Tetrahedron 69 (2013) 1427–1433

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Efficient one-pot synthesis of substituted pyrazoles

Meng Tang [a,*], Fu-Min Zhang [b,*]

[a] School of Pharmacy, Lanzhou University, Lanzhou 730000, PR China
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 17 September 2012
Received in revised form 31 October 2012
Accepted 14 December 2012
Available online 21 December 2012

Keywords:
Substituted pyrazoles
Regioselectivity
Synthesis

ABSTRACT

An efficient, one-pot synthesis of substituted pyrazoles from enones, hydrazides, and halides was developed. In comparison with the classical Knorr pyrazole synthesis, this methodology gave a different type of product ($R^3 \geq R^5$). A range of substituted pyrazoles were prepared in good to high yields with complete regioselectivity.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Pyrazoles and their derivatives represent an important class of compounds that are used extensively in the pharmaceutical and agrochemical industries.[1] Compounds containing the pyrazole moiety have a wide range of biological activities, such as the HIV-1 reverse transcriptase inhibitor PNU-32945,[2] cyclooxygenase-2 (COX-2) inhibitor Celecoxib,[3] herbicide Fluazolate,[1b] and fungicide Pyraclostrobin[4] (Fig. 1).

One of the most important methods for constructing pyrazole rings[5,6] is the classical Knorr pyrazole synthesis.[7] The Knorr synthesis suffers from a regioselectivity issue,[8] which arise for pyrazoles with $R^3 \neq R^5$. When considering the sizes of the substituents, Knorr synthesis products typically have R^5 larger than R^3 (Scheme 1a), such as in PNU-32945 and Celecoxib. To prepare a product with R^3 larger than R^5, such as Fluazolate and Pyraclostrobin, this method is usually unsuitable. Therefore, a general and convenient method for synthesis of pyrazoles with $R^3 > R^5$ is required.

2. Results and discussion

In the course of our study on the synthesis of substituted allenes from enones,[9] we found that when using inorganic Brønsted bases, the reaction led to a different product, which was 1*H*-pyrazoles **A** and/or **B** (Scheme 2). This kind of transformation has been reported several times,[10] however, to the best of our knowledge, this method has not been widely used in pyrazole synthesis. It is well known that under basic conditions, tautomerism between 1*H*-pyrazoles **A** and **B** occurs easily. Therefore, we investigated sequential synthesis of 1-position substituted pyrazoles by combining several elementary steps. Here, we report a three-step, one-pot synthesis of 1-position substituted pyrazole derivatives from readily available and simple starting materials, such as enones, *p*-toluenesulfonyl hydrazide ($TsNHNH_2$) and halides (R^1–X) (Scheme 1b).

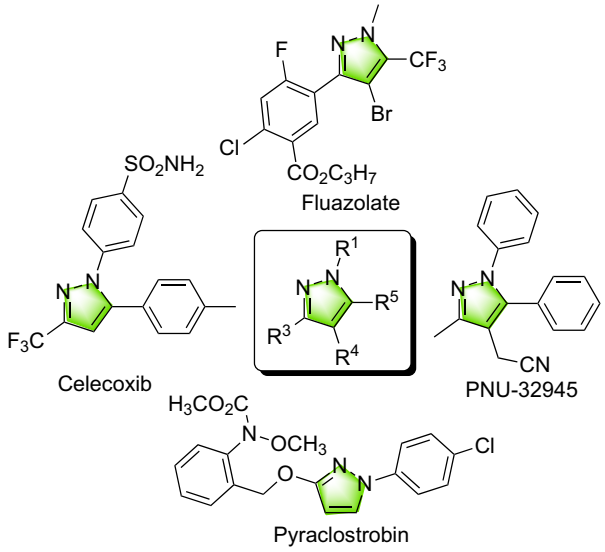
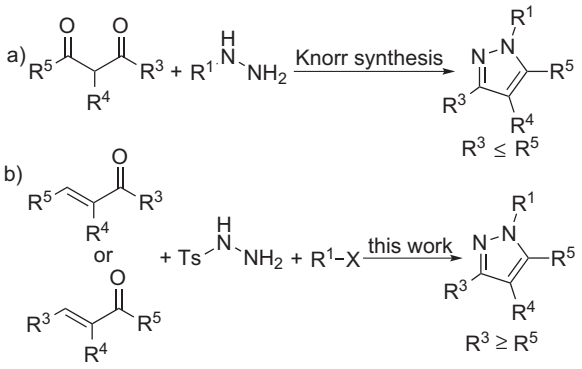


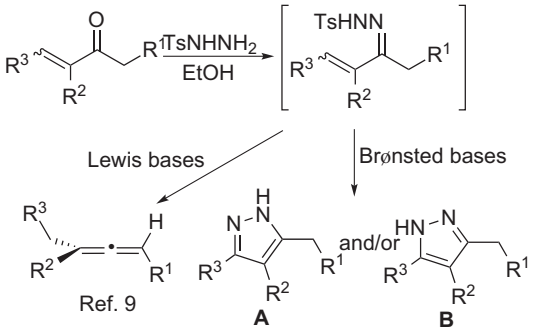
Fig. 1. Representative pyrazole derivatives.

* Corresponding authors. E-mail addresses: tangmeng@lzu.edu.cn (M. Tang), zhangfm@lzu.edu.cn (F.-M. Zhang).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.038



Scheme 1. Regioselectivity in the construction of pyrazole rings.

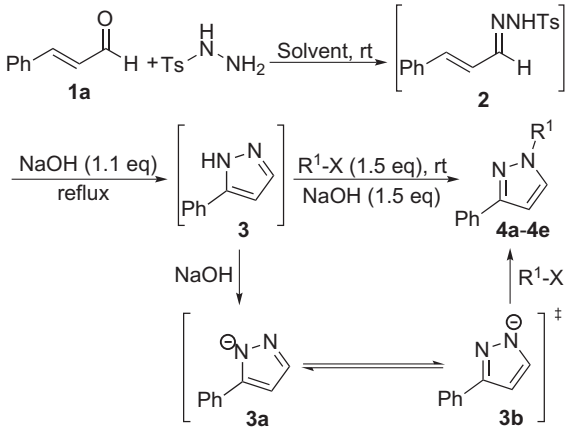


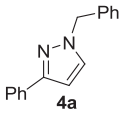
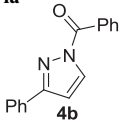
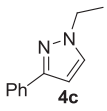
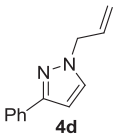
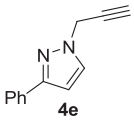
Scheme 2. α,β-Unsaturated tosylhydrazones as versatile synthetic intermediates lead to allenes or pyrazoles.

Encouraged by previous results,[9] our study was performed with cinnamaldehyde (**1a**) as a model substrate and NaOH as the base in EtOH (Table 1). First, trapping of the intermediate 5-phenyl-1*H*-pyrazole (**3**)[11] with benzyl bromide was attempted. The progress of pyrazole **3** formation was monitored by TLC, and when complete, NaOH and benzyl bromide were added. Under basic conditions, deprotonation of the NH moiety and rapid tautomerism resulted in **3a** and/or **3b**. Then **4a** was obtained by a nucleophilic substitution reaction of **3b** with benzyl bromide. The structure of **4a** was unambiguously established by NMR and single-crystal X-ray analysis (Fig. 2). However, the reaction of pyrazole **3** with benzyl bromide was quite slow, and the yield was only 44% after two days (entry 1, Table 1). Of the solvents screened, acetonitrile gave an excellent yield within 2 h (91%, entry 2, Table 1). We then investigated the scope of R^1–X, and found benzoyl chloride, iodoethane, allyl bromide, and propargyl bromide all gave the corresponding pyrazole derivatives (**4b**–**e**) in good to high yields (entries 3–6, Table 1). The reaction showed consistent, complete regioselectivity, with only single isomers obtained in all reactions. This regioselectivity could be a result of repulsion between the phenyl substituent and R^1.

Syntheses of a variety of pyrazoles were attempted to investigate the scope of the method. As shown in Table 2, different di-, tri- and tetrasubstituted pyrazole derivatives were obtained in good yields. However, the substituent R^5 apparently affected the formation of tosylhydrazone. Compared with benzalacetone (**1e**) as the substrate, tosylhydrazone production was very slow in acetonitrile with chalcone (**1d**) and **1f** as substrates (entries 9–13, 16, 17, Table 2). EtOH was used in the initial stage of the reaction, and after the pyrazole formed, it was removed under reduced pressure and acetonitrile was used to complete the procedure. When **1e** was used as the substrate, the bulk of R^1 apparently affected the regioselectivity of the reaction, benzyl bromide and benzoyl chloride could trap the intermediate 1*H*-pyrazole with complete

Table 1
One-pot synthesis of 1,3-disubstituted pyrazoles and the scope of the halides



Entry	Solvent	R^1–X	Product	Yield[a] (%)
1	EtOH		 **4a**	44[b]
2	CH_3CN		**4a**	91
3	CH_3CN		 **4b**	89
4	CH_3CN		 **4c**	87
5	CH_3CN		 **4d**	86
6	CH_3CN		 **4e**	71

[a] The yields are for the isolated product.
[b] 5-Phenyl-1*H*-pyrazole **3** was isolated in 51% yield.

regioselectivity, and only one product (**4s** or **4t**) was isolated, (entries 14, 15, Table 2) however, iodoethane gave a disappointing result, and the ratio of **4v**:**4w**[12] was 2.2:1 (Scheme 3). Moreover, substrates **1e** and **1f** led to the same product **4s** or **4t** when trapped with benzyl bromide or benzoyl chloride (entries 14–17, Table 2).

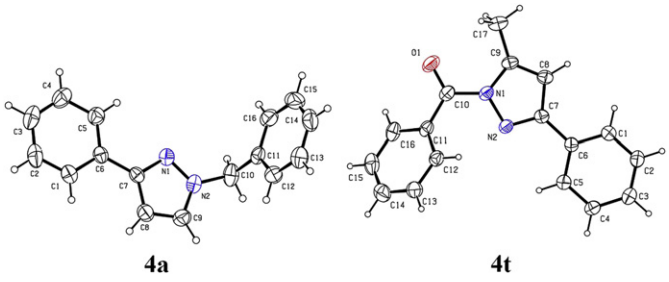
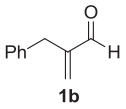
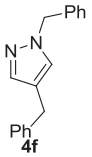
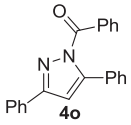
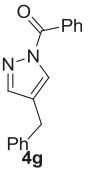
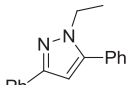
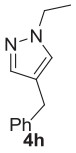
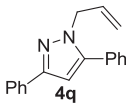
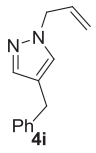
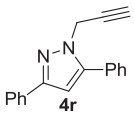
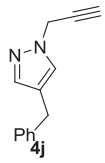
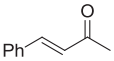
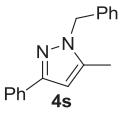
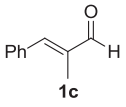
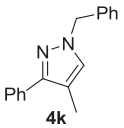
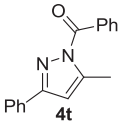
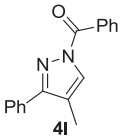
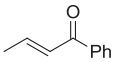
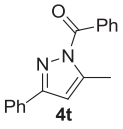
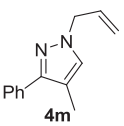
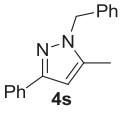
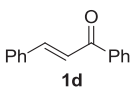
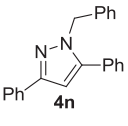
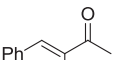
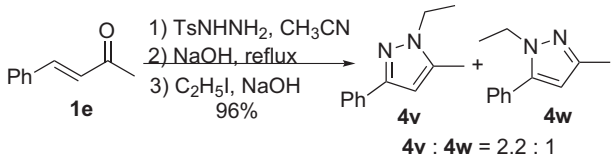


Fig. 2. X-ray structure of **4a** and **4t**.

Table 2
Preparation of substituted pyrazoles

Entry	Enone **1**	R^1–X	Product	Yield[a] (%)	Entry	Enone **1**	R^1–X	Product	Yield[a] (%)
1	 **1b**		 **4f**	88	10	**1d**		 **4o**	85
2	**1b**		 **4g**	89	11	**1d**		 **4p**	98
3	**1b**		 **4h**	93	12	**1d**		 **4q**	96
4	**1b**		 **4i**	89	13	**1d**		 **4r**	74
5	**1b**		 **4j**	82	14	 **1e**		 **4s**	78
6	 **1c**		 **4k**	94	15	**1e**		 **4t**	76
7	**1c**		 **4l**	95	16	 **1f**		 **4t**	73
8	**1c**		 **4m**	78	17	**1f**		 **4s**	65
9	 **1d**		 **4n**	89	18	 **1g**		**4u**	73

[a] The yields are for the isolated product.



Scheme 3. Regioselectivity in preparation of 1,3,5-trisubstituted pyrazoles.

3. Conclusions

In conclusion, an efficient, one-pot, three-step synthesis of substituted pyrazoles was developed. A series of 1,3-disubstituted, 1,4-disubstituted, 1,3,4-trisubstituted, 1,3,5-trisubstituted and 1,3,4,5-tetrasubstituted pyrazole derivatives were synthesized in good yields. This efficient and highly modular one-pot procedure is practical and useful. Further studies on the biological activities of the products and application of this methodology to other interesting pyrazole derivatives are underway in our laboratory.

4. Experimental section

4.1. General remarks

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (bp 60–90 °C) are used. All organic extracts were dried over anhydrous $MgSO_4$. IR spectra were recorded on a Nicolet FT-170SX spectrometer. ^1H and ^{13}C NMR spectra were taken on a Bruker AVANCE III 400 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. The HRMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer.

4.2. Typical representative procedure for the synthesis 1-benzyl-3-phenyl-1*H*-pyrazole (4a)

A mixture of **1a** (132 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in CH_3CN (2 mL) were stirred at room temperature for 3 h and then CH_3CN (2 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 15 h, then NaOH (60 mg, 1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4a** as a white crystalline solid (213 mg, 91%). Mp 60–62 °C; δ_H (400 MHz, $CDCl_3$) 5.32 (2H, s), 6.55 (1H, d, *J* 2.4 Hz), 7.20–7.23 (2H, m), 7.25–7.33 (5H, m), 7.35–7.39 (2H, m), 7.81–7.82 (2H, m); δ_C (100 MHz, $CDCl_3$) 56.0, 103.2, 125.6, 127.5, 127.6, 127.9, 128.5, 128.7, 130.5, 133.5, 136.6, 151.5; HRMS (ESI): MH^+, found 235.1232. $C_{16}H_{15}N_2$ requires 235.1230, ν_{max} (liquid film) 3126, 3107, 3062, 3033, 2936, 1498, 1455, 1078 cm^{-1}.

*4.2.1. Preparation of phenyl(3-phenyl-1H-pyrazol-1-yl)methanone (**4b**).* Compound **4b** (221 mg, 89%) was prepared following the procedure described for **4a** by using **1a** (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 6.84 (1H, d, *J* 2.8 Hz), 7.35–7.44 (3H, m), 7.49–7.53 (2H, m), 7.59–7.63 (1H, m), 7.85–7.88 (2H, m), 8.24–8.27 (2H, m), 8.45 (1H, d, *J* 2.8 Hz); δ_C (100 MHz, $CDCl_3$) 107.1, 126.4, 128.0, 128.7, 129.1, 131.5, 131.7, 131.78, 131.84, 132.9, 155.9, 166.0; HRMS (ESI): MNa^+, found: 271.0838. $C_{16}H_{12}N_2ONa$ requires 271.0842; ν_{max} (liquid film) 3150, 3125, 3062, 1697, 1541, 1451, 1403, 1351, 1275 cm^{-1}.

*4.2.2. Preparation of 1-ethyl-3-phenyl-1H-pyrazole (**4c**).* Compound **4c** (150 mg, 87%) was prepared following the procedure described for **4a** by using **1a** (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and iodoethane (234 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.6 Hz), 4.17 (2H, q, *J* 7.6 Hz), 6.51 (1H, d, *J* 2.0 Hz), 7.26 (1H, t, *J* 7.2 Hz), 7.36–7.39 (3H, m), 7.80 (2H, d, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 15.6, 47.0, 102.5, 125.5, 127.3, 128.5, 129.4, 133.7, 151.1; HRMS (ESI): MH^+, found: 173.1070. $C_{11}H_{13}N_2$ requires 173.1073; ν_{max} (liquid film) 3063, 3035, 2982, 2939, 1605, 1500, 1457, 1352, 1225 cm^{-1}.

*4.2.3. Preparation of 1-allyl-3-phenyl-1H-pyrazole (**4d**).* Compound **4d** (158 mg, 86%) was prepared following the procedure described for **4a** by using **1a** (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and allyl bromide (180 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 4.75 (2H, dt, *J* 5.6, 1.2 Hz), 5.17–5.26 (2H, m), 5.99–6.08 (1H, m), 6.55 (1H, d, *J* 2.4 Hz), 7.25–7.29 (1H, m), 7.35–7.39 (3H, m), 7.79–7.81 (2H, m); δ_C (100 MHz, $CDCl_3$) 54.7, 102.9, 118.4, 125.5, 127.4, 128.5, 130.1, 132.9, 133.5, 151.4; HRMS (ESI): MH^+, found: 185.1070. $C_{12}H_{13}N_2$ requires 185.1073; ν_{max} (liquid film) 3066, 3035, 2985, 2925, 1500, 1458, 1355, 1327, 1226, 1074 cm^{-1}.

*4.2.4. Preparation of 3-phenyl-1-(prop-2-yn-1-yl)-1H-pyrazole (**4e**).* Compound **4e** (129 mg, 71%) was prepared following the procedure described for **4a** by using **1a** (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and propargyl bromide (177 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 2.49 (1H, t, *J* 2.8 Hz), 4.95 (2H, d, *J* 2.8 Hz), 6.57 (1H, d, *J* 2.4 Hz), 7.26–7.30 (1H, m), 7.36–7.39 (2H, m), 7.60 (1H, d, *J* 2.4 Hz), 7.78 (2H, dd, *J* 8.0, 1.2 Hz); δ_C (100 MHz, $CDCl_3$) 41.5, 74.7, 76.7, 103.3, 125.6, 127.7, 128.5, 130.0, 133.2, 152.0; HRMS (ESI): MH^+, found: 183.0919. $C_{12}H_{11}N_2$ requires 183.0917; ν_{max} (liquid film) 3290, 3063, 3037, 2925, 2127, 1500, 1459, 1337, 1227 cm^{-1}.

4.3. Typical representative procedure for the synthesis 1,4-dibenzyl-1*H*-pyrazole (4f)

A mixture of 2-benzylacrylaldehyde (**1b**)[13] (146 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in CH_3CN (2 mL) were stirred at room temperature for 2 h and then CH_3CN (2 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 15 h, then NaOH (60 mg, 1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4f** as colorless oil (218 mg, 88%). δ_H (400 MHz, $CDCl_3$) 3.79 (2H, s), 5.21 (2H, s), 7.11 (1H, s), 7.17–7.21 (5H, m), 7.24–7.33 (5H, m), 7.37 (1H, s); δ_C (100 MHz, $CDCl_3$) 30.6, 55.9, 121.0, 126.0, 127.5, 127.9, 128.0, 128.36, 128.39, 128.7, 136.7, 139.3, 141.0; HRMS (ESI): MH^+, found 249.1381. $C_{17}H_{17}N_2$ requires 249.1386, ν_{max} (liquid film) 3061, 3028, 2922, 2848, 1494, 1450, 1396, 1152 cm^{-1}.

*4.3.1. Preparation of (4-benzyl-1H-pyrazol-1-yl)(phenyl)methanone (**4g**).* Compound **4g** (233 mg, 89%) was prepared following the procedure described for **4f** by using **1b** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 3.88 (2H, s), 7.22–7.26 (3H, m), 7.31–7.34 (2H, m), 7.45–7.50 (2H, m), 7.56–7.61 (1H, m), 7.63 (1H, s), 8.06–8.08 (2H, m), 8.16 (1H, d, *J* 0.4 Hz); δ_C (100 MHz, $CDCl_3$) 30.5, 124.8, 126.6, 128.0, 128.3, 128.5, 128.7, 131.3, 131.6, 132.8, 139.3, 145.2, 166.3; HRMS (ESI): MNa^+, found: 285.1002. $C_{17}H_{14}N_2ONa$ requires 285.0998; ν_{max} (liquid film) 3062, 3028, 2919, 2850, 1697, 1365, 1244 cm^{-1}.

*4.3.2. Preparation of 4-benzyl-1-ethyl-1H-pyrazole (**4h**).* Compound **4h** (173 mg, 93%) was prepared following the procedure described

for **4f** by using **1b** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and iodoethane (234 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.2 Hz), 3.81 (2H, s), 4.09 (2H, q, *J* 7.2 Hz), 7.12 (1H, s), 7.17–7.21 (3H, m), 7.24–7.30 (2H, m), 7.33 (1H, s); δ_C (100 MHz, $CDCl_3$) 15.5, 30.6, 46.8, 120.4, 126.0, 127.0, 128.37, 128.43, 138.7, 141.2; HRMS (ESI): MH^+, found: 187.1237. $C_{12}H_{15}N_2$ requires 187.1230; ν_{max} (liquid film) 3082, 3061, 3026, 2981, 2934, 1494, 1449, 1397, 1356, 1157 cm^{-1}.

*4.3.3. Preparation of 1-allyl-4-benzyl-1H-pyrazole (**4i**).* Compound **4i** (176 mg, 89%) was prepared following the procedure described for **4f** by using **1b** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and allyl bromide (180 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 3.81 (2H, s), 4.66 (2H, dt, *J* 6.0, 1.2 Hz), 5.15–5.24 (2H, m), 5.94–6.04 (1H, m), 7.13 (1H, s), 7.17–7.20 (3H, m), 7.24–7.29 (2H, m), 7.35 (1H, s); δ_C (100 MHz, $CDCl_3$) 30.6, 54.6, 118.3, 120.8, 126.0, 127.7, 128.37, 128.39, 133.0, 139.1, 141.1; HRMS (ESI): MH^+, found: 199.1232. $C_{13}H_{15}N_2$ requires 199.1230; ν_{max} (liquid film) 3083, 3026, 2919, 2849, 1494, 1446, 1397, 1328, 1152 cm^{-1}.

*4.3.4. Preparation of 4-benzyl-1-(prop-2-yn-1-yl)-1H-pyrazole (**4j**).* Compound **4j** (161 mg, 82%) was prepared following the procedure described for **4f** by using **1b** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and propargyl bromide (177 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 2.45 (1H, t, *J* 2.4 Hz), 3.81 (2H, s), 4.85 (2H, d, *J* 2.4 Hz), 7.18–7.21 (3H, m), 7.24–7.30 (2H, m), 7.33–7.35 (2H, m); δ_C (100 MHz, $CDCl_3$) 30.5, 41.4, 74.4, 76.9, 121.3, 126.1, 127.5, 128.4, 139.8, 140.8; HRMS (ESI): MH^+, found: 197.1074. $C_{13}H_{13}N_2$ requires 197.1073; ν_{max} (liquid film) 3289, 3084, 3061, 3027, 2916, 2126, 1602, 1494, 1446, 1395, 1349, 1152 cm^{-1}.

4.4. Typical representative procedure for the synthesis 1-benzyl-4-methyl-3-phenyl-1*H*-pyrazole (4k)

A mixture of (*E*)-2-methyl-3-phenylacrylaldehyde (**1c**) (146 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in CH_3CN (2 mL) were stirred at room temperature for 3 h and then CH_3CN (2 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 15 h, then NaOH (60 mg, 1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4k** as colorless oil (233 mg, 94%). δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s), 5.27 (2H, s), 7.15 (1H, s), 7.21–7.35 (6H, m), 7.38–7.42 (2H, m), 7.69–7.71 (2H, m); δ_C (100 MHz, $CDCl_3$) 10.1, 55.9, 114.2, 127.1, 127.4, 127.7, 127.9, 128.3, 128.7, 129.7, 134.1, 136.8, 149.7; HRMS (ESI): MH^+, found 249.1380. $C_{17}H_{17}N_2$ requires 249.1386, ν_{max} (liquid film) 3061, 3030, 2926, 2867, 1603, 1552, 1496, 1444, 1343, 1162 cm^{-1}.

*4.4.1. Preparation of (4-methyl-3-phenyl-1H-pyrazol-1-yl)(phenyl) methanone (**4l**).* Compound **4l** (249 mg, 95%) was prepared following the procedure described for **4k** by using **1c** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s), 7.37–7.51 (5H, m), 7.58 (1H, t, *J* 7.2 Hz), 7.75 (2H, d, *J* 7.2 Hz), 8.21–8.25 (3H, m); δ_C (100 MHz, $CDCl_3$) 10.4, 118.8, 127.8, 128.0, 128.5, 128.6, 130.0, 131.67, 131.72, 132.5, 132.7, 155.5, 165.9; HRMS (ESI): MNa^+, found: 285.0997. $C_{17}H_{14}N_2ONa$ requires 285.0998; ν_{max} (liquid film) 3061, 3030, 2925, 2867, 1603, 1552, 1495, 1447, 1343, 1162 cm^{-1}.

*4.4.2. Preparation of 1-allyl-4-methyl-3-phenyl-1H-pyrazole (**4m**).* Compound **4m** (155 mg, 78%) was prepared following the procedure described for **4k** by using **1c** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and allyl bromide (180 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 2.22 (3H, d, *J* 0.8 Hz), 4.71 (2H, dt, *J* 4.4, 1.2 Hz), 5.20–5.25 (2H, m), 5.99–6.09 (1H, m), 7.21 (1H, s), 7.27–7.31 (1H, m), 7.37–7.41 (2H, m), 7.67–7.69 (2H, m); δ_C (100 MHz, $CDCl_3$) 10.0, 54.5, 113.9, 118.3, 127.0, 127.4, 128.3, 129.4, 133.1, 134.1, 149.7; HRMS (ESI): MH^+, found: 199.1232. $C_{13}H_{15}N_2$ requires 199.1230; ν_{max} (liquid film) 3062, 3024, 2922, 2868, 1604, 1552, 1438, 1340, 1165 cm^{-1}.

4.5. Typical representative procedure for the synthesis 1-benzyl-3,5-diphenyl-1*H*-pyrazole (4n)

A mixture of chalcone (**1d**) (208 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in EtOH (2 mL) were stirred at room temperature for 48 h and then EtOH (2 mL), NaOH (44.0 mg, 1.1 mmol) were added and the mixture was heated at reflux for 15 h, then the solvent was removed under reduced pressure, then CH_3CN (4 mL), NaOH (60 mg, 1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4n** as white crystalline solid (276 mg, 89% yield). Mp 114–117 °C; δ_H (400 MHz, $CDCl_3$) 5.38 (2H, s), 6.66 (1H, s), 7.09 (2H, d, *J* 7.2 Hz), 7.21–7.30 (4H, m), 7.32–7.42 (7H, m), 7.87 (2H, d, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 53.2, 103.7, 125.6, 126.7, 127.4, 127.6, 128.55, 128.56, 128.6, 128.8, 130.6, 133.4, 137.7, 145.4, 150.9; HRMS (ESI): MH^+, found 311.1536. $C_{22}H_{19}N_2$ requires 311.1543, ν_{max} (liquid film) 3060, 2955, 2924, 2853, 1452, 1361, 1307 cm^{-1}.

*4.5.1. Preparation of (3,5-diphenyl-1H-pyrazol-1-yl)(phenyl)methanone (**4o**).* Compound **4o** (276 mg, 85%) was prepared following the procedure described for **4n** by using **1d** (208 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 6.86 (1H, s), 7.35–7.44 (6H, m), 7.47–7.51 (4H, m), 7.59–7.63 (1H, m), 7.86 (2H, dd, *J* 8.0, 1.2 Hz), 8.11–8.13 (2H, m); δ_C (100 MHz, $CDCl_3$) 108.9, 126.3, 128.0, 128.2, 128.5, 128.7, 129.1, 130.8, 131.8, 131.9, 132.5, 133.1, 148.6, 153.5, 167.4; HRMS (ESI): MNa^+, found: 347.1158. $C_{22}H_{16}N_2ONa$ requires 347.1155; ν_{max} (liquid film) 3061, 2924, 2856, 1709, 1560, 1488, 1453, 1331, 1305 cm^{-1}.

*4.5.2. Preparation of 1-ethyl-3,5-diphenyl-1H-pyrazole (**4p**).* Compound **4p** (243 mg, 98%) was prepared following the procedure described for **4n** by using **1d** (208 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and iodoethane (234 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.2 Hz), 4.20 (2H, q, *J* 7.2 Hz), 6.57 (1H, s), 7.29 (1H, t, *J* 7.6 Hz), 7.38–7.48 (7H, m), 7.84–7.86 (2H, m); δ_C (100 MHz, $CDCl_3$) 15.9, 44.6, 103.3, 125.6, 127.5, 128.48, 128.54, 128.7, 128.8, 130.9, 133.6, 144.4, 150.5; HRMS (ESI): MH^+, found: 249.1384. $C_{17}H_{17}N_2$ requires 249.1386; ν_{max} (liquid film) 3060, 2976, 2937, 1605, 1548, 1481, 1460, 1373, 1304 cm^{-1}.

*4.5.3. Preparation of 1-allyl-3,5-diphenyl-1H-pyrazole (**4q**).* Compound **4q** (250 mg, 96%) was prepared following the procedure described for **4n** by using **1d** (208 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and allyl bromide (180 mg, 1.5 mmol) as colorless oil. δ_H (400 MHz, $CDCl_3$) 4.77 (2H, dd, *J* 3.2, 1.6 Hz), 5.03 (1H, dd, *J* 16.8, 1.2 Hz), 5.20 (1H, dd, *J* 10.4, 1.2 Hz), 6.00–6.09 (1H, m), 6.61 (1H, s), 7.29 (1H, t, *J* 7.6 Hz), 7.37–7.46 (7H, m), 7.84–7.86 (2H, m); δ_C (100 MHz, $CDCl_3$) 52.0, 103.3, 117.2, 125.6, 127.6, 128.52, 128.56, 128.59, 128.7, 130.6, 133.4, 133.8, 145.1, 150.9; HRMS (ESI): MH^+, found: 261.1385. $C_{18}H_{17}N_2$

requires 261.1386; ν_{max} (liquid film) 3062, 2986, 2928, 1605, 1549, 1483, 1459, 1438, 1367, 1304 cm^{-1}.

*4.5.4. Preparation of 3,5-diphenyl-1-(prop-2-yn-1-yl)-1H-pyrazole (**4r**).* Compound **4r** (191 mg, 74%) was prepared following the procedure described for **4n** by using **1d** (208 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol) and propargyl bromide (177 mg, 1.5 mmol) as white crystalline solid. Mp 93–95 °C; δ_H (400 MHz, $CDCl_3$) 2.42 (1H, t, *J* 2.4 Hz), 4.90 (2H, d, *J* 2.4 Hz), 6.62 (1H, s), 7.28–7.32 (1H, m), 7.38–7.50 (5H, m), 7.55–7.58 (2H, m), 7.84–7.86 (2H, m); δ_C (100 MHz, $CDCl_3$) 39.7, 73.6, 78.4, 103.7, 125.7, 127.8, 128.5, 128.7, 128.8, 130.1, 133.1, 145.0, 151.4; HRMS (ESI): MH^+, found: 259.1223. $C_{18}H_{15}N_2$ requires 259.1230; ν_{max} (liquid film) 3294, 3063, 2963, 2932, 1482, 1458, 1432 cm^{-1}.

4.6. Typical representative procedure for the synthesis 1-benzyl-5-methyl-3-phenyl-1*H*-pyrazole (4s)

A mixture of (*E*)-4-phenylbut-3-en-2-one (**1e**) (146 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in CH_3CN (2 mL) were stirred at room temperature for 3 h and then CH_3CN (2 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 17 h, then NaOH (60 mg, 1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4s** as white crystalline solid (194 mg, 78% yield). Mp 86–87 °C; δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s), 5.32 (2H, s), 6.37 (1H, s), 7.11 (2H, d, *J* 6.8 Hz), 7.22–7.31 (4H, m), 7.36–7.39 (2H, m), 7.80–7.82 (2H, m); δ_C (100 MHz, $CDCl_3$) 11.2, 53.1, 103.2, 125.5, 126.6, 127.4, 127.5, 128.5, 128.6, 133.7, 137.0, 139.8, 150.3; HRMS (ESI): MH^+, found 249.1385. $C_{17}H_{17}N_2$ requires 249.1386, ν_{max} (liquid film) 3063, 3027, 2914, 1547, 1480, 1451, 1427, 1310 cm^{-1}.

*4.6.1. Preparation of (5-methyl-3-phenyl-1H-pyrazol-1-yl)(phenyl) methanone (**4t**).* Compound **4t** (199 mg, 76%) was prepared following the procedure described for **4s** by using **1e** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as white crystalline solid. Mp 81–83 °C; δ_H (400 MHz, $CDCl_3$) 2.72 (3H, d, *J* 0.8 Hz), 6.57 (1H, d, *J* 0.8 Hz), 7.23–7.41 (3H, m), 7.46–7.50 (2H, m), 7.56–7.60 (1H, m), 7.78–7.81 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.5, 107.9, 126.2, 127.8, 128.6, 128.9, 131.7, 132.0, 132.5, 133.1, 145.7, 153.4, 168.5; HRMS (ESI): MNa^+, found: 285.0991. $C_{17}H_{14}N_2ONa$ requires 285.0998; ν_{max} (liquid film) 3112, 3061, 3031, 2970, 2925, 1690, 1597, 1577, 1469, 1446, 1349 cm^{-1}.

*4.6.2. Preparation of 1-ethyl-5-methyl-3-phenyl-1H-pyrazole (**4v**) and 1-ethyl-3-methyl-5-phenyl-1H-pyrazole (**4w**).* Compound **4v** (123 mg, 66%) and **4w** (56 mg, 30%) were prepared following the procedure described for **4s** by using **1e** (146 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and iodoethane (234 mg, 1.5 mmol) as colorless oil. For **4v**: δ_H (400 MHz, $CDCl_3$) 1.43 (3H, t, *J* 7.2 Hz), 2.29 (3H, s), 4.12 (2H, q, *J* 7.2 Hz), 6.29 (1H, s), 7.24–7.27 (1H, m), 7.34–7.38 (2H, m), 7.75–7.77 (2H, m); δ_C (100 MHz, $CDCl_3$) 11.0, 15.5, 44.0, 102.6, 125.4, 127.2, 128.4, 133.9, 138.7, 150.0; HRMS (ESI): MH^+, found: 187.1225. $C_{12}H_{15}N_2$ requires 187.1320; ν_{max} (liquid film) 3059, 2980, 2938, 2875, 1550, 1444, 1372, 1315 cm^{-1}. For **4w**: δ_H (400 MHz, $CDCl_3$) 1.39 (3H, t, *J* 7.2 Hz), 2.32 (3H, s), 4.09 (2H, q, *J* 7.2 Hz), 6.05 (1H, s), 7.36–7.46 (5H, m); δ_C (100 MHz, $CDCl_3$) 13.5, 15.9, 44.1, 105.6, 128.3, 128.6, 128.7, 131.2, 143.9, 147.7; HRMS (ESI): MH^+, found: 187.1227. $C_{12}H_{15}N_2$ requires 187.1320; ν_{max} (liquid film) 3059, 2976, 2932, 2876, 1548, 1495, 1453, 1423, 1379 cm^{-1}.

4.7. Procedure for the synthesis (4,5-dimethyl-3-phenyl-1*H*-pyrazol-1-yl)(phenyl)methanone (4u)

A mixture of (*E*)-3-methyl-4-phenylbut-3-en-2-one (**1g**) (160 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg, 1.1 mmol) in CH_3CN (2 mL) were stirred at room temperature for 24 h and then CH_3CN (2 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 24 h, then NaOH (60 mg, 1.5 mmol) and benzoyl chloride (256 mg, 1.5 mmol) were subsequently added and the mixture was stirred at room temperature for 2 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product **4u** as white crystalline solid (202 mg, 73%). Mp 143–146 °C; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s), 2.63 (3H, s), 7.33–7.46 (5H, m), 7.52–7.68 (1H, m), 7.67 (2H, d, *J* 7.2 Hz), 8.06 (2H, d, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 9.2, 12.4, 116.5, 127.7, 128.1, 128.4, 131.5, 132.3, 132.9, 133.4, 141.5, 153.8, 168.5; HRMS (ESI): MNa^+, found 299.1146. $C_{18}H_{16}N_2ONa$ requires 299.1155, ν_{max} (liquid film) 3061, 2960, 2925, 1694, 1450, 1338 cm^{-1}.

Acknowledgements

We are grateful for financial support from NSFC (Nos. 21002044) and the Fundamental Research Funds for the Central Universities (lzujbky-2012-89). We also acknowledge Prof. Yong-Qiang Tu and Prof. Chun-An Fan of Lanzhou University for their helpful discussions.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.12.038.

References and notes

1. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5; (b) Hirai, K.; Uchida, A.; Ohno, R. In *Herbicide Classes in Development*; Boger, P., Hirai, K., Wakabyashi, K., Eds.; Springer: Heidelberg, Germany, 2002; pp 179–289; (c) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52; (d) Seltzman, H. H. *Drug Dev. Res.* **2009**, *70*, 601; (e) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222; (f) Jones, L. H.; Allan, G.; Corbau, R.; Middleton, D. S.; Mowbray, C. E.; Newman, S. D.; Phillips, C.; Webster, R.; Westby, M. *Chem. Biol. Drug Des.* **2011**, *77*, 393.
2. Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J. Med. Chem.* **2000**, *43*, 1034.
3. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W. *J. Med. Chem.* **1997**, *40*, 1347.
4. Mercader, J. V.; Suárez-Pantaleón, C.; Agulló, C.; Abad-Somovilla, A.; Abad-Fuentes, A. *J. Agric. Food Chem.* **2008**, *56*, 7682.
5. For reviews, see: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984; (b) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253; (c) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1999**, *36*, 321; (d) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *35*, 489.
6. Recent examples about synthesis of pyrazole, see: (a) Kumar, R.; Namboothiri, I. N. N. *Org. Lett.* **2011**, *13*, 4016; (b) Zhu, Y.; Wen, S.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 3553; (c) Willy, B.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2082; (d) Shan, G.; Liu, P.; Rao, Y. *Org. Lett.* **2011**, *13*, 1746; (e) Wang, Y.; Bi, X.; Li, W.-Q.; Li, D.; Zhang, Q.; Liu, Q.; Ondon, B. S. *Org. Lett.* **2011**, *13*, 1722; (f) Avila, B.; Solano, D. M.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 1060; (g) Verma, D.; Mobin, S.; Namboothiri, I. N. N. *J. Org. Chem.* **2011**, *76*, 4764; (h) Surmont, R.; Verniest, G.; Schrijver, M. D.; Thuring, J. W.; Holte, P. t.; Deroose, F.; Kimpe, N. D. *J. Org. Chem.* **2011**, *76*, 4015; (i) Mateos, C.; Mendiola, J.; Carpintero, M.; Mínguez, J. M. *Org. Lett.* **2010**, *12*, 4924; (j) Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506; (k) Surmont, R.; Verniest, G.; Kimpe, N. D. *Org. Lett.* **2010**, *12*, 4648; (l) Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Org. Lett.* **2010**, *12*, 3328; (m) Mohanan, K.; Martin, A. R.; Toupet, L.; Smietana, M.; Vasseur, J.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3196; (n) Neumann, J. J.; Suri,

M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790; (o) Cheng, X.; Ma, S. *Chem. Commun.* **2009**, 4263.
7. (a) Gerstenberger, B. S.; Rauckhorst, M. R.; Starr, J. T. *Org. Lett.* **2009**, *11*, 2097; (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675; (c) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030; (d) Patel, M. V.; Bell, R.; Majest, S.; Henry, R.; Kolasa, T. *J. Org. Chem.* **2004**, *69*, 7058; (e) Knorr, L. *Ber.* **1883**, *16*, 2587.
8. (a) Norris, T.; Colon-Cruz, R.; Ripin, D. H. B. *Org. Biomol. Chem.* **2005**, *3*, 1844; (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; (c) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43; (d) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.* **1993**, *30*, 755.
9. Tang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, W.-X.; Wang, A.-X. *Org. Lett.* **2008**, *10*, 5585.
10. The behaviour of α,β-unsaturated tosylhydrazone towards bases has not been exhaustively examined. Isolated examples of cyclization to pyrazole isomers can be found in: (a) Closs, G. L.; Böll, W. A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 399; (b) Closs, G. L.; Closs, L. E.; Böll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3796; (c) Sharp, J. T.; Findlay, R. H.; Thorogood, P. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 102; (d) Almirante, N.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Tetrahedron Lett.* **1998**, *39*, 3287; (e) Doyle, M. P.; Yan, M. *J. Org. Chem.* **2002**, *67*, 602; (f) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926; (g) Corradi, A.; Leonelli, C.; Rizzuti, A.; Rosa, R.; Veronesi, P.; Grandi, R.; Baldassari, S.; Villa, C. *Molecules* **2007**, *12*, 1482; (h) Wen, J.; Fu, Y.; Zhang, R.-Y.; Zhang, J.; Chen, S.-Y.; Yu, X.-Q. *Tetrahedron* **2011**, *67*, 9618.
11. The spectral data for compound 5-phenyl-1*H*-pyrazole **3** is in agreement with the literature values. For the related reference, see: Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.
12. The spectral data for compounds **4v** and **4w** is in agreement with the literature values. For the related reference, see: Montoya, V.; Pons, J.; Branchadellb, V.; Ros, J. *Tetrahedron* **2005**, *61*, 12377.
13. Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.