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An Efficient One-pot Synthesis of Aryl-substituted 1-(Thiazol-2-yl)-1*H*-pyrazole-3-carboxylates via a Hantzsch Synthesis-Knorr Reaction Sequence

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The treatment of α-bromoalkyl aryl ketones and 2-(propan-2-ylidene)hydrazine carbothioamide afforded 4-aryl-2-(2-(propan-2-ylidene)hydrazinyl)thiazoles via a Hantzsch-thiazole synthesis, which reacted with 4-aryl-2,4-diketoesters via a sequential Knorr-pyrazole reaction to deliver a variety of aryl-substituted ethyl 1-(thiazol-2-yl)-1*H*-pyrazole-3-carboxylates in a one-pot fashion with moderate to high yields. The key intermediates 4-aryl-2,4-diketoesters, existing as its enolic lithium salt, were synthesized *in situ* by a high-yield *tert*-BuOLi-mediated Claisen condensation of alkylphenones and diethyl oxalate. This class of elegant molecule comprises aryl groups on the two different heterocyclic cores, and the configurations of two representative molecules were determined by single crystal X-ray crystallography.

Keywords one-pot synthesis, Claisen condensation, Hantzsch synthesis, Knorr reaction, 1-(thiazol-2-yl)pyrazole-3-carboxylates

Introduction

Recently, a number of organic molecular architectures comprising polyheterocyclic moieties have attracted considerable attention due to their wide spectrum of biological activities.[1] Among polyheteroatomic rings, pyrazoles and thiazoles have exhibited a great variety of biological properties and practical applications. Furthermore, the combination of the pyrazole and thiazole into a N^1,C^2-tethered scaffold [referred to as 1-(thiazol-2-yl)pyrazole] imparts distinct and interesting structural characteristics with unique diheterocycle's functionality and more molecular diversity. Of the 1-(thiazol-2-yl)pyrazole compounds, a variety of bioactivities such as analgesic,[2] anti-inflammatory,[3] antibacterial,[4] antiviral[5] as well as inhibitors of *Candida elegans*[6] and fibrinogen-mediated platelet aggregation[7] (Figure 1a), have been revealed.

Although several investigations have assured a continuous attention on 1-(thiazol-2-yl)pyrazole derivatives,[8] the approach to functionalized 1-(thiazol-2-yl)pyrazole-3-carboxylates was still sparse. Concretely speaking, the two reports relying on intermediates thiazol-2-ylhydrazonyl chlorides were inconvenient and step-uneconomical.[9] On the other hand, the pyrazole-3-carboxylate scaffold has been a focus in medicinal chemistry, in particular, it has served as cannabinoid-1 (CB1) receptor antagonists[10] (Figure 1b). The synthesis of the promising drug scaffold with highly structural diversity is greatly desirable for drug discovery. As a part of our program aimed at constructing functionalized pyrazoles[11a,11c] and thiazoles,[11b] we attempted to synthesize new aryl-substituted 1-(thiazol-2-yl)pyrazole-3-carboxylates in an efficient and step-economical manner. Generally, novel and important polyheterocyclic compounds would have enhanced biological activity or vagarious property. There are two traditional methods to concisely create the 1-(thiazol-2-yl)pyrazoles by means of hydrazine carbothioamide as an initial molecular backbone (Scheme 1): (a) Knorr-pyrazole reaction with 4-aryl-2,4-diketoesters, followed by Hantzsch-thiazole synthesis using α-bromoalkyl aryl ketones; (b) Hantzsch-thiazole synthesis of intermediate **B** using α-bromoalkyl aryl ketones, followed by Knorr-pyrazole reaction with 4-aryl-2,4-diketoesters. Herein, we reported an efficient one-pot synthesis of ethyl 1-(4-arylthiazol-2-yl)-5-aryl-1*H*-pyrazole-3-carboxylates (**1**) in moderate to high yields via a Hantzsch synthesis-Knorr reaction sequence, based on the recent work.[11]

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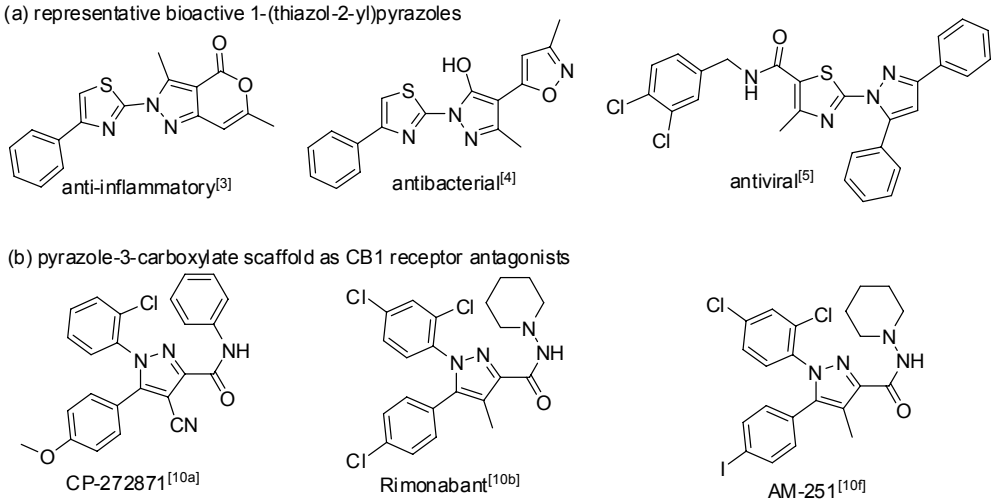
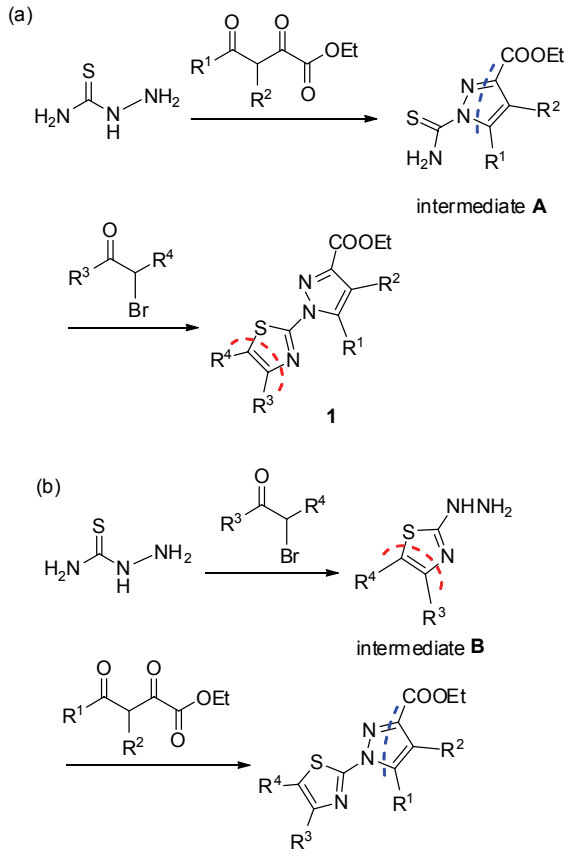


Figure 1 Structure of 1-(thiazol-2-yl)pyrazoles and CB1 receptor antagonists.

Scheme 1 Two possible methods for the synthesis of aryl-substituted 1-(thiazol-2-yl)-1*H*-pyrazole-3-carboxylates (**1**, R^1, R^3= aryl)



Results and Discussion

Firstly, following the route of Scheme 1a, the enolic lithium salt of ethyl 2,4-dioxo-4-phenylbutanoate (**3a**), freshly prepared via *tert*-BuOLi-mediated Claisen condensation of acetophenone (**2a**) and diethyl oxalate in THF,[11a] was added to an EtOH solution of hydrazinecarbothioamide and concentrated hydrochloric acid in order to prepare the pivotal ethyl 1-thiocar-bamoyl-5-phenyl-1*H*-pyrazole-3-carboxylate (**A'**, Scheme 2a).[10d,11c,12] However, the unexpected dethiocarbamoylation overwhelmingly occurred, with ethyl 5-phenyl-1*H*-pyrazole-3-carboxylate (**4**) as a major product in 87% yield. It was found that N^1-thiocarbamoyl group is susceptible to acidic reaction conditions giving rise to an unusual dethiocarbamoylation. Any desired **A'** was not observed indicating that the route was difficult to pursue the set goal. Next, we turned our attention to the reaction of α-bromoacetophenone (**5a**) with hydrazine carbothioamide (Scheme 1b). Likewise, to our disappointment, the dominant Hantzsch 1,3,4-thiadiazine synthesis suppressed the desired Hantzsch-thiazole synthesis leading to the undesired **6** in 78% yield, without detectable target product 2-hydrazino-4-phenylthiazole (**B'**, Scheme 2b, see Supporting Information).[13]

To avoid the unwanted 1,3,4-thiadiazines **6**, an alternative molecular backbone 2-(propan-2-ylidene)hydrazinecarbothioamide was employed to carry out the desired Hantzsch-thiazole synthesis. Indeed, **5a** smoothly reacted in EtOH to accomplish the target thiazoles **7a** in an excellent yield of 91%, fully excluding **6** (Scheme 2c). But, subsequent deisopropylidenation with hydrazine hydrate only afforded **B'** in a low yield of 53%, as reported.[14] On the other hand, the desired ethyl 5-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1aa**) was achieved highly efficiently through a hydrochloric acid-promoted Knorr-pyrazole reaction of the resultant **B'** and the preprepared **3a** in 94% yield.[11c]

Note that ketone exchange reactions of ketimines with other ketones directly provided a new ketimines.[15] Reasonably, we concluded that the desired **1aa** might also be afforded via reaction of ethyl 2,4-dioxo-4-phenylbutanoate (free **3a**) and **7a**, with no need for an additional deisopropylidenation (Scheme 2c). As expected, the treatment of **3a** and **7a**, under the mediation of hydrochloric acid, efficiently achieved **1aa** in an excellent yield of 93%. To clarify the selectivity of the

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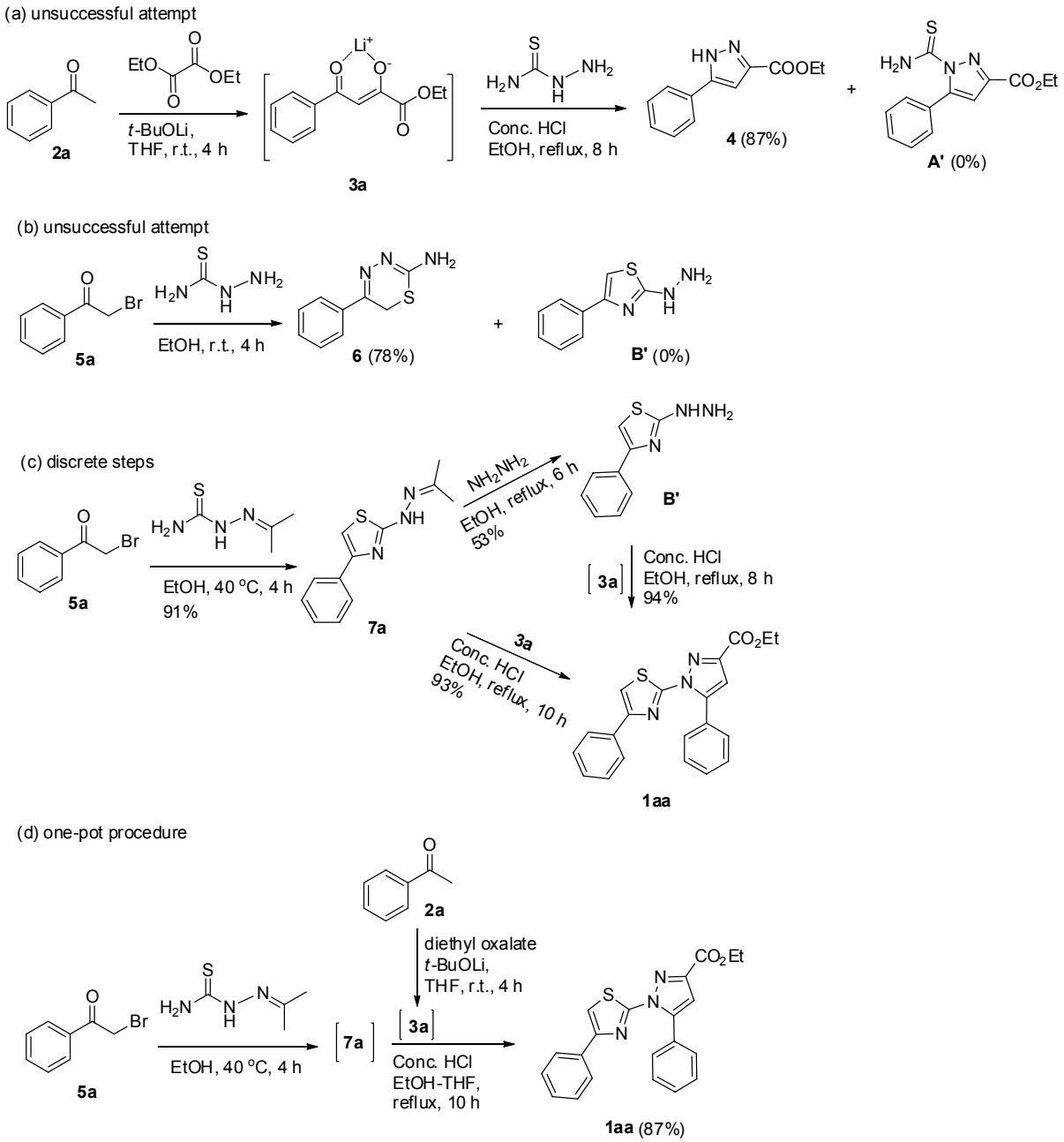
Scheme 2 Tentative approaches for the target product **1aa**



reaction, the NMR-based structure of **1aa** was further determined by single crystal X-ray crystallography (Figure 2). The acquired results unambiguously confirmed its 1-(thiazol-2-yl)pyrazole-3-carboxylate motif as a result of the regioselective Knorr reaction (Figure S1, see Supporting Information). Additionally, the isomeric 1-(thiazol-2-yl)-1*H*-pyrazole-5-carboxylate product was undetected in the reaction.[16]

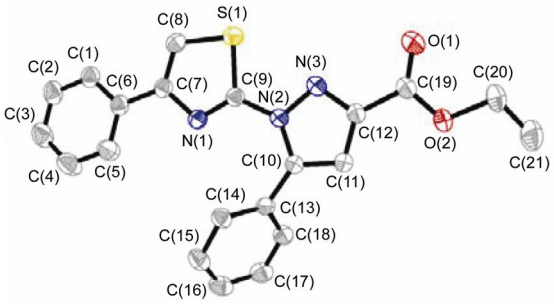


Figure 2 Single crystal structure of **1aa**.

It was noticed that, THF, used in the Claisen condensation, was well compatible with EtOH, used in Hantzsch synthesis and Knorr reaction.[17] Besides, the acidic conditions were uniformly required for the formation of the thiazole and pyrazole rings. Naturally, we attempted to assemble the discrete reaction steps into a one-pot procedure. To our delight, the reaction of **5a** with 2-(propan-2-ylidene)hydrazinecarbothioamide was conducted in EtOH at 40 ℃ for 4 h, followed by a direct cyclization with freshly prepared **3a** (unseparated),

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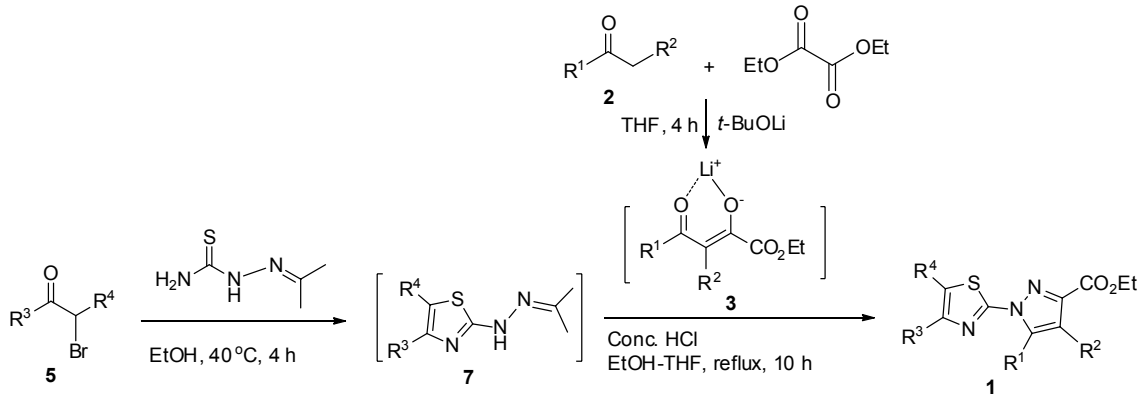
under the mediation of hydrochloric acid and reflux for a prolonged time of 10 h, to ultimately deliver the desired **1aa** in a yield of 87%. The combination of sequential Hantzsch synthesis and Knorr reaction, wherein making use of the unseparated **3a** arisen from the Claisen condensation, virtually attained a step-, energy-, separation- and purification-economical one-pot procedure with a higher combined yield, in comparison with the discrete steps (Scheme 2d).

With the convenient one-pot procedure in hand, the scope of the substrates alkylphenones (**2**) and α-bromoalkyl aryl ketones (**5**) was evaluated to identify the feasibility of the procedure for synthesis of **1** (Table 1). Firstly, alkylphenones **2b**—**2i** containing different R^1 and R^2 were assessed based on α-bromoacetophenone (**5a**) (Entries 1—8). Compared to unsubstituted acetophenone (**2a**, $R^1=C_6H_5$, $R^2=H$; Scheme 2d), as for the acetophenones **2b** and **2c**, the procedure delivered the desired products **1ba** and **1ca** in slightly low yields of 83% and 81%, respectively (Entries 1 and 2). The results indicated that the steric hindrance of substituent(s), particularly an *ortho*-substituent at benzene ring, expressed an impact on the Claisen condensation and Knorr reaction. Next, the products **1da**—**1fa** were obtained in lower yields of 72%—75% from propiophenones **2d**—**2f**, showing that the steric hindrance of R^2 ($R^2=CH_3$) possessed a striking impact on the efficacy of the procedure (Entries 3—5). Furthermore, when R^2 was designated as larger substituents ($R^2=C_2H_5$, C_6H_5), the yields of the products **1ga** and **1ha** sharply reduced to 68% and 60%, respectively (Entries 6 and 7), comparing with the yield of **1aa** (Scheme 2d). In contrast, the steric effect was not observed in a rigid cycloketones 1-tetralone (**2i**), and the procedure offered the corresponding product **1ia** in a high yield of 85% (Entry 8).

Afterwards, α-bromoalkyl aryl ketones **5b**—**5h** containing different R^3 and R^4 were evaluated based on acetophenone (**2a**) (Entries 9—15). As for α-bromo-substituted acetophenones **5b** ($R^3=4\text{-}ClC_6H_4$, $R^4=H$) and **5c** ($R^3=3,4\text{-}O(CH_2)_3OC_6H_3$, $R^4=H$), the procedure efficiently afforded the corresponding prod-

Table 1 One-pot synthesis of aryl-substituted 1-(thiazol-2-yl)-1*H*-pyrazole-3-carboxylates[a]



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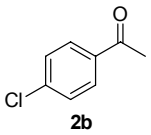
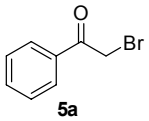
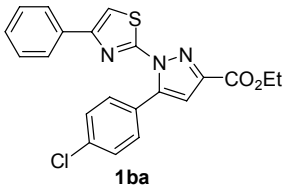
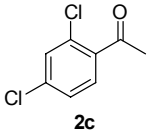
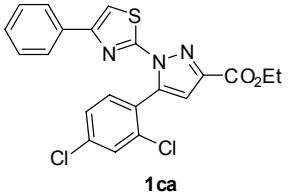
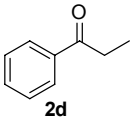
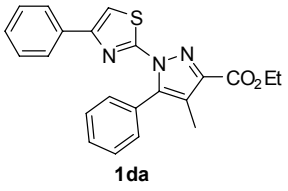
1	 **2b**	 **5a**	 **1ba**	83
2	 **2c**	**5a**	 **1ca**	81
3	 **2d**	**5a**	 **1da**	75

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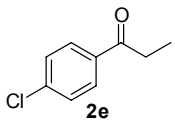
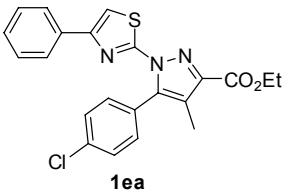
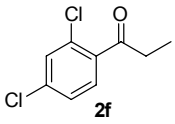
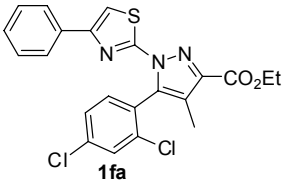
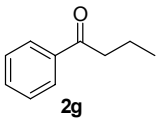
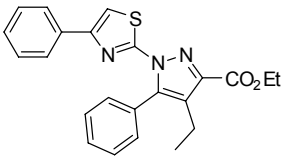
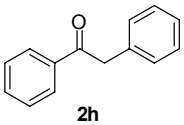
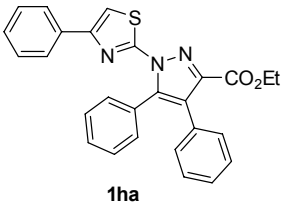
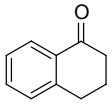
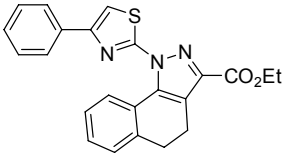
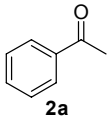
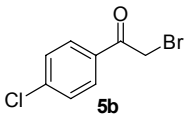
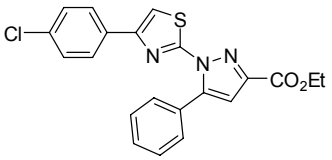
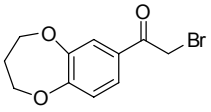
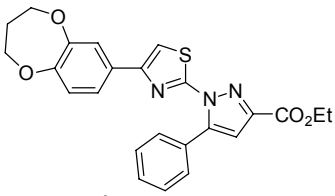
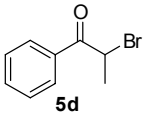
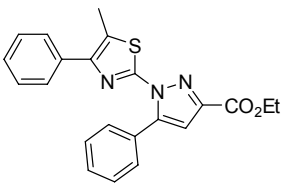
Continued

Entry	2	5	1	Yield[b]/%
4	 **2e**	**5a**	 **1ea**	73
5	 **2f**	**5a**	 **1fa**	72
6	 **2g**	**5a**	 **1ga**	68
7	 **2h**	**5a**	 **1ha**	60
8	 **2i**	**5a**	 **1ia**	85
9	 **2a**	 **5b**	 **1ab**	86
10	**2a**	 **5c**	 **1ac**	83
11	**2a**	 **5d**	 **1ad**	78

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Continued

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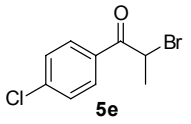
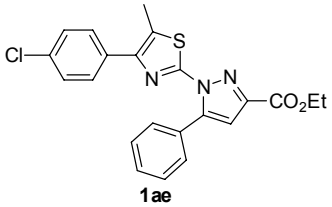
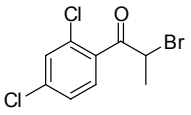
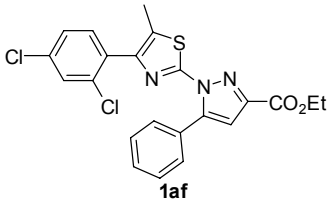
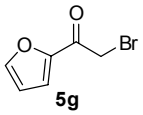
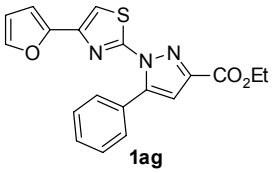
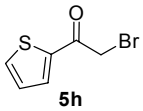
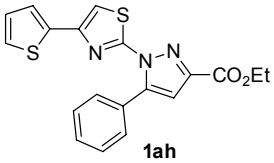
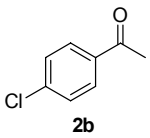
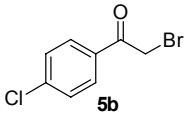
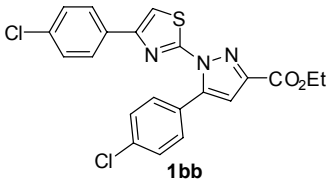
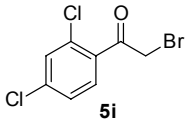
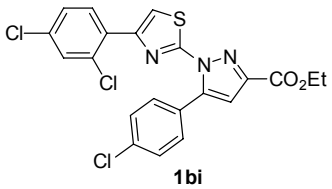
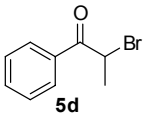
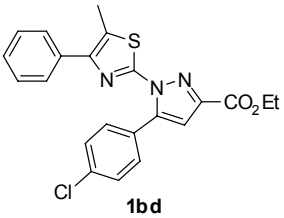
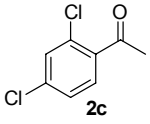
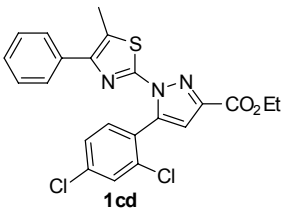
12	**2a**	 **5e**	 **1ae**	76
13	**2a**	 **5f**	 **1af**	72
14	**2a**	 **5g**	 **1ag**	82
15	**2a**	 **5h**	 **1ah**	84
16	 **2b**	 **5b**	 **1bb**	82
17	**2b**	 **5i**	 **1bi**	80
18	**2b**	 **5d**	 **1bd**	74
19	 **2c**	**5d**	 **1cd**	72

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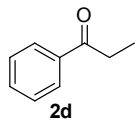
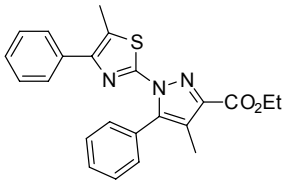
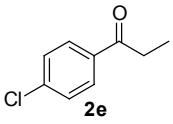
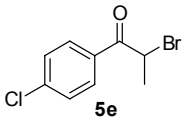
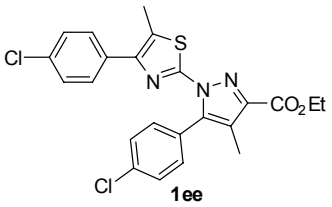
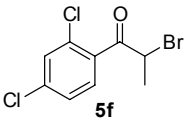
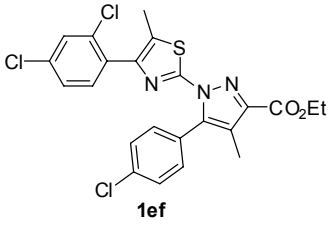
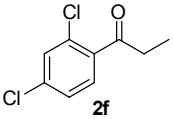
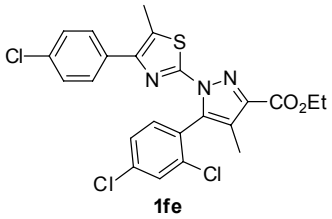
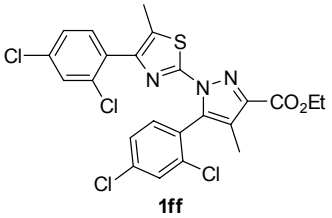
Continued

Entry	2	5	1	Yield[b]/%
20	 **2d**	**5d**	 **1dd**	68
21	 **2e**	 **5e**	 **1ee**	65
22	**2e**	 **5f**	 **1ef**	64
23	 **2f**	**5e**	 **1fe**	64
24	**2f**	**5f**	 **1ff**	59

[a] For the pre-prepared **3** (unseparated, via Claisen condensation): alkylphenones (**2**, 5.0 mmol), diethyl oxalate (6.0 mmol, 0.88 g), *t*-BuOLi (6.5 mmol, 0.52 g) in anhydrous THF (15mL), r.t., 4 h. The one-pot procedure: α-bromoalkyl aryl ketones (**5**, 5.0 mmol), 2-(propan-2-ylidene)hydrazinecarbothioamide (5.0 mmol, 0.66 g) in EtOH (15mL), 40 ℃, 4 h; followed by addition of the pre-prepared **3** and conc. HCl (12.5 mmol, 1.0 mL), reflux, 10 h. [b] Isolated yield.

ucts **1ab** and **1ac** in high yields of 86% and 83%, respectively (Entries 9 and 10). However, with respect to α-bromo-substituted propiophenones **5d**—**5f** (R^4=CH_3), the desired products **1ad**—**1af** were obtained in markedly reduced yields of 72%—78% (Entries 11—13). These results clearly demonstrated that a major steric hindrance of R^4 and minor hindrance of the substitutent(s) at the benzene ring emerged in the Hantzsch-thiazole synthesis. It was noteworthy that the α-bromoethyl heteroaryl ketones **5g** and **5h** were smoothly subjected to the procedure resulting in the elegant triheterocyclic molecules **1ag** and **1ah** in high yields of 82% and 84%, respectively (Entries 14 and 15).

To further explore the generality of this one-pot procedure, more densely substituted 1-(thiazol-2-yl)-pyrazole-3-carboxylates (**1**) were synthesized by examining both **5** and **2** (Entries 16—24). With regard to α-bromo-substituted acetophenones **5b** and **5i**, the procedure still took effect well to afford the desired **1bb** and **1bi** in good yields of 82% and 80%, respectively, from the same substrate **2b** (Entries 16 and 17), once again suggesting the slight steric hindrance of the sub-

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stitutent(s) at the benzene ring of R^3. Next, when α-bromo-substituted propiophenones **5d** was used, acetophenones **2b** and **2c** were converted to the corresponding products **1bd** and **1cd** in significantly reduced yields of 74% and 72%, respectively (Entries 18 and 19), consistently indicating the major detrimental influence of the R^4. Moreover, with larger steric hindrance-containing propiophenones (**2d**, **2e** and **2f**) and α-bromo-substituted propiophenones (**5d**, **5e** and **5f**) being employed, the procedure provided fully substituted 1-(thiazol-2-yl)pyrazoles **1dd**, **1ee**, **1ef**, **1fe** and **1ff** in moderate yields of 59% — 68% (Entries 20 — 24), wherein the drastically reduced yields should be attributed to the dual impacts of R^2 and R^4. These results also clearly demonstrated that the one-pot procedure was qualified for constituting more complex molecular architecture of 1-(thiazol-2-yl)pyrazoles.

Finally, the geometrical configuration of a fully substituted product **1ee** was also determined by single crystal X-ray crystallography, and the asymmetrical unit consists of two crystallographically independent molecules of **1ee** (Figure 3).[18] The crystal structure is further stabilized by an intermolecular π···π interaction and an intramolecular edge-to-face C—H···π interaction (Figure S2, see Supporting Information).

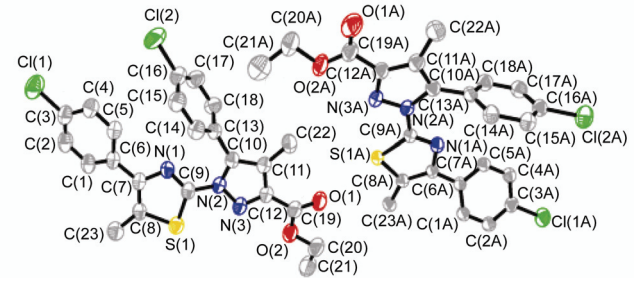

Figure 3 Single crystal structure of **1ee** (Table 1, Entry 21).

Conclusions

In summary, an efficient one-pot synthesis of aryl-substituted ethyl 1-(thiazol-2-yl)pyrazole-3-carboxylates has been developed for the first time. We successfully combined the Hantzsch-thiazole synthesis and Knorr-pyrazole reaction into a one-pot procedure, by using the preformed enolic lithium salt of 4-aryl-2,4-diketoesters resulting from the Claisen condensation. The procedure provides a general and practical method for the regioselective construction of multi-substituted 1-(thiazol-2-yl)-pyrazoles from readily available diethyl oxalate, alkylphenones, 2-(propan-2-ylidene)hydrazinecarbothioamide and α-bromoalkyl aryl ketones. In addition, the geometrical configurations of two representative products were determined by the single crystal X-ray crystallography. Considering availability of the feedstocks, simplicity of the procedure, broad scope of the substrates and importance of the products, the methodology is expected to have synthetically potential applications in medicinal chemistry.

Experimental

General information

Unless otherwise indicated, all reagents were obtained from commercial sources and used as received without further purification. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (TLC, precoated silica gel plates containing HF_{254}). All solvents were only dried over 4 Å molecular sieves. Melting points were determined using an open capillaries and uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. HRMS were carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer and Micromass GCTTM gas chromatograph-mass spectrometer. Crystal data of **1aa** and **1ee** were collected on a Brüker Smart APEX II CCD diffractometer with monochromated Mo Kα radiation (λ=0.71073 Å) at 293 K, and operating in the ϕ-ω scan mode. The structures were solved by direct methods and refined on F^2 by full matrix least-squares methods using SHELXTL.

Tentative approaches for the target product 1aa

The tentative approaches were carefully conducted in Supporting Information with the detailed procedures and data confirmation.

One-pot synthesis of ethyl 1-(thiazol-2-yl)-5-aryl-1*H*-pyrazole-3-carboxylates

24 products of various aryl-substituted 1-(thiazol-2-yl)-1*H*-pyrazole-3-carboxylates were further synthesized in the yields of 59%—86% with the one-pot procedure.

Preparation of 3 via Claisen condensation

Diethyl oxalate (6.0 mmol, 0.88 g) was added to a solution of alkylphenones (**2**, 5.0 mmol) and *tert*-BuOLi (6.5 mmol, 0.52 g) in anhydrous THF (15 mL), and the resulting mixture was allowed to stir at room temperature for 4 h. Subsequently, the prepared solution of **3** was subjected to the one-pot synthesis as below.

One-pot synthesis of 1

2-(Propan-2-ylidene)hydrazinecarbothioamide (5 mmol, 0.66 g) was added to a solution of α-bromoalkyl aryl ketones (**5**, 5.0 mmol) in EtOH (15 mL), and the mixture was stirred at 40 ℃ for 4 h. Then, the preprepared solution of **3** and conc. HCl (12.5 mmol, 1.0 mL) were added at room temperature to the reaction mixture, and the resulting mixtures were refluxed for another 10 h. After completion of the reaction as monitored by TLC, the reaction solution was concentrated *in vacuo* to remove EtOH and THF affording a residue, to which were added H_2O (15 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×2). Finally, the combined organic phase was washed with brine (35 mL),

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dried over anhydrous sodium sulfate, and concentrated to give a crude product, which was purified by column chromatography (200—300 mesh silica gel, petroleum ether/ethyl acetate, *V*∶ *V*=2∶1) to give the corresponding **1**.

Ethyl 5-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1aa**): pale yellow solid, 1.76 g (94%), m.p. 120—122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.59—7.50 (m, 4H), 7.48—7.42 (m, 3H), 7.35—7.27 (m, 4H), 7.00 (s, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 1.45 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.7, 159.7, 152.4, 146.0, 145.6, 133.6, 129.8 (2C), 129.4, 129.2, 128.6 (2C), 128.3, 128.0 (2C), 125.9 (2C), 111.7, 111.4, 61.5, 14.4; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{21}H_{18}N_3O_2S$ 376.1120, found 376.1111.

Ethyl 5-(4-chlorophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ba**): pale yellow solid, 1.70 g (83%), m.p. 122—123 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.53 (d, *J*=7.2 Hz, 2H), 7.49 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.38—7.27 (m, 4H), 6.99 (s, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.5, 159.6, 152.4, 145.6, 144.6, 135.4, 133.5, 131.2 (2C), 128.7 (2C), 128.4, 128.2 (2C), 127.8, 125.8 (2C), 111.8, 111.3, 61.6, 14.3; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{21}H_{17}ClN_3O_2S$ 410.0730, found 410.0729.

Ethyl 5-(2,4-dichlorophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ca**): pale yellow solid, 1.80 g (81%), m.p. 134—135 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.54 (s, 1H), 7.42—7.35 (m, 4H), 7.33—7.27 (m, 4H), 7.00 (s, 1H), 4.48 (q, *J*=7.2 Hz, 2H), 1.45 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.4, 159.3, 152.3, 145.6, 140.8, 136.2, 135.8, 133.5, 132.5, 129.3, 128.7 (2C), 128.5, 128.3, 127.0, 125.7 (2C), 112.6, 110.5, 61.6, 14.3; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{21}H_{16}Cl_2N_3O_2S$ 444.0340, found 444.0336.

Ethyl 4-methyl-5-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1da**): pale yellow solid, 1.46 g (75%), m.p. 143—144 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.51—7.46 (m, 3H), 7.46—7.39 (m, 4H), 7.31—7.23 (m, 4H), 4.47 (q, *J*=7.2 Hz, 2H), 2.25 (s, 3H), 1.46 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.5, 159.9, 152.2, 143.7, 143.0, 133.7, 130.6 (2C), 129.4, 128.9, 128.6 (2C), 128.2 (3C), 125.8 (2C), 121.4, 110.6, 61.2, 14.4, 9.5; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{22}H_{20}N_3O_2S$ 390.1276, found 390.1280.

Ethyl 5-(4-chlorophenyl)-4-methyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ea**): pale yellow solid, 1.55 g (73%), m.p. 127—129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.52—7.43 (m, 4H), 7.40—7.29 (m, 5H), 7.28 (s, 1H), 4.50 (q, *J*=7.2 Hz, 2H), 2.27 (s, 3H), 1.48 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.3, 159.8, 152.2, 143.7, 141.7, 135.2, 133.6, 132.0 (2C), 128.7 (2C), 128.4 (2C), 128.3, 128.0, 125.8 (2C), 121.6, 110.4, 61.3, 14.4, 9.4; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{22}H_{19}ClN_3O_2S$ 424.0887, found 424.0890.

Ethyl 5-(2,4-dichlorophenyl)-4-methyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1fa**): pale yellow solid, 1.65 g (72%), m.p. 138—140 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.57 (d, *J*=2.0 Hz, 1H), 7.43 (dd, *J*=8.2, 2.0 Hz, 1H), 7.37—7.28 (m, 6H), 7.24 (s, 1H), 4.48 (q, *J*=7.2 Hz, 2H), 2.20 (s, 3H), 1.47 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.2, 159.6, 152.2, 143.6, 138.5, 136.3, 136.1, 133.6, 132.9, 129.4, 128.7 (2C), 128.2, 128.1, 127.1, 125.7 (2C), 122.5, 110.0, 61.3, 14.4, 9.2; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{22}H_{18}Cl_2N_3O_2S$ 458.0497, found 458.0492.

Ethyl 4-ethyl-5-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ga**): pale yellow solid, 1.37 g (68%), m.p. 135—136 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.53—7.48 (m, 3H), 7.42—7.38 (m, 4H), 7.30—7.22 (m, 4H), 4.48 (q, *J*=7.2 Hz, 2H), 2.67 (q, *J*=7.6 Hz, 2H), 1.46 (t, *J*=7.2 Hz, 3H), 1.15 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.3, 159.8, 152.2, 143.2, 142.7, 133.7, 130.5 (2C), 129.6, 128.9, 128.5 (2C), 128.20 (2C), 128.15, 127.9, 125.8 (2C), 110.4, 61.2, 17.1, 15.6, 14.3; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{23}H_{22}N_3O_2S$ 404.1433, found 404.1434.

Ethyl 4,5-diphenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ha**): pale yellow solid, 1.35 g (60%), m.p. 181—183 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.50—7.47 (d, *J*=6.8 Hz, 2H), 7.37—7.22 (m, 14H), 4.34 (q, *J*=7.2 Hz, 2H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.9, 159.6, 152.4, 143.2, 143.1, 133.6, 130.9 (2C), 130.8, 130.5 (2C), 128.86, 128.40, 128.6 (2C), 128.3, 128.0 (2C), 127.7 (2C), 127.4, 126.2, 125.9 (2C), 111.1, 61.3, 14.1; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{27}H_{22}N_3O_2S$ 452.1433, found 452.1430.

Ethyl 1-(4-phenylthiazol-2-yl)-4,5-dihydro-1*H*-benzo[g]indazole-3-carboxylate (**1ia**): pale yellow solid, 1.70 g (85%), m.p. 164—165 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.94 (d, *J*=7.2 Hz, 1H), 7.86 (d, *J*=7.2 Hz, 2H), 7.50 (s, 1H), 7.42 (t, *J*=7.2 Hz, 2H), 7.35 (t, *J*=7.2 Hz, 2H), 7.29 (t, *J*=7.2 Hz, 1H), 7.21 (t, *J*=7.2 Hz, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 3.10—2.99 (m, 4H), 1.45 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 162.2, 160.7, 152.5, 141.9, 141.4, 137.7, 133.8, 128.9 (3C), 128.5, 128.4, 126.2, 126.1 (2C), 125.8, 125.2, 124.3, 112.6, 61.3, 30.1, 20.1, 14.4; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{23}H_{20}N_3O_2S$ 402.1276, found 402.1273.

Ethyl 1-(4-(4-chlorophenyl)thiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1ab**): pale yellow solid, 1.76 g (86%), m.p. 124—125 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.53—7.50 (m, 2H), 7.49—7.41 (m, 5H), 7.31 (s, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 6.99 (s, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.6, 159.9, 151.2, 145.9, 145.6, 134.0, 132.1, 129.8 (2C), 129.3, 129.2, 128.8 (2C), 128.0 (2C), 127.1 (2C), 111.8, 111.6, 61.5, 14.3; HRMS (ESI) *m*/*z*: [M+H$^+$] calcd for $C_{21}H_{17}ClN_3O_2S$ 410.0730, found 410.0722.

Ethyl 1-(4-(3,4-dihydro-2*H*-benzo[b]1,4-dioxepin-

7-yl)thiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1ac**): pale yellow solid, 1.86 g (83%), m.p. 108—109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54—7.40 (m, 5H), 7.20 (s, 1H), 7.17 (d, J=2.0 Hz, 1H), 7.09 (dd, J=8.4, 2.0 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J=8.4 Hz, 1H), 4.46 (q, J=7.2 Hz, 2H), 4.21 (t, J=5.6 Hz, 4H), 2.19 (quint, J=5.6 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7, 159.5, 151.7, 151.4, 151.2, 146.0, 145.5, 129.8 (2C), 129.3 (2C), 129.2, 128.0 (2C), 121.7, 121.1, 119.2, 111.6, 110.6, 70.5 (2C), 61.5, 31.7, 14.4; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{24}H_{22}N_3O_4S$ 448.1331, found 448.1334.

Ethyl 1-(5-methyl-4-phenylthiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1ad**): pale yellow solid, 1.52 g (78%), m.p. 174—176 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52—7.49 (m, 2H), 7.45—7.36 (m, 5H), 7.33 (t, J=7.2 Hz, 2H), 7.28 (d, J=7.2 Hz, 1H), 7.00 (s, 1H), 4.46 (q, J=7.2 Hz, 2H), 2.58 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8, 155.2, 147.9, 145.8, 145.4, 134.2, 129.6 (2C), 129.3, 129.1, 128.3 (2C), 128.2 (2C), 128.1 (2C), 128.1, 127.6, 111.2, 61.4, 14.4, 12.8; HRMS (ESI) *m/z*: [M+ H$^+$] calcd for $C_{22}H_{20}N_3O_2S$ 390.1276, found 390.1274.

Ethyl 1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1ae**): pale yellow solid, 1.61 g (76%), m.p. 143—144 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50—7.39 (m, 5H), 7.32—7.27 (m, 4H), 6.99 (s, 1H), 4.46 (q, J=7.2 Hz, 2H), 2.56 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7, 155.4, 146.5, 145.7, 145.4, 133.5, 132.7, 129.6 (2C), 129.3 (2C), 129.3, 129.1, 128.4 (2C), 128.2, 128.1 (2C), 111.3, 61.4, 14.3, 12.8; HRMS (ESI) *m/z*: [M+ H$^+$] calcd for $C_{22}H_{19}ClN_3O_2S$ 424.0887, found 424.0884.

Ethyl 1-(4-(2,4-dichlorophenyl)-5-methylthiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1af**): pale yellow solid, 1.65 g (72%), m.p. 138—140 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45—7.42 (m, 3H), 7.39—7.35 (m, 3H), 7.23 (dd, J=8.4, 2.1 Hz, 1H), 7.11 (d, J=8.4 Hz, 1H), 7.00 (s, 1H), 4.45 (t, J=7.2 Hz, 2H), 2.33 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8, 155.7, 146.2, 145.6, 145.4, 135.0, 134.6, 132.6, 132.2, 131.5, 129.6, 129.2 (2C), 129.2, 128.7, 128.3 (2C), 126.9, 110.8, 61.4, 14.3, 12.3; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{22}H_{18}Cl_2N_3O_2S$ 458.0497, found 458.0495.

Ethyl 1-(4-(furan-2-yl)thiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1ag**): pale yellow solid, 1.50 g (82%), m.p. 120—121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52—7.40 (m, 5H), 7.37 (s, 1H), 7.24 (s, 1H), 6.99 (s, 1H), 6.38 (d, J=3.2 Hz, 1H), 6.30 (d, J=3.2 Hz, 1H), 4.46 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 160.1, 149.6, 146.1, 145.7, 144.1, 142.4, 129.8 (2C), 129.3, 129.1, 128.0 (2C), 111.7, 111.5, 110.4, 107.6, 61.6, 14.4; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{19}H_{16}N_3O_3S$ 366.0912, found 366.0912.

Ethyl 5-phenyl-1-(4-(thiophen-2-yl)thiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1ah**): pale yellow solid, 1.60 g (84%), m.p. 104—105 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56—7.53 (m, 2H), 7.47—7.43 (m, 3H), 7.21—7.15 (m, 3H), 6.99 (s, 1H), 6.97 (d, J=4.0 Hz 1H), 4.47 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 159.8, 147.1, 146.1, 145.7, 137.7, 129.9 (2C), 129.3, 129.1, 128.0 (2C), 127.7, 125.6, 124.3, 111.8, 109.9, 61.6, 14.4; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{19}H_{16}N_3O_2S_2$ 382.0684, found 382.0682.

Ethyl 5-(4-chlorophenyl)-1-(4-(4-chlorophenyl)-thiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1bb**): pale yellow solid, 1.82 g (82%), m.p. 162—163 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, J=8.4 Hz, 2H), 7.43 (dd, J=8.4, 2.8 Hz, 4H), 7.31 (s, 1H), 7.30 (d, J=7.6 Hz, 2H), 6.98 (s, 1H), 4.46 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.4, 159.8, 151.2, 145.7, 144.6, 135.5, 134.2, 132.0, 131.2 (2C), 128.9 (2C), 128.2 (2C), 127.8, 127.0 (2C), 111.9, 111.5, 61.6, 14.3; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{21}H_{16}Cl_2N_3O_2S$ 444.0340, found 444.0349.

Ethyl 5-(4-chlorophenyl)-1-(4-(2,4-dichlorophenyl)-thiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1bi**): pale yellow solid, 1.92 g (80%), m.p. 169—170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (s, 1H), 7.46—7.42 (m, 5H), 7.32 (d, J=8.4 Hz, 1H), 7.19 (dd, J=7.6, 1.6 Hz, 1H), 6.99 (s, 1H), 4.47 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.4, 158.8, 147.8, 145.8, 144.6, 135.5, 134.2, 132.1, 132.0, 131.1 (2C), 130.4, 130.3, 128.4 (2C), 127.9, 127.3, 117.3, 112.0, 61.7, 14.3; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{21}H_{15}Cl_3N_3O_2S$ 477.9951, found 477.9954.

Ethyl 5-(4-chlorophenyl)-1-(5-methyl-4-phenyl-thiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1bd**): pale yellow solid, 1.57 g (74%), m.p. 199—201 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=8.8 Hz, 2H), 7.41—7.34 (m, 6H), 7.32—7.29 (m, 1H), 6.98 (s, 1H), 4.46 (q, J=7.2 Hz, 2H), 2.59 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 155.2, 147.8, 145.4, 144.5, 135.3, 134.1, 131.0 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 128.0, 127.8, 127.7, 111.4, 61.5, 14.3, 12.8; HRMS (ESI) *m/z*: [M+H$^+$] calcd for $C_{22}H_{19}ClN_3O_2S$ 424.0887, found 424.0883.

Ethyl 5-(2,4-dichlorophenyl)-1-(5-methyl-4-phenyl-thiazol-2-yl)-1*H*-pyrazole-3-carboxylate (**1cd**): pale yellow solid, 1.65 g (72%), m.p. 124—126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 7.36 (s, 2H), 7.34—7.27 (m, 3H), 7.23 (d, J=8.0 Hz, 2H), 6.96 (s, 1H), 4.45 (q, J=7.2 Hz, 2H), 2.57 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 155.1, 147.4, 145.3, 140.5, 136.0, 135.7, 134.3, 132.5, 129.3, 128.5, 128.3 (2C), 127.9 (2C), 127.6, 127.0, 126.9, 112.4, 61.5, 14.3, 12.8; HRMS (ESI) *m/z*: [M+ H$^+$] calcd for $C_{22}H_{18}Cl_2N_3O_2S$ 458.0497, found 458.0495.

Ethyl 4-methyl-1-(5-methyl-4-phenylthiazol-2-yl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**1dd**): pale yellow solid, 1.37 g (68%), m.p. 116—118 ℃; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ: 7.47－7.45 (m, 3H), 7.40－7.37 (m, 2H), 7.31－7.23 (m, 5H), 4.46 (q, J=7.2 Hz, 2H), 2.54 (s, 3H), 2.26 (s, 3H), 1.45 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6, 155.4, 147.5, 143.4, 142.8, 134.3, 130.5 (2C), 129.3, 128.8, 128.19 (2C), 128.16 (2C), 128.1 (2C), 127.5, 127.1, 121.0, 61.1, 14.4, 12.7, 9.5; HRMS (ESI) *m/z*: [M＋H$^+$] calcd for $C_{23}H_{22}N_3O_2S$ 404.1433, found 404.1434.

Ethyl 5-(4-chlorophenyl)-1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylate (**1ee**): pale yellow solid, 1.54 g (65%); m.p. 155－156 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=8.0 Hz, 2H), 7.33－7.29 (m, 4H), 7.22 (d, J=8.4 Hz, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.54 (s, 3H), 2.23 (s, 3H), 1.45 (t, J=7.2 Hz, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 162.4, 155.6, 146.3, 143.6, 141.5, 135.2, 133.5, 132.7, 131.9 (2C), 129.2 (2C), 128.50 (2C), 128.47 (2C), 127.9, 127.3, 121.4, 61.2, 14.4, 12.8, 9.4; HRMS (ESI) *m/z*: [M＋H$^+$] calcd for $C_{23}H_{20}Cl_2N_3O_2S$ 472.0653, found 472.0654.

Ethyl 5-(4-chlorophenyl)-1-(4-(2,4-dichlorophenyl)-5-methylthiazol-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylate (**1ef**): pale yellow solid, 1.62 g (64%), m.p. 134－135 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J=1.6 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 7.23 (dd, J=8.0, 1.6 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 4.45 (q, J=7.2 Hz, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 155.8, 145.2, 143.6, 141.8, 135.1, 134.9, 134.5, 132.6, 131.8 (2C), 131.5, 131.3, 129.6, 128.5 (2C), 127.2, 126.9, 121.0, 61.2, 14.4, 12.3, 9.5; HRMS (ESI) *m/z*: [M＋H$^+$] calcd for $C_{23}H_{19}Cl_3N_3O_2S$ 506.0264, found 506.0264.

Ethyl 1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)-5-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (**1fe**): pale yellow solid, 1.62 g (64%), m.p. 174－176 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, J=1.6 Hz, 1H), 7.39 (dd, J=8.4, 1.6 Hz, 1H), 7.31－7.27 (m, 3H), 7.15 (d, J=8.4 Hz, 2H), 4.47 (q, J=7.2 Hz, 2H), 2.54 (s, 3H), 2.18 (s, 3H), 1.46 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 155.5, 146.1, 143.4, 138.2, 136.2, 136.0, 133.4, 132.9, 132.8, 129.3, 129.0 (2C), 128.4 (2C), 128.1, 127.1, 126.6. 122.4, 61.3, 14.4, 12.8, 9.2; HRMS (ESI) *m/z*: [M＋H$^+$] calcd for $C_{23}H_{19}Cl_3N_3O_2S$ 506.0264, found 506.0264.

Ethyl 5-(2,4-dichlorophenyl)-1-(4-(2,4-dichlorophenyl)-5-methylthiazol-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylate (**1ff**): pale yellow solid, 1.60 g (59%), m.p. 146－148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.40 (d, J=1.6 Hz, 1H), 7.32－7.26 (m, 2H), 7.21 (dd, J=8.4, 1.6 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 4.46 (q, J=7.4 Hz, 2H), 2.29 (s, 3H), 2.16 (s, 3H), 1.45 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 156.0, 145.1, 143.4, 138.5, 136.0, 135.9, 134.8, 134.4, 133.1, 132.5, 131.6, 130.3, 129.6, 129.4, 127.3, 127.1, 126.8, 122.3, 61.2, 14.4, 12.4, 9.3; HRMS (ESI) *m/z*: [M＋H$^+$] calcd for $C_{23}H_{18}Cl_4N_3O_2S$ 539.9874, found 539.9879.

X-ray crystallography of 1aa and 1ee

See Supporting Information.

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[18] CCDC 970392 (**1aa**) and 970393 (**1ee**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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