindered rotation of the corresponding groups arising from a steric effect of the neighboring substituents or from additional hydrogen bonding; (b) Crystallographic data for **6d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-872146. Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

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