Tetrahedron 69 (2013) 627–635

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

'One-pot' synthesis of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates via lithium *tert*-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction

Jian-An Jiang [a], Wei-Bin Huang [a], Jiao-Jiao Zhai [a], Hong-Wei Liu [a], Qi Cai [a], Liu-Xin Xu [a], Wei Wang [a,b,*], Ya-Fei Ji [a,*]

[a] School of Pharmacy, East China University of Science & Technology, Campus P.O. Box 363, 130 Meilong Road, Shanghai 200237, PR China
[b] Department of Chemistry & Chemical Biology, University of New Mexico, MSC03 2060, Albuquerque, NM 87131-0001, USA

ARTICLE INFO

Article history:
Received 14 September 2012
Received in revised form 27 October 2012
Accepted 2 November 2012
Available online 8 November 2012

Keywords:
Lithium *tert*-butoxide
Sterically hindered Claisen condensation
3-Substituted 4-aryl-2,4-diketoesters
Knorr reaction
4-Substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates

ABSTRACT

A concise 'one-pot' synthesis of a variety of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates has been developed in moderate to good yields with excellent regioselectivity. Less cost lithium *tert*-butoxide has been identified as a base for sterically hindered Claisen condensation to efficiently generate the labile 3-substituted 4-aryl-2,4-diketoesters. Furthermore, extensive studies lead to a 'one-pot' process by combination of the Claisen condensation and the Knorr reaction for the synthesis of highly valuable 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates.

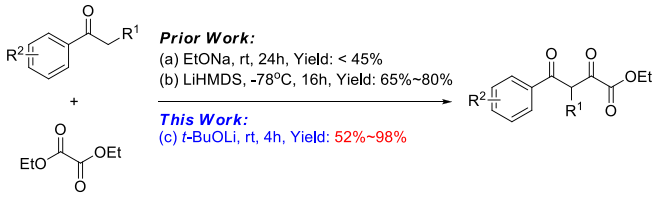
1. Introduction

Pyrazoles have a rich chemistry with numerous applications.[1–6] Of these, particularly interesting to medicinal chemists are highly substituted pyrazoles, which constitute the core structures of clinically used drugs, such as Celebrex,[7] Viagra,[8] and Rimonabant,[9] as well as many developing molecules across a wide spectrum of therapeutic areas including anti-inflammation,[10] analgesia,[10b,11] anti-infection,[12] and anti-cancer.[13] These factors have assured a continually increasing attention on the synthesis of functionalized pyrazole derivatives and their biological explorations.[10–14] Notably, the recent discoveries in 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylate derivatives as cannabinoid-1 (CB1) receptor antagonist,[15] Iκβ kinase β (IKKβ or IKK-2) inhibitor,[16a] analgesic,[16b] and anti-inflammatory agent[16b,c] prompted us to explore a sustainable chemistry-oriented synthesis[17] to the fully substituted 1*H*-pyrazole-3-carboxylates. As our continuing efforts toward 'one-pot' synthesis of functionalized heterocycles,[18] in this context, we wish to report a general and efficient approach to create 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates.

There have been two prevalent strategies for constructing 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates deriving from Knorr reaction[15a,b,d,e,g,i] and 1,3-dipolar cycloaddition of 2-chloro-2-(2-aryl-hydrazono)acetates with 1-aryl-1-enamines.[15l] The Knorr reaction involving a [3+2]-cyclization between 3-substituted 4-aryl-2,4-diketoesters and arylhydrazines has proven to be more effective in terms of convenience and versatility.[15a,b,d,e,g,i,19] However, the main limitation of this reaction relies on the use of non-readily accessible 3-substituted 4-aryl-2,4-diketoesters. These versatile 2,4-diketoesters are also pivotal in the synthesis of pharmaceutically significant heterocycles; yet their mild and cost-effective synthesis is rare. The most straightforward synthesis of 3-substituted 4-aryl-2,4-diketoesters is the employment of the base-mediated Claisen condensation of alkylphenones with diethyl oxalate.[15b,d,e,i,16b] However, the steric hindrance of the alkyl groups often leads to low chemical yields in sodium ethoxide-mediated procedure (Scheme 1(a)).[15b,16b] Therefore, a much stronger base lithium hexamethyldisilazide (LiHMDS) has been frequently employed to effectively execute a sterically hindered Claisen condensation (SHCC).[15d,e,i] Although yields generally improve, the troublesome operation and high cost of

* Corresponding authors. Tel./fax: +86 21 6425 3314; e-mail addresses: wwang@unm.edu (W. Wang), jyf@ecust.edu.cn (Y.-F. Ji).

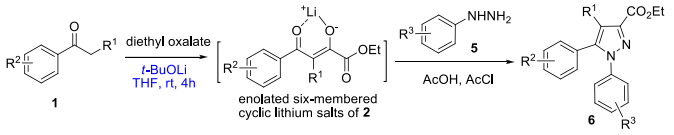
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.012



Scheme 1. Base-mediated SHCC of alkylphenones with diethyl oxalate.

LiHMDS inevitably limit the procedure on large-scale preparation (Scheme 1(b)).

Accordingly, development of a mild SHCC using robust and low cost base for 3-substituted 4-aryl-2,4-diketoesters becomes essential, but still remains a challenge. Toward this end, herein, we wish to report a concise 'one-pot' procedure, which comprises lithium *tert*-butoxide-mediated SHCC of alkylphenones with diethyl oxalate, and subsequent Knorr reaction of the resulting 2,4-diketoesters with arylhydrazines, to construct a wide range of fully substituted 1*H*-pyrazole-3-carboxylates (Scheme 2). Notably, cyclization of the diketoesters generated in situ and arylhydrazines effectively leads to the desired 1*H*-pyrazole-3-carboxylates in moderate to good yields with excellent regioselectivity. The ready availability of reactants, the employment of robust and cost-effective lithium *tert*-butoxide,[20] as well as high yields make this procedure particularly appealing for synthesis of the pharmaceutically relevant pyrazole compounds with highly structural diversity (alkyl, two or three aryl and carboxyl functionalities).



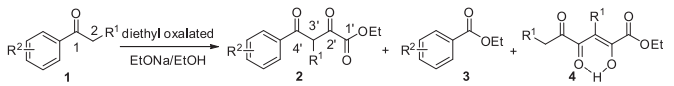
Scheme 2. A 'one-pot' procedure to construct fully substituted 1*H*-pyrazole-3-carboxylates.

2. Results and discussion

2.1. Investigation of sodium ethoxide-mediated SHCC

It is well known that the yield of sodium ethoxide-mediated SHCC is low.[15b,16b] To shed new light on the nature of the sodium ethoxide-mediated SHCC, we investigated three model reactions of representative alkylphenones **1** and diethyl oxalate (Table 1), by following the EtONa procedure described by Zhang and co-workers.[15b] These reactions uniformly generated unexpected benzoates **3** and triketoesters **4**[21] as major products, whereas the originally desired **2**[22] was obtained in low yields (20–38%). The results again clearly showed that sodium ethoxide-mediated SHCC is difficult to achieve **2** in yield at a useful level. We attributed the formation

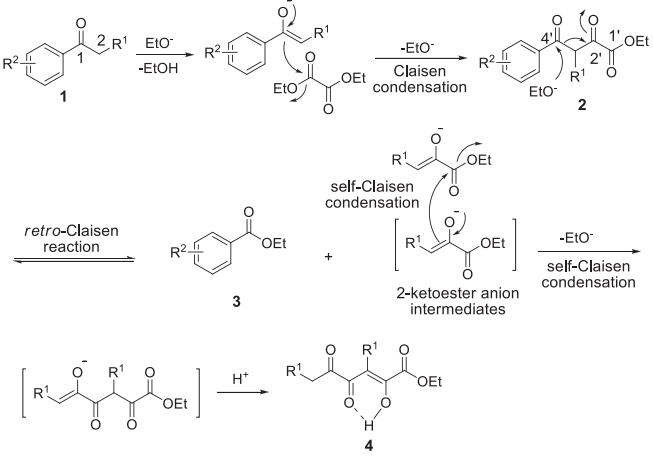
Table 1
Sodium ethoxide-mediated SHCC[a]



Entry	R^1	R^2	**2** (Yield[b])	**3** (Yield[b])	**4** (Yield[b])
1	Me	H	**2a** (38%)	**3a** (45%)	**4a** (43%)
2	Et	H	**2f** (23%)	**3a** (63%)	**4f** (62%)
3	*n*-Pr	H	**2g** (20%)	**3a** (62%)	**4g** (61%)

[a] Reactions were performed in an oven-dried vial with alkylphenones **1** (5.0 mmol), diethyl oxalate (6.5 mmol), and sodium ethoxide (10.0 mmol) in anhydrous ethanol (15 mL) at room temperature for 24 h.
[b] Isolated yields via column chromatography.

of concomitants **3** and **4** to the well-studied *retro*-Claisen reaction[22] and a rare self-Claisen condensation process, respectively (Scheme 3). Ethoxide anion attacking 4′-carbonyl group of the resultant **2** of the Claisen condensation triggers a *retro*-Claisen reaction to yield **3** and 2-ketoester anion intermediates. Surprisingly, the intermediates, not detected, were converted into **4** by a self-Claisen condensation under the reaction conditions. These investigations suggest that a base not only plays an important role in the product formation but also has a pronounced impact on stability of product(s). Therefore, LiHMDS has often been used as a favorable base in SHCC.[15d,e,i] We hypothesized that surrogates for sodium ethoxide and LiHMDS might offer an opportunity to identify a suitable base for the preparation of **2** efficiently and sustainably.



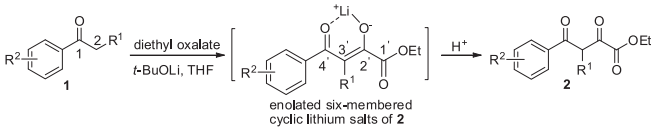
Scheme 3. A proposed reaction pathway for sodium ethoxide-mediated SHCC.

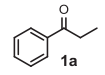
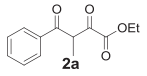
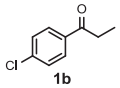
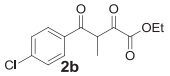
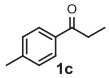
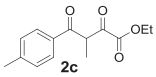
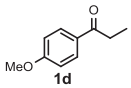
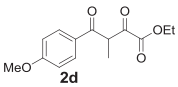
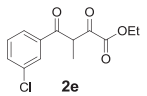
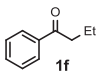
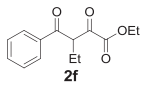
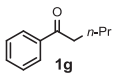
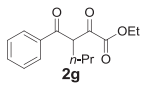
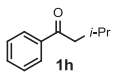
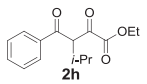
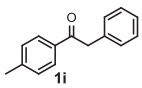
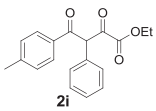
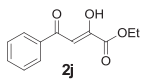
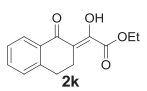
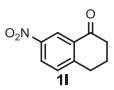
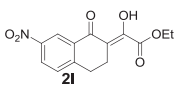
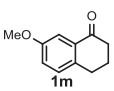
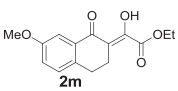
2.2. Substrate generality of the lithium *tert*-butoxide-mediated SHCC

Given the fact that LiHMDS functions as both a strong base and an oxygenphilic reagent to bring about enolated six-membered cyclic lithium salts[15d,i] based on stronger affinity of lithium with oxygen than sodium and potassium,[23] *t*-BuOLi should improve the efficiency of SHCC. Indeed, desired **2a** was exclusively obtained in a yield of 95% under the optimized reaction conditions: 5.0 mmol alkylphenones, 6.0 mmol diethyl oxalate, and 6.5 mmol *t*-BuOLi at room temperature for 4 h (Table 2, entry 1). We then examined the scope of the lithium *tert*-butoxide-mediated SHCC. It was found that it serves as a general strategy for the preparation of structurally diverse 3-substituted 4-aryl-2,4-diketoesters **2** (Table 2). The electron-deficient propiophenones **1b** and **1e** with chlorine atom at the *para*- or *meta*-position smoothly formed **2b** and **2e** in good yields (82% and 86%, respectively, entries 2 and 5). The same trend was observed for electron-rich **1c** and **1d** containing methyl or methoxyl group on the benzene ring (85% and 84%, respectively, entries 3 and 4).

A difficult challenge for the synthesis of 3-substituted 4-aryl-2,4-diketoesters is the steric hindrance. The size of the substituents (R^1) at C2 position of alkylphenones has a significant influence on the reaction. The studies have shown that the relatively smaller methyl group could participate in the process smoothly (entry 1). We further examined the influence of larger R^1 of chain alkylphenones **1f**–**i**. It was found that the corresponding steric hindrance expressed a powerful impact on reaction yields. For example, *n*-butyrophenone (**1f**), *n*-valerophenone (**1g**) and isovalerophenone (**1h**) gave rise to **2f**, **2g**, and **2h** in yields of 69%, 58%, and 52%, respectively (entries 6–8). What is more, for 2-phenyl-1-*p*-tolylethanone (**1i**) with bulky phenyl group at C2 position, the sterically more hindered product **2i**

Table 2
Substrate generality of lithium *tert*-butoxide-mediated SHCC[a]



Entry	1	2	Yield[b] (%)
1			95
2			82
3			85
4			84
5			86
6			69
7			58
8			52
9			—[c]
10			98
11			97
12			96
13			97

[a] The reactions were performed in an oven-dried vial with alkylphenones **1** (5.0 mmol), diethyl oxalate (6.0 mmol), and *t*-BuOLi (6.5 mmol) in anhydrous THF (15 mL) at room temperature for 4 h.
[b] Isolated yields via column chromatography.
[c] No product obtained for its instability.

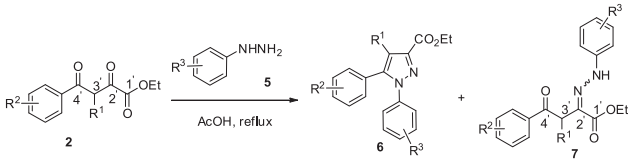
is difficult to reach owing to its instability under the reaction conditions (entry 9), albeit the product **2i** could be observed with TLC monitoring. Indeed, acetophenone (**1j**) with no substituent at C2 position gave enolated diketoesters **2j** with nearly quantitative yield (entry 10).

In contrast, benzocyclohexanones **1k**–**m** displayed excellent outcomes for the formation of enolated diketoesters **2k**–**m** in nearly quantitative yields (entries 11–13). With regard to the partially rigid aromatic cycloketones (e.g., 1-benzocyclopentanones, 1-tetralones and 1-benzosuberones), the Claisen condensations could be implemented with good yields even in the presence of EtONa.[15a] It is reasonably understood that such stable cycloketone structures of **2k**–**m** inherently suppress potential decomposition. Thus, we concluded that the SHCC is more suitable for defining the condensation pattern of chain alkylphenones (except acetophenone). In general, *t*-BuOLi instead of LiHMDS can equally efficiently accomplish SHCC for **2**.

2.3. Further insight for the Knorr reaction

Having established an efficient protocol for 3-substituted 4-aryl-2,4-diketoesters, we made our efforts on the construction of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates **6** (1,5-isomers) from freshly prepared **2** and arylhydrazines **5** via Knorr reaction (Table 3). The diketoesters **2a**, **2b**, and **2f** were converted into the desired 1,5-isomers **6aa**, **6ab**, **6bd**, and **6fa** in the yields of 60–66%. Meanwhile, *N*-arylhydrazones **7aa**, **7ab**, **7bd**, and **7fa** were obtained in the yields of 24–31%. These facts support a mechanism starting at the attack of arylhydrazines at more active 2′-carbonyl group of **2** followed by an intramolecular dehydrating cyclization.[24–26] With the 1,5-isomer overwhelmingly exceeding 4-substituted-1,3-diaryl-1*H*-pyrazole-5-carboxylate (1,3-isomer) in a 33/1 ratio detected by ^{1}H NMR for **6ab** (entry 2),[27] indeed, the Knorr reactions fulfill excellent regioselectivity to 1,5-isomers. The previous report has unequivocally confirmed the proximity of the two aromatic rings in the 1,5-isomer by a nuclear Overhauser effect (NOE) interaction.[26] Furthermore, our ^{1}H NMR spectra demonstrated that **7** were composed of comparable *E*/*Z*-isomers, while *Z*-isomers were considered impossible for intramolecular dehydrating cyclization.[26]

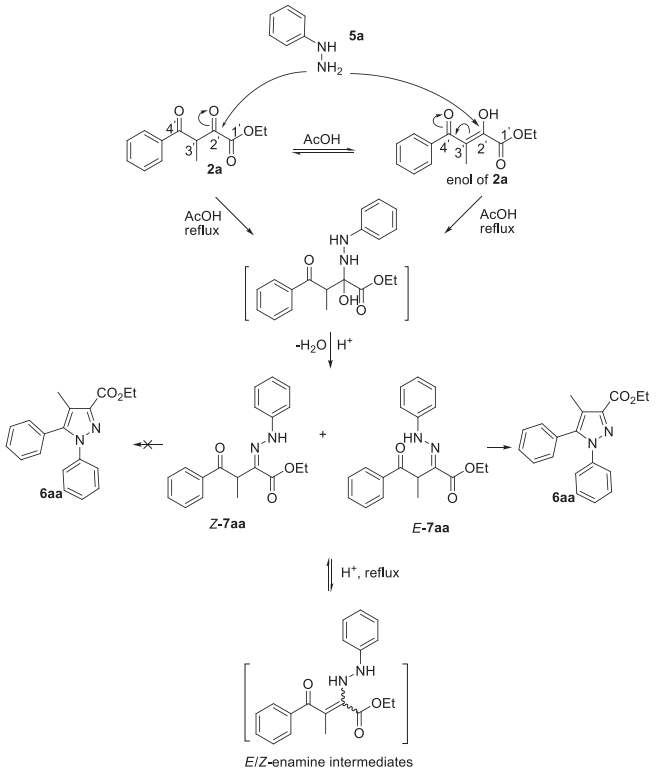
Table 3
Knorr reactions of some representative **2** and **5**[a]



Entry	R^1	R^2	R^3	**6** (Yield[b])	**7** (Yield[b])
1	Me	H	H	**6aa** (60%)	**7aa** (31%)
2	Me	H	4-Cl	**6ab** (65%, 33/1[c])	**7ab** (26%)
3	Me	4-Cl	2,4-Cl_2	**6bd** (66%)	**7bd** (27%)
4	Et	H	H	**6fa** (61%)	**7fa** (24%)

[a] Reactions were performed in an oven-dried vial with freshly prepared 3-substituted 4-aryl-2,4-diketoesters **2** (4.0 mmol) and arylhydrazines **5** (4.0 mmol) in glacial acetic acid (8 mL) at reflux for 12 h.
[b] Isolated yields via column chromatography.
[c] Ratio of 1,5-isomer/1,3-isomer determined by ^{1}H NMR.

A plausible mechanism (Scheme 4) for the formation of **6aa** was proposed. Initially, under acidic conditions, the reaction begins with an attack of more nucleophilic NH_2 of **5a** at the more electrophilic 2′-carbonyl group of **2a**,[25] or a conjugate addition of terminal nitrogen of **5a** with the acid-promoted enolate of **2a**,[28] followed by a rapid acid-catalyzed dehydration irreversibly to result in *E*/*Z*-**7aa**, of which *E*-**7aa** having geometrically closeness of NH and 4′-carbonyl group can be cyclized into **6aa**. Meantime, acetic acid probably undertakes another role to convert noncyclizable *Z*-**7aa** into cyclizable *E*-**7aa** via *E*/*Z*-enamine intermediates arising from an acid-promoted double bond-migration. Accordingly, the regenerated *E*-**7aa** from *Z*-**7aa** was again transformed into **6aa**. Therefore, the yield of Knorr reaction largely depends on a conversion of noncyclizable *Z*-**7** into cyclizable *E*-**7**.



Scheme 4. A plausible mechanism for the Knorr reaction.

2.4. Optimization of the Knorr reaction and exploration of 'one-pot' procedure

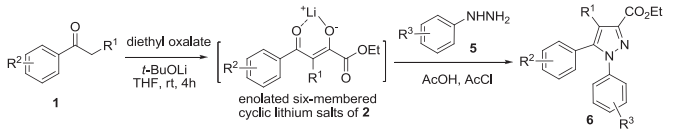
To further improve efficiency of the Knorr reaction, materials **2a** and **5a** were chosen to explore optimum conditions for the preparation of **6aa**. Control experiments revealed that the desired **6aa** was achieved in a higher yield of 76% (vs 60%, Table 3, entry 1) when **2a** reacted with equimolar **5a** in glacial acetic acid at reflux for 8 h, followed by a treatment of 2.0 equiv of acetyl chloride for another 8 h. On the one hand, the addition of acetyl chloride would use up all water generated in the reaction to facilitate the formation of **6aa**. On the other hand, it is likely that the resulting hydrogen chloride further propels *Z*-**7aa** into *E*-**7aa** to increase the yield of **6aa**. Nonetheless, the isolation of unstable **2** still brings about some disadvantages to decrease the applicability of the Knorr reaction.

With the insights to the SHCC and Knorr reaction in mind, we sought to combine two descrete reaction steps into a 'one-pot' fashion. Thus, we achieved an optimized 'one-pot' procedure in terms of the model reaction for **6aa**. The reaction of **1a** (1.0 equiv), diethyl oxalate (1.2 equiv) and *t*-BuOLi (1.3 equiv) was performed in THF at room temperature for 4 h to completely transform **1a** into the lithium salt of **2a**. Upon removal of THF, glacial acetic acid, and **5a** (1.0 equiv) were added to carry out the following condensation of **2a** and **5a** at reflux for 8 h. Then, addition of 2.0 equiv of acetyl chloride, the reaction proceeded another 8 h in order at reflux. Finally, the desired **6aa** was obtained in 75% yield, indicating a favorable increase by comparison with the total yield of 72% for the discrete steps (95% (Table 2, entry 1)×76%).

2.5. Substrate generality of the 'one-pot' procedure for 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates 6

With the established 'one-pot' procedure in hand, we investigated the scope for the synthesis of **6** with commercially available **1** and **5** (Table 4). First, compounds **5a**–**n** bearing various electronic properties of substituents at benzene ring were used to

Table 4
Substrate generality of the 'one-pot' procedure



Entry[a]	1	5	6	Ratio[b] (1,5-/1,3-)	Yield[c] (%)
1	**1a**	**5a**	**6aa**	No[d]	75
2	**1a**	**5b**	**6ab**	33/1	76
3	**1a**	**5c**	**6ac**	No	78
4	**1a**	**5d**	**6ad**	18/1	78
5	**1a**	**5e**	**6ae**	No	60
6	**1a**	**5f**	**6af**	14/1	77
7	**1a**	**5g**	**6ag**	No	77
8	**1a**	**5h**	**6ah**	22/1	76
9	**1a**	**5i**	**6ai**	No	51
10	**1a**	**5j**	**6aj**	No	72
11	**1a**	**5k**	**6ak**	No	73
12	**1a**	**5l**	**6al**	No	73
13	**1a**	**5m**	**6am**	No	67
14	**1a**	**5n**	**6an**	No	72
15	**1b**	**5a**	**6ba**	No	62
16	**1c**	**5a**	**6ca**	No	69
17	**1d**	**5a**	**6da**	No	71
18	**1e**	**5a**	**6ea**	No	67
19	**1f**	**5a**	**6fa**	No	61
20	**1g**	**5a**	**6ga**	No	52
21	**1h**	**5a**	**6ha**	No	48
22	**1i**	**5a**	**6ia**	No	47

Table 4 (*continued*)

Entry[a]	1	5	6	Ratio[b] (1,5-/1,3-)	Yield[c] (%)
23	**1j**	**5a**	**6ja**	No	91
24	**1k**	**5a**	**6ka**	No	90
25	**1l**	**5f**	**6lf**	No	87
26	**1m**	**5a**	**6ma**	No	92

[a] Reactions were performed in an oven-dried vial with alkylphenones **1** (5.0 mmol), diethyl oxalate (6.0 mmol), *t*-BuOLi (6.5 mmol), arylhydrazines **5** (5.0 mmol), anhydrous THF (15 mL), glacial acetic acid (10 mL), and then acetyl chloride (10 mmol) following the typical 'one-pot' procedure.
[b] Ratios of 1,5-/1,3-isomer determined by ^{1}H NMR.
[c] Isolated yields via column chromatography.
[d] No 1,3-isomer observed.

evaluate the generality of arylhydrazines (entries 1–14). Compared to electron-neutral **5a**, a feebly beneficial influence of **5b**–**d** and **5f**–**h** on chemical outcomes was generally displayed with the yields of 76–78% for **6ab**–**ad** and **6af**–**ah** (entries 2–4, 6–8) by changing the nature and number of electron-withdrawing substituent with chlorine, fluorine or nitro group(s). However, arylhydrazines bearing electron-donating methyl or ethyl group(s) on benzene ring conversely gave the products **6aj**–**al** and **6an** in slightly low yields of 72–73% (entries 10–12 and 14). It should be also noted that, despite of the electronic effect of substituents, the di-*ortho*-substituted steric hindrance of **5e** and **5m** delivers a strong impact on the products **6ae** and **6am** in low yields of 60% and 67%, respectively (entries 5 and 13). Furthermore, the reduced yield of 51% for **6ai** appeared in the case of **5i** with nitro group at *ortho*-position (entry 9). We reasoned that the conceivable intramolecular NH$\cdots$O$_2$N hydrogen bond as well as decreased nucleophilicity of NH by NO_2 block the cyclization in the Knorr reaction.[29] Again it is suggested that the influence on the efficiency of the 'one-pot' procedure might be more expected from steric effect.

On the basis of the aforementioned substrate generality of the lithium *tert*-butoxide-mediated SHCC (Table 2), a variety of alkylphenones were again investigated to evaluate the scope of **1** in the 'one-pot' procedure (Table 4, entries 15–26). In comparison with **1a** (entry 1), the substituted propiophenones **1b**–**e** with electron-withdrawing or electron-donating group at benzene ring all reacted smoothly to provide **6ba**–**ea** in respected yields of 62–71% (entries 15–18). Again we witnessed the steric effect associated with C2 position of chain alkylphenones. For instance, chain alkylphenones **1f**–**i** afforded the corresponding **6fa**, **6ga**, **6ha**, and **6ia**, in relatively lower yields of 61%, 52%, 48%, and 47%, respectively (entries 19–22). However, it should be noted that the 'one-pot' procedure can achieve sterically overcrowded 1,4,5-triaryl-1*H*-pyrazole-3-carboxylate **6ia** (entry 22), which would be inaccessible by discrete protocol due to the inaccessibility of precursor **2i** (Table 2, entry 9). In addition, very high yields were obtained with acetophenone (**1j**) and benzocyclohexanones **1k**–**m** in the 'one-pot' process (Table 4, entries 23–26, 91%, 90%, 87%, and 92%, respectively) based on the excellent results of the above stepwise approach (Table 2, entries 10–13, **2j**–**m**). Finally, critically the 'one-pot' procedure offered excellent regioselectivity to the desired **6** without 1,3-isomer observed in most of cases. High regioselectivity (33/1, 18/1, 14/1, and 22/1 of 1,5-/1,3-isomer ratios detected by ^{1}H NMR, respectively) for **6ab**, **6ad**, **6af**, and **6ah** was also observed (Table 4, entries 2, 4, 6, and 8).

3. Summary

In summary, a concise 'one-pot' synthesis of synthetically and biologically important 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates **6** has been developed in moderate to good yields with excellent regioselectivity from readily available diethyl oxalate, alkylphenones **1** and arylhydrazines **5**. The procedure involves a newly expounded SHCC reaction and subsequent optimized Knorr reaction. The cost-effective process possesses two notable features: (i) the use of inexpensive, robust, safe, and easier-to-handle *t*-BuOLi in place of LiHMDS to conduct SHCC reaction; (ii) no need to isolate intractable **2** to achieve the valuable pyrazole compounds in a 'one-pot' manner. The synthetic versatility and pharmaceutical importance of **2** and **6** greatly highlight the usefulness of this methodology. We believe that this operationally simple protocol holds application potential in the field of organic synthesis and medicinal chemistry.

4. Experimental section

4.1. General methods

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, pre-coated silica gel plates containing HF_{254}). All solvents were only dried over 4 Å molecular sieves. Reaction products were purified by silica gel column chromatography with elution of petroleum ether/ethyl acetate. Melting points were determined using an open capillaries and uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ with TMS as internal standard for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. MS were recorded on Micromass GCTTM gas chromatograph-mass spectrometer. HRMS were carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer and Micromass GCTTM gas chromatograph-mass spectrometer.

4.2. General 'one-pot' procedure for the preparation of ethyl 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates 6 (Table 4)

An oven-dried vial equipped with a stir bar was charged with a mixture of lithium *tert*-butoxide (0.52 g, 6.5 mmol) and diethyl oxalate (0.88 g, 6.0 mmol) in anhydrous THF (10 mL), and the mixture was then stirred at 0 °C under a nitrogen atmosphere. Ten minutes later, a solution of alkylphenones **1** (5.0 mmol) in anhydrous THF (5 mL) was added dropwise to the mixture, and the resulting mixture was allowed to stir at room temperature for 4 h. After completion of the reaction as monitored by TLC, the mixture was concentrated to remove THF giving a residual. Glacial acetic acid (10 mL) and arylhydrazines **5** (5.0 mmol) were added to the residual at room temperature, followed by reflux for 8 h. Then to the reaction solution was added acetyl chloride (0.78 g, 10.0 mmol), and stirred at reflux for another 8 h. Next, the solution was concentrated in vacuo to remove glacial acetic acid affording a residual, to which were added water (10 mL) and methylene chloride (15 mL) to make the solution partitioned into organic and aqueous layers. The aqueous layer was extracted with methylene chloride (10 mL×2). Finally, the combined organic phase was washed with water (20 mL×2), dried over anhydrous sodium sulfate, and concentrated to give a crude oil, which was purified by column chromatography (200–300 mesh silica gel, petroleum ether/ethyl acetate 10:1) to offer the corresponding **6**.

*4.2.1. Ethyl 1,5-diphenyl-4-methyl-1H-pyrazole-3-carboxylate (**6aa**).*[30] Yellow solid, 1.15 g (75% yield), mp 104–106 °C (lit.[30] mp 105–106 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.38–7.35 (m, 3H), 7.30–7.22 (m, 5H), 7.17–7.14 (m, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.33 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.2, 142.2, 142.1, 139.6, 130.1 (2C), 129.6, 128.8 (2C), 128.6, 128.5 (2C), 127.8, 125.4 (2C), 119.9, 60.8, 14.5, 9.7; MS (EI): m/z (%)=306.1 (93) [M$^+$], 260.1 (53), 233.1 (100), 180.1 (50), 77.0 (24); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1442.

*4.2.2. Ethyl 1-(4-chlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6ab**).* Yellow powder, 0.88 g (65% yield), mp

69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40–7.36 (m, 3H), 7.23 (d, J=8.8 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.17–7.12 (m, 2H), 4.46 (q, J=7.2 Hz, 2H), 4.46 (q, J=7.2 Hz, 0.06H, as 1,3-isomer), 2.31 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.1, 142.5, 142.1, 138.1, 133.6, 130.1 (2C), 129.3, 128.9 (2C), 128.8, 128.7 (2C), 126.4 (2C), 120.1, 60.9, 14.5, 9.7; MS (EI): m/z (%)=340.1 (100) [M^+], 294.1 (78), 267.1 (96), 231.1 (43), 214.0 (62), 111.0 (21); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1055; m/z [M+Na$^+$] calcd for $C_{19}H_{17}ClN_2NaO_2$ 363.0876, found 363.0877; m/z [M+K$^+$] calcd for $C_{19}H_{17}ClN_2KO_2$ 379.0616, found 379.0612.

*4.2.3. Ethyl 1-(3-chlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6ac**).* Yellow powder, 1.33 g (78% yield), mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 (t, J=2.0 Hz, 1H), 7.40–7.35 (m, 3H), 7.24 (d, J=8.4 Hz, 1H), 7.18–7.12 (m, 3H), 7.02 (d, J=8.0 Hz, 1H), 4.47 (q, J=7.2 Hz, 2H), 2.31 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.0, 142.6, 142.2, 140.5, 134.6, 130.0 (2C), 129.6, 129.2, 128.9, 128.8 (2C), 127.9, 125.5, 123.3, 120.2, 60.9, 14.5, 9.7; MS (EI): m/z (%)=340.1 (100) [M^+], 294.1 (85), 267.1 (74), 231.1 (46), 214.0 (57), 111.0 (19); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1053; m/z [M+K$^+$] calcd for $C_{19}H_{17}ClKN_2O_2$ 379.0616, found: 379.0611.

*4.2.4. Ethyl 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6ad**).*[31] Yellow powder, 1.46 g (78% yield), mp 90–92 °C (lit.[31] 80–82 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (d, J=2.0 Hz, 1H), 7.35–7.30 (m, 4H), 7.26–7.24 (m, 1H), 7.16–7.12 (m, 2H), 4.46 (q, J=7.2 Hz, 2H), 4.36 (q, J=7.2 Hz, 0.11H, as 1,3-isomer), 2.35 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.9, 144.1, 142.9, 136.2, 135.8, 133.2, 130.8, 130.0, 129.7 (2C), 128.7, 128.6, 128.5 (2C), 127.6, 119.0, 60.9, 14.5, 9.7; MS (EI): m/z (%)=374.1 (100) [M^+], 328.0 (87), 301.0 (86), 267.1 (94), 248.0 (80), 77.0 (24); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{17}Cl_2N_2O_2$ 375.0667, found 375.0670; m/z [M+Na$^+$] calcd for $C_{19}H_{16}Cl_2N_2NaO_2$ 397.0487, found 397.0483.

*4.2.5. Ethyl 4-methyl-5-phenyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-3-carboxylate (**6ae**).* Yellow powder, 1.23 g (60% yield), mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37–7.31 (m, 5H), 7.25–7.21 (m, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.34 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.6, 143.2, 142.4, 135.0, 134.6 (2C), 133.3, 128.0 (2C), 127.9, 127.3 (2C), 127.2 (2C), 127.1, 117.7, 59.7, 13.3, 8.5; MS (EI): m/z (%)=408.0 (57) [M^+], 364.0 (58), 336.0 (55), 301.0 (100), 282.0 (54), 77.0 (19); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{16}Cl_3N_2O_2$ 409.0277, found 409.0279; m/z [M+Na$^+$] calcd for $C_{19}H_{15}Cl_3N_2NaO_2$ 431.0097, found 431.0100.

*4.2.6. Ethyl 1-(4-fluorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6af**).* White powder, 1.25 g (77% yield), mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36 (t, J=3.2 Hz, 3H), 7.25–7.20 (m, 2H), 7.16–7.12 (m, 2H), 6.97 (t, J=8.4 Hz, 2H), 4.46 (q, J=7.2 Hz, 2H), 4.42 (q, J=7.2 Hz, 0.14H, as 1,3-isomer), 2.32 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.1, 161.8 (d, J_{C-F}=246.6 Hz), 142.3, 142.2, 135.8 (d, J_{C-F}=3.1 Hz), 130.1 (2C), 129.3, 128.7, 128.7 (2C), 127.2 (d, J_{C-F}=8.6 Hz, 2C), 119.9, 115.7 (d, J_{C-F}=22.8 Hz, 2C), 60.8, 14.5, 9.7; MS (EI): m/z (%)=324.1 (100) [M^+], 278.1 (66), 251.1 (86), 198.1 (64), 95.0 (15); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{18}FN_2O_2$ 325.1352, found 325.1350; m/z [M+Na$^+$] calcd for $C_{19}H_{17}FN_2NaO_2$ 347.1172, found 347.1164.

*4.2.7. Ethyl 4-methyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**6ag**).* Yellow powder, 1.35 g (77% yield), mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16–8.11 (m, 2H), 7.46–7.40 (m, 5H), 7.19–7.15 (m, 2H), 4.47 (q, J=7.2 Hz, 2H), 2.30 (s, 3H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.7, 146.3, 144.3, 143.7, 142.4, 130.0 (2C), 129.3, 129.1 (2C), 129.0, 125.1 (2C), 124.4 (2C), 121.1, 61.2, 14.4, 9.6; MS (EI): m/z (%)=351.1 (72) [M^+], 305.1 (100), 277.1 (42), 225.1 (57), 179.1 (21); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}N_3O_4$ 351.1219, found 351.1217.

*4.2.8. Ethyl 4-methyl-1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**6ah**).* Yellow powder, 1.33 g (76% yield), mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.18 (t, J=2.0 Hz, 1H), 8.13 (dd, J=1.2, 8.4 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.43–7.38 (m, 3H), 7.20–7.15 (m, 2H), 4.48 (q, J=7.2 Hz, 2H), 4.29 (q, J=7.2 Hz, 0.09H, as 1,3-isomer), 2.32 (s, 3H), 1.46 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.8, 148.3, 143.3, 142.4, 140.4, 130.5, 130.0 (2C), 129.6, 129.3, 129.1 (2C), 128.8, 122.3, 120.7, 120.1, 61.1, 14.4, 9.6; MS (EI): m/z (%)=351.1 (71) [M^+], 305.1 (100), 277.1 (31), 225.1 (50), 179.1 (11); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}N_3O_4$ 351.1219, found: 351.1214.

*4.2.9. Ethyl 1-(2,4-dinitrophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6ai**).* Red powder, 1.01 g (51% yield), mp 128–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.71 (d, J=2.4 Hz, 1H), 8.40 (dd, J=8.8, 2.4 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 7.43–7.35 (m, 3H), 7.14 (dd, J=8.0, 1.6 Hz, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.35 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.3, 146.7, 145.2, 144.8, 143.5, 137.8, 130.7, 129.9 (2C), 129.6, 129.2 (2C), 127.5, 127.4, 120.9, 120.6, 61.3, 14.4, 9.6; MS (EI): m/z (%)=396.1 (58) [M^+], 379.1 (13), 350.1 (100), 229.1 (15), 105.0 (40); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{17}N_4O_6$ 397.1148, found 397.1154; m/z [M+Na$^+$] calcd for $C_{19}H_{16}N_4NaO_6$ 419.0968, found 419.0964; m/z [M+K$^+$] calcd for $C_{19}H_{16}KN_4O_6$ 435.0707, found: 435.0713.

*4.2.10. Ethyl 4-methyl-5-phenyl-1-p-tolyl-1H-pyrazole-3-carboxylate (**6aj**).* Yellow powder, 1.15 g (72% yield), mp 73–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37–7.31 (m, 3H), 7.17–7.10 (m, 4H), 7.06 (d, J=8.4 Hz, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.32 (s, 3H), 2.31 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.3, 142.1, 141.9, 137.7, 137.2, 130.1 (2C), 129.7, 129.3 (2C), 128.5 (2C), 128.4, 125.2 (2C), 119.7, 60.7, 21.1, 14.5, 9.7; MS (EI): m/z (%)=320.2 (83) [M^+], 274.1 (36), 247.1 (100), 194.1 (35), 145.1 (6), 91.1 (13); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1601; m/z [M+Na$^+$] calcd for $C_{20}H_{20}N_2NaO_2$ 343.1422, found 343.1437; m/z [M+K$^+$] calcd for $C_{20}H_{20}KN_2O_2$ 359.1162, found 359.1166.

*4.2.11. Ethyl 1-(2,4-dimethylphenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6ak**).* Yellow powder, 1.22 g (73% yield), mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31–7.25 (m, 3H), 7.15–7.09 (m, 3H), 6.94 (d, J=11.2 Hz, 2H), 4.45 (q, J=7.2 Hz, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.88 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.4, 143.4, 141.7, 139.0, 136.4, 135.0, 131.3, 129.7 (2C), 129.3, 128.3 (2C), 128.3, 128.0, 126.9, 118.5, 60.7, 21.1, 17.5, 14.5, 9.9; MS (EI): m/z (%)=334.2 (100) [M^+], 289.1 (22), 259.1 (90); HRMS (EI): m/z [M^+] calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found: 334.1682.

*4.2.12. Ethyl 1-(2,5-dimethylphenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6al**).* Yellow powder, 1.22 g (73% yield), mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31–7.25 (m, 3H), 7.15–7.09 (m, 3H), 7.05 (d, J=8.0 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 4.45 (q, J=7.2 Hz, 2H), 2.38 (s, 3H), 2.28 (s, 3H), 1.81 (s, 3H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.3, 143.3, 141.8, 138.6, 136.1, 131.9, 130.4, 129.9, 129.6 (2C), 129.2, 128.7, 128.3 (3C), 118.5, 60.7, 20.7, 17.1, 14.5, 9.9; MS (EI): m/z (%)=334.2 (100) [M^+], 289.1 (21), 259.1 (92); HRMS (EI): m/z [M^+] calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1677.

*4.2.13. Ethyl 1-(2,6-dimethylphenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6am**).* Yellow powder, 1.12 g (67% yield), mp

94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31–7.25 (m, 3H), 7.14 (t, *J*=7.6 Hz, 1H), 7.11–7.06 (m, 2H), 6.99 (d, *J*=7.6 Hz, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 2.40 (s, 3H), 1.95 (s, 6H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.4, 143.1, 142.0, 138.0, 136.2 (2C), 129.1, 129.1 (2C), 129.0, 128.4, 128.3 (2C), 128.0 (2C), 118.4, 60.7, 17.8 (2C), 14.5, 10.1; MS (EI): *m*/*z* (%)=334.2 (100) [M$^+$], 289.1 (37), 259.1 (81); HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1675.

*4.2.14. Ethyl 1-(2-ethylphenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylate (**6an**).* Yellow powder, 1.20 g (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32–7.25 (m, 4H), 7.20 (d, *J*=7.6 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 1H), 7.14–7.09 (m, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 2.38 (s, 3H), 2.26 (q, *J*=7.6 Hz, 2H), 143 (t, *J*=7.2 Hz, 3H), 0.97 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.3, 143.4, 141.7, 141.0, 138.3, 129.8 (2C), 129.3, 129.1, 128.9, 128.4, 128.3, 128.3 (2C), 126.1, 118.6, 60.7, 23.7, 14.5, 13.8, 9.9; MS (EI): *m*/*z* (%)=334.2 (100) [M$^+$], 305.1 (40), 259.1 (55), 245.1 (54), 206.1 (25); HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1682.

*4.2.15. Ethyl 5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (**6ba**).* Yellow powder, 1.05 g (62% yield), mp 94–96 °C 7.30 (dd, *J*=5.2, 2.0 Hz, 3H), 7.25–7.20 (m, 2H), 7.08 (d, *J*=8.8 Hz, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 2.31 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.1, 142.3, 140.9, 139.4, 134.7, 131.3 (2C), 128.9 (4C), 128.1, 128.0, 125.4 (2C), 120.0, 60.8, 14.5, 9.7; MS (EI): *m*/*z* (%)=340.1 (100) [M$^+$], 294.1 (69), 267.1 (93), 214.1 (52), 77.0 (35); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1058; *m*/*z* [M+Na$^+$] calcd for $C_{19}H_{17}ClN_2NaO_2$ 363.0876, found 363.0883; *m*/*z* [M+K$^+$] calcd for $C_{19}H_{17}ClKN_2O_2$ 379.0616, found 379.0626.

*4.2.16. Ethyl 4-methyl-1-phenyl-5-p-tolyl-1H-pyrazole-3-carboxylate (**6ca**).* Yellow powder, 1.10 g (69% yield), mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29–7.22 (m, 5H), 7.15 (d, *J*=8.0 Hz, 2H), 7.03 (d, *J*=8.0 Hz, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.3, 142.2, 142.1, 139.7, 138.5, 129.9 (2C), 129.3 (2C), 128.7 (2C), 127.7, 126.6, 125.4 (2C), 119.7, 60.7, 21.3, 14.5, 9.7; MS (EI): *m*/*z* (%)=320.2 (94) [M$^+$], 274.1 (44), 247.1 (100), 194.1 (52), 77.0 (15); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1601; *m*/*z* [M+Na$^+$] calcd for $C_{20}H_{20}N_2NaO_2$ 343.1422, found 343.1423; *m*/*z* [M+K$^+$] calcd for $C_{20}H_{20}KN_2O_2$ 359.1162, found 359.1162.

*4.2.17. Ethyl 5-(4-methoxyphenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (**6da**).*[32] Yellow powder, 1.19 g (71% yield), mp 156–158 °C (lit.[32] 148–150 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31–7.23 (m, 5H), 7.07 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 3.81 (s, 3H), 2.31 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.3, 159.6, 142.1, 142.0, 139.7, 131.4 (2C), 128.7 (2C), 127.7, 125.4 (2C), 121.7, 119.6, 114.1 (2C), 60.8, 55.2, 14.5, 9.8; MS (EI): *m*/*z* (%)=336.1 (100) [M$^+$], 290.1 (30), 263.1 (62), 210.1 (44), 77.0 (12); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{20}H_{21}N_2O_3$ 337.1552, found 337.1551; *m*/*z* [M+Na$^+$] calcd for $C_{20}H_{20}N_2NaO_3$ 359.1372, found 359.1371; *m*/*z* [M+K$^+$] calcd for $C_{20}H_{20}KN_2O_3$ 375.1111, found 375.1127.

*4.2.18. Ethyl 5-(3-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (**6ea**).* Yellow powder, 1.14 g (67% yield), mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35–7.31 (m, 2H), 7.31–7.28 (m, 2H), 7.26–7.23 (m, 3H), 7.19 (d, *J*=1.6 Hz, 1H), 7.00 (d, *J*=7.6 Hz, 1H), 4.46 (q, *J*=7.2 Hz, 2H), 2.33 (s, 3H), 1.44 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.0, 142.3, 140.6, 139.2, 134.5, 131.3, 129.9, 129.8, 128.9 (2C), 128.8, 128.3, 128.1, 125.4 (2C), 120.2, 60.9, 14.5, 9.7; MS (EI): *m*/*z* (%)=340.1 (95) [M$^+$], 294.1 (76), 267.1 (100), 231.1 (23), 214.0 (48), 77.0 (31); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1052; *m*/*z* [M+Na$^+$] calcd for $C_{19}H_{17}ClN_2NaO_2$ 363.0876, found 363.0877; *m*/*z* [M+K$^+$] calcd for $C_{19}H_{17}ClKN_2O_2$ 379.0616, found: 379.0606.

*4.2.19. Ethyl 1,5-diphenyl-4-ethyl-1H-pyrazole-3-carboxylate (**6fa**).*[33] Yellow powder, 0.78 g (61% yield), mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39–7.32 (m, 3H), 7.30–7.22 (m, 5H), 7.20–7.13 (m, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 2.73 (q, *J*=7.6 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H), 1.19 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.0, 141.9, 141.6, 139.5, 130.1 (2C), 129.7, 128.7 (2C), 128.64, 128.60 (2C), 127.8, 126.5, 125.4 (2C), 60.8, 17.3, 15.8, 14.4; MS (EI): *m*/*z* (%)=320.2 (56) [M$^+$], 274.1 (100), 245.1 (70), 231.1 (23), 180.1 (58), 77.0 (26); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1606.

*4.2.20. Ethyl 1,5-diphenyl-4-propyl-1H-pyrazole-3-carboxylate (**6ga**).* Yellow powder, 0.87 g (52%), mp 44–46 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.38–7.34 (m, 3H), 7.30–7.24 (m, 5H), 7.19–7.15 (m, 2H), 4.47 (q, *J*=7.2 Hz, 2H), 2.70 (quint, *J*=7.6, 5.6 Hz, 2H), 1.63–1.54 (m, 2H), 1.45 (t, *J*=7.2 Hz, 3H), 0.89 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.0, 142.2, 141.8, 139.6, 130.1 (2C), 129.9, 128.7 (2C), 128.7, 128.6 (2C), 127.7, 125.3 (2C), 125.0, 60.8, 25.9, 24.5, 14.4, 14.2; MS (EI): *m*/*z* (%)=334.2 (55) [M$^+$], 305.1 (64), 288.1 (100), 259.1 (68), 180.1 (34), 77.0 (19); HRMS (ESI): *m*/*z* [M+Na$^+$] calcd for $C_{21}H_{22}N_2NaO_2$ 357.1579, found 357.1578; *m*/*z* [M+K$^+$] calcd for $C_{21}H_{22}KN_2O_2$ 373.1318, found 373.1328.

*4.2.21. Ethyl 4-isopropyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**6ha**).* Yellow oil, 0.80 g (48%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.36–7.33 (m, 3H), 7.25–7.20 (m, 5H), 7.19–7.15 (m, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 3.26 (quint, *J*=7.2 Hz, 1H), 1.45 (t, *J*=7.2 Hz, 3H), 1.27 (d, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.2, 141.7, 141.3, 139.5, 130.7 (2C), 130.5, 130.1, 128.7, 128.6 (2C), 128.4 (2C), 127.7, 125.5 (2C), 60.9, 24.7, 22.3 (2C), 14.4; MS (EI): *m*/*z* (%)=334.2 (42) [M$^+$], 305.1 (16), 288.1 (91), 259.1 (100), 245.1 (39), 77.0 (21); HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1678.

*4.2.22. Ethyl 1,4-diphenyl-5-p-tolyl-1H-pyrazole-3-carboxylate (**6ia**).* White powder, 0.90 g (47% yield), mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31 (s, 5H), 7.28–7.25 (m, 3H), 7.24–7.22 (m, 2H), 6.97 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=8.0 Hz, 2H), 4.33 (q, *J*=7.2 Hz, 2H), 2.27 (s, 3H), 1.26 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.6, 142.3, 141.6, 139.6, 138.4, 132.0, 130.7 (2C), 130.2 (2C), 129.0 (2C), 128.8 (2C), 128.0, 127.6 (2C), 127.0, 125.9, 125.7 (2C), 124.7, 60.9, 21.3, 14.2; MS (EI): *m*/*z* (%)=382.2 (100) [M$^+$], 337.1 (16), 309.1 (44), 194.1 (39), 77.0 (7); HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{25}H_{23}N_2O_2$ 383.1760, found 383.1754.

*4.2.23. Ethyl 1,5-diphenyl-1H-pyrazole-3-carboxylate (**6ja**).* Yellow powder, 1.33 g (91%), mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.38–7.28 (m, 8H), 7.23–7.20 (m, 2H), 7.05 (s, 1H), 4.46 (q, *J*=7.2 Hz, 2H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.4, 144.6, 144.3, 139.5, 129.5, 128.9 (2C), 128.7 (2C), 128.69, 128.6 (2C), 128.3, 125.7 (2C), 109.9, 61.1, 14.4; MS (EI): *m*/*z* (%)=292.1 (81) [M$^+$], 247.1 (54), 220.1 (100), 193.1 (16), 180.1 (18), 77.0 (19); HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{22}N_2O_2$ 292.1212, found 292.1210.

*4.2.24. Ethyl 1-phenyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate (**6ka**).*[31] Brown powder, 1.43 g (90% yield), mp 154–156 °C (lit.[31] 152–154 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55–7.51 (m, 2H), 7.51–7.46 (m, 3H), 7.30 (d, *J*=7.2 Hz, 1H), 7.17 (t, *J*=7.6 Hz, 1H), 6.98 (t, *J*=7.2 Hz, 1H), 6.74 (d, *J*=7.6 Hz, 1H), 4.45 (q, *J*=7.2 Hz, 2H), 3.12–3.07 (m, 2H), 3.03–2.99 (m, 2H), 1.43 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.9, 140.4,

140.2, 139.6, 137.4, 129.4 (2C), 129.1, 128.7, 128.0, 126.3, 126.2, 126.1, 122.9 (2C), 122.9, 60.9, 30.1, 20.1, 14.5; MS (EI): m/z (%)=318.1 (35) [M^+], 271.1 (23), 245.1 (100); HRMS (ESI): m/z [M+H^+] calcd for $C_{20}H_{19}N_2O_2$ 319.1447, found 319.1445.

*4.2.25. Ethyl 1-(4-fluorophenyl)-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate (**6lf**).* Brown powder, 1.66 g (87% yield), mp 194–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (dd, J=8.4, 2.4 Hz, 1H), 7.55 (d, J=2.4 Hz, 1H), 7.54–7.48 (m, 2H), 7.46 (d, J=8.4 Hz, 1H), 7.26–7.22 (m, 2H), 4.45 (q, J=7.2 Hz, 2H), 3.17–3.08 (m, 4H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.1 (d, J_{C-F}=249.6 Hz), 162.4, 146.7, 144.5, 140.5, 137.9, 135.6 (d, J_{C-F}=3.1 Hz), 129.6, 128.0 (d, J_{C-F}=8.9 Hz, 2C), 127.1, 123.5, 122.7, 117.3, 116.9 (d, J_{C-F}=22.8 Hz, 2C), 61.18, 30.21, 19.57, 14.42; MS (EI): m/z (%)=381.1 (51) [M^+], 335.1 (54), 308.1 (100), 262.1 (24); HRMS (ESI): m/z [M+H^+] calcd for $C_{20}H_{17}FN_3O_4$ 382.1203, found 382.1202.

*4.2.26. Ethyl 8-methoxy-1-phenyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate (**6ma**).* Brown powder, 1.18 g (85% yield), mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.56–7.45 (m, 5H), 7.19 (d, J=8.4 Hz, 1H), 6.71 (dd, J=8.4, 2.8 Hz, 1H), 6.27 (d, J=2.8 Hz, 1H), 4.45 (d, J=7.2 Hz, 2H), 3.44 (s, 3H), 3.07 (t, J=7.2 Hz, 2H), 2.94 (t, J=7.2 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.9, 157.8, 140.2, 140.2, 139.6, 129.5, 129.4 (2C), 129.3, 126.8, 126.5 (2C), 126.2, 123.1, 113.8, 108.4, 60.9, 54.9, 29.2, 20.4, 14.5; MS (EI): m/z (%)=348.1 (53) [M^+], 301.1 (35), 275.1 (100), 232.1 (13); HRMS (ESI): m/z [M+H^+] calcd for $C_{21}H_{21}N_2O_3$ 349.1552, found: 349.1551.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (Project No. 21176074) for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.012. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For general reviews, see, e.g.: (a) Kost, A. N. I.; Grandberg, I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347–429; (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Springer: New York, NY, 2002; Vol. 6, pp 52–98; (c) Yet, L. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, pp 1–141; (d) Fustero, S.; Sanchez-Rosell, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984–7034.
2. For selected examples on pyrazoles as active ingredients in medicinal chemistry, see: (a) Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; R. Baldwin, M.; G. Tamagnan, D.; Conn, P. J. *J. Med. Chem.* **2006**, *49*, 3332–3344; (b) Chimenti, F.; Fioravanti, R.; Bolasco, A.; Manna, F.; Chimenti, P.; Secci, D.; Befani, O.; Turini, P.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2007**, *50*, 425–428; (c) Wyatt, P. G.; Woodhead, A. J.; Berdini, V.; J. Boulstridge, A.; Carr, M. G.; Cross, D. M.; Davis, D. J.; Devine, L. A.; Early, T. R.; Feltell, R. E.; Lewis, E. J.; MsMenamin, R. L.; Navarro, E. F.; O'Brien, M. A.; O'Reilly, M.; Reule, M.; Saxty, G.; Seavers, L. A.; Smith, D.-M.; Squires, M.; Trewartha, G.; Walker, M. T.; Woolford, A. J.-A. *J. Med. Chem.* **2008**, *51*, 4986–4999; (d) Mowbray, C. E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D. A.; Quinton, F. J.; Selby, M. D.; Stupple, P. A.; Webster, R.; Wood, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857–5860.
3. For selected examples on pyrazoles as agrochemicals, see: (a) Vicentini, C. B.; Romagnoli, C.; Andreotti, E.; Mares, D. *J. Agric. Food Chem.* **2007**, *55*, 10331–10338; (b) Fustero, S.; Roman, R.; Sanz-Cervera, J. F.; Simon-Fuentes, A.; Bueno, J.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545–8552; (c) Lahm, G. P.; Cordova, D.; Barry, J. D. *Bioorg. Med. Chem.* **2009**, *17*, 4127–4133.
4. For selected examples on pyrazoles as ligands in coordination chemistry, see: (a) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151–218; (b) Ward, M. D.; McCleverty, J. A.; Jeffery, J. C. *Coord. Chem. Rev.* **2001**, *222*, 251–272; (c) Trofimenko, S. *Polyhedron* **2004**, *23*, 197–203; (d) Kırkar, B. T.; Türkmen, H.; Kani, İ.; Çetinkaya, B. *Tetrahedron* **2012**, *68*, 8655–8662.
5. For a selected example on pyrazoles as UV stabilizers, see: Catalan, J.; Fabero, F.; Claramunt, R. M.; Maria, M. D. S.; Foces-Foces, M. C.; Cano, F. H.; Martinez-Ripoll, M.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1992**, *114*, 5039–5048.
6. For recent examples on pyrazoles as units in supramolecular entities, see: (a) Gemming, S.; Schreiber, M.; Thiel, W.; Heine, T.; Seifert, G.; Avelino de Abreu, H.; Anderson Duarte, H. *J. Lumin.* **2004**, *108*, 143–147; (b) Maeda, H.; Ito, Y.; Kusunose, Y.; Nakanishi, T. *Chem. Commun.* **2007**, 1136–1138; (c) Sachse, A.; Penkova, L.; Noel, G.; Dechert, S.; Varzatskii, O. A.; Fritsky, I. O.; Meyer, F. *Synthesis* **2008**, 800–806.
7. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
8. Terrett, N. K.; A. Bell, S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
9. Barth, F.; Rinaldi-Carmona, M. *Curr. Med. Chem.* **1999**, *6*, 745–755.
10. (a) Sui, Z.; Guan, J.; Ferro, M. P.; McCoy, K.; Wachter, M. P.; Murray, W. V.; Singer, M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601–604; (b) Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935–1945; (c) Selvam, C.; Jachak, S. M.; Thilagavathi, R.; Chakraborti, A. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1793–1797.
11. Katoch-Rouse, R.; L. Pavlova, A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem.* **2003**, *46*, 642–645.
12. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J.-I. *Bioorg. Med. Chem.* **2004**, *12*, 5515–5524.
13. (a) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934–4947; (b) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 141–150.
14. For recent pyrazole syntheses, see, e.g.: (a) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079–7082; (b) Bagley, M. C.; Lubinu, M. C.; Mason, C. *Synlett* **2007**, 704–708; (c) Dang, T. T.; Dang, T. T.; Fischer, C.; Gorls, H.; Langer, P. *Tetrahedron* **2008**, *64*, 2207–2215; (d) Liu, H.-L.; Jiang, H.-F.; Zhang, M.; Yao, W.-J.; Zhu, Q.-H.; Tang, Z. *Tetrahedron Lett.* **2008**, *49*, 3805–3809; (e) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691–1694; (f) Deng, X.; Mani, N. S. *Org. Lett.* **2008**, *10*, 1307–1310; (g) Deng, X.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2412–2415; (h) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 12104–12107; (i) Dadiboyena, S.; Valente, E. J.; Hamme, A. T. *Tetrahedron Lett.* **2010**, *51*, 1341–1343; (j) Meng, L.; Lorsbach, B. A.; Sparks, T. C.; Fettiger, J. C.; Kurth, M. J. *J. Comb. Chem.* **2010**, *12*, 129–136; (k) Janin, Y. L. *Mini-Rev. Org. Chem.* **2010**, *7*, 314–323; (l) Chandanshive, J. Z.; Bonini, B. F.; Gentili, D.; Fochi, M.; Bernardi, L.; Franchini, M. C. *Eur. J. Org. Chem.* **2010**, 6440–6447; (m) Li, Y.; Hong, D.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2011**, *52*, 4161–4163; (n) Willy, B.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2082–2085; (o) Wu, X.-F.; Neumann, H.; Beller, M. *Eur. J. Org. Chem.* **2011**, 4919–4924; (p) Vazquez, N.; Gomez-Vallejo, V.; Llop, J. *Tetrahedron Lett.* **2012**, *53*, 4743–4746; (q) Rüger, A. J.; Nieger, M.; Bräse, S. *Tetrahedron* **2012**, *68*, 8823–8829.
15. For selected examples, see: (a) Murineddu, G.; Lazzari, P.; Ruiu, S.; Sanna, A.; Loriga, G.; Manca, I.; Falzoi, M.; Dessi, C.; Curzu, M. M.; Chelucci, G.; Pani, R. L.; Pinna, G. A. *J. Med. Chem.* **2006**, *49*, 7502–7512; (b) Zhang, Y.; Burgess, J. P.; Brackeen, M.; Gilliam, A.; Mascarella, S. W.; Page, K.; Seltzman, H. H.; Thomas, B. F. *J. Med. Chem.* **2008**, *51*, 3526–3539; (c) Dow, R. L.; Carpino, P. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; DaSilva-Jardine, P.; Schneider, S. R.; Paight, E. S.; Griffith, D. A.; Scott, D. O.; O'Connor, R. E.; Nduaka, C. I. *J. Med. Chem.* **2009**, *52*, 2652–2655; (d) Spivey, A. C.; Tseng, C.-C.; Jones, T. C.; Kohler, A. D.; Ellames, G. J. *Org. Lett.* **2009**, *11*, 4760–4763; (e) Wu, C.-H.; Hung, M.-S.; Song, J.-S.; Yeh, T.-K.; Chou, M.-C.; Chu, C.-M.; Jan, J.-J.; Hsieh, M.-T.; Tseng, S.-L.; Chang, C.-P.; Hsieh, W.-P.; Lin, Y.; Yeh, Y.-N.; Chung, W.-L.; Kuo, C.-W.; Lin, C.-Y.; Shy, H.-S.; Chao, Y.-S.; Shia, K.-S. *J. Med. Chem.* **2009**, *52*, 4496–4510; (f) Griffith, D. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; Carpino, P. A.; DaSilva-Jardine, P.; Day, R.; DiBrino, J.; Dow, R. L.; Landis, M. S.; O'Connor, R. E.; Scott, D. O. *J. Med. Chem.* **2009**, *52*, 234–237; (g) Szabo, G.; Varga, B.; Payer-Lengyel, D.; Szemzo, A.; Erdelyi, P.; Vukics, K.; Szikra, J.; Hegyi, E.; Vastag, M.; Kiss, B.; Laszy, J.; Gyertyan, I.; Fischer, J. *J. Med. Chem.* **2009**, *52*, 4329–4337; (h) Seo, H. J.; Kim, M. J.; Lee, S. H.; Lee, S.-H.; Jung, M. E.; Kim, M.-S.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 1149–1162; (i) Cooper, M.; Receveur, J.-M.; Bjurling, E.; Nørregaard, P. K.; Nielsen, P. A.; Sköld, N.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2067–2070; (j) Yan, L.; Huo, P.; Debenham, J. S.; Madsen-Duggan, C. B.; Lao, J.; Chen, R. Z.; Xiao, J. C.; Shen, C.-P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Tsou, N.; Ball, R. G.; Wang, J.; Tong, X.; Bateman, T. J.; Reddy, V. B. G.; Fong, T. M.; Hale, J. J. *J. Med. Chem.* **2010**, *53*, 4028–4037; (k) Lange, J. H. M.; Coolen, H. K. A. C.; Neut, M. A. W.; Borst, A. J. M.; Stork, B.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2010**, *53*, 1338–1346; (l) Donohue, S. R.; Dannals, R. F.; Halldin, C.; Pike, V. W. *J. Med. Chem.* **2011**, *54*, 2961–2970.
16. (a) Xie, J.; Poda, G. I.; Hu, Y.; Chen, N. X.; Heier, R. F.; Wolfson, S. G.; Reding, M. T.; Lennon, P. J.; Kurumbail, R. G.; Selness, S. R.; Li, X.; Kishore, N. N.; Sommers, C. D.; Christine, L.; Bonar, S. L.; Venkatraman, N.; Mathialagan, S.; Brustkern, S. J.; Huang, H.-C. *Bioorg. Med. Chem.* **2011**, *19*, 1242–1255; (b) Nassar, E.; Abdel-Aziz, H. A.; Ibrahim, H. S.; Mansour, A. M. *Sci. Pharm.* **2011**, *79*, 507–524; (c) Abd-E1 Gawad, N. M.; Hassan, G. S.; Georgey, H. H. *Med. Chem. Res.* **2012**, *21*, 983–994.
17. (a) Kotagiri, V. K.; Suthrapu, S.; Reddy, J. M.; Rao, C. P.; Bollugoddu, V.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2007**, *11*, 910–912; (b) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703–2802; (c) Ji, Y. -F.; Zhang, P. -Z.; Wan, H.; Duan, M. -L.; Xu,

X.; Wang, Y. CN Patent 101585810A (101585810B), 2009; *Chem. Abstr.* **2009**, *152*, 57302. (d) Climent, M. J.; Corma, A.; Iborra, S. *Chem. Rev.* **2011**, *111*, 1072–1133.
18. (a) Zhang, Y.-N.; Yu, C.-G.; Ji, Y.-F.; Wang, W. *Chem.—Asian J.* **2010**, *5*, 1303–1306; (b) Yu, C.-G.; Zhang, Y.-N.; Song, A.-G.; Ji, Y.-F.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 770–774; (c) Jiang, J.-A.; Zhai, J.-J.; Yu, X.-H.; Teng, X.; Ji, Y.-F. *Synthesis* **2012**, *44*, 207–214; (d) Jiang, J.-A.; Ji, Y.-F. *Synth. Commun.* **2013**, *43*, 72–79.
19. Sakya, S. M. In *Name Reactions in Heterocyclic Chemistry*; Li, J.-J., Corey, E. J., Eds.; Wiley: Hoboken, 2005; pp 292–300.
20. (a) http://onlinelibrary.wiley.com/o/eros/articles/rl063/sect0-fs.html. (b) http://onlinelibrary.wiley.com/o/eros/articles/rl117m/frame.html. (c) http://www.aladdin-reagent.com/thir.asp?Rea_SubID=14146. (d) http://www.aladdin-reagent.com/thir.asp?Rea_SubID=16627.
21. ^{1}H NMR showed that the intramolecular hydrogen bond-bound hydroxyl proton of enolated **4** resonated at a higher field (around 6 ppm) due to less deshielding effect in contrast with freely enolated hydroxyl proton (generally around 16 ppm).
22. The achieved **2** and **4** is badly unstable under the reaction conditions, similar instability and related retro-Claisen reactions see: (a) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60; (b) Cvetovich, R. J.; Pipik, B.; Hartner, F. W.; Grabowski, E. J. J. *Tetrahedron Lett.* **2003**, *44*, 5867–5870; (c) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971; (d) Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623–3625; (e) Biswas, S.; Maiti, S.; Jana, U. *Eur. J. Org. Chem.* **2010**, 2861–2866; (f) Grenning, A. J.; Tunge, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 14785–14794.
23. (a) Sannigrahi, A. B.; Kar, T.; Guha Niyogi, B.; Hobza, P.; Ragu Schleyer, P. *Chem. Rev.* **1990**, *90*, 1061–1076; (b) Izatt, R. M.; Bradshaw, J. S.; Kent Dalley, N. *Chem. Rev.* **1991**, *91*, 137–164; (c) Paquette, L. A.; Ra, C. S.; Gallucci, J. C.; Kang, H.-J.; Ohmori, N.; Arrington, M. P.; David, W.; Brodbelt, J. S. *J. Org. Chem.* **2001**, *66*, 8629–8639.
24. (a) Singh, S. P.; Kumar, D.; Batra, H.; Naithani, R.; Rozas, I.; Elguero, J. *Can. J. Chem.* **2000**, *78*, 1109–1120; (b) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2004**, 4348–4356; (c) Fustero, S.; Simon-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253–290.
25. (a) Murray, W. V.; Wachter, M. P. *J. Heterocycl. Chem.* **1989**, *26*, 1389–1392; (b) Ashton, W. T.; Doss, G. A. *J. Heterocycl. Chem.* **1993**, *30*, 307–311.
26. Selttman, H. H.; Carroll, F. I.; Burgess, J. P.; Wyrick, C. D.; Burch, D. F. *J. Chem. Soc., Chem. Commun.* **1995**, 1549–1550.
27. The two regioisomers in the case of **6ab** were indistinguishable on chromatographic analysis, only detected by a careful recognition of ^{1}H NMR (see Supplementary data). Similar pyrazole regioisomers had been mentioned as an inseparable mixture, see: Singh, S. K.; Srinivasa Reddy, M.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Moses Babu, J.; Sivalakshmidevi, A.; Koteswar Rao, Y. *Tetrahedron Lett.* **2004**, *45*, 7679–7682.
28. Singh, S. P.; Kapoor, J. K.; Kumar, D.; Threadgill, M. D. *J. Fluorine Chem.* **1997**, *83*, 73–79.
29. Szczesna, B.; Urbanczyk-Lipkowska, Z. *Supramol. Chem.* **2001**, *13*, 247–251.
30. Alkorta, I.; Goya, P.; Pérez-Fernández, R.; Alvarado, M.; Elguero, J.; García-Granda, S.; Menéndez-Taboada, L. *J. Mol. Struct.* **2009**, 10–15.
31. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769–776.
32. Donohue, S. R.; Halldin, C.; Pike, V. W. *Bioorg. Med. Chem.* **2006**, *14*, 3712–3720.
33. Schmidt, A.; Muenster, N.; Dreger, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2790–2793 and Supplementary data therein.