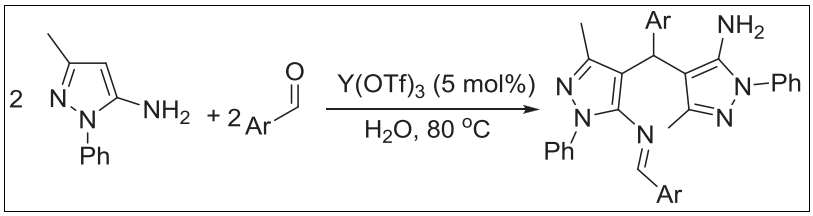
Efficient Domino Strategy for the Synthesis of Substituted Bipyrazole Derivatives

Xi Zhang, Kai Long, Jiayi He, Jialian Fu, Furen Zhang,* and Chunmei Li*

School of Chemistry and Chemical Engineering, Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing, Zhejiang Province 312000, China
*E-mail: frzhang@usx.edu.cn; lchm@usx.edu.cn

Received August 29, 2017
DOI 10.1002/jhet.3096
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



An efficient domino strategy for the synthesis of bipyrazole derivatives has been established successfully using $Y(OTf)_3$ as catalyst. This new reaction allows direct formation of highly functionalized bipyrazole derivatives with a wide diversity in substituents in a one-pot manner. The present synthesis shows attractive characteristics, such as the use of water as reaction media, simple one-pot operation, highly efficient catalyst, and mild reaction conditions.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

In recent years, assembly of molecular diversity from easily available starting materials with regard to environmental and economic aspects constitutes a great challenge in modern organic synthesis chemistry. Then, the multicomponent domino reaction for the synthesis of biologically and pharmacologically important active molecules has become useful tools because of their efficiency and green chemistry characteristic [1–4]. These reactions avoid time-consuming and costly processes for separation and purification of precursors and tedious steps of protection procedures [5–8]. Therefore, the development of new domino reactions for diversity of active molecules is a continuing challenge for modern organic synthesis.

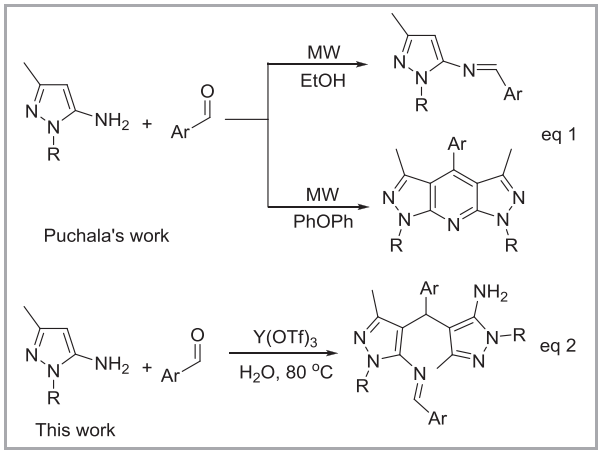
Heterocycles containing pyrazole rings belong to important building blocks because of their diversity of biological and pharmacological activities [9]. These compounds show anxiolytic [10], cholesterol formation-inhibiting compounds [11], treatment of Alzheimer's disease, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction, and infertility activities [12]. In addition, they have also been reported as potent and selective inhibitors of A1 adenosine receptor [13], inhibitors in immune and inflammatory cells [14], and kinase inhibitors as anti-inflammatory drugs [15]. Because of the important biological activities of them, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance [16–18]. Thus, the development of new strategy for these compounds has attracted considerable attention. A diversity of pyrazole and bipyrazole derivatives has been synthesized using different starting materials by various methods [19–23].

In recent years, our group has developed a series of multicomponent domino reaction that can provide a lot of multi-functionalized heterocyclic structures with chemical and pharmaceutical interest [24]. Recently, Puchala and co-workers have reported a microwave-assisted reaction between 1*H*-pyrazol-5-amines and aldehydes affording structurally diverse pyrazole and dipyrazole derivatives (Scheme 1, eq 1) [25]. However, a new compound was obtained when the 1*H*-pyrazol-5-amines, aldehydes, and cyclohexanone were submitted to reaction system [24b]. As a continuation of our research, in this manuscript, we would like to report a new chemistry approach for bipyrazole derivatives that may be of potential chemical and biomedical activities (Scheme 1, eq 2). This reaction was carried out by mixing 1*H*-pyrazol-5-amines and aldehydes in aqueous phase using Lewis acid $Y(OTf)_3$ as catalyst at 80°C.

RESULTS AND DISCUSSION

An appropriate catalyst is of crucial importance in successful organic transformations. First of all, we started this methodology by mixing 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and benzaldehyde for goal product **3a** as model reaction with different catalysts (Scheme 2). The results were summarized in Table 1. As shown in Table 1, none of the product **3a** was given without any catalysts. Good yields (77–85%) of goal product **3a** was obtained,

Scheme 1. The reaction of 1*H*-pyrazol-5-amine and aldehydes.



Scheme 2. The model reaction for the synthesis of compound **3a**.

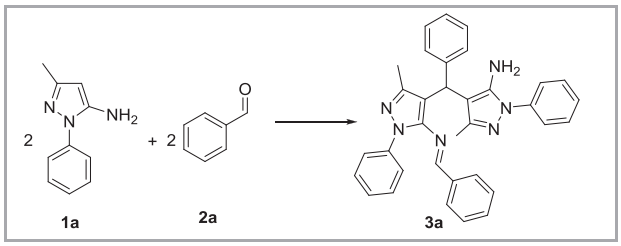


Table 1

Reaction conditions for the synthesis of model goal product **3a**.[a]

Entry	Catalyst (mg)	Solvent	T (°C)	Yield (%)[b]
1	–	H_2O	80	0
2	$Sc(OTf)_3$ (10)	H_2O	80	85
3	$Y(OTf)_3$ (10)	H_2O	80	82
4	$Yb(OTf)_3$ (10)	H_2O	80	77
5	TsOH (10)	H_2O	80	25
6	TFA (10)	H_2O	80	18
7	HOAc (10)	H_2O	80	31
8	H_2SO_4 (10)	H_2O	80	21
9	Et_3N (10)	H_2O	80	0
10	Pyridine (10)	H_2O	80	0
11	$Y(OTf)_3$ (20)	H_2O	80	83
12	$Y(OTf)_3$ (5)	H_2O	80	80
13	$Y(OTf)_3$ (3)	H_2O	80	67
14	$Y(OTf)_3$ (5)	EtOH	reflux	76
15	$Y(OTf)_3$ (5)	$CHCl_3$	reflux	25
16	$Y(OTf)_3$ (5)	CH_3CN	80	35
17	$Y(OTf)_3$ (5)	THF	reflux	30
18	$Y(OTf)_3$ (5)	Toluene	80	19
19	$Y(OTf)_3$ (5)	H_2O	20	0
20	$Y(OTf)_3$ (5)	H_2O	40	<10
21	$Y(OTf)_3$ (5)	H_2O	60	41
22	$Y(OTf)_3$ (5)	H_2O	100	82

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), $Y(OTf)_3$ (X mol%), and solvent (3.0 mL) in the sealed tube in 4 h.
[b]Isolated yields.

when Lewis acids, such as $Sc(OTf)_3$, $Y(OTf)_3$, and $Yb(OTf)_3$ were chosen to catalyze the model reaction, respectively. However, Brønsted acids, such as TsOH, TFA, HOAc, and H_2SO_4 only exhibited poor activities and gave 18–31% of goal product. The alkali catalysts Et_3N and pyridine did not show any activities. Considering the cost and catalytic activity, the $Y(OTf)_3$ was chosen to catalyze the following reactions. Subsequently, the model reaction was repeated many times with different amount of catalyst loading. The results indicated $Y(OTf)_3$ (5 mol%) was enough to push the reaction forward successfully.

The use of water as reaction media allowed the direct conversion of model substrates into the corresponding product **3a** in a chemical yield of 80% (Table 1, entry 12). Other organic solvents, such as ethanol, chloroform, acetonitrile, tetrahydrofuran, and toluene gave much lower yields of 19–76% (Table 1 entries 14–18). Then, the examination of the reaction temperature led to a regulation that the model reaction proceeded more smoothly at an elevated temperature because the model reaction became much faster when the temperature was increased from 20°C to 80°C (Table 1, entries 12, 19–21). However, no significant improvement in yield was obtained, when further increased the temperature to 100°C. Therefore, 80°C was chosen as the reaction temperature for all the further studies.

With the optimized reaction condition in hand, we next set out to explore its scope using various readily available starting materials (Scheme 3). The reaction of various aromatic aldehydes bearing different substituents were submitted to water with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine for a given time under the conditions described above, respectively. The results are summarized in Table 2. Obviously, not only aromatic aldehydes **1b**–**1c** (Table 2, entries 2–3), which possess electron-donating substituents, such as methyl and methoxy groups at the para position of the benzene ring but also **1d**–**1j** (Table 2, entries 4–10) having electron-withdrawing substituents, such as fluoro, chloro, bromo, trifluoromethyl, and nitro groups produced the corresponding bipyrazole derivatives in

Scheme 3. Synthesis of bipyrazole derivatives **3**.

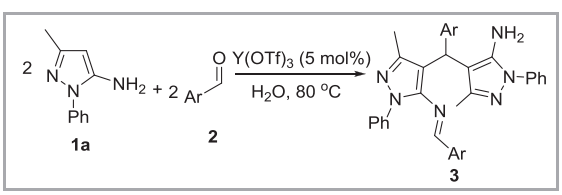


Table 2

Domino synthesis of multi-substituted bipyrazole derivatives **3**.[a]

Entry	3	Ar	Time	Yield (%)[b]
1	**3a**	C_6H_5	4	80
2	**3b**	4-MeC_6H_4	4	77
3	**3c**	4-$OMeC_6H_4$	4	81
4	**3d**	4-FC_6H_4	4	76
5	**3e**	4-ClC_6H_4	4	79
6	**3f**	4-BrC_6H_4	4	72
7	**3g**	4-$CF_3C_6H_4$	6	69
8	**3h**	4-$NO_2C_6H_4$	6	67
9	**3i**	2,4-$Cl_2C_6H_3$	6	69
10	**3j**	2,6-$Cl_2C_6H_3$	6	61
11	**3k**	1-Naphthyl	6	67
12	**3l**	2-Thienyl	6	76

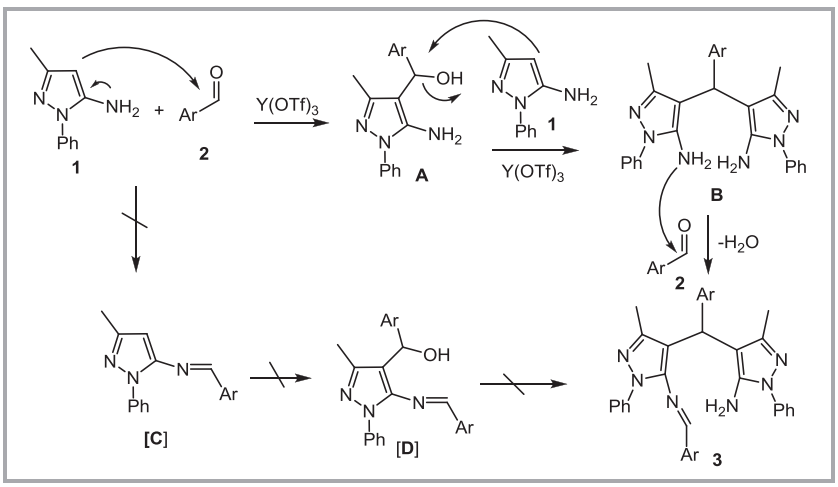
[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), $Y(OTf)_3$ (5 mol%), and water (3.0 mL) in the sealed tube in 4–6 h.
[b]Isolated yields.

good to high yields. We also noted that the aromatic aldehydes bearing electron-donating substituents showed higher activities and gave higher yields than those bearing electron-withdrawing groups. The substituents on the *ortho*-position of the ring of the aromatic aldehydes hampered the reaction process and gave slightly low yields of goal products. The 2,6-dichlorobenzaldehyde only gave 61% yields of goal product (Table 2, entry 10). Particularly noteworthy was the fact that the bulky aromatic aldehyde, such as 1-naphthaldehyde and less reactive heterocyclic aldehyde, such as thiophene-2-carbaldehyde, also exhibited good reactivity and gave corresponding products with 67% and 76% yields, respectively. In all cases, the reaction occurred at a very fast speed; in fact, all cases can be finished within 6 h. The results exhibit the scope and generality of the novel multicomponent domino reaction with respect to a range of aromatic aldehyde substrates.

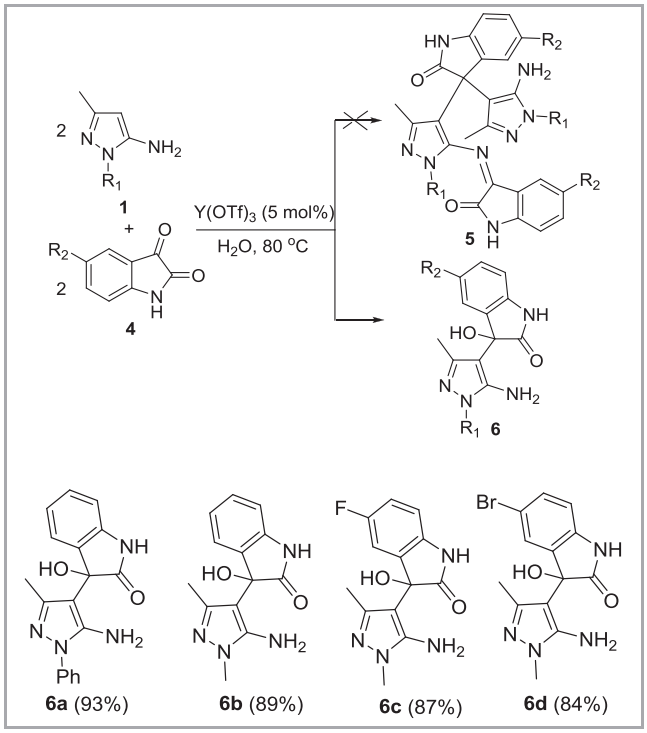
On the basis of literature reports [21e, 22a, d] and our experimental results, a possible mechanism for the formation of compound **3** was proposed and is depicted in Scheme 4. The competing reaction between 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** and aldehyde occurs to generate intermediate **A**, which favors the following coordination and reaction in the presence of $Y(OTf)_3$. Intermediate **A** then smoothly reacted with another 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** to yield intermediate **B**. Subsequently, the intermediate **B** condensed with redundant aldehyde and gave desired product **3**.

In view of these results, we then turned our attention to investigate other substrates. To study the scope of this methodology, isatin (**4**) was submitted to react with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**) under the same conditions. Unfortunately, the corresponding goal product (**5**) was not obtained under similar reaction conditions, probably because of the low reactivity or large steric hindrance of isatin [21e]. Then, to further explore the possibility of the multicomponent domino reaction, we used 1,3-dimethyl-1*H*-pyrazol-5-amine to replace 3-methyl-1-phenyl-1*H*-pyrazol-5-amine to investigate the possibility of the domino reaction. As anticipated, 3-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one was obtained instead of domino product. Then, 3-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one derivatives bearing different substituents were obtained with different yields (Scheme 5).

Scheme 4. Proposed mechanism for the synthesis of products **3**.



Scheme 5. The synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one **6**.



CONCLUSIONS

In conclusion, we have discovered a novel domino reaction for the synthesis of bipyrazole derivatives by varying the substituents on the ring of aromatic aldehydes. The mild conditions, the maximum efficiency of a process, and short reaction periods as well as operational simplicity are clearly represented in this one-pot transformation that provides an elegant methodology for the synthesis of highly functionalized bipyrazole derivatives. The reactions were conducted in water using readily available and inexpensive substrates. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates and to synthesize closely related natural-like products and test their biological activity.

EXPERIMENTAL

General. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF254 plates. Flash column chromatography was performed on silica gel (300–400 mesh). Melting points were measured on an X-4 melting point apparatus. ^{1}H–NMR spectra were recorded on a 400 MHz instrument (Bruker Avance 400 Spectrometer). Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, with coupling constants (J) in Hz. ^{13}C–NMR spectra were recorded at 100 MHz. Chemical shift were reported in ppm with the internal chloroform signal at 77.0 ppm at as a standard. Elemental analysis was carried out on EuroEA elemental analyzer.

General procedure for the synthesis of bipyrazole derivatives 3a–3l. 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**, 1.0 mmol), aromatic aldehyde (**2**, 1.0 mmol), $Y(OTf)_3$ (0.05 mmol), and water (3.0 mL) were mixed and heated at 80°C for 4–6 h. When the reaction was finished indicated by TLC monitoring, the reaction mixture was cooled to room temperature and exacted with ethyl acetate (5 mL × 3). The resulting residue was purified by column chromatography on silica gel with the eluent (ethyl acetate/petroleum ether = 1:10–1:4) to afford the pure product. **3a-3l**. The compounds were characterized using spectroscopic techniques (^{1}H–NMR, ^{13}C NMR, and elemental analyzer).

(E)-4-((5-(benzylideneamino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3a). Yellow plates. Mp 123–124°C. IR (KBr) ν: 3446, 3360, 2961, 2921, 1716, 1617, 1594, 1490, 1341, 1017, 758, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.02 (s, 1H, NH), 7.65 (d, 2H, J = 7.2 Hz, ArH), 7.53 (d, 2H, J = 7.2 Hz, ArH), 7.36–7.40 (m, 11H, ArH), 7.30–7.35 (m, 5H, ArH), 5.21 (s, 1H, CH), 3.35 (br, s,

2H, NH_2), 2.05 (s, 3H, CH_3), 1.98 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.5, 148.4, 147.5, 146.4, 142.7, 139.5, 138.4, 131.1, 131.0, 129.9, 130.1, 129.4, 128.6, 127.3, 126.1, 123.9, 123.6, 116.2, 116.1, 115.6, 115.4, 108.7, 101.5, 13.6, 12.5. *Anal*. Calcd for $C_{34}H_{30}N_6$ (522.66): C 78.13, H 5.79, N 16.08; Found: C 77.89, H 5.47, N 15.87.

(E)-3-methyl-4-((3-methyl-5-((4-methylbenzylidene)amino)-1-phenyl-1H-pyrazol-4-yl)(p-tolyl)methyl)-1-phenyl-1H-pyrazol-5-amine (3b). Yellow powder. Mp 95–96°C. IR (KBr) ν: 3448, 3365, 2962, 2921, 1717, 1619, 1594, 1491, 1341, 1089, 1015, 816, 759, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.01 (s, 1H, NH), 7.67 (d, 2H, J = 8.4 Hz, ArH), 7.52 (d, 2H, J = 8.0 Hz, ArH), 7.37–7.40 (m, 5H, ArH), 7.13–7.24 (m, 6H, ArH), 5.22 (s, 1H, CH), 3.33 (br, s, 2H, NH_2), 2.39 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.8, 148.5, 147.6, 146.8, 142.8, 139.5, 138.3, 131.1, 131.0, 130.1, 130.1, 129.5, 128.8, 127.4, 126.2, 123.9, 123.6, 116.2, 116.1, 115.5, 115.4, 108.8, 101.6, 15.3, 14.9, 13.5, 12.6. *Anal*. Calcd for $C_{36}H_{34}N_6$ (550.71): C 78.52, H 6.22, N 15.26; Found: C 78.86, H 5.99, N 15.50.

(E)-4-((5-((4-methoxybenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-methoxyphenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3c). Yellow powder. Mp 92–94°C. IR (KBr) ν: 3445, 3363, 3132, 2961, 2923, 1716, 1619, 1595, 1492, 1087, 1016, 812, 756, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 7.97 (s, 1H, NH), 7.67 (d, 2H, J = 8.0 Hz, ArH), 7.57 (d, 2H, J = 8.4 Hz, ArH), 7.36–7.40 (m, 6H, ArH), 7.23–7.28 (m, 2H, ArH), 6.86–6.90 (m, 4H, ArH), 5.20 (s, 1H, CH), 3.84 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.39 (br, s, 2H, NH_2), 2.06 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 163.2, 148.8, 147.7, 146.9, 142.8, 139.4, 138.5, 131.0, 130.7, 130.3, 130.0, 129.4, 128.8, 127.1, 126.4, 123.9, 123.5, 116.2, 116.1, 115.7, 109.1, 101.5, 53.4, 52.8, 13.5, 12.7. *Anal*. Calcd for $C_{36}H_{34}N_6O_2$ (582.71): C 74.20, H 5.88, N 14.42; Found: C 73.88, H 6.01, N 14.23.

(E)-4-((5-((4-fluorobenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-fluorophenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3d). Yellow needles. Mp 126–127°C. IR (KBr) ν: 3446, 3365, 3135, 2962, 2921, 1719, 1618, 1595, 1492, 1399, 1087, 1013, 818, 750, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 7.99 (s, 1H, NH), 7.59–7.64 (m, 4H, ArH), 7.38–7.42 (m, 4H, ArH), 7.00–7.09 (m, 4H, ArH), 5.24 (s, 1H, CH), 3.50 (br, s, 2H, NH_2), 2.05 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.8, 148.7, 147.9, 146.9, 142.8, 139.4, 138.4, 131.0, 130.9, 130.1, 130.0, 129.4, 128.8, 127.1, 126.4, 123.9, 123.4, 116.2, 116.0, 115.6, 115.4, 108.9, 101.6, 13.5, 12.7. *Anal*. Calcd for $C_{34}H_{28}F_2N_6$ (558.64): C 73.10, H 5.05, N 15.04; Found: C 72.87, H 4.87, N 15.30.

(E)-4-((5-((4-chlorobenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-chlorophenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3e). Yellow needles. Mp 94–95°C. IR (KBr) ν: 3442, 3367, 3135, 2961, 2922, 1716, 1619, 1595, 1491, 1399, 1088, 1015, 816, 757, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 7.96 (s, 1H, NH), 7.61 (d, 2H, J = 8.0 Hz, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.37–7.45 (m, 8H, ArH), 7.25–7.30 (m, 6H, ArH), 5.23 (s, 1H, CH), 3.50 (br, s, 2H, NH_2), 2.06 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.2, 148.5, 147.9, 146.8, 142.8, 139.4, 138.3, 131.1, 131.2, 130.1, 130.1, 129.4, 128.8, 127.3, 126.2, 123.9, 123.5, 116.2, 116.1, 115.5, 115.4, 108.8, 101.5, 13.5, 12.6. *Anal*. Calcd for $C_{34}H_{28}Cl_2N_6$ (591.54): C 69.04, H 4.77, N 14.21; Found: C 68.78, H 4.59, N 13.95.

(E)-4-((5-((4-bromobenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-bromophenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3f). Yellow needles. Mp 110–112°C. IR (KBr) ν: 3444, 3366, 3135, 2961, 2920, 1716, 1619, 1594, 1492, 1341, 1085, 1015, 818, 758, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 7.94 (s, 1H, NH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.32–7.46 (m, 11H, ArH), 7.25–7.30 (m, 1H, ArH), 7.19 (d, 2H, J = 8.4 Hz, ArH), 5.21 (s, 1H, CH), 3.50 (br, s, 2H, NH_2), 2.06 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.7, 148.8, 147.9, 146.9, 142.6, 139.4, 138.4, 131.0, 130.9, 130.1, 130.1, 129.3, 128.7, 127.1, 126.5, 123.9, 123.3, 116.3, 116.1, 115.7, 115.4, 108.7, 101.6, 13.6, 12.7. *Anal*. Calcd for $C_{34}H_{28}Br_2N_6$ (680.45): C 60.02, H 4.15, N 12.35; Found: C 59.85, H 3.97, N 12.55.

(E)-3-methyl-4-((3-methyl-1-phenyl-5-((4-(trifluoromethyl) benzylidene)amino)-1H-pyrazol-4-yl)(4-(trifluoromethyl) phenyl)methyl)-1-phenyl-1H-pyrazol-5-amine (3g). Yellow powder. Mp 107–108°C. IR (KBr) ν: 3447, 3367, 3133, 2962, 2920, 1716, 1619, 1595, 1493, 1341, 1086, 1015, 755, 692 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.02 (s, 1H, NH), 7.56–7.66 (m, 8H, ArH), 7.28–7.46 (m, 10H, ArH), 5.36 (s, 1H, CH), 3.60 (br, s, 2H, NH_2), 2.10 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.8, 148.8, 147.8, 146.9, 142.7, 139.4, 138.4, 131.0, 130.8, 130.1, 139.9, 129.4, 128.7, 127.1, 126.5, 123.9, 123.4, 116.1, 116.0, 115.6, 115.4, 109.1, 101.5, 13.6, 12.7. *Anal*. Calcd for $C_{36}H_{28}F_6N_6$ (658.65): C 65.65, H 4.29, N 12.76; Found: C 65.81, H 4.00, N 12.93.

(E)-3-methyl-4-((3-methyl-5-((4-nitrobenzylidene)amino)-1-phenyl-1H-pyrazol-4-yl)(4-nitrophenyl)methyl)-1-phenyl-1H-pyrazol-5-amine (3h). Yellow powder. Mp 150–152°C. IR (KBr) ν: 3447, 3364, 3135, 2961, 1716, 1621, 1594, 1494, 1086, 1011, 820, 758, 692 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.17–8.22 (m, 4H, ArH), 8.10 (s, 1H, NH), 7.71 (d, 2H, J = 8.4 Hz, ArH), 7.56 (d, 2H, J = 8.0 Hz, ArH), 7.49 (d, 2H, J = 8.4 Hz, ArH), 7.41–7.46 (m, 6H, ArH), 7.33–7.36

(m, 2H, ArH), 5.38 (s, 1H, CH), 3.68 (br, s, 2H, NH_2), 2.07 (s, 3H, CH_3), 2.04 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 174.7, 161.2, 160.3, 150.2, 150.0, 149.4, 146.7, 142.9, 139.0, 129.6, 129.4, 129.1, 127.5, 127.2, 124.1, 123.9, 101.6, 13.6, 12.8. *Anal*. Calcd for $C_{34}H_{28}N_8O_4$ (612.65): C 66.66, H 4.61, N 18.29; Found: C 66.83, H 4.80, N 17.96.

(E)-4-((5-((2,4-dichlorobenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(2,4-dichlorophenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3i). Yellow needles. Mp 126–128°C. IR (KBr) ν: 3445, 3364, 3135, 2961, 1716, 1617, 1593, 1492, 1085, 1018, 814, 761, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.44 (s, 1H, NH), 7.86 (d, 1H, J = 8.8 Hz, ArH), 7.56 (d, 2H, J = 8.0 Hz, ArH), 7.43–7.50 (m, 4H, ArH), 7.44–7.50 (m, 4H, ArH), 7.15 (d, 1H, J = 9.6 Hz, ArH), 5.36 (s, 1H, CH), 3.62 (br, s, 2H, NH_2), 2.04 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.9, 148.9, 148.1, 146.8, 142.5, 139.4, 139.2, 138.4, 131.1, 130.9, 130.7, 130.3, 130.1, 129.3, 128.7, 127.2, 126.5, 123.9, 123.5, 116.2, 116.1, 115.8, 115.4, 108.5, 101.4, 13.6, 12.8. *Anal*. Calcd for $C_{34}H_{26}Cl_4N_6$ (660.42): C 61.84, H 3.97, N 12.73; Found: C 61.66, H 4.24, N 12.94.

(E)-4-((5-((2,6-dichlorobenzylidene)amino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)(2,6-dichlorophenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3j). Yellow powder. Mp 104–105°C. IR (KBr) ν: 3446, 3365, 3135, 2923, 1716, 1619, 1597, 1492, 1086, 1013, 818, 755, 692 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.53 (s, 1H, NH), 7.69–7.71 (m, 2H, ArH), 7.38–7.63 (m, 6H, ArH), 7.14–7.33 (m, 10H, ArH), 6.05 (s, 1H, CH), 3.60 (br, s, 2H, NH_2), 2.03 (s, 3H, CH_3), 1.93 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 164.0, 149.3, 148.5, 146.8, 142.5, 141.2, 139.5, 139.2, 138.6, 131.2, 130.9, 130.6, 130.4, 130.1, 129.3, 128.7, 127.2, 126.5, 123.9, 123.2, 116.0, 116.1, 115.9, 115.2, 108.1, 101.6, 13.6, 12.6. *Anal*. Calcd for $C_{34}H_{26}Cl_4N_6$ (660.42): C 61.84, H 3.97, N 12.73; Found: C 61.57, H 3.87, N 12.48.

(E)-3-methyl-4-((3-methyl-5-((naphthalen-1-ylmethylene)amino)-1-phenyl-1H-pyrazol-4-yl)(naphthalen-1-yl)methyl)-1-phenyl-1H-pyrazol-5-amine (3k). Yellow powder. Mp 127–128°C. IR (KBr) ν: 3444, 3364, 3135, 2961, 1716, 1617, 1595, 1492, 1342, 1087, 1012, 755, 693 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.68 (s, 1H, NH), 7.97 (t, 2H, J = 7.6 Hz, ArH), 7.87 (d, 2H, J = 8.4 Hz, ArH), 7.81 (d, 2H, J = 8.0 Hz, ArH), 7.38–7.62 (m, 15H, ArH), 7.25–7.37 (m, 1H, ArH), 7.06 (m, 1H, J = 7.6 Hz, ArH), 5.90 (s, 1H, CH), 3.18 (br, s, 2H, NH_2), 2.08 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 162.5, 149.0, 148.2, 146.8, 142.6, 139.4, 139.1, 138.5, 131.1, 130.9, 130.6, 130.7, 130.0, 129.3, 128.7, 127.3, 126.6, 123.9, 123.4, 116.2, 116.2, 115.7, 115.4, 108.6, 101.8, 13.6, 12.7. *Anal*. Calcd for $C_{42}H_{34}N_6$ (622.78): C 81.00, H 5.50, N 13.49; Found: C 81.35, H 5.25, N 13.72.

(E)-3-methyl-4-((3-methyl-1-phenyl-5-((thiophen-2-ylmethylene)amino)-1H-pyrazol-4-yl)(thiophen-2-yl)methyl)-1-phenyl-1H-pyrazol-5-amine (3l). Brown powder. Mp 140–142°C. IR (KBr) ν: 3449, 3364, 3135, 2961, 2922, 1598, 1498, 1403, 1259, 1074, 1044, 809, 760, 692 cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$, δ ppm): 8.16 (s, 1H, NH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 7.52 (d, 2H, J = 4.8 Hz, ArH), 7.38–7.43 (m, 6H, ArH), 7.25–7.31 (m, 2H, ArH), 7.22 (d, 2H, J = 6.0 Hz, ArH), 7.06 (t, 1H, J = 4.4 Hz, ArH), 6.93–6.96 (m, 2H, ArH), 5.46 (s, 1H, CH), 3.65 (br, s, 2H, NH_2), 2.18 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). ^{13}C–NMR (100 MHz, $CDCl_3$, δ ppm): 156.8, 149.3, 149.0, 146.8, 145.3, 144.2, 133.6, 131.8, 129.4, 128.8, 128.1, 127.0, 126.3, 124.8, 124.0, 123.4, 106.7, 105.2, 103.2, 13.3, 12.6. *Anal*. Calcd for $C_{30}H_{26}N_6S_2$ (534.70): C 67.39, H 4.90, N 15.72; Found: C 67.66, H 5.21, N 15.98.

General procedure for the synthesis of compound 6a–6d. 3-Methyl-1*H*-pyrazol-5-amine (**1**, 1.0 mmol), isatin (**4**, 1.0 mmol), $Y(OTf)_3$ (0.05 mmol), and water (3.0 mL) were mixed and heated at 80°C for 4 h. When the reaction was finished indicated by TLC monitoring, the reaction mixture was cooled to room temperature. The solid product was collected by Büchner filtration and subsequently recrystallized from hot EtOH (95%) to give the pure product **6**.

3-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-hydroxyindolin-2-one (6a). Yellow powder. Mp 234–236°C. IR (KBr) ν: 3440, 3364, 3138, 2832, 1714, 1619, 1515, 1385, 1188, 1115, 1051, 934, 745, 693 cm^{-1}. ^{1}H–NMR (400 MHz, DMSO-d_6, δ ppm): 10.42 (s, 1H, NH), 7.56 (d, 2H, J = 8.0 Hz, ArH), 7.46 (t, 2H, J = 7.6 Hz, ArH), 7.23–7.31 (m, 3H, ArH), 6.98 (t, 1H, J = 7.2 Hz, ArH), 7.46 (d, 1H, J = 7.6 Hz, ArH), 5.30 (br, s, 1H, NH_2), 1.44 (s, 3H, CH_3). *Anal*. Calcd for $C_{18}H_{16}N_4O_2$ (320.35): C 67.49, H 5.03, N 17.49; Found: C 67.24, H 4.79, N 17.23.

3-(5-Amino-1,3-dimethyl-1H-pyrazol-4-yl)-3-hydroxyindolin-2-one (6b). Light yellow powder. Mp 196–197°C. IR (KBr) ν: 3440, 3364, 3138, 2832, 1714, 1619, 1515, 1385, 1188, 1115, 1051, 934, 745, 693 cm^{-1}. ^{1}H–NMR (400 MHz, DMSO-d_6, δ ppm): 10.31 (s, 1H, NH), 7.20 (d, 2H, J = 8.0 Hz, ArH), 6.95 (t, 1H, J = 7.6 Hz, ArH), 6.80 (t, 1H, J = 7.2 Hz, ArH), 6.37 (s, 1H, OH), 5.03 (br, s, 1H, NH_2), 3.41 (s, 3H, NCH_3), 1.33 (s, 3H, CH_3). *Anal*. Calcd for $C_{13}H_{14}N_4O_2$ (258.28): C 60.45, H 5.46, N 21.69; Found: C 60.61, H 5.11, N 21.98.

3-(5-Amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-3-hydroxyindolin-2-one (6c). Light yellow crystal. Mp 195–196°C. IR (KBr) ν: 3445, 3365, 3135, 2830, 1714, 1617, 1515, 1382, 1189, 1116, 1051, 932, 745, 692 cm^{-1}. ^{1}H–NMR (400 MHz, DMSO-d_6, δ ppm): 10.32 (s, 1H, NH), 7.03–7.08 (m, 2H, ArH), 6.81–6.84 (m, 1H, ArH), 6.59 (s, 1H, OH), 5.10 (br, s, 1H, NH_2), 3.44 (s, 3H, NCH_3), 1.37 (s, 3H, CH_3). *Anal*. Calcd for $C_{13}H_{13}FN_4O_2$ (276.27): C 56.52, H 4.74, N 20.28; Found: C 56.22, H 5.01, N 19.87.

3-(5-Amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-bromo-3-hydroxyindolin-2-one (6d). Light yellow powder. Mp 200–202°C. IR (KBr) ν: 3445, 3364, 3138, 2830, 1714, 1619, 1516, 1385, 1184, 1115, 1052, 934, 746, 693 cm^{-1}. ^1H–NMR (400 MHz, DMSO-d_6, δ ppm): 10.05 (s, 1H, NH), 7.31 (d, 1H, J = 3.2 Hz, ArH), 7.23 (dd, 1H, J = 2.0, 8.4 Hz, ArH), 6.70 (d, 1H, J = 8.4 Hz, ArH), 6.37 (s, 1H, OH), 4.76 (br, s, 2H, NH_2), 3.45 (s, 3H, NCH_3), 1.44 (s, 3H, CH_3). *Anal*. Calcd for $C_{13}H_{13}BrN_4O_2$ (337.18): C 46.31, H 3.89, N 16.62; Found: C 46.71, H 4.11, N 16.51.

Acknowledgment. We are grateful for the financial support from the science and technology innovation program for college students in Zhejiang province (grant no. 2017R428016). We are also grateful to Shaoxing University for spiritual support.

REFERENCES AND NOTES

[1] Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. Nature 2006, 441, 861.

[2] Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. J Am Chem Soc 2009, 131, 1753.

[3] Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. J Am Chem Soc 2005, 127, 2836.

[4] Schreiber, S. L. Science 2000, 287, 1964.

[5] deMeijere, A.; von Zezschwitz, P.; Brüase, S. Acc Chem Res 2005, 38, 413.

[6] Lu, M.; Zhu, D.; Lu, Y.; Hou, B.; Tan, B.; Zhong, G. Angew Chem Int Ed 2008, 47, 10187.

[7] Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. Angew Chem Int Ed 2008, 47, 4177.

[8] Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. Pure Appl Chem 2003, 75, 143.

[9] Beutner, G. L.; Kuethe, J. T.; Kim, M. M.; Yasuda, N. J Org Chem 2009, 74, 789.

[10] Meiners, B. A.; Salama, A. I. Eur J Pharmacol 1982, 78, 315.

[11] Fujikama, Y.; Suzuki, M.; Iwasaki, H.; Sakashita, M.; Kitahara, M. Chem Abstr 1990, 113, 23903.

[12] Chen, Y. L.; WO9534563 A1, 1995; Chem Abstr 1995, 124, 232447.

[13] Manetti, F.; Schenone, S.; Bondavalli, F.; Brullo, C.; Bruno, O.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Trincavelli, M. L.; Martini, C.; Martinelli, A.; Tintori, C.; Botta, M. J Med Chem 2005, 48, 7172.

[14] Hamblin, J. N.; Angell, T. D. R.; Ballantine, S. P.; Cook, C. M.; Cooper, A. W. J.; Dawson, J.; Delves, C. J.; Jones, P. S.; Lindvall, M.; Lucas, F. S.; Mitchell, C. J.; Neu, M. Y.; Ranshaw, L. E.; Solanke, Y. E.; Somers, D. O.; Wiseman, J. O. Bioorg Med Chem Lett 2008, 18, 4237.

[15] Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Neumann, U.; Rucklin, G. Bioorg Med Chem Lett 2006, 16, 262.

[16] Lee, S.; Park, S. B. Org Lett 2009, 11, 5214.

[17] Zhong, Y.-L.; Lindale, M. G.; Yasuda, N. Tetrahedron Lett 2009, 50, 2293.

[18] Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Cobo, J. Tetrahedron Lett 2008, 49, 2689.

[19] (a) Wang, S.-L.; Liu, Y.-P.; Xu, B.-H.; Wang, X.-H.; Jiang, B.; Tu, S.-J. Tetrahedron 2011, 67, 9417; (b) Jiang, B.; Liu, Y.-P.; Tu, S.-J. Eur J Org Chem 2011, 3026.

[20] (a) Drizin, I.; Altenbach, R. J.; Buckner, S. A.; Whiteaker, K. L.; Scott, V. E.; Darbyshire, J.; Jayanti, F. V.; Henry, R. F.; Coghlan, M. J.; Gopalakrishnan, M.; Carroll, W. A. Bioorg Med Chem 2004, 12, 1895; (b) Quiroga, J.; Mejia, D.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sanchez, A.; Cobo, J.; Low, J. N. Tetrahedron 2001, 57, 6947; (c) Quiroga, J.; Hormaza, A.; Insuasty, B.; Saitz, C.; Jullian, C. J Heterocyclic Chem 1998, 35, 575.

[21] (a) Szlachcic, P.; Kucharek, M.; Jarosz, B.; Danel, A.; Stadnicka, K. J Heterocyclic Chem 2017, 54, 1729; (b) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Shishkina, S. V.; Shishkin, O. V.; Kobzar, K. M.; Kappe, C. O. Org Lett 2007, 9, 1691; (c) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. J Org Chem 2008, 73, 5110; (d) Hennig, L.; Hofmann, J.; Alva-Astudillo, M.; Mann, G. J Prakt Chem 1990, 332, 351; (e) Esteves-Souza, A.; Echevarría, A.; Vencato, I.; Jimeno, M. L.; Elguero, J. Tetrahedron 2001, 57, 6147.

[22] (a) Quiroga, J.; Portilla, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sortino, M.; Zacchino, S. J Heterocyclic Chem 2005, 42, 61; (b) Shi, D. Q.; Yang, F. J Chin Chem Soc 2008, 55, 755; (c) Lezana, N.; Matus-Pérez, M.; Galdámez, A.; Lühr, S.; Vilches-Herrera, M. Green Chem 2016, 18, 3712; (d) Zhang, X.-Y.; Li, X.-Y.; Fan, X.-S.; Wang, X.; Qu, G.-R.; Wang, J.-J. Heterocycles 2009, 78, 923.

[23] (a) Reddy, M. V.; Jeong, Y. T. RSC Adv 2016, 6, 103838; (b) Castillo, J.-C.; Quiroga, J.; Abonia, R.; Rodriguez, J.; Coquerel, Y. Org Lett 2015, 17, 3374; (c) Galvez, J.; Castillo, J.-C.; Quiroga, J.; Rajzmann, M.; Rodriguez, J. Org Lett 2014, 16, 4126; (d) Abonia, R.; Castillo, J.; Insuasty, B.; Quiroga, J.; Nogueras, M.; Cobo, J. Eur J Org Chem 2010, 6454.

[24] (a) Zhang, F. R.; Li, C. M.; Qi, C. Z. RSC Adv 2016, 6, 102924; (b) Chen, Z.; Shi, Y. X.; Shen, Q. Q.; Xu, H. X.; Zhang, F. R. Tetrahedron Lett 2015, 56, 4749; (c) Li, C. M.; Liang, X. Z.; Zhang, F. R.; Qi, C. Z. Catal Commun 2015, 62, 6; (d) Luo, J.; Zhong, Z. J.; Ji, H. F.; Chen, J. Y.; Zhao, J.; Zhang, F. R. J Sulfur Chem 2016, 37, 438; (e) Li, C. M.; Zhang, F. R. RSC Adv 2016, 6, 75359; (f) Zhang, F. R.; Li, C. M.; Wang, C.; Qi, C. Z. Org Biomol Chem 2015, 13, 5022; (g) Lin, J. L.; Chen, J. M.; Ji, H. F.; Zhao, J.; Zhang, F. R.; Li, C. M. J Heterocyclic Chem 2017, 54, 2022.

[25] Puchala, A.; Marcinkowska, M.; Rasala, D. Current Micro Chem 2016, 3, 97.