An Efficient One-Pot Synthesis of 3,5-Diaryl-4-bromopyrazoles by 1,3-Dipolar Cycloaddition of In Situ Generated Diazo Compounds and 1-Bromoalk-1-ynes

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Abstract: A simple, highly efficient, one-pot synthesis of 3,5-diaryl-4-bromopyrazoles via 1,3-dipolar cycloaddition of diazo compounds and alkynyl bromides has been developed. The diazo compounds and alkynyl bromides were generated in situ from tosylhydrazones and *gem*-dibromoalkenes, respectively. When ketone-derived hydrazones were used, 3,5-diaryl-4-bromo-3*H*-pyrazoles were obtained and the isomerization products 3,5-diaryl-4-bromo-1*H*-pyrazoles were formed when using aldehyde-derived hydrazones. The reaction system exhibited high regioselectivity and good functional group tolerance. Both electron-rich and electron-deficient substituents on the aromatic ring of the hydrazones or the *gem*-dibromoalkenes gave desired products in moderate to good yields (67–86%).

Key words: cycloaddition, diazo compounds, hydrazones, pyrazoles, *gem*-dibromoalkenes

Pyrazoles and their derivatives have important applications in the pharmaceutical and agricultural industries due to their diverse bioactivity.[1] Thus, they have attracted much attention and many methods have been developed for their synthesis[2] and chemical structural modifications.[3]

Among these, the most practical method is the condensation of hydrazines with 1,3-diketones or their derivatives.[4] However, the reactions often give undesired isomers as major products. Another important method is the 1,3-dipolar cycloaddition of diazo compounds to triple bonds,[5] however diazo compounds without an electron-withdrawing group are usually unstable and thus difficult to handle.[6] These factors significantly limit the scope of these reactions.

In 2003, Aggarwal et al. prepared 1*H*-pyrazoles by 1,3-dipolar cycloaddition reactions of diazo compounds generated in situ from aldehyde-derived tosylhydrazones.[7] The reaction was carried out in acetonitrile with sodium hydroxide as the base and took 48 hours to go to completion; in most cases moderate yields of the products were obtained. Recently, Chen and co-workers improved the reaction by using a stronger base, sodium ethoxide, instead of sodium hydroxide and carried out the reaction in toluene instead of acetonitrile in a one-pot procedure.[8] The method of generating diazo compounds in situ has been widely used in organic synthesis in recent years, and many synthetic protocols have been developed to expand the scope of this type of reaction.[9]

To the best of our knowledge, most reported syntheses of pyrazoles use aldehyde-derived tosylhydrazones and terminal alkynes. Reports on the cycloaddition between diazo compounds and alkynyl halides are rare. Field and Atherton reported a cycloaddition reaction between bromoacetylene and trifluorodiazoethane; the reaction was not fully regioselective and gave a mixture of isomers.[10] Hanamoto and co-workers reported a one-pot preparation of 4-fluoro-5-(tributylstannyl)-1*H*-pyrazole via 1,3-dipolar cycloaddition between diazomethane and fluoro(tributylstannyl)acetylene generated in situ.[11] The reaction between iodoalkynes and diazomethane reported in 1988 by Dzhuraev et al. led to 3-iodopyrazoles in 91–93% yields.[12] All of these reactions used only aldehyde-derived hydrazones or the corresponding diazo compounds.

gem-Dibromoalkenes are used as an alkynyl donor in organic reactions.[13] Generating alkynyl bromides from *gem*-dibromoalkenes in situ is an easy and economic way for the preparation of alkynyl bromides, which are usually malodorous and expensive.

The preparation of 3,5-diaryl-4-bromopyrazoles by traditional methods requires two steps, synthesis of 3,5-diarylpyrazoles first and bromination of the pyrazoles using *N*-bromosuccinimide[14] or bromine[15] in a separate step or through the condensation of hydrazine hydrate with 2-bromo-substituted 1,3-diarylpropane-1,3-diones.[16] However these methods can only be used to synthesize 3,5-diaryl-4-bromo-1*H*-pyrazoles. In this article, we would like to report a novel, one-pot 1,3-dipolar cycloaddition reaction between diazo compounds and alkynyl bromides. The diazo compounds are generated in situ from ketone- or aldehyde-derived tosylhydrazones and the alkynyl bromides are generated in situ from *gem*-dibromoalkenes. The reaction was carried out in tetrahydrofuran in the presence of sodium hydroxide under mild conditions (80 °C, 10 h) and gave the corresponding products in moderate to good yields. Of the two possible regioisomers, **3** and **4**, isomer **3** was obtained with high regioselectivity. It was found that if the diazo compound was generated in situ from an aldehyde-derived tosylhydrazone **1** (R^1 = H), the isolated product is **5**, which was formed through the isomerization of the initially formed addition product **3** (Scheme 1). Both of isomer **3** and **5** can be used as intermediates toward the synthesis of other important compounds.[17] In particular, they are of special interest,

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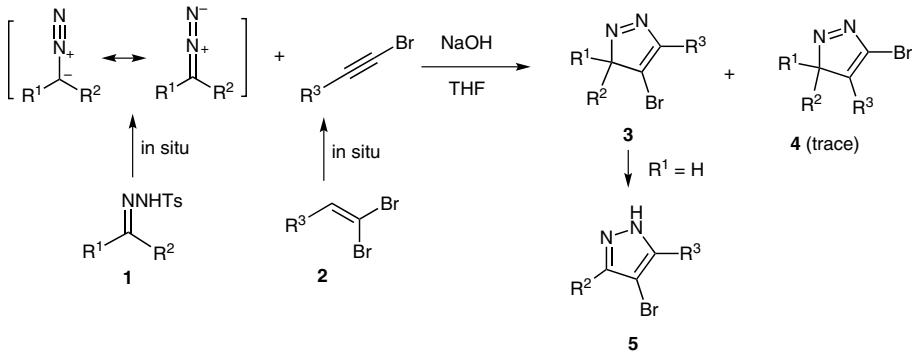
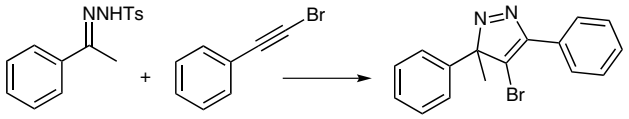


Scheme 1 1,3-Dipolar cycloaddition between substituted tosylhydrazones and *gem*-dibromoethenes

because the halogen atom provides an opportunity for further functionalization to form a variety of C–C, C–X (X = N, O, S, etc.) bonds.

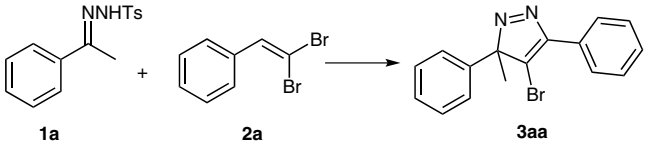
We initiated our studies by examining the reaction of acetophenone tosylhydrazone (**1a**) with 1-(2-bromoethynyl)benzene in dioxane with lithium *tert*-butoxide as the base (Scheme 2, conditions A). To our delight, the reaction proceeded with high regioselectivity and gave product **3aa** in 65% yield.



Scheme 2 The reaction of acetophenone tosylhydrazone (**1a**) with 1-(2-bromoethynyl)benzene: Conditions A: **1a** (0.3 mmol), 1-(2-bromoethynyl)benzene (0.3 mmol), LiO*t*-Bu (3 equiv), dioxane (3 mL), 110 °C, 10 h (65%). Conditions B: **1a** (0.3 mmol), 1-(2-bromoethynyl)benzene (0.3 mmol), NaOH (3 equiv), THF (3 mL), 80 °C, 10 h (84%)

Inspired by these results, we decided to replace alkynyl bromides by using inexpensive and easy prepared *gem*-dibromoalkenes. For the optimization of the reaction conditions, the cycloaddition between acetophenone tosylhydrazone (**1a**) and (2,2-dibromovinyl)benzene (**2a**) was selected as a model reaction (Table 1). The desired product **3aa** was obtained in 59% yield in dioxane with lithium *tert*-butoxide as the base (entry 2). Following this encouraging result, further optimization of the reaction conditions was performed. A series of bases, including potassium *tert*-butoxide, potassium carbonate, cesium carbonate, and sodium hydroxide, were screened first. With potassium *tert*-butoxide as the base instead of lithium *tert*-butoxide, the yield of **3aa** decreased from 59% to 42% (entry 3). When the reaction was carried out using potassium or cesium carbonate as the base, only trace amounts of **3aa** were detected (entries 1 and 5). Without the presence of a base, no reaction took place (entry 13). However, when sodium hydroxide was used, the yield of the product increased to 72% (entry 4). A range of solvents including toluene, tetrahydrofuran, 1,2-dichloroethane, and dioxane were then screened, and tetrahydrofuran was found to be most suitable (entries 6–8). Finally the reaction temperature and time were investigated and it was found that reaction at 80 °C for 10 hours gave the highest yield of **3aa** (entries 9–12). Using these conditions for the reaction of tosylhydrazone **1a** and 1-(2-bromoethynyl)benzene, the yield of **3aa** also increased to 84% (Scheme 2, conditions B).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	K_2CO_3	dioxane	110	12	trace
2	LiO*t*-Bu	dioxane	110	12	59
3	KO*t*-Bu	dioxane	110	12	42
4	NaOH	dioxane	110	12	72
5	Cs_2CO_3	dioxane	110	12	trace
6	NaOH	toluene	110	12	55
7	NaOH	THF	110	12	85
8	NaOH	DCE	110	12	trace
9	NaOH	THF	80	12	86
10	NaOH	THF	60	12	52
11	NaOH	THF	80	10	85
12	NaOH	THF	80	8	70
13	–	THF	80	10	NR

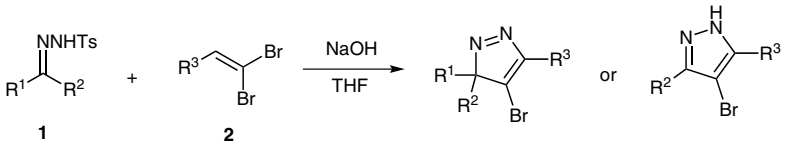
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), base (3 equiv), solvent (3 mL), under air.
[b] Isolated yields.

With the optimized conditions in hand, the scope of this cycloaddition reaction was investigated (Table 2). When ketone-derived hydrazones were used, both electron-neutral **2a** and electron-rich **2b** *gem*-dibromoalkenes gave

the desired products in good yields. For electron-deficient *gem*-dibromoalkenes, the type of electron-withdrawing group on the aromatic ring was important. Substrate bearing a weak electron-withdrawing group on the aromatic ring, such as chloro-substituted **2d**, still gave a high product yield. Substrates bearing strong electron-withdrawing groups on the aromatic ring, such as nitro-substituted **2c** and **2h**, gave much lower product yields. However, the yield of product increased to 84% when the reaction was carried out in dioxane with lithium *tert*-butoxide as the base. Heteroaromatic *gem*-dibromoalkenes **2e**–**g** were also tested in the reaction and gave good yields. The reaction also proceeded well with different tosylhydrazones **1b**–**e**. Then the use of the aldehyde hydrazones **1e**–**h** was examined, and isomerized products **5** were obtained in good yields. Various functional groups of the hydrazones and *gem*-dibromoalkenes were also investigated. The aromatic moiety tolerated electron-donating as well as electron-withdrawing groups (entries 12–18).

Tosylhydrazones **1** were prepared via condensation of tosylhydrazine and the corresponding aldehydes or ketones. If the tosylhydrazones **1** can be generated in situ, the procedure may simplified further. Therefore, we tried the cycloaddition reaction with (2,2-dibromovinyl)benzene (**2a**), tosylhydrazine, and acetophenone (**6a**) as the starting materials. Unfortunately, the desired product **3aa** was obtained in only 23% yield. Compared with the reaction of using hydrazones directly, the only difference is the generation of one equivalent of water during the condensation of the tosylhydrazine with a ketone or aldehyde to form the tosylhydrazone. Hence 4 Å molecular sieves were added to the reaction mixture to remove the in situ formed water. To our delight, the tandem reaction with (2,2-dibromovinyl)benzene (**2a**), tosylhydrazine, and acetophenone (**6a**) proceeded well and cycloaddition product **3aa** was obtained in 76% yield (Table 3, entry 1). Then electron-rich and electron-deficient ketones **6b** and **6c**

Table 2 1,3-Dipolar Cycloaddition between a Variety of Substituted Tosylhydrazones and *gem*-Dibromoethenes[a]

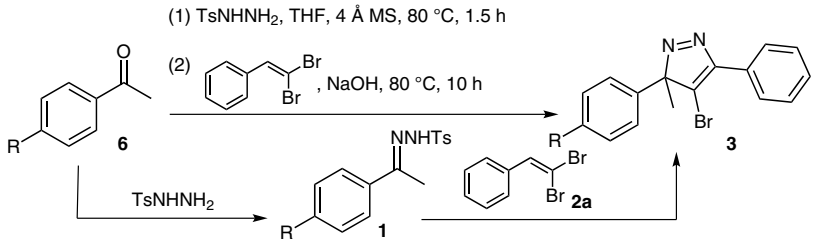


1 **2** **3** **5**

Entry	Hydrazone	R^1	R^2	*gem*-Dibromoalkene	R^3	Product	Yield[b] (%)
1	**1a**	Ph	Me	**2a**	Ph	**3aa**	85
2	**1a**	Ph	Me	**2b**	4-$MeOC_6H_4$	**3ab**	76
3	**1a**	Ph	Me	**2c**	4-$O_2NC_6H_4$	**3ac**	42 (84[b])
4	**1a**	Ph	Me	**2d**	4-ClC_6H_4	**3ad**	82
5	**1a**	Ph	Me	**2e**	2-pyridyl	**3ae**	75
6	**1a**	Ph	Me	**2f**	2-furyl	**3af**	86
7	**1a**	Ph	Me	**2g**	2-thienyl	**3ag**	81
8	**1a**	Ph	Me	**2h**	2-$O_2NC_6H_4$	**3ah**	48 (80[c])
9	**1b**	4-$MeOC_6H_4$	Me	**2a**	Ph	**3ba**	81
10	**1c**	Ph	Et	**2a**	Ph	**3ca**	83
11	**1d**	4-NCC_6H_4	Me	**2a**	Ph	**3da**	73
12	**1e**	Ph	H	**2a**	Ph	**5ea**	76
13	**1e**	Ph	H	**2b**	4-$MeOC_6H_4$	**5eb**	75
14	**1e**	Ph	H	**2c**	4-$O_2NC_6H_4$	**5ec**	79
15	**1e**	Ph	H	**2d**	4-ClC_6H_4	**5ed**	80
16	**1f**	4-ClC_6H_4	H	**2a**	Ph	**5fa**	67
17	**1g**	4-$Me_2NC_6H_4$	H	**2a**	Ph	**5ga**	78
18	**1h**	4-$MeOC_6H_4$	H	**2a**	Ph	**5ha**	81

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), NaOH (0.9 mmol), THF (3 mL), 80 °C, 10 h.
[b] Isolated yield.
[c] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), LiO*t*-Bu (0.9 mmol), dioxane (3 mL), 110 °C, 4 h.

Table 3 The Tandem Reaction of Carbonyl Compounds with *gem*-Dibromoalkenes[a]



Entry	Ketone	R	Product	Yield[b] (%)
1	**6a**	H	**3aa**	76 (23[c])
2	**6b**	OMe	**3ba**	78
3	**6c**	CN	**3da**	72

[a] Reaction conditions: ketone **6** (0.3 mmol), $TsNHNH_2$ (0.3 mmol), 4 Å MS (0.1 g), (2,2-dibromovinyl)benzene (**2a**) (0.3 mmol), NaOH (0.9 mmol), THF (3 mL), 80 °C.
[b] Isolated yields.
[c] Without the use of 4 Å MS.

were used, and the yields of products were also good (entries 2 and 3).

Theoretically, the reaction may give two products, **3** and **4** (Scheme 1). In order to make sure of the exact structure of the product, product **3ac** was selected as an example. Firstly, the structure of **3ac** was determined by 2D NMR HMBC techniques. It was found from the HMBC spectrum that there was correlation between H1 and C_a (designation as shown in Figure 1) and no correlation between H1 and C_b (for HMBC and NOESY spectra see the Supporting Information). If the product is another isomer **4ac**, there must be correlation between H1 and C_b, because these two atoms are three bonds apart (Figure 1). Then, the structure was further examined by the NOESY experiment. It was found that there were NOE correlations between H1 and H2 and no NOE correlations between H1 and H3 (Figure 1). The distance of H2, H3, and H4 to H1 in isomer **4ac** was then calculated according to Gaussian 03 package using the B3LYP method. Obviously, the distance of H1 to H3 (3.888 Å) is shorter than 5 Å (Figure 2). So if the product is the isomer **4ac**, there must be NOE correlations between H1 and H3. All the above discussion supported the structure of the product as isomer **3ac**.

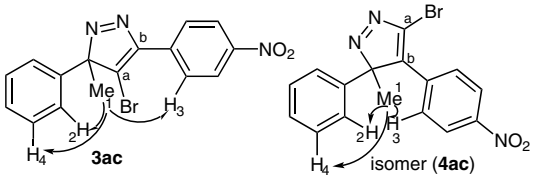


Figure 1 The structure of **3ac** and its potential isomer

Among the eighteen products, only **5ea** has been previously reported in literature. This could also give the evidence for the structure of the products. We synthesized **5ea** according to the literature method.[8,14] The ^1H and ^{13}C

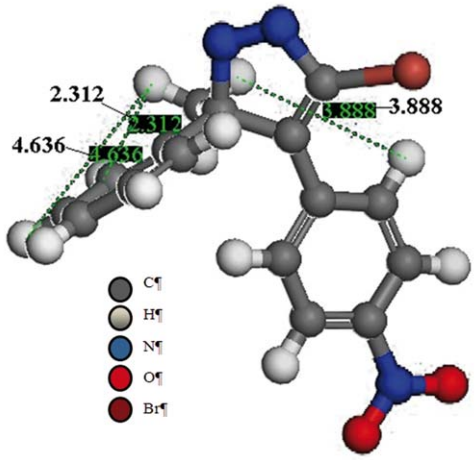


Figure 2 The calculated distance of hydrogen atoms of isomer **4ac**. Computations were performed according to Gaussian 03 package using the B3LYP method. The optimizations were performed without any symmetry restrictions using the default convergence criteria in the programs. The optimized structure was characterized to be true local energy minima on the potential energy surfaces without imaginary frequencies.

NMR spectra of **5ea** synthesized by the literature method were exactly the same as our sample (see the Supporting Information). We found that the ^{13}C spectra of **5ea** differed widely when using different solvents (see Figure 3 and the Supporting Information) as reported in literature.[18] When using DMSO-d_6, ten signals were present in the ^{13}C spectrum. However when using $CDCl_3$, only six signals were present. From the ^{13}C spectra, we drew the conclusion that there is fast tautomerism of **5ea** in $CDCl_3$ and slow tautomerism in DMSO-d_6.

In summary, a simple, highly efficient, and regioselective procedure for the synthesis of 3,5-diaryl-4-bromopyrazoles via the reaction of hydrazones and *gem*-dibromoalkenes was developed. The diazo compounds and 1-

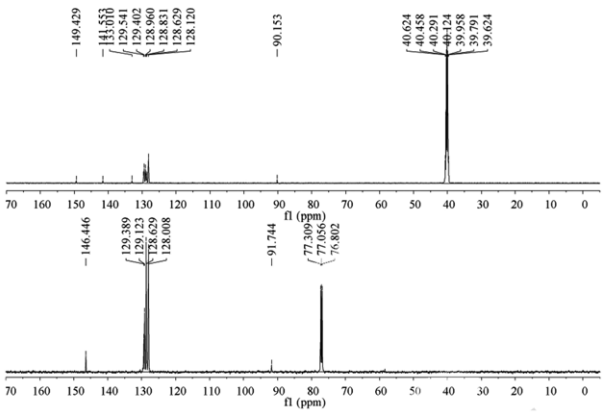


Figure 3 The different ^{13}C spectra of **5ea**

bromoalk-1-ynes were both generated in situ. The reaction may also be carried out in a tandem manner starting from a 1-bromoalk-1-yne, tosylhydrazine, and a ketone or aldehyde. The reaction system exhibits tolerance with various functional groups not only on the aromatic ring of the hydrazones but also on the aromatic ring of the *gem*-dibromoalkenes, and gives 3,5-diaryl-4-bromo-3*H*-pyrazoles or 3,5-diaryl-4-bromo-1*H*-pyrazoles with high regioselectivity and in good yields (67–86%). The structure of the product was determined by HMBC spectra and NOESY experiments. Studies on further applications of this methodology are now in progress.

All solvents were distilled prior to use. 1,4-Dioxane, toluene, and THF were dried over Na, DCE was dried over CaH_2, other chemicals (AR grade) were obtained from commercial sources and were used without further purification. Petroleum ether (PE) refers to the fraction bp 60–90 °C. The progress of the reactions was monitored by TLC (silica gel, Polygram SILG/UV 254 plates). Column chromatography was performed on Silicycle silica gel (200–300 mesh). Melting points were obtained using a Yamato melting point apparatus Model MP-21 and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX 500 (500 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard.

Tosylhydrazones 1; General Procedure[19]
A soln of pure $TsNHNH_2$ (1.72 g, 10 mmol) in MeOH (10 mL) was stirred at 60 °C until the $TsNHNH_2$ was completely dissolved. Then carbonyl compounds (10.5 mmol) were added dropwise slowly to the mixture, and it was then refluxed for 2 h. The mixture was allowed to cool to r.t.; the crude products were obtained as solid precipitates. The precipitates were washed with cold petroleum ether then dried to give the pure products. The general yield was ~80%.

(Dibromovinyl)benzene (2a); Typical Procedure[20]
To a stirred mixture of benzaldehyde (1.06 g, 10 mmol), CBr_4 (6.6 g, 20 mmol), and CH_2Cl_2 (25 mL) at 0 °C was added Ph_3P (10.5 g, 40 mmol) in portions over 15 min; the resulting brown-colored soln was stirred at 0 °C for 2 h. The reaction was quenched with petroleum ether (100 mL), the precipitate was filtered through silica gel pad, and the filtrate was evaporated. The crude product was further purified by column chromatography (silica gel, 1% EtOAc–PE) to give **2a** as a yellow liquid; yield: 2.27 g (87%).

1-(2,2-Dibromovinyl)-4-methoxybenzene (2b)[20]
White solid; yield: 2.84 g (98%); mp 37–38 °C.

1-(2,2-Dibromovinyl)-4-nitrobenzene (2c)[20]
Yellow solid; yield: 2.68 g (88%); mp 93–94 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.61 (d, *J* = 8.5 Hz, 2 H), 8.15 (d, *J* = 8.5 Hz, 2 H).

1-Chloro-4-(2,2-dibromovinyl)benzene (2d)[20]
Light green solid; yield: 2.23 g (76%); mp 35–36 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.5 Hz, 2 H), 7.43 (s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H).

4-Bromo-3-methyl-3,5-diphenyl-3*H*-pyrazole (3aa) by Cycloaddition of Acetophenone Tosylhydrazone (1a) with 1-(2-Bromoethynyl)benzene
A Schlenk tube with a magnetic stirrer bar charged with hydrazone **1a** (0.3 mmol), 1-(2-bromoethynyl)benzene (0.3 mmol), NaOH (0.9 mmol), and THF (3 mL). The system was heated at 80 °C with stirring for 10 h, The mixture was then allowed to cool to r.t., and diluted with EtOAc (20 mL), and washed with brine (15 mL), H_2O (15 mL), and then the organic layer was dried (Na_2SO_4). After concentrated in vacuo, the crude product was purified by column chromatography; yield: 78.7 mg (84%).

4-Bromo-3-methyl-3,5-diphenyl-3*H*-pyrazole (3aa) by Cycloaddition of Acetophenone Tosylhydrazone (1a) with 1-(2-Bromovinyl)benzene (2a); Typical Procedure
A Schlenk tube with a magnetic stir bar charged with hydrazone **1a** (0.3 mmol), 1-(2-bromovinyl)benzene (**2a**, 0.3 mmol), NaOH (0.9 mmol), and THF (3 mL). The system was heated at 80 °C with stirring for 10 h, The mixture was then allowed to cool to r.t., and diluted with EtOAc (20 mL), and washed with brine (15 mL) and H_2O (15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the crude product was purified by column chromatography; yield: 79.6 mg (85%).

4-Bromo-3-methyl-3,5-diphenyl-3*H*-pyrazole (3aa) by One-Pot Cycloaddition of Acetophenone (6a) with 1-(2-Bromovinyl)benzene (2a); Typical Procedure
A Schlenk tube with a magnetic stir bar charged with acetophenone (**6a**, 0.036 g, 0.3 mmol), $TsNHNH_2$ (0.056 g, 0.3 mmol), 4 Å MS (0.1 g), and THF (3 mL). The system was heated at 80 °C with stirring for 1.5 h, then NaOH (0.036 g, 0.9 mmol) and 1-(2,2-dibromovinyl)benzene (**2a**, 0.078 g, 0.3 mmol) were added, the mixture was heated at 80 °C with stirring for 10 h. The mixture was then allowed to cool to r.t., and diluted EtOAc (20 mL) and washed with brine (15 mL) and H_2O (15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the crude product was purified by column chromatography; yield: 71.2 mg (76%).

4-Bromo-3-methyl-3,5-diphenyl-3*H*-pyrazole (3aa)
Yellow solid; yield: 79.6 mg (85%); mp 47–50 °C; R_f = 0.55 (PE–EtOAc, 10:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 7.5 Hz, 2 H), 7.57–7.49 (m, 3 H), 7.39–7.36 (m, 3 H), 7.22 (dd, *J* = 7.9, 1.9 Hz, 2 H), 1.91 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.47, 136.67, 133.01, 129.78, 129.69, 128.99, 128.75, 128.38, 128.05, 126.25, 100.81, 19.69.

GC-MS (EI, 70 eV): *m*/*z* = 311.9.

Anal. Calcd for $C_{16}H_{13}BrN_2$ (312.03): C, 61.36; H, 4.18; N, 8.94. Found: C, 61.52; H, 4.21; N, 8.89.

4-Bromo-5-(4-methoxyphenyl)-3-methyl-3-phenyl-3*H*-pyrazole (3ab)
Yellow solid; yield: 78.0 mg (76%); mp 84–87 °C; R_f = 0.37 (PE–EtOAc, 10:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 7.5 Hz, 2 H), 7.39–7.35 (m, 3 H), 7.22 (d, *J* = 7.5 Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 3.90 (s, 3 H), 1.89 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.69, 149.29, 134.04, 133.44, 129.69, 129.03, 128.72, 126.37, 122.49, 114.28, 100.63, 55.50, 19.86.

GC-MS (EI, 70 eV): *m*/*z* = 341.9.

Anal. Calcd for $C_{17}H_{15}BrN_2O$ (342.04): C, 59.49; H, 4.41; N, 8.16. Found: C, 59.56; H, 4.43; N, 8.09.

4-Bromo-3-methyl-5-(4-nitrophenyl)-3-phenyl-3*H*-pyrazole (3ac)
Yellow solid; yield: 89.9 mg (84%); mp 154–157 °C; R_f = 0.34 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.5 Hz, 2 H), 8.37 (d, *J* = 8.5 Hz, 2 H), 7.40–7.37 (m, 3 H), 7.19–7.17 (m, 2 H), 1.91 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.00, 147.47, 141.04, 135.84, 132.31, 129.18, 129.08, 128.81, 126.17, 123.99, 101.88, 19.76.

GC-MS (EI, 70 eV): *m*/*z* = 356.8.

Anal. Calcd for $C_{16}H_{12}BrN_3O_2$ (357.01): C, 53.65; H, 3.38; N, 11.73. Found: C, 54.54; H, 3.46; N, 11.82.

4-Bromo-5-(4-chlorophenyl)-3-methyl-3-phenyl-3*H*-pyrazole (3ad)
Yellow liquid; yield: 85.1 mg (82%); R_f = 0.62 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34–8.33 (m, 2 H), 7.53–7.53 (m, 2 H), 7.39–7.37 (m, 3 H), 7.22–7.20 (m, 2 H), 1.90 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.45, 137.12, 135.66, 132.82, 129.32, 129.20, 129.05, 128.84, 128.25, 126.22, 101.10, 19.72.

GC-MS (EI, 70 eV): *m*/*z* = 345.8.

Anal. Calcd for $C_{16}H_{12}BrClN_2$ (345.99): C, 55.28; H, 3.48; N, 8.06. Found: C, 55.41; H, 3.45; N, 7.93.

4-Bromo-3-methyl-3-phenyl-5-(2-pyridyl)-3*H*-pyrazole (3ae)
Brown liquid; yield: 70.4 mg (75%); R_f = 0.22 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.84–8.82 (m, 1 H), 8.41 (d, *J* = 8 Hz, 1 H), 7.91–7.88 (m, 1 H), 7.42–7.34 (m, 4 H), 7.23–7.21 (m, 2 H), 1.91 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.94, 149.26, 149.20, 141.23, 137.15, 132.72, 129.12, 128.93, 126.41, 124.13, 123.94, 101.40, 19.81.

GC-MS (EI, 70 eV): *m*/*z* = 312.8.

Anal. Calcd for $C_{15}H_{12}BrN_3$ (313.02): C, 57.34; H, 3.85; N, 13.37. Found: C, 57.44; H, 3.91; N, 13.33.

4-Bromo-5-(2-furyl)-3-methyl-3-phenyl-3*H*-pyrazole (3af)
Brown liquid; yield: 77.9 mg (86%); R_f = 0.55 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.67 (m, 1 H), 7.39–7.33 (m, 4 H), 7.23–7.20 (m, 2 H), 6.64–6.63 (m, 1 H), 1.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.82, 144.20, 143.52, 133.06, 132.27, 129.00, 128.76, 126.28, 112.74, 111.86, 100.51, 19.91.

GC-MS (EI, 70 eV): *m*/*z* = 301.8.

Anal. Calcd for $C_{14}H_{11}BrN_2O$ (302.01): C, 55.47; H, 3.66; N, 9.24. Found: C, 55.53; H, 3.71; N, 9.27.

4-Bromo-3-methyl-3-phenyl-5-(2-thienyl)-3*H*-pyrazole (3ag)
Gray solid; yield: 77.3 mg (81%); mp 115–117 °C; R_f = 0.54 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 3.5 Hz, 1 H), 7.58–7.56 (m, 1 H), 7.40–7.36 (m, 3 H), 7.27–7.23 (m, 3 H), 1.91 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.47, 133.37, 132.33, 129.11, 128.86, 128.23, 127.92, 126.39, 100.89, 20.11.

GC-MS (EI, 70 eV): *m*/*z* = 317.8.

Anal. Calcd for $C_{14}H_{11}BrN_2S$ (317.98): C, 52.68; H, 3.47; N, 8.78. Found: C, 52.59; H, 3.55; N, 8.91.

4-Bromo-3-methyl-5-(2-nitrophenyl)-3-phenyl-3*H*-pyrazole (3ah)
Gray solid; yield: 85.7 mg (80%); mp 133–136 °C; R_f = 0.19 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23–8.21 (m, 1 H), 7.80–7.77 (m, 1 H), 7.75–7.73 (m, 1 H), 7.70–7.67 (m, 1 H), 7.44–7.38 (m, 3 H), 7.31–7.27 (m, 2 H), 1.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.64, 148.61, 140.38, 133.58, 132.40, 132.17, 130.78, 129.25, 129.07, 126.45, 125.37, 125.25, 100.43, 19.26.

GC-MS (EI, 70 eV): *m*/*z* = 356.9.

Anal. Calcd for $C_{16}H_{12}BrN_3O_2$ (357.01): C, 53.65; H, 3.38; N, 11.73. Found: C, 53.58; H, 3.39; N, 11.80.

4-Bromo-3-(4-methoxyphenyl)-3-methyl-5-phenyl-3*H*-pyrazole (3ba)
Yellow liquid; yield: 83.1 mg (81%); R_f = 0.40 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 7 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 2 H), 7.50 (t, *J* = 7 Hz, 1 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 6.91 (d, *J* = 9 Hz, 2 H), 3.81 (s, 3 H), 1.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.85, 149.16, 136.98, 129.84, 129.68, 128.77, 128.03, 127.56, 114.38, 100.52, 55.34, 19.76.

GC-MS (EI, 70 eV): *m*/*z* = 341.8.

Anal. Calcd for $C_{17}H_{15}BrN_2O$ (342.04): C, 59.49; H, 4.41; N, 8.16. Found: C, 59.53; H, 4.46; N, 8.11.

4-Bromo-3-ethyl-3,5-diphenyl-3*H*-pyrazole (3ca)
Yellow solid; yield: 81.2 mg (83%); mp 50–53 °C; R_f = 0.55 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40–8.38 (m, 2 H), 7.58–7.55 (m, 2 H), 7.53–7.50 (m, 1 H), 7.39–7.36 (m, 3 H), 7.32–7.30 (m, 2 H), 3.01–2.94 (m, 1 H), 2.37–2.30 (m, 1 H), 0.71 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.55, 134.92, 133.63, 129.89, 129.79, 129.07, 128.86, 128.73, 128.21, 126.64, 104.22, 27.48, 7.50.

GC-MS (EI, 70 eV): *m*/*z* = 325.9.

Anal. Calcd for $C_{17}H_{15}BrN_2$ (326.04): C, 62.40; H, 4.62; N, 8.56. Found: C, 62.56; H, 4.54; N, 8.49.

4-(4-Bromo-3-methyl-5-phenyl-3*H*-pyrazol-3-yl)benzonitrile (3da)
Yellow solid; yield: 73.8 mg (73%); mp 45–47 °C; R_f = 0.22 (PE–EtOAc, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37–8.34 (m, 2 H), 7.68–7.67 (m, 2 H), 7.55–7.51 (m, 3 H), 7.35–7.33 (m, 2 H), 1.90 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.43, 138.50, 135.14, 12.86, 130.20, 129.36, 128.98, 128.20, 127.31, 118.37, 112.37, 100.25, 19.90.

GC-MS (EI, 70 eV): *m*/*z* = 336.8.

Anal. Calcd for $C_{17}H_{12}BrN_3$ (337.02): C, 60.37; H, 3.58; N, 12.42. Found: C, 60.46; H, 3.62; N, 12.33.

4-Bromo-3,5-diphenyl-1*H*-pyrazole (5ea)
White solid; yield: 67.9 mg (76%); mp 207–208 °C (Lit.[14] 199–200 °C, Lit.[15] 195 °C); R_f = 0.38 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79–7.78 (m, 4 H), 7.45–7.41 (m, 6 H), 5.16 (s, 1 H).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.75 (s, 1 H), 7.85–7.76 (m, 4 H), 7.55–7.41 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.45, 129.39, 129.12, 128.63, 128.01, 91.74.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 149.43, 141.53, 133.01, 129.54, 129.40, 128.96, 128.83, 128.63, 128.12.

GC-MS (EI, 70 eV): *m*/*z* = 298.0.

Anal. Calcd for $C_{15}H_{11}BrN_2$ (298.01): C, 60.22, H, 3.71, N, 9.36. Found: C, 60.31; H, 3.68; N, 9.29.

4-Bromo-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (5eb)
White solid; yield: 73.8 mg (75%); mp 204–207 °C; R_f = 0.22 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.63 (s, 1 H), 7.85–7.70 (m, 4 H), 7.53–7.41 (m, 3 H), 7.09–7.05 (m, 2 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.29, 159.72, 149.29, 141.45, 133.13, 129.41, 128.94, 128.56, 128.08, 125.46, 121.16, 114.84, 114.41, 89.85, 89.61, 55.82.

GC-MS (EI, 70 eV): *m*/*z* = 328.0.

Anal. Calcd for $C_{16}H_{13}BrN_2O$ (328.02): C, 58.38; H, 3.98; N, 8.51. Found: C, 58.51; H, 4.01; N, 3.89.

4-Bromo-5-(4-nitrophenyl)-3-phenyl-1*H*-pyrazole (5ec)
Yellow solid; yield: 81.3 mg (79%); mp 221–224 °C; R_f = 0.30 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 14.06 (s, 1 H), 8.37–8.31 (m, 2 H), 8.17–8.05 (m, 2 H), 7.83–7.74 (m, 2 H), 7.55–7.48 (m, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.08, 149.46, 147.73, 147.37, 147.18, 142.34, 139.39, 134.91, 132.58, 129.76, 129.42, 128.99, 128.65, 128.26, 126.38, 125.76, 124.58, 124.30, 90.75.

GC-MS (EI, 70 eV): *m*/*z* = 343.0.

Anal. Calcd for $C_{15}H_{10}BrN_3O_2$ (343.00): C, 52.35; H, 2.93; N, 12.21. Found: C, 52.44; H, 2.99; N, 12.08.

4-Bromo-5-(4-chlorophenyl)-3-phenyl-1*H*-pyrazole (5ed)
White solid; yield: 79.7 mg (80%); mp 226–230 °C; R_f = 0.43 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.83 (s, 1 H), 7.88–7.76 (m, 4 H), 7.61–7.48 (m, 5 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 149.59, 148.23, 141.80, 140.43, 134.32, 133.40, 132.87, 131.84, 129.68, 129.41, 129.08, 128.68, 127.64, 127.36, 125.69, 90.18.

GC-MS (EI, 70 eV): *m*/*z* = 332.0.

Anal. Calcd for $C_{15}H_{10}BrClN_2$ (331.97): C, 54.00; H, 3.02; N, 8.40. Found: C, 53.87; H, 3.08; N, 8.43.

4-Bromo-3-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole (5fa)
White solid; yield: 66.7 mg (67%); mp 210–213 °C; R_f = 0.40 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.83 (s, 1 H), 7.89–7.74 (m, 4 H), 7.64–7.42 (m, 5 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 149.47, 148.13, 141.71, 140.34, 134.21, 133.30, 131.73, 129.77, 129.35, 129.01, 128.57, 128.08, 127.52.

GC-MS (EI, 70 eV): *m*/*z* = 332. 0.

Anal. Calcd for $C_{15}H_{10}BrClN_2$ (331.97): C, 54.00; H, 3.02; N, 8.40. Found: C, 53.89; H, 3.07; N, 8.47.

4-(4-Bromo-5-phenyl-1*H*-pyrazol-3-yl)-*N*,*N*-dimethylaniline (5ga)
Yellow solid; yield: 79.8 mg (78%); mp 196–200 °C; R_f = 0.23 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.49 (s, 1 H), 7.86–7.64 (m, 4 H), 7.48–7.40 (m, 3 H), 6.815 (d, *J* = 8 Hz, 2 H), 2.94 (s, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.92, 149.07, 141.93, 133.21, 129.29, 128.82, 128.69, 128.39, 127.96, 115.92, 112.40, 88.68, 60.25.

GC-MS (EI, 70 eV): *m*/*z* = 341.1.

Anal. Calcd for $C_{11}H_{16}BrN_3$ (341.05): C, 59.66; H, 4.71; N, 12.28. Found: C, 59.54; H, 4.73; N, 12.17.

4-Bromo-3-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole (5ha)
White solid; yield: 79.7 mg (81%); mp 205–208 °C; R_f = 0.24 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.67 (s, 1 H), 7.84–7.77 (m, 4 H), 7.50–7.42 (m, 3 H), 7.07 (d, *J* = 7 Hz, 2 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.05, 149.11, 141.44, 133.09, 131.99, 129.49, 129.11, 128.09, 121.16, 114.63, 89.75, 55.76.

GC-MS (EI, 70 eV): *m*/*z* = 328.0.

Anal. Calcd for $C_{16}H_{13}BrN_2O$ (328.02): C, 58.38; H, 3.98, N, 8.51. Found: C, 58.51; H, 4.01; N, 3.89.

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

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