Facile One-Pot Synthesis of 3,5-Disubstituted 1*H*-Pyrazoles from Propargylic Alcohols via Propargyl Hydrazides

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Abstract: A new and efficient metal-free, two-component, one-pot approach to a variety of 3,5-disubstituted 1*H*-pyrazoles has been developed from propargylic alcohols. This transformation proceeds via an acid-catalyzed propargylation of N,N-diprotected hydrazines followed by base-mediated 5-*endo*-dig cyclization leading to 3,5-disubstituted 1*H*-pyrazoles in good overall yields.

Key words: pyrazole, propargylic alcohol, one-pot reaction, acid catalysis, hydrazines

Pyrazoles are a key core heterocyclic structural moieties present in many pharmaceutically active compounds for various therapeutic activities including metabolic diseases, CNS disorders, and anti-obesity etc.[1] For instance, Celecoxib (Celebrex), Linazolac, Rimonabant, and Mepiprazole are representative clinical drugs having pyrazole as a key framework (Figure 1). Accordingly, pyrazoles have attracted the attention of synthetic chemists and to date several methods have been reported for the synthesis of substituted pyrazoles[2] including the traditional Knorr reaction involving the condensation of hydrazines with 1,3-dicarbonyls,[3] 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines to alkenes or alkynes,[4] and others.[5] All of these methods, while offering advantages, also suffer from disadvantages, such as the formation of undesired isomers, structural limitations, the use of expensive catalysts, and toxic and explosive starting materials. Thus, the development of new approaches to pyrazoles from readily available starting materials under mild and efficient reaction conditions is welcome.

In the past decade, π-activated alcohols (benzylic/allylic/propargylic) have gained prominence as alkylating agents in green and atom-economic approaches, as they generate only water as the byproduct in the reaction.[6] In particular, propargylic alcohols have received substantial attention in alkylation reactions involving nucleophilic substitution, since the obtained propargylated compounds can be easily transformed to various heterocycles with the help of the alkyne functionality.[6,7] The efficacy of propargylic alcohols as carbon electrophiles has been explored in direct nucleophilic S_N1-type reactions with various carbon, oxygen, nitrogen, and sulfur nucleophiles and further conversion into the heterocycles.[8,9] We also have successfully explored the propargylation of a variety of nucleophiles under acid catalysis in the synthesis of benzofurans, isoxazoles, dihydroisoxazoles, and furans.[10] These results encouraged us to investigate the direct propargylation of hydrazines to propargyl hydrazides, which are expected to provide 3,5-disubstituted 1*H*-pyrazoles. While this manuscript was in preparation, Yoshimatsu et al. and Zhan et al. independently reported the synthesis of pyrazoles from propargylic alcohols.[11] Although these are attractive one-pot methods employing tosylhydrazine as the nucleophile, the use of a metal catalyst [AgOTf or $Sc(OTf)_3$ or $La(OTf)_3$] is essential for C–N bond formation (nucleophilic substitution). In contrast, the present paper describes a novel method for the synthesis of 3,5-disubstituted 1*H*-pyrazoles **4** from propargylic alcohols **1** using *N*-acetyl-*N*-tosylhydrazine (**2**) as a nucleophile under metal-free reaction conditions, via propargyl hydrazides **3** (Scheme 1).

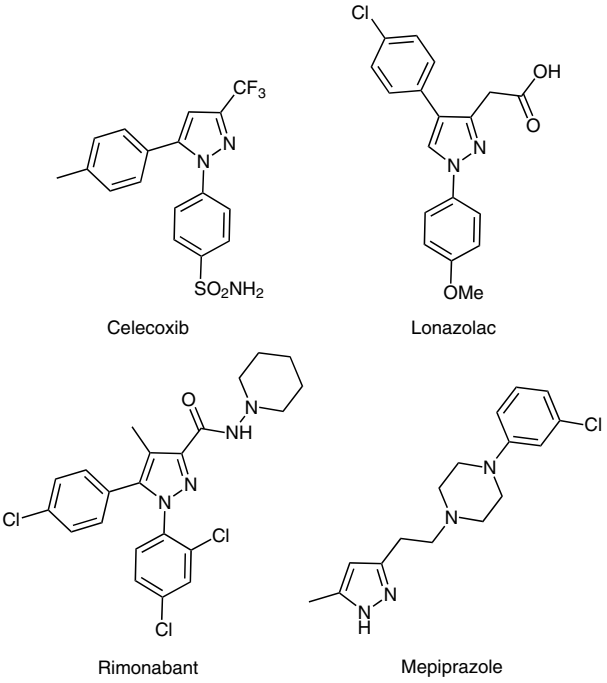

Figure 1 Structures of representative pyrazole drugs

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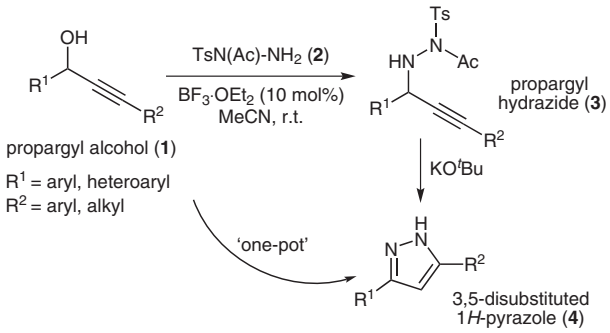
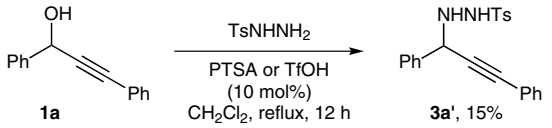


Scheme 1 Approach to 3,5-disubstituted 1*H*-pyrazoles

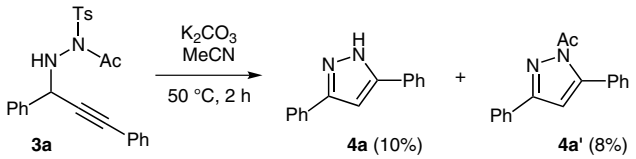
We initiated our investigation by examining the reaction of propargylic alcohol (**1a**) with tosylhydrazine in the presence of various acid catalysts (PTSA, $BF_3{\cdot}OEt_2$, and TfOH) in dichloromethane. However, the expected propargyl hydrazide was formed in very low yields even under reflux conditions. In the case of boron trifluoride–diethyl ether complex, the formation of a complex mixture was observed. The reaction of **1a** with tosylhydrazine in the presence of 4-toluenesulfonic acid or triflic acid provided the propargyl hydrazide **3a′**[11a] in only 15% yield (Scheme 2). This may be due to nucleophilic as well as more basic nature of tosylhydrazine, which could neutralize the acidic catalysts.

Therefore, we next considered *N*-acetyl-*N*-tosylhydrazine (**2**)[12] as the nucleophile, which is anticipated to have a milder basic character. Accordingly, the N-propargylation



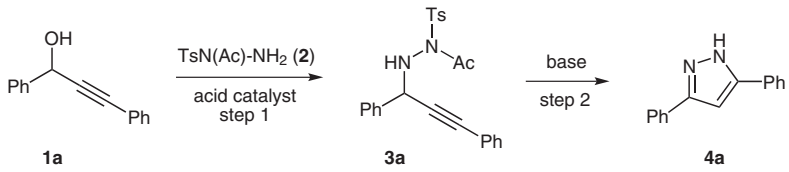
Scheme 2

of **2** with **1a** was examined using 10 mol% 4-toluenesulfonic acid in dichloromethane at room temperature. To our delight, the formation of the desired *N*-propargyl hydrazide **3a** was observed in 73% yield (Table 1, entry 1). In order to improve the yield, other catalysts were screened and the results are summarized in Table 1. Among the catalysts tested, boron trifluoride–diethyl ether complex was found to give **3a** in an improved 87% yield (entry 2). After the successful formation of **3a**, our aim was to convert it into the pyrazole. We envisioned that a base-mediated detosylation/deacetylation would induce cyclization to give the pyrazole **4a**. Consequently, the isolated **3a** was treated with potassium carbonate in acetonitrile at 50 °C to provide 3,5-diphenyl-1*H*-pyrazole (**4a**) in 10% yield together with 1-acetyl-3,5-diphenyl-1*H*-pyrazole (**4a′**) (8%) (Scheme 3).



Scheme 3

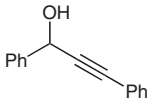
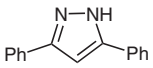
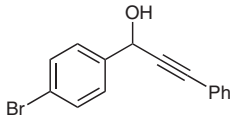
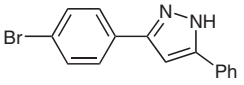
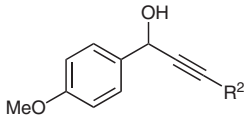
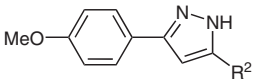
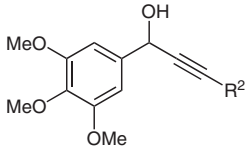
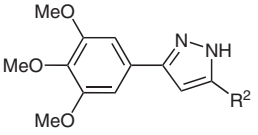
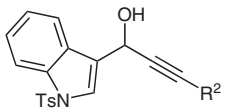
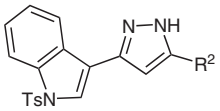
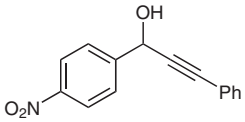
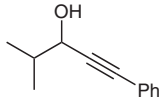
Table 1 Optimization of the Reaction Conditions



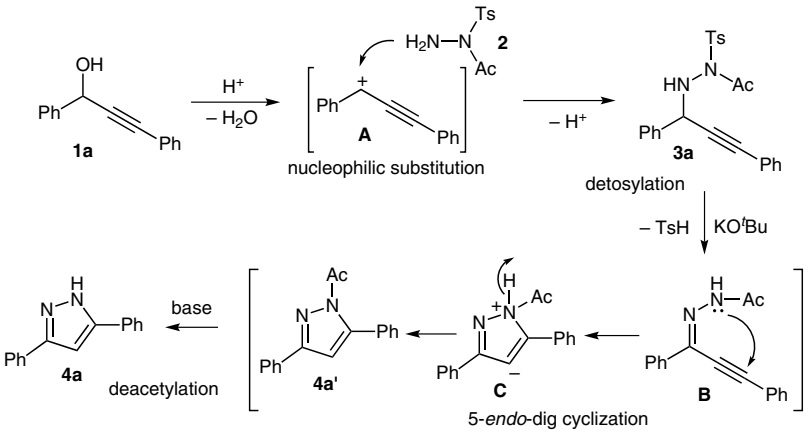
Entry	Nucleophilic substitution[a] (step 1)	Deprotection/cyclization[b] (step 2)	Product	Yield[c] (%)
1	PTSA, CH_2Cl_2, r.t., 15 min	–	**3a**	73
2	$BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t., 10 min	–	**3a**	87
3	$B(C_6F_5)_3$, CH_2Cl_2, r.t., 5 h	–	**3a**	0[d]
4	–	K_2CO_3, 50 °C 8 h	**4a**	10[e]
5	–	Cs_2CO_3, 50 °C, 8 h	**4a**	12[e]
6	–	TBAF, 50 °C, 8 h	**4a**	15[e]
7	–	KO*t*-Bu, r.t., 0.5 h	**4a**	85
8[f]	$BF_3{\cdot}OEt_2$, MeCN, r.t. 10 min	KO*t*-Bu, r.t., 0.5 h	**4a**	82

[a] Catalyst (10 mol%).
[b] Catalyst (3 equiv) in MeCN.
[c] Isolated yields.
[d] After 12 h at refluxing temperature 10% **3a** was formed.
[e] The formation of 4**a′** was also observed (see Scheme 3).
[f] One-pot reaction.

Table 2 One-Pot Synthesis of 3,5-Disubstituted 1*H*-Pyrazoles[a]

Entry	Propargylic alcohol	Time (min) Step 1	Step 2	Pyrazole[b]	Yield[c] (%)
1	 **1a**	10	15	 **4a**	82
2	 **1b**	15	30	 **4b**	85
3	 R^2 = Ph, **1c**	15	30	 R^2 = Ph, **4c**	78
4	R^2 = CH_2OBn, **1d**	15	20[d]	R^2 = CH_2OBn, **4d**	76
5	R^2 = Pr, **1e**	10	20[d]	R^2 = Pr, **4e**	75
6	 R^2 = Ph, **1f**	10	30	 R^2 = Ph, **4f**	81
7	R^2 = CH_2OBn, **1g**	15	30[d]	R^2 = CH_2OBn, **4g**	77
8	R^2 = Pr, **1h**	5	20[d]	R^2 = Pr, **4h**	74
9	 R^2 = Ph, **1i**	10	30	 R^2 = Ph, **4i**	76
10	R^2 = CH_2OBn, **1j**	10	25[d]	R^2 = CH_2OBn, **4j**	83
11	R^2 = Pr, **1k**	10	20[d]	R^2 = Pr, **4k**	73
12[e]	 **1l**	120	0	–	–
13[e]	 **1m**	120	0	–	–

[a] Reaction conditions: (step 1) propargyl alcohol **1** (1 mmol), **2** (0.95 mmol), $BF_3{\cdot}OEt_2$ (10 mol%), r.t.; (step 2) KO*t*-Bu (3 equiv), r.t. or 50 °C.
[b] Characterized by ^1H and ^{13}C NMR, and MS.
[c] Isolated yields.
[d] Step 2 was successful at 50 °C.
[e] Nucleophilic substitution reaction did not proceed.



Scheme 4 Proposed mechanism

To improve the yield of the reaction, various bases (Cs_2CO_3, TBAF, KO*t*-Bu) were examined and it was found that potassium *tert*-butoxide provided the best yield (85%, Table 1, entry 7). Having optimized the reaction conditions for the synthesis of propargyl hydrazide **3a** and its conversion into 3,5-disubstituted 1*H*-pyrazole **4a**, performing both the reactions in a one-pot procedure would be attractive. Hence, propargylic alcohol **1a** was treated first with *N*-acetyl-*N*-tosylhydrazine (**2**) in presence of 10 mol% boron trifluoride–diethyl ether in acetonitrile and after 10 minutes, potassium *tert*-butoxide (3 equiv) was added and stirring continued for a further 30 minutes at room temperature, which gave clean formation of 3,5-diphenyl-1*H*-pyrazole (**4a**) in 82% yield (entry 8).

Encouraged by the above results, the generality of this one-pot method was studied for the synthesis of various 3,5-disubstituted 1*H*-pyrazoles from different propargylic alcohols. As can be seen from Table 2, propargylic alcohol **1b** (bearing 4-bromophenyl in the benzylic position) provided the corresponding 3,5-disubstituted 1*H*-pyrazole **4b** in 85% yield using the one-pot reaction conditions (entry 2). Next, alcohols **1c**–**e**, derived from the reaction of 4-methoxybenzaldehyde with aryl- or alkylacetylenes, were reacted with nucleophile **2** followed by treatment with base to afford the corresponding pyrazoles **4c**–**e** in good yields (entries 3–5). Similarly, propargylic alcohols obtained from 3,4,5-trimethoxybenzaldehyde **1f**–**h** and 1-tosyl-1*H*-indole-3-carbaldehyde **1i**–**k** also efficiently participated in the one-pot reaction to give 3,5-disubstituted 1*H*-pyrazoles, **4f**–**k** (entries 6–11). In the case of propargylic alcohols with an alkyl group on the alkyne, the cyclization (Step 2) was successful at 50 °C and in good yields.

However, propargylic alcohols **1l** and **1m** failed to give the expected products, because the initial nucleophilic substitution did not proceed in the presence of boron trifluoride–diethyl ether complex even under refluxing conditions. These results obviously reveal that the direct propargylation of hydrazine **2** was successful only in the case of propargylic alcohols generated from aromatic (without electron-withdrawing groups)/heteroaromatic aldehydes and not with alcohols generated from aliphatic aldehydes. This may be due to the benzylic group, which can facilitate the formation of the carbenium ion.

A possible reaction mechanism is shown in Scheme 4. In the first step, propargylic alcohol **1a** reacts with nucleophile **2** in the presence of an acid catalyst to give the *N*-propargyl hydrazide **3a** via carbocation **A**. Next, a base can induce either detosylation or deacetylation to provide the hydrazone. Based on our observation (formation of **4a′**, Scheme 3), we suggest that the detosylation takes place first to give the *N*-acetylhydrazone **B** and subsequent 5-*endo*-dig cyclization produces the intermediate **C** which afford *N*-acetylpyrazole **4a′**. A final base-mediated deacetylation furnishes the product **4a**.

In conclusion, we have developed a new one-pot, acid-catalyzed N-propargylation of *N*-acetyl-*N*-tosylhydrazine using propargylic alcohols to propargyl hydrazides followed by their base-mediated conversion into 3,5-disubstituted 1*H*-pyrazoles. The reaction conditions are metal-free, mild, and efficient, and provide the products in good yields.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 500 MHz or 75 MHz spectrometer at r.t. with TMS as an internal standard. FTIR spectra were recorded as KBr thin films or neat. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade EtOAc and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of N_2 in oven-dried glassware with magnetic stirring.

N-Acetyl-*N*-tosylhydrazine (**2**) was prepared using the literature procedure.[12b]

1-Substituted Alk-2-yn-1-ols 1a–m; General Procedure

To the alkyne (1.1 mmol) in anhyd THF (5 mL) was added BuLi (1 mmol) slowly at –78 °C. After 40 min, the aromatic aldehyde (1 mmol) in THF (5 mL) was added at –78 °C to the mixture. The mixture was stirred at –78 °C until complete consumption of the aldehyde, then the reaction was quenched by the addition of aq sat. NH_4Cl soln and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel) to afford pure

propargylic alcohols **1a**–**m**. The products obtained were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy.

The spectral data of **1a**,[8g] **1c**,[9a] **1d**,[13a] **1e**,[13b] **1i**,[13c] **1l**,[13d] and **1m**[13e] were in full agreement with the literature data.

1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol (1b)
Viscous liquid; yield: 1.1 g (74%).

IR (KBr): 3365, 2196, 1485, 1068, 1011, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.44 (m, 6 H, Ar), 7.36–7.30 (m, 3 H, Ar), 5.65 (s, 1 H, CH), 2.36 (s, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.4, 131.6, 131.5, 128.6, 128.3, 128.2, 122.2, 122.0, 88.1, 86.8, 64.2.

3-Phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (1f)
Viscous liquid; yield: 1.1 g (76%).

IR (KBr): 3431, 2939, 2216, 1595, 1461, 1127 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2 H, Ar), 7.35–7.30 (m, 3 H, Ar), 6.87 (s, 2 H, Ar), 5.63 (s, 1 H, CH), 3.90 (s, 6 H, OCH_3), 3.86 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0, 137.4, 136.3, 131.4, 128.4, 128.1, 122.1, 103.5, 88.7, 86.1, 64.7, 60.6, 55.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}NaO_4$: 321.1097; found: 321.1097.

4-(Benzyloxy)-1-(3,4,5-trimethoxyphenyl)but-2-yn-1-ol (1g)
Viscous liquid; yield: 1.4 g (81%).

IR (KBr): 3433, 2939, 2841, 1594, 1234, 1125 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5 H, Ar), 6.78 (s, 2 H, Ar), 5.46 (s, 1 H, CH), 4.61 (s, 2 H, $PhCH_2$), 4.27 (d, *J* = 1.7 Hz, 2 H, OCH_2), 3.86 (s, 6 H, OCH_3), 3.84 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8, 137.3, 136.8, 136.1, 128.1, 127.7, 103.3, 86.4, 81.8, 71.3, 64.0, 60.5, 57.1, 55.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}NaO_5$: 3651359; found: 365.1361.

1-(3,4,5-Trimethoxyphenyl)hex-2-yn-1-ol (1h)
Viscous liquid; yield: 1.0 g (79%).

IR (KBr): 3446, 2963, 2226, 1594, 1460, 1420, 1331, 1233 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (s, 2 H, Ar), 5.37 (s, 1 H, ArCH), 3.85 (s, 6 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.24 (td, *J* = 2.0, 6.9 Hz, 2 H, CH_2), 1.59–1.51 (m, 2 H, CH_2CH_3), 0.99 (t, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 137.1, 136.9, 103.3, 86.5, 80.0, 64.1, 60.2, 55.5, 21.6, 20.3, 13.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_4$: 287.1253; found: 287.1252.

4-(Benzyloxy)-1-(1-tosyl-1*H*-indol-3-yl)but-2-yn-1-ol (1j)
Viscous liquid; yield: 1.2 g (85%).

IR (KBr): 3521, 2856, 1447, 1369, 1173, 748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1 H, Ar), 7.76 (t, *J* = 8.3 Hz, 3 H, Ar), 7.70 (s, 1 H, N-CH), 7.37–7.16 (m, 9 H, Ar), 5.72 (s, 1 H, CH), 4.60 (s, 2 H, $PhCH_2$), 4.28 (d, *J* = 2.2 Hz, 2 H, CH_2O), 2.32 (s, 3 H, CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{23}NO_4NaS$: 468.1240; found: 468.1233.

1-(1-Tosyl-1*H*-indol-3-yl)hex-2-yn-1-ol (1k)
Viscous liquid; yield: 1.0 g (83%).

IR (KBr): 2964, 2232, 1917, 1447, 1374, 1174, 972, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99–7.66 (m, 5 H, Ar), 7.36–7.18 (m, 4 H, Ar), 5.65 (s, 1 H, CH), 2.28–2.23 (m, 5 H, CH_3Ts, CH_2), 1.68–1.53 (m, 2 H, CH_2CH_3), 1.01 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 129.8, 126.9, 125.6, 124.9, 124.7, 123.0, 120.5, 113.3, 88.1, 62.7, 61.7, 22.0, 21.5, 20.8, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{21}NNaO_3S$: 390.1134; found: 390.1132.

***N*-Acetyl-*N*′-(1,3-diphenylprop-2-ynyl)-4-methylbenzenesulfonohydrazide (3a) (Table 1, Entry 2)**
To a mixture of propargylic alcohol **1a** (1.0 mmol) and *N*-acetyl-*N*-tosylhydrazine (**2**, 0.9 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (5 mol%) at r.t. and the mixture was stirred for 10 min (Table 1, entry 2). The mixture was diluted with sat. aq $NaHCO_3$ soln (5 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and dried (anhyd Na_2SO_4), concentrated in vacuo and purified by column chromatography to afford **3a** as a white solid; yield: 174.8 mg (87%); mp 120–122 °C.

IR (KBr): 3312, 2237, 1707, 1491, 1358, 1164, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.9 Hz, 2 H, Ar), 7.65 (s, 2 H, Ar), 7.50–7.14 (m, 10 H, Ar), 5.68 (s, 1 H, CH), 5.31 (s, 1 H, NH), 2.51 (s, 3 H, CH_3), 2.41 (s, 3 H, $COCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 144.9, 136.2, 131.3, 129.2, 128.9, 128.8, 128.5, 128.4, 128.1, 87.6, 85.2, 57.5, 23.9, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_3S$: 419.1423; found: 419.1426.

3,5-Diphenyl-1*H*-pyrazole (4a); Procedure from 3a (Table 1, Entry 7)
To a soln of **3a** (1.0 mmol) in MeCN (5 mL) was added KO*t*-Bu (3 mmol) at r.t. and the mixture was stirred for 30 min (Table 1, entry 7). The solvent was removed on a rotary evaporator and the crude product was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 15 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by column chromatography to afford **4a** as a viscous liquid; yield: 44.7 mg (85%).

IR (KBr): 3097, 2923, 1461, 1181, 972, 753 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.70 (m, 4 H, Ar), 7.44–7.31 (m, 6 H, Ar), 6.85 (s, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 131.2, 128.3, 127.4, 125.1, 99.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1072.

1-(3,5-Diphenyl-1*H*-pyrazol-1-yl)ethanone (4a′)
Viscous liquid; yield: 5 mg (8%).

IR (KBr): 3055, 1742, 1324, 941, 763 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.88 (m, 2 H, Ar), 7.49–7.39 (m, 8 H, Ar), 6.72 (s, 1 H, CH), 2.80 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 153.3, 147.1, 131.7, 131.0, 129.1, 128.9, 128.8, 128.7, 127.8, 126.1, 109.8, 23.7.

MS (ESI): *m*/*z* = 263 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2O$: 263.1179; found: 263.1196.

One-Pot Synthesis of 3,5-Disubstituted 1*H*-Pyrazoles 4; General Procedure
To a stirred soln of propargyl alcohol **1** (1 mmol) in MeCN (5 mL) was added *N*-acetyl-*N*-tosylhydrazine (**2**, 0.95 mmol) and $BF_3{\cdot}OEt_2$ (10 mol%) and the mixture was stirred at r.t. (see Table 2). Then, KO*t*-Bu (3 mmol) was added and the stirring was continued at r.t. or 50 °C (see Table 2). After completion of the reaction (for reaction time, see Table 2), the mixture was evaporated in vacuo and the

crude mixture was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and brine (5 mL). The EtOAc layer was evaporated and the residue was purified by column chromatography (silica gel, EtOAc–hexanes) to give the corresponding pyrazole **4**.

3-(4-Bromophenyl)-5-phenyl-1*H*-pyrazole (4b)
White solid; yield: 88.5 mg (85%); mp 210–213 °C.

IR (KBr): 3448, 2922, 1488, 1453, 1067, 759 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.82–7.71 (m, 4 H, Ar), 7.54 (d, *J* = 8.3 Hz, 2 H, Ar), 7.42 (t, *J* = 7.5 Hz, 2 H, Ar), 7.32 (t, *J* = 7.5 Hz, 1 H, Ar), 6.88 (s, 1 H, CH=).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 130.2, 127.3, 126.4, 125.6, 123.9, 119.6, 98.0.

MS (ESI): *m*/*z* = 299 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}BrN_2$: 299.0178; found: 299.0188.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrazole (4c)
White solid; yield: 81.9 mg (78%); mp 150–154 °C.

IR (KBr): 2925, 2854, 1461, 1252, 1176, 764 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.1 Hz, 2 H, Ar), 7.63 (d, *J* = 8.6 Hz, 2 H, Ar), 7.43–7.30 (m, 3 H, Ar), 6.91 (d, *J* = 8.5 Hz, 2 H, Ar), 6.75 (s, 1 H, =CH), 3.83 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 147.8, 131.4, 128.1, 127.1, 126.2, 124.9, 113.5, 98.2, 54.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}NO_2$: 251.1178; found: 251.1178.

5-[(Benzyloxy)methyl]-3-(4-methoxyphenyl)-1*H*-pyrazole (4d)
White solid; yield: 79.2 mg (76%); mp 97–100 °C.

IR (KBr): 2925, 2855, 1511, 1251, 1029, 835 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.7 Hz, 2 H, Ar), 7.39–7.29 (m, 5 H, Ar), 6.95 (d, *J* = 7.8 Hz, 2 H, Ar), 6.49 (s, 1 H, =CH), 4.64 (s, 2 H, CH_2O), 4.60 (s, 2 H, CH_2Ph), 3.85 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 148.1, 145.8, 137.6, 128.4, 127.9, 127.7, 126.8, 124.1, 114.1, 101.4, 72.2, 64.3, 55.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2$: 295.1441; found: 295.1440.

3-(4-Methoxyphenyl)-5-propyl-1*H*-pyrazole (4e)
Viscous liquid; yield: 79.4 mg (75%).

IR (KBr): 2960, 2871, 1457, 1249, 1177, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.3 Hz, 2 H, Ar), 6.93 (d, *J* = 8.3 Hz, 2 H, Ar), 6.30 (s, 1 H, =CH), 3.84 (s, 3 H, OCH_3), 2.64 (t, *J* = 7.5 Hz, 2 H, N=CH_2), 1.77–1.64 (m, 2 H, C$H_2$$CH_3$), 0.99 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 149.2, 147.8, 126.9, 125.1, 114.0, 100.4, 55.2, 28.3, 22.4, 13.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}NO_2$: 217.1335; found: 217.1335.

5-Phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (4f)
Viscous liquid; yield: 84.2 mg (81%).

IR (KBr): 2929, 1590, 1468, 1239, 1127, 765 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.3 Hz, 2 H, Ar), 7.37–7.29 (m, 3 H, Ar), 6.94 (s, 2 H, Ar), 6.74 (s, 1 H, =CH), 3.86 (s, 3 H, OCH_3), 3.81 (s, 6 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 149.4, 147.6, 137.8, 130.4, 128.6, 128.0, 127.0, 125.3, 102.5, 99.4, 60.7, 55.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1390; found: 311.1388.

5-[(Benzyloxy)methyl]-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (4g)
Viscous liquid; yield: 79.7 mg (77%).

IR (KBr): 2932, 1589, 1468, 1126, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H, Ar), 6.95 (s, 2 H, Ar), 6.50 (s, 1 H, =CH), 4.63 (s, 2 H, $PhCH_2$), 4.59 (s, 2 H, CH_2O), 3.90 (s, 6 H, OCH_3), 3.87 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 149.3, 144.5, 137.9, 137.3, 128.4, 127.8, 127.5, 104.1, 102.8, 101.8, 72.3, 63.8, 60.8, 56.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_4$: 355.1652; found: 355.1652.

5-Propyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (4h)
Viscous liquid; yield: 77.3 mg (74%).

IR (KBr): 2959, 2933, 1590, 1467, 1236, 1126, 1004 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.97 (s, 2 H, Ar), 6.33 (s, 1 H, =CH), 3.90 (s, 6 H, OCH_3), 3.87 (s, 3 H, OCH_3), 2.64 (t, *J* = 7.5 Hz, 2 H, CH_2), 1.78–1.64 (m, 2 H, C$H_2$$CH_3$), 0.99 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 150.0, 147.4, 137.8, 128.4, 102.9, 100.7, 60.7, 55.9, 28.1, 22.4, 13.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3$: 277.1546; found: 277.1546.

3-(5-Phenyl-1*H*-pyrazol-3-yl)-1-tosyl-1*H*-indole (4i)
Viscous liquid; yield: 78.2 mg (76%).

IR (KBr): 2926, 2207, 1683, 1445, 1372, 1174, 1134, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (t, *J* = 7.9 Hz, 2 H, Ar), 7.91 (s, 1 H, NCH=), 7.81 (d, *J* = 7.9 Hz, 2 H, Ar), 7.70 (t, *J* = 7.9 Hz, 2 H, Ar), 7.45 (t, *J* = 6.9 Hz, 2 H, Ar), 7.38 (t, *J* = 6.9 Hz, 2 H, Ar), 7.34–7.29 (m, 1 H, Ar), 7.22 (d, *J* = 7.9 Hz, 2 H, Ar), 6.86 (s, 1 H, =CH), 2.33 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0, 145.0, 143.2, 135.2, 134.9, 131.9, 130.3, 129.8, 128.8, 128.5, 128.4, 126.8, 125.5, 125.0, 123.7, 123.3, 121.2, 115.0, 113.6, 101.1, 21.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_2S$: 414.1270; found: 414.1274.

3-{5-[(Benzyloxy)methyl]-1*H*-pyrazol-3-yl}-1-tosyl-1*H*-indole (4j)
Viscous liquid; yield: 85.2 mg (83%).

IR (KBr): 3064, 2924, 1597, 1446, 1371, 1174 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (t, *J* = 6.7 Hz, 2 H, Ar), 7.86 (s, 1 H, NCH), 7.78 (d, *J* = 8.3 Hz, 2 H, Ar), 7.39–7.28 (m, 7 H, Ar), 7.19 (d, *J* = 8.3 Hz, 2 H, Ar), 6.54 (s, 1 H, =CH), 4.66 (s, 2 H, $PhCH_2$), 4.60 (s, 2 H, CH_2O), 2.31 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 143.8, 137.3, 135.1, 134.8, 129.8, 128.4, 126.7, 125.0, 123.6, 123.2, 121.3, 115.1, 113.5, 102.9, 72.3, 63.6, 21.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{24}N_3O_3S$: 458.1532; found: 458.1532.

3-(5-Propyl-1*H*-pyrazol-3-yl)-1-tosyl-1*H*-indole (4k)
Viscous liquid; yield: 75.3 mg (73%).

IR (KBr): 2926, 2868, 1371, 1174, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.4 Hz, 1 H, Ar), 8.01 (d, *J* = 8.1 Hz, 1 H, Ar), 7.84 (s, 1 H, NCH), 7.78 (d, *J* = 8.7 Hz, 2 H, Ar), 7.35 (t, *J* = 7.4 Hz, 1 H, Ar), 7.29 (t, *J* = 7. 4 Hz, 1 H, Ar), 7.20 (d, *J* = 8.1 Hz, 2 H, Ar), 6.37 (s, 1 H, =CH), 2.68 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.32 (s, 3 H, CH_3Ts), 1.76–1.70 (m, 2 H, C$H_2$$CH_3$), 1.01 (t, *J* = 7. 4 Hz, 3 H, C$H_3$$CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 144.9, 143.9, 135.2, 135.0, 129.8, 128.6, 126.8, 124.9, 123.6, 123.2, 121.5, 115.9, 113.5, 102.0, 27.9, 22.3, 21.4, 13.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2S$: 380.1427; found: 380.1425.

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