A Complementary Approach to 3,5-Substituted Pyrazoles with Tosylhydrazones and Terminal Alkynes Mediated by TfOH

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Abstract: A complementary method for the preparation of 3,5-substituted pyrazoles in moderate to high yields has been explored via TfOH-induced addition of tosylhydrazones to the terminal alkynes. This acid-induced addition procedure might be an operationally safe alternative compared to typical 1,3-dipolar cycloaddition as there is no involvement of diazo compounds.

Key words: alkynes, tosylhydrazones, cycloaddition, heterocyclics, pyrazoles

Pyrazole has emerged as one of the important heterocyclic motifs due to its widespread application in material, food, agrochemical, and especially pharmaceutical industries, exemplified by the launched drugs such as Celebrex,[1] Viagra,[2] and Zometapine.[3] Thus the heterocycle has attracted continuous interest of many chemists in multiple disciplines over a long time,[4,5] resulting in a repertoire of methodologies for the pyrazoles with various substituted patterns.[6] Among them, 1,3-dipolar cycloaddition of diazo compounds onto triple bonds is one of the typical methods for the pyrazoles in medicinal chemistry due to readily available reaction components, however, this method seems to be less applicable for preparative purposes due to toxicity and potential explosion of diazo compounds. Thus, the recent efforts have been devoted to developing the safer procedures for generation and handling of diazo compounds, and the problem has been elegantly solved by in situ generation of diazo compounds from tosylhydrazone salts in the presence of phase-transfer catalyst (PTC).[7] Despite the great progress made, it is still highly desirable to develop intrinsic safer alternatives for the preparation of pyrazoles from the same starting materials: tosylhydrazones and alkynes.

As a standard method, under the basic conditions, tosylhydrazones can be converted into diazo compounds, which subsequently undergo 1,3-dipolar cycloaddition with alkynes to produce pyrazoles (Scheme 1, path a).[8] In contrast to this, less attention seems to be paid on acidic conditions with hydrazone chemistry.[9] Traced back to the previous literatures, Padwa[10] and Wilson[11] reported that the tosylhydrazones could react with the intramolecular double bond under acidic conditions and resulted in pyrazolines; noteworthy, the authors suggested that the acid-induced reaction might involve a stepwise carbocation addition of tosylhydrazones to the intramolecular double bond, but not involving the corresponding diazo intermediates. Inspired by the findings neglected for about 30 years, we hypothesize that the carbocation resulting from tosylhydrazones under acidic conditions might undergo intermolecular addition to the triple bond and produces the pyrazole ring if alkynes, instead of alkenes, are used (Scheme 1, path b). We believe that this route to pyrazole might be a mechanically safer process than that involving diazo compounds. Herein, we are willing to present our primary work on the issue.

Initially, we performed **1a** with **2a** in the presence of various Brønsted or Lewis acids (0.2 equiv) in refluxing 1,2-dichloroethane (DCE), and observed that some acids indeed promoted the reaction (Table 1), even though in most cases the starting material could not be consumed. In the cases of Brønsted acids, concentrated H_2SO_4 gave the desired product in 29% yield but accompanied with several complicated side products, in contrast to that, TfOH seemed to result in a cleaner reaction with a yield of 30% (Table1, entries 2 and 3). The other strong Brønsted acids such as $HClO_4$ and PTSA except concentrated hydrogen chloride also promoted the desired reaction with lower yields, but the weak Brønsted acids, for example, TFA and AcOH, did not initiate the reaction (Table 1, entries 1, 4–7).

As expected, some Lewis acids also promoted the transformation under the same conditions (Table 1, entries 8–16). Among them, $BF_3{\cdot}OEt_2$, $InCl_3$, $MoCl_5$, $ZnCl_2$, and TMSOTf gave reasonable yields of about 30%. However, compared with TfOH, those Lewis acids usually gave more side products in spite of more consumption of the starting materials. Thus TfOH was chosen to optimize the transformation, as shown in Table 2.

At first, the amounts of TfOH and the alkyne were found to have an evident influence on the reaction (Table 2, entries 1–6), and the best result was found when one equivalent of TfOH was used, and in that case, the tosylhydrazone was consumed and provided **3a** in 66% yield. To our surprise, the yield could be increased to 78% if the tosylhydrazone and TfOH were premixed (Table 2, entry 7 and footnote b), and it was also necessary to keep a small excess of the alkyne for higher yields (Table 2, entries 7–10). In addition, the transformation did not proceed at a lower temperature (Table 2, entries 11 and 12); furthermore, other solvents, such as MeCN, EtOH, and THF, were not suitable for the reaction due to poor solu-

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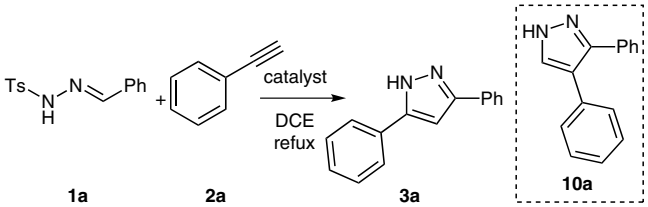
bility of a mixture of the reagents or intervention in the protonation of the tosylhydrazone. Unexpectedly, the regioisomer **10a**[12] (Table 1) could never be isolated during the whole period, suggesting the reaction might be highly regioselective or regiospecific.

Table 1 Screening of Various Acids for the Model Reaction of **1a** and **2a** under Different Conditions[a]



Entry	Catalyst (0.2 equiv)[b]	Yield of **3a** (%)[c]
1	HCl (concd)	trace
2	H_2SO_4 (concd)	29
3	TfOH	30
4	$HClO_4$	19
5	PTSA	17
6	TFA	0
7	AcOH	0
8	$BF_3{\cdot}OEt_2$	26
9	$AlCl_3$	20
10	$ZnCl_2$	38
11	$InCl_3$	22
12	$FeCl_3$	15
13	$BiCl_3$	16
14	$MoCl_5$	24
15	$SnCl_2$	11
16	TMSOTf	31

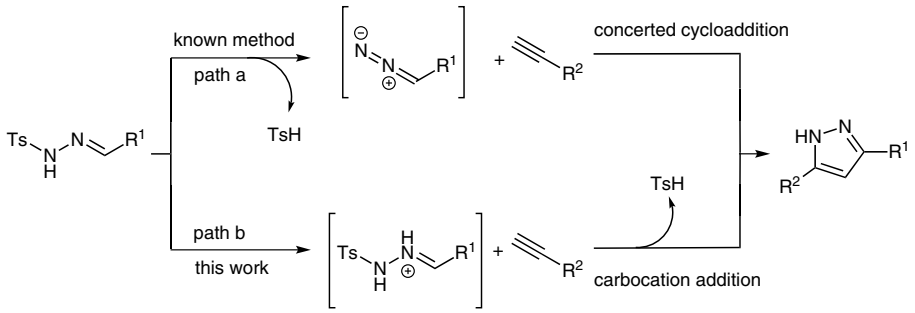
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), acid (0.2 equiv), DCE (2 mL), refluxing under Ar atmosphere for 12 h.
[b] Other Lewis acids were also tested, such as $CrCl_3$, $Cu(OTf)_2$, $CdCl_2$, $CuBr_2$, CuI, and CuCl.
[c] Isolated yield.

With the optimal conditions in hand, we next examined the scope and limitation of the reaction, as shown in Table 3. In general, for the aryl-substituted tosylhydrazones, the electronic effect on the aromatic ring had little influence on the reaction and resulted in good yields (Table 3, products **3a**–**i**). However, for the heteroaryl-substituted tosylhydrazones the yields were not good enough (Table 3, products **3j**,**k**). When alkyl tosylhydrazones were used, the reaction gave excellent yields (Table 3, products **3l**,**m**), but trifluoromethyl tosylhydrazone did not work (Table 3, product **3n**). If the substituent effect was switched to aryl-substituted alkynes, the reaction appeared to be very sensitive to the electronic effect (Table 3, products **3o**–**s**). Especially, the electron-rich aryl alkyne might not be compatible with the reaction (Table 3, product **3q**) possibly due to its instability under the acidic conditions, whereas the electron-poor aryl alkynes led to slightly low yields (Table 3, products **3r**,**s**). Unfortunate-

Table 2 Optimizing the Conditions for the Model Reaction[a]

Entry	TfOH (equiv)	**1a**/**2a** (equiv)	Temp (°C)	Yield of **3a** (%)[c]
1	0.2	1.0/1.2	85	30
2	0.5	1.0/1.2	85	54
3	0.5	1.0/1.5	85	54
4	1.0	1.0/1.5	85	66
5	1.5	1.0/1.5	85	48
6	2.0	1.0/1.5	85	20
7	1.0	1.0/1.5	85	78[b]
8	1.0	1.0/1.4	85	75[b]
9	1.0	1.0/1.2	85	56[b]
10	1.0	1.0/1.0	85	50[b]
11	1.0	1.0/1.5	r.t.	n.r.[b,d]
12	1.0	1.0/1.5	50	n.r.[b,d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a**, acid, DCE (2 mL), refluxing under Ar atmosphere for 12 h.
[b] Reaction conditions: A mixture of **1a** (0.5 mmol) and acid (1.0 equiv) in DCE (2 mL) was stirred at r.t. for 10 min, then **2a** was injected, and the mixture was stirred under Ar atmosphere for 12 h under the indicated condition in Table 2.
[c] Isolated yields.

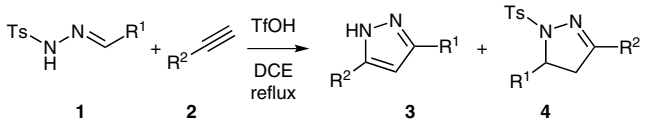


Scheme 1 The two complementary accesses to pyrazoles

ly, the alkyl-substituted alkyne also resulted in a low yield (Table 3, product **3t**), and additionally, the strong electron-withdrawing carboxylate group on the alkyne was not suitable in the transformation (Table 3, product **3u**).

An attempt to extend the reaction in the preparation of polysubstituted pyrazoles failed (Scheme 2). When the reaction of **1a** with the internal alkynes such as **2w** or **2x** was performed, the desired pyrazoles were not observed; furthermore, if the N1-substituted tosylhydrazone **1y** and **2a** were subjected to our conditions, the corresponding product was also not isolated. Those results suggested that the reaction was very sensitive to the steric hindrance between the two partners.

Table 3 Synthesis of 3,5-Substituted Pyrazoles via Cycloaddition of Tosylhydrazones and Alkynes[a]

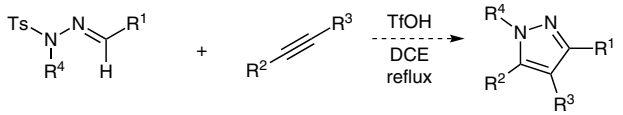


1 **2** **3** **4**

Product	R^1	R^2	Yield of **3** (**4**) (%)[b]
3a	Ph	Ph	78
3b	4-MeC_6H_4	Ph	66
3c	4-$MeOC_6H_4$	Ph	66
3d	4-FC_6H_4	Ph	66 (25)
3e	4-ClC_6H_4	Ph	60 (13)
3f	4-BrC_6H_4	Ph	63 (14)
3g	3-$O_2NC_6H_4$	Ph	66
3h	3-$F_3CC_6H_4$	Ph	47
3i	α-naphthyl	Ph	63
3j	2-thienyl	Ph	35 (12)
3k	2-furanyl	Ph	37
3l	cyclohexyl	Ph	90
3m	Et_2CH	Ph	90
3n	CF_3	4-MeC_6H_4	n.d.
3o	Ph	4-MeC_6H_4	59
3p	4-BrC_6H_4	4-MeC_6H_4	68 (9)
3q	4-BrC_6H_4	4-$MeOC_6H_4$	trace
3r	4-BrC_6H_4	4-FC_6H_4	52 (14)
3s	4-BrC_6H_4	3-ClC_6H_4	40
3t	Ph	*n*-Bu	42
3u	Ph	CO_2Et	n.d.[c]

[a] Reaction conditions: A mixture of **1a** (0.5 mmol) and TfOH (1.0 equiv) in DCE (2 mL) was stirred at r.t. for 10 min, then **2a** (0.75 mmol) was injected, and the mixture was refluxed under Ar atmosphere for 12 h.
[b] Isolated yields.
[c] n.d. = not determined.

It is noteworthy that tautomerism was evident in NMR experiments of the 3,5-substituted pyrazoles and sometimes led to difficulty in assigning the corresponding ^{13}C NMR signals.[13] In general, the signals of ^{13}C NMR in $CDCl_3$ are simpler than those in DMSO, but without the signals of the quaternary carbons near the nitrogen atoms in the pyrazole ring (Figure 1). The reason for this might be a longer relaxation time which is a consequence of the neighboring nitrogen atoms present in the highly conjugated system.[7b] To clarify the existence of the quaternary carbons, we treated **3a**[14] with NaH and subsequent MeI in dry THF or with K_2CO_3 and MeI in DMSO, respectively, obtaining the quantitative N-methylated product **11a**, whose signals in the ^1H NMR and ^{13}C NMR spectra, including the quaternary carbons, were in good agreement with the literature.[7b,16] Unfortunately, some pyrazoles were not soluble enough in $CDCl_3$, but in DMSO the ^{13}C NMR signals became more complicated at room temperature, meanwhile, the data of some known pyrazoles were found to be obviously inconsistent with each other.[15] Thus, the ^{13}C NMR experiment of the sample **3a** in DMSO was done at 90 °C, and the result showed that the signals of the quaternary carbons disappeared similar to those in $CDCl_3$. At last, the problem was overcome by the addition of a drop of concentrated HCl to the sample solution for the NMR experiment in DMSO at room temperature, which simplified the ^{13}C NMR signals and exhibited signals of the quater-



1a: R^1 = Ph; R^4 = H **2w**: R^2 = Ph, R^3 = Ph **3w**
1a: R^1 = Ph; R^4 = H **2x**: R^2 = Ph, R^3 = Me **3x**
1y: R^1 = Ph; R^4 = *i*-Pr **2a**: R^2 = Ph, R^3 = H **3y**

Scheme 2 The attempt to extend the reaction in the preparation of polysubstituted pyrazoles

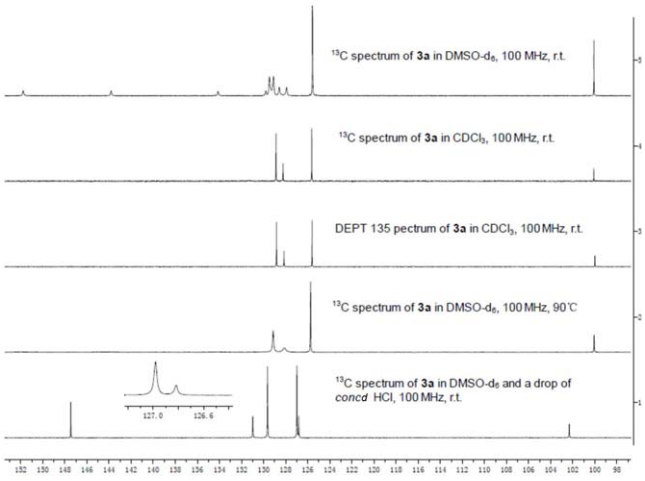


Figure 1 ^{13}C NMR spectra of **3a** in $CDCl_3$ or DMSO at different temperatures

nary carbons due to elimination of the tautomerism through protonation of the pyrazoles.[17]

In addition, in some cases we could isolate tosylated pyrazoline as the major side product **4** (Table 3, **3d**–**f**,**j**,**p**,**r**). For example, in the preparation of compound **3p**, the side product **4p** was isolated in 9% yield. Unexpectedly, by analyzing the data of the 2D NMR spectrum including NOESY, H–H COSY, HSQC, HMBC, the corresponding side product was assigned to the structure of **4p** instead of **5p** (see Figure 2 and Supporting Information), strongly supported by the obvious NOESY correlations between the H-5 on the pyrazoline or the H-15 on the tosyl ring and H-7 on the bromophenyl ring as well as no NOE signals between the H-5 and the H-11 on the tolyl ring.

Finally, based on our results and that of others,[10,11] a plausible mechanism for the transformation was proposed (Scheme 3). The tosylhydrazone was first protonated in the presence of TfOH, and the resulting protonated tosylhydrazone underwent carbocation addition to the alkyne **2**, leading to **Int-1**, followed by the attack of N1 atom of **Int-1** to intramolecular vinyl carbocation to give **Int-2** accompanied with the release of a proton. However, **Int-2** might also be produced from the protonated tosylhydrazone and the alkyne in the concerted manner similar to [3+2] mechanism of the hydrazones.[9] Because this reaction seemed to be very sensitive to the steric hindrance between the two partners, supported by the high regioselectivities with the terminal alkynes and the failures of the reaction with the internal alkynes. Subsequently, **Int-2** might undergo Ts elimination or migration. As shown in path a, **Int-2** was converted into **4** possibly through **Int-3**, resembling the reported 1,2-migration of Ts.[18] As shown in path b, **Int-2** could be converted into **Int-4** with the elimination of 4-methylbenzenesulfinic acid and resulted in the stable pyrazole **3** after resonance. It is noteworthy that when **4p** (Table 3) was subjected to the standard conditions (TfOH, DCE, reflux), only a trace amount of **3p** was observed, suggesting that path a might

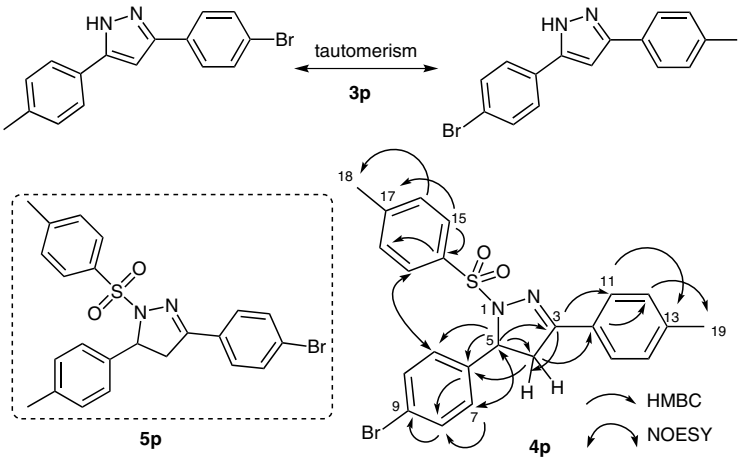
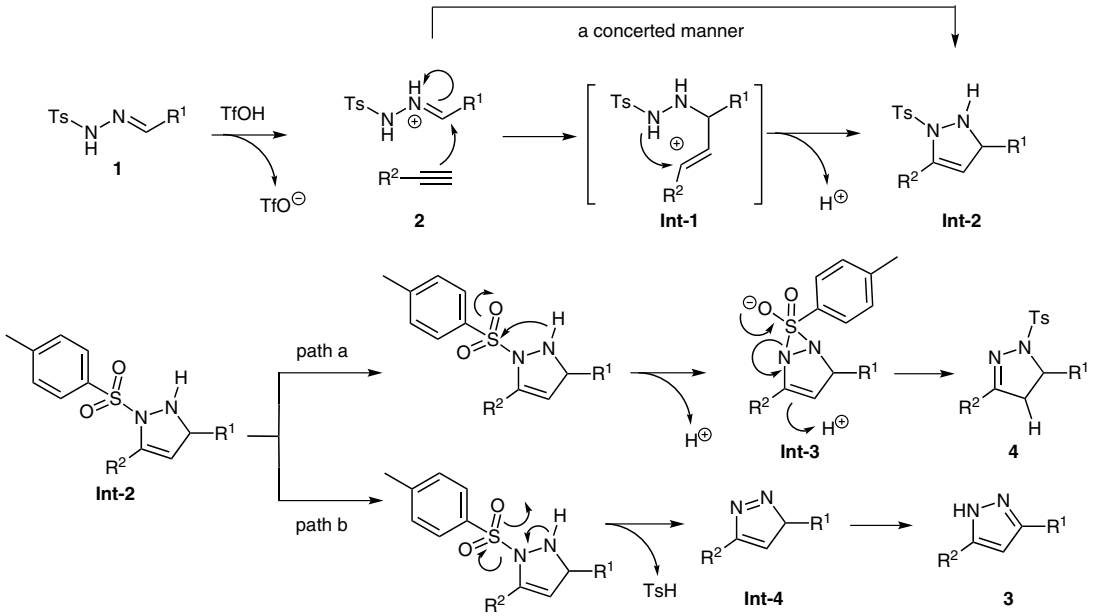
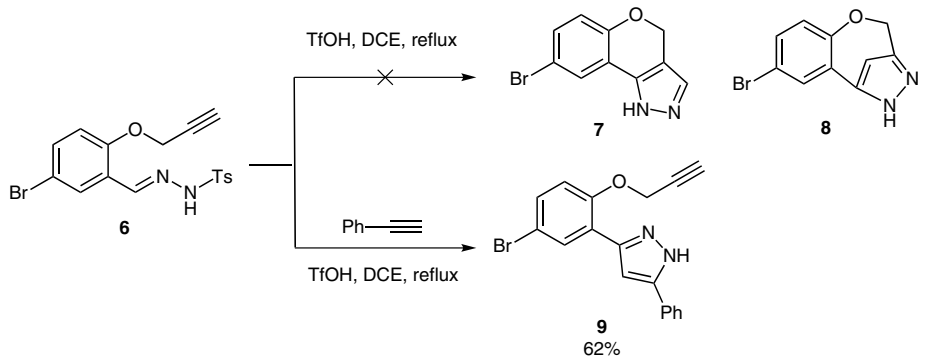


Figure 2 Key HMBC and NOESY correlations of compounds **4p** and structures of compounds **3p** and **5p**



Scheme 3 One plausible mechanism for the reaction



Scheme 4 Controlled experiments for the mechanism

be a competitive side process while path b is a main process.

In order to rule out the possible diazo intermediate existed in the reaction, we performed compound **6** under standard conditions. In the absence of phenylacetylene, the intramolecular carbocation cycloaddition was almost prohibited probably due to the serious steric hindrance (Scheme 4, compound **8**), but we could not detect compound **7** via the intramolecular 1,3-dipolar cycloaddition of the diazo intermediate (Scheme 1, path a);[19] on the other hand, in the presence of phenylacetylene, we could isolate the intermolecular cycloaddition product **9** in 62% yield. All these results strongly suggested that our process did not involve the diazo intermediate.

In summary, a TfOH-induced addition involving a carbocation addition of tosylhydrazones to the terminal alkynes has been explored, which leads to 3,5-substituted pyrazoles in moderate to high yields.[20] This acid-induced addition might be an intrinsically safer operation compared to the typical 1,3-dipolar cycloaddition involving diazo compounds.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) **General Procedure for the TfOH-Mediated Reaction of Tosylhydrazones with Terminal Alkynes**
To a solution of tosylhydrazones (0.5 mmol, 1.0 equiv) in dry DCE (2 mL) was added TfOH (0.5 mmol, 1.0 equiv) dropwise at r.t. under Ar atmosphere. After stirring for about 10 min, the alkynes (0.75 mmol, 1.5 equiv) were added. The reaction flask was refluxed for 12 h, and then it was cooled to r.t. and quenched with sat. Na_2CO_3 (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE–EtOAc = 4:1) to afford the corresponding products **3**. In some cases, compound **4** can be obtained by basic Al_2O_3 (100–200 mesh) column chromatography (PE–EtOAc = 6:1).

3,5-Diphenyl-1*H*-pyrazole (3a)
Yield: 78%; mp 197–199 °C; R_f = 0.31 (PE–EtOAc = 4:1); light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.3 Hz, 4 H), 7.25–7.38 (m, 6 H), 6.82 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.9, 128.2, 125.6, 100.1. ESI-LRMS: *m/z* = 221.2 $[M + H]^+$. CAS registry no. 1145-01-3.

3-(4-Bromophenyl)-5-*p*-tolyl-1*H*-pyrazole (3p)
Yield: 68%; mp 239–241 °C; R_f = 0.49 (PE–EtOAc = 3:1); white solid. ^{1}H NMR (400 MHz, DMSO-d_6 with a drop of concd HCl): δ = 7.90 (d, *J* = 8.6 Hz, 2 H), 7.82 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.40 (s, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6 with a drop of concd HCl): δ = 147.3, 147.0, 138.9, 132.3, 130.0, 128.1, 126.9, 126.1, 122.2, 100.8, 21.3. ESI-LRMS: *m/z* = 313.0 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{14}BrN_2^+$ $[M + H]^+$: 313.0340; found: 313.0337.

3-(4-Bromophenyl)-5-(4-fluorophenyl)-1*H*-pyrazole (3r)
Yield: 52%; mp 228–229 °C; R_f = 0.58 (PE–EtOAc = 3:1); white solid. ^{1}H NMR (400 MHz, DMSO-d_6 with a drop of concd HCl): δ = 7.95–7.99 (m, 2 H), 7.88 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.32–7.37 (m, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6 with a drop of concd HCl): δ = 162.6 (d, $^1J_{CF}$ = 245.7 Hz), 146.9, 146.6, 132.3, 130.1, 128.2 (d, $^3J_{CF}$ = 8.4 Hz), 128.0, 127.1 (d, $^4J_{CF}$ = 3.1 Hz), 122.0, 116.3 (d, $^2J_{CF}$ = 21.8 Hz), 100.91. ESI-LRMS: *m/z* = 316.9 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{15}H_{11}BrFN_2^+$ $[M + H]^+$: 317.0090; found: 317.0062.

5-(4-Bromophenyl)-3-*p*-tolyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (4p)
Yield: 9%; R_f = 0.35 (PE–EtOAc = 5:1); light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.2 Hz, 2 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.25–7.28 (m, 4 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 4.84 (dd, *J* = 11.1, 9.3 Hz, 1 H), 3.49 (dd, *J* = 17.2, 11.3 Hz, 1 H), 3.05 (dd, *J* = 17.2, 9.2 Hz, 1 H), 2.39 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.5, 144.2, 141.2, 139.9, 132.4, 131.8, 129.5, 129.4, 128.5, 128.5, 127.7, 126.8, 121.9, 64.5, 43.7, 21.6, 21.5. ESI-LRMS: *m/z* = 469.0 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{23}H_{22}BrN_2O_2S^+$ $[M + H]^+$: 469.0585; found: 469.0587.

