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Synthesis of β-tosylethylhydrazine and its use in preparation of N-protected pyrazoles and 5-aminopyrazoles

David M. Dastrup,[a] Amy H. Yap,[a] Steven M. Weinreb,[a,*] James R. Henry[b,*] and Andrew J. Lechleiter[b]

[a]*Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA*
[b]*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*

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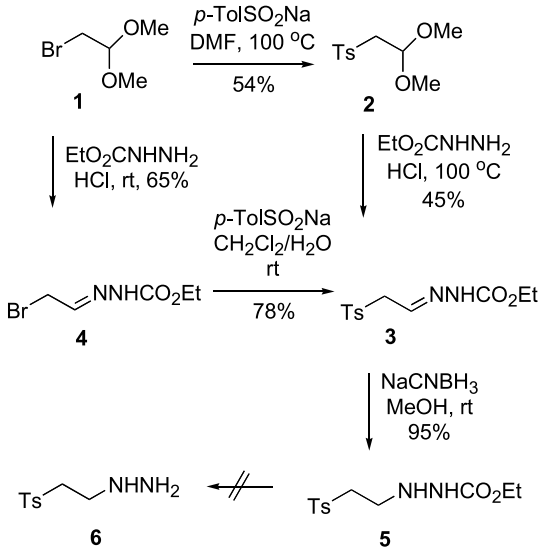
Abstract—β-Tosylethylhydrazine (**6**) can be prepared efficiently in one step from commercially available *p*-tolyl vinyl sulfone (**7**) and hydrazine hydrate. This hydrazine reacts with both 1,3-diketones and conjugated ynones in glacial acetic acid to provide a variety of N-tosylethyl-protected (TSE) pyrazoles in good yields. The TSE group can be removed from the pyrazoles using potassium *t*-butoxide in THF at −30 °C–rt. In addition, hydrazine **6** condenses with β-ketonitriles and β-aminoacrylonitriles to afford 5-aminopyrazoles, which can be deprotected by brief treatment with NaOEt in EtOH/DMSO at 45 °C.

1. Introduction

A few years ago we demonstrated that the β-tosylethyl group (TSE) is useful in N-protection of various types of amides, carbamates and lactams (including β-lactams), and can be removed via a β-elimination upon treatment with potassium *t*-butoxide in THF under mild conditions.[1] This protecting group can be easily introduced using the readily prepared reagent β-tosylethylamine.[1a,b] We subsequently described the synthesis of β-tosylethylhydroxylamine and its use in synthesis of TSE-protected γ-lactams via our amidyl radical cyclization methodology.[1c] In addition, a few scattered examples have appeared on the use of the TSE and β-phenylsulfonylethyl groups for N-protection of heteroaromatics including tetrazoles,[2a] pyrroles,[2b] imidazoles,[2c] and indoles.[3d] In these cases, the protecting groups were usually installed onto a preformed heterocycle. In the latter example, the N-protection could also be effected prior to indole ring construction.[2d] Once again, TSE removal is effected in these cases with various bases. In this article we describe a new extension of our work which involves the synthesis of β-tosylethylhydrazine (**6**)[3] and its application to synthesis of TSE-protected pyrazoles and 5-aminopyrazoles.[4]

2. Results and discussion

The initial approach to this hydrazine was patterned after our synthesis of β-tosylethylhydroxylamine.[2c] Thus, commercially available bromo acetal **1** reacts with sodium *p*-toluenesulfinate to afford sulfone acetal **2** in 54% yield (Scheme 1).[5] Treatment of acetal **2** with ethyl carbazate under aqueous acidic conditions then leads directly to acylhydrazone **3** (45%). A more efficient variation of this route was also developed which involved initial conversion of bromo acetal **1** to acylhydrazone **4** (65%), which reacts with sodium *p*-toluenesulfinate to produce sulfone intermediate **3** in 78% yield. It was then possible to reduce hydrazone **3** with sodium cyanoborohydride to *N*-carbamoylhydrazine **5** in high yield. Unfortunately, despite some



Scheme 1.

Keywords: Protecting groups; Nitrogen heterocycles.
* Corresponding authors. Tel.: +1-814-8630189; fax: +1-814-8638403; e-mail address: smw@chem.psu.edu

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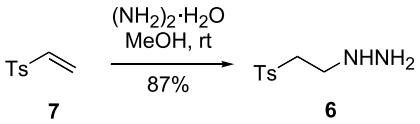
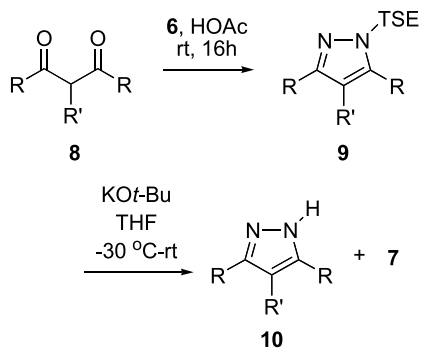
effort the acyl group of **5** could not be removed hydrolytically to afford the desired TSE–hydrazine (**6**).[6]

We therefore turned to an alternative route for preparation of the requisite hydrazine **6** which proved to be simpler and considerably more efficient than the one attempted above. Thus, by analogy with the work of Hill and Vederas,[7] commercially available tosyl vinyl sulfone (**7**)[8] was found to react smoothly with hydrazine hydrate in methanol at room temperature for about 15 min to afford **6** in a single step (Eq. 1).



(1)

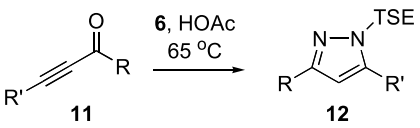
Two equivalents of hydrazine hydrate are used here in order to minimize dialkylation. Hydrazine **6** is rather difficult to purify but the crude material is sufficiently pure for use directly in the condensation reactions.



Scheme 2.

Two well known types of condensations were investigated for construction of the N-TSE-protected pyrazoles.[4] In the first series, TSE-hydrazine (**6**) was found to combine with 1,3-diketones **8** in glacial acetic acid at room temperature to generate the pyrazoles **9** in good yields (Scheme 2). Since this condensation is known to generally produce regioisomeric mixtures of pyrazoles with most unsymmetrical 1,3-diketones,[4a] the reaction was tested with a series of symmetrical substrates as outlined in Table 1.

These pyrazoles can be deprotected by treatment with potassium *t*-butoxide in THF starting at −30 °C and allowing the reaction mixture slowly warm to room temperature. In general, the yields of deprotected pyrazoles **10** were good, as is shown in Table 1. The vinyl sulfone **7** by-product appears to polymerize under these reaction conditions.



(2)

In addition, conjugated ynones are also known to condense with hydrazines, often producing pyrazoles regioselectively depending upon the substrate and reaction conditions.[9] It was found that TSE-hydrazine (**6**) reacts with ynones **11** in glacial HOAc, but the condensations require higher temperatures (65 °C) than the 1,3-diketones to produce the pyrazoles **12** (Eq. 2). This pyrazole synthesis has been explored with a few different ynone systems and the results are listed in Table 2. In the case of ynone **11a**, it was found that a single regioisomeric pyrazole **12a** was formed whose structure was proven by X-ray crystallography.[10] The

Table 1. Preparation of TSE-protected pyrazoles from TSE–$NHNH_2$/1,3-diketones, and deprotection with KO–*t*-Bu/THF

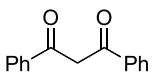
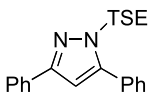
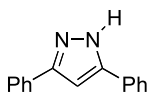
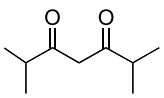
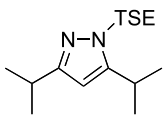
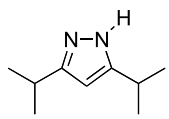
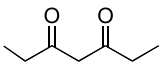
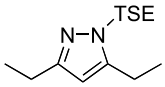
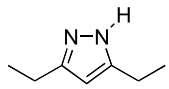
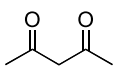
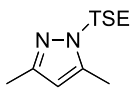
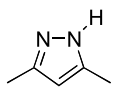
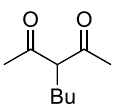
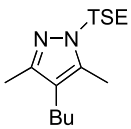
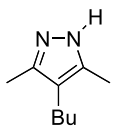
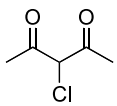
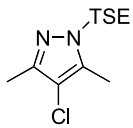
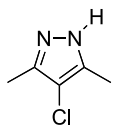
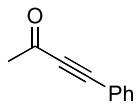
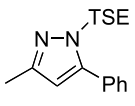
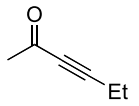
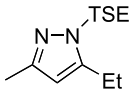
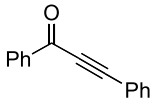
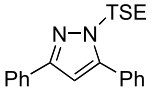
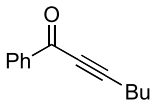
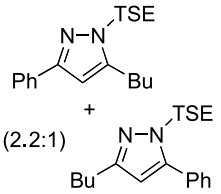
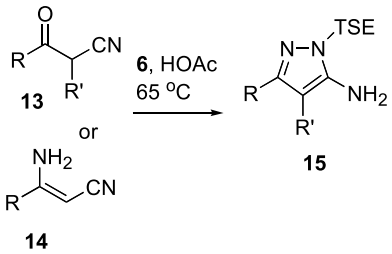
Entry	1,3-Diketone **8**	TSE-protected pyrazole **9**	Isolated yield (%)	Deprotected pyrazole **10**	Isolated yield (%)
a			81		89
b			77		80
c			86		71
d			89		68
e			92		75
f			69		81

Table 2. Preparation of TSE-protected pyrazoles from TSE–$NHNH_2$ and ynones

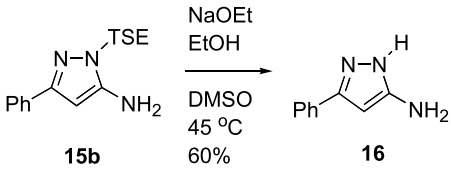
Entry	Ynone **11**	TSE-protected pyrazole **12**	Isolated yield (%)
a			92
b			59
c			62
d			84



Scheme 3.

regiochemistry of the protected pyrazole **12b** was established to be as shown by ^{1}H NMR NOE experiments. With the ynone in entry d, however, an inseparable 2.2:1 mixture of regioisomeric pyrazoles was formed.

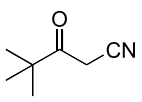
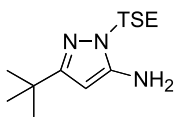
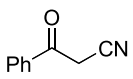
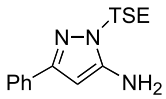
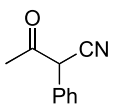
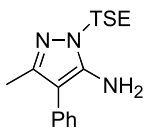
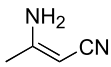
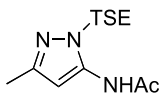
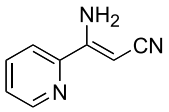
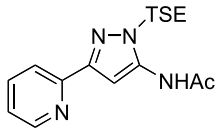
In addition, β-ketonitriles **13** react with hydrazine **6** to produce 5-aminopyrazoles **15** (Scheme 3). Alternatively, β-aminoacrylonitriles **14** can also be used in this reaction. Several substrates were screened in this reaction and the results are listed in Table 3. For the compounds in entries d and e, it was best to N-acetylate the crude, highly polar products with acetyl chloride before chromatographic purification. The deprotection of these products is sluggish, perhaps due to additional acidic protons within the molecules, and does not proceed using the conditions described above for the pyrazoles. However, if the deprotection of TSE-substituted aminopyrazole **15b** is conducted with two equivalents of 1 M NaOEt in ethanol using DMSO as solvent at 45 °C for 30 min, the parent 5-aminopyrazole **16** is produced (Eq. 3).



(3)

In conclusion, a convenient one-step synthesis of β-tosylethylhydrazine (**6**) has been developed from *p*-tolyl vinyl sulfone (**7**). This hydrazine condenses with both β-diketones and alkynyl ketones to directly afford TSE-protected pyrazoles, often with good regioslectivity in the latter case. Similarly, TSE-protected 5-aminopyrazoles can be prepared regioselectively by condensation of **6** with either β-ketonitriles or β-aminoacrylonitriles. The N-TSE protecting

Table 3. Preparation of TSE-protected 5-aminopyrazoles

Entry	β-Ketonitrile **13** or β-aminoacrylate **14**	TSE-protected 5-aminopyrazole **15**	Isolated yield (%)
a			58
b			50
c			70
d			88[a]
e			78[a]

[a] For ease of isolation the condensation product was converted to the *N*-acetyl derivative before purification.

group on the heterocycles produced in these reactions can be removed by exposure to base under mild conditions.

3. Experimental

3.1. Data for compounds

3.1.1. 1-(2,2-Dimethoxyethyl)-(*p*-tolyl)sufone (2). To a solution of sodium *p*-toluenesulfinate (2.00 g, 11.2 mmol) in DMF (32 mL) was added bromoacetaldehyde dimethyl acetal (**1**, 1.06 mL, 9.35 mmol). The resulting solution was stirred overnight at 100 °C, cooled to rt, and diluted with ether (30 mL). The ether layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the known tosyl acetal **2**[6] as pale yellow solid (1.33 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J=6.6, 1.7 Hz, 2H), 7.34 (d, J=7.9 Hz, 2H), 4.85 (t, J=5.3 Hz, 1H), 3.40 (d, J=5.3 Hz, 2H), 3.23 (s, 6H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 137.1, 129.8, 128.4, 99.3, 59.0, 53.6, 21.8.

3.1.2. *N*′-(2-Bromoethylidene)-hydrazinecarboxylic acid ethyl ester (4). To a solution of ethyl carbazate (9.01 g, 86.6 mmol) in aqueous HCl (1 M, 300 mL) was added bromoacetaldehyde dimethyl acetal (**1**, 5.00 mL, 43.3 mmol). The solution was stirred overnight, and was extracted with CH_2Cl_2. The extract was dried with $MgSO_4$, and concentrated in vacuo to afford the bromide **4** as a white solid (5.87 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of geometric isomers) δ 8.05 (br s, 1H), 7.24 (br s, 1H), 4.28 (m, 2H), 4.21 (d, J=5.8 Hz, 1.2H), 4.08 (d, J=6.2 Hz, 0.8H), 1.30 (m, 3H); HRMS ($C_5H_9BrN_2O_2$) calcd 208.9926 (MH^+), found 208.9914.

3.1.3. *N*′-[2-(*p*-Tosyl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (3). Sodium *p*-toluenesulfinate (7.45 g, 41.8 mmol) was added in one portion to the bromide **4** (5.83 g, 27.9 mmol) in CH_2Cl_2–H_2O (1:1, 100 mL). The mixture was stirred rapidly at rt overnight, diluted with H_2O, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated in vacuo to give the hydrazone **3** as a light yellow solid (6.18 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) (mixture of geometric isomers) δ 8.35 (br s, 1H), 7.74 (m, 2H), 7.33 (m, 3H), 4.24 (m, 2H), 4.09 (m, 2H), 2.44 (m, 3H), 1.27 (m, 3H).

Alternatively, a solution of sulfone **2** (2.40 g, 10.1 mmol) and ethyl carbazate (3.15 g, 104.1 mmol) in aqueous HCl (1 M, 60 mL) was heated for 6 h at 100 °C. After the solution was cooled the precipitated hydrazone was removed by filtration as a light yellow solid (1.30 g, 45%).

3.1.4. *N*′-[2-(*p*-Tosyl)-ethyl]-hydrazinecarboxylic acid ethyl ester (5). To a solution of hydrazone **3** (1.29 g, 4.54 mmol) and a trace of methyl orange in methanol (17 mL) at 0 °C was added sodium cyanoborohydride (570 mg, 9.08 mmol). The pH was adjusted periodically to the red–yellow transition point (pH 3.2–4.4) by addition of 25% HCl in methanol (prepared from acetyl chloride/MeOH). The reaction was followed by TLC (ethyl acetate/hexanes, 7/3), until the hydrazone was consumed (~1 h). The solution was basified with 1 M NaOH and extracted with Et_2O. The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ethyl acetate/hexanes, 7/3) to give the hydrazine ethyl ester **5** as a white solid, mp 85–89 °C (1.23 g, 95%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.82 (d, J=8.3 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 6.20 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.48 (s, 1H), 3.27 (m, 4H), 2.45 (s, 3H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 145.0, 136.2, 130.0, 128.1, 61.6, 54.7, 45.5, 21.7, 14.6; HRMS ($C_{12}H_{18}N_2O_4S$) calcd 287.1066 (MH^+), found 287.1065.

3.1.5. [2-(*p*-Tosyl)-ethyl]-hydrazine (6). To a rapidly stirred solution of hydrazine monohydrate (107 μL, 2.20 mmol) in methanol (4 mL) was added dropwise a solution of *p*-tolyl vinyl sulfone (**7**) (200 mg, 1.10 mmol) in methanol (4 mL). After stirring for 15 min at rt, the solution was diluted with H_2O and extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. The resulting thick colorless oil was used immediately without further purification (204 mg, 87%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.76 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 3.36 (s, 3H), 3.30 (m, 2H), 3.11 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.6, 130.3, 128.5, 54.4, 47.9, 22.0; HRMS ($C_9H_{14}N_2O_2S$) calcd 215.0842 (MH^+), found 215.0848.

3.2. General procedure for the formation of TSE-protected pyrazoles 9 from 1,3-diketones 8

A solution of TSE–$NHNH_2$ (**6**, 154 mg, 0.719 mmol) and 1,3-diketone **8** (0.497 mmol) in glacial acetic acid (4 mL) was stirred at rt for 16 h. The solution was concentrated in vacuo and the residue was purified by flash silica gel chromatography (ethyl acetate/hexanes, 3/7) to give the corresponding TSE-protected pyrazole **9** (Table 1).

3.2.1. 3,5-Diphenyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9a/12c). Gummy yellow foam (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.17 (m, 14H), 6.48 (s, 1H), 4.51 (m, 2H), 3.78 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 145.4, 145.0, 136.0, 133.0, 130.0, 129.1, 128.9, 128.7, 128.4, 128.0, 127.9, 125.6, 103.8, 55.4, 43.5, 21.6; HRMS ($C_{24}H_{22}N_2O_2S$) calcd 403.1480 (MH^+), found 403.1468.

3.2.2. 3,5-Diphenyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9b). White solid (77% yield); mp 76–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.6 (m, 2H), 7.31–7.28 (m, 2H), 5.72 (s, 1H), 4.38–4.34 (m, 2H), 3.72–3.67 (m, 2H), 2.98–2.87 (m, 1H), 2.81–2.70 (m, 1H), 2.41 (s, 3H), 1.22–1.20 (m, 6H), 1.13–1.11 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 150.4, 145.3, 136.6, 130.3, 128.5, 99.0, 56.2, 42.2, 28.3, 25.6, 23.1, 22.1; HRMS ($C_{18}H_{26}N_2O_2S$) calcd 335.1788 (MH^+), found 335.1770.

3.2.3. 3,5-Diethyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9c). Yellow oil (86% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.29 (m, 2H), 5.72 (s, 1H), 4.33 (m, 2H), 3.65 (m, 2H), 2.56 (m, 2H), 2.44 (m, 5H), 1.22 (t, J=7.5 Hz, 3H), 1.11 (t, J=7.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.6, 145.6, 145.0, 136.4, 130.0, 127.9, 102.0, 55.8, 42.0,

21.8, 21.5, 18.8, 13.9, 12.9; HRMS ($C_{16}H_{22}N_2O_2S$) calcd 307.1475 (MH^+), found 307.1487.

3.2.4. 3,5-Dimethyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9d). White solid (89% yield). Mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 5.68 (s, 1H), 4.33 (m, 2H), 3.65 (m, 2H), 2.42 (s, 3H), 2.23 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 144.9, 139.4, 136.2, 129.9, 127.8, 105.4, 55.6, 41.9, 21.7, 13.4, 10.9; HRMS ($C_{14}H_{18}N_2O_2S$) calcd 279.1167 (MH^+), found 279.1141.

3.2.5. 4-Butyl-3,5-dimethyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9e). Pale yellow solid (92% yield); mp 81–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.33 (m, 2H), 3.65 (m, 2H), 2.42 (s, 3H), 2.22 (t, J=7.1 Hz, 2H), 2.14 (s, 3H), 2.00 (s, 3H), 1.33–1.26 (m, 4H), 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 144.8, 136.2, 136.1, 129.8, 127.8, 117.0, 55.6, 42.1, 33.1, 23.2, 22.5, 21.7, 14.1, 11.8, 9.5; HRMS ($C_{18}H_{26}N_2O_2S$) calcd 335.1793 (MH^+), found 335.1770.

3.2.6. 4-Chloro-3,5-dimethyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (9f). White solid (69% yield); mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (d, J=8.1 Hz, 2H), 7.29–7.27 (d, J=8.1 Hz, 2H), 4.35–4.31 (m, 2H), 3.71–3.67 (m, 2H), 2.43 (s, 3H), 2.12 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 144.9, 135.9, 129.7, 127.6, 107.9, 55.1, 43.0, 21.7, 11.2, 9.3; HRMS ($C_{14}H_{17}N_2O_2SCl$) calcd 313.0757 (MH^+), found 313.0772.

3.3. General procedure for deprotection of TSE-protected pyrazoles

To a solution of a TSE protected pyrazole **9** (0.107 mmol) in THF (5 mL) at −30 °C was added *t*-BuOK (428 μL, 1 M in THF). The solution was warmed slowly to rt, and stirred for an additional 1 h. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ethyl acetate/hexanes, 2/3) to give the deprotected pyrazole **10** (Table 1).

3.4. General procedure for the formation of TSE-protected pyrazoles 12 from ynones 11

A solution of TSE–$NHNH_2$ (**6**, 154 mg, 0.719 mmol) and ynone **11** (0.497 mmol) in glacial acetic acid (4 mL) was stirred at 65 °C for 14 h. The solution was concentrated in vacuo and the residue was purified by flash silica gel chromatography (ethyl acetate/hexanes, 3/7) to give the corresponding TSE-protected pyrazole **12** (Table 2).

3.4.1. 5-Phenyl-3-methyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (12a). White solid, mp 89–92 °C (92% yield). A sample for X-ray analysis was crystallized from CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.18 (m, 9H), 5.92 (s, 1H), 4.33 (m, 2H), 3.58 (m, 2H), 2.35 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 145.0, 144.9, 136.0, 130.2, 130.0, 129.1, 128.9, 128.8, 128.1, 106.5, 55.6, 43.1, 21.8, 13.6; HRMS ($C_{19}H_{20}N_2O_2S$) calcd 341.1318 (MH^+), found 341.1319.

3.4.2. 5-Ethyl-3-methyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (12b). Yellow oil (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.30 (m, 2H), 5.69 (s, 1H), 4.31 (m, 2H), 3.64 (m, 2H), 2.56 (q, J=7.5 Hz, 2H), 2.42 (s, 3H), 2.06 (s, 3H), 1.21 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 145.9, 145.2, 136.4, 130.2, 128.2, 103.9, 55.6, 42.1, 22.0, 19.0, 13.8, 13.1; HRMS ($C_{15}H_{20}N_2O_2S$) calcd 293.1318 (MH^+), found 293.1295.

3.4.3. 5-Butyl-3-phenyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole and 3-butyl-5-phenyl-1-[2-(*p*-tosyl)-ethyl]-1*H*-pyrazole (12, entry d). Yellow oil (84% yield), 2.2:1 inseparable mixture of regioisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.18 (m, 37H), 6.11 (s, 1H), 5.93 (s, 2.3H), 4.33 (m, 6.6H), 3.63 (m, 2.4H), 3.57 (m, 4.7H), 3.00 (m, 1.4H), 2.43 (m, 15.9H), 2.18 (s, 3.6H), 1.3 (m, 17.9H), 0.87 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 151.0, 145.0, 144.9, 144.7, 136.1, 135.9, 133.4, 130.3, 130.0, 129.9, 129.1, 128.9, 128.8, 128.6, 128.3, 128.0, 127.7, 127.6, 125.5, 105.4, 101.8, 55.6, 50.8, 43.0, 42.4, 31.8, 30.7, 28.0, 25.2, 22.7, 22.5, 21.8, 21.6, 14.1, 14.0; HRMS ($C_{22}H_{26}N_2O_2S$) calcd 383.1788 (MH^+), found 383.1783.

3.5. General procedure for formation of TSE-protected 5-aminopyrazoles from β-ketonitriles or β-amino-acrylonitriles

A solution of TSE–$NHNH_2$ (**6**, 154 mg, 0.719 mmol) and the β-ketonitrile or β-aminoacrylonitrile (0.497 mmol) in glacial acetic acid (4 mL) was stirred at 65 °C for 14 h. The solution was concentrated in vacuo and the residue was purified by flash silica gel chromatography to give the corresponding TSE-protected 5-aminopyrazole.

3.5.1. 5-*tert*-Butyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-ylamine (15a). 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J=8.3 Hz, 2H), 7.25 (d, J=7.9 Hz, 2H), 5.28 (s, 1H), 4.33 (t, J=6.2 Hz, 2H), 3.77 (s, 2H), 3.68 (t, J=6.4 Hz, 2H), 2.40 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 144.9, 144.6, 136.4, 129.8, 127.4, 88.4, 55.7, 40.6, 32.2, 30.4, 21.8; HRMS ($C_{16}H_{23}N_3O_2S$) calcd 322.1589 (MH^+), found 322.1564.

3.5.2. 5-Phenyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-ylamine (15b). 50%. ^{1}H NMR, (400 MHz, d_6-DMSO) δ 7.75 (d, J=8.3 Hz, 2H), 7.54 (dd, J=8.1, 1.5 Hz, 2H), 7.36 (d, J=7.9 Hz, 2H), 7.28 (d, J=7.9 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 5.64 (s, 1H), 5.25 (s, 2H), 4.18 (t, J=7.0 Hz, 2H), 3.77 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 148.5, 144.9, 136.5, 134.4, 130.3, 128.7, 128.1, 127.5, 125.2, 86.6, 54.2, 41.2, 21.5; HRMS ($C_{18}H_{19}N_3O_2S$) calcd 342.1198 (MH^+), found 342.1257.

3.5.3. 5-Methyl-4-phenyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-ylamine (15c). 70%. ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.63 (d, J=8.3 Hz, 2H), 7.39 (t, J=7.5 Hz, 2H), 7.26–7.17 (m, 5H), 4.37 (t, J=6.4 Hz, 2H), 3.96 (s, 2H), 3.72 (t, J=6.2 Hz, 2H), 2.40 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 144.6, 142.5, 136.1, 133.3, 129.7, 128.8, 128.4, 127.4, 125.9, 105.3, 55.3, 40.9, 21.8, 13.0; HRMS ($C_{19}H_{21}N_3O_2S$) calcd 356.1432 (MH^+), found 356.1444.

The following compounds were isolated as acetamides to

simplify purification. After heating for 14 h, the crude reaction mixtures were cooled to rt and 4 equiv. of acetyl chloride were added to the acetic acid solution. After 1 h, the reactions were worked up as above to give the title compounds.

3.5.4. *N*-{5-Methyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-yl}-acetamide (15d). 88%. ^{1}H NMR, (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.63 (d, J=7.9 Hz, 2H), 7.30 (d, J=7.9 Hz, 2H), 6.02 (s, 1H), 4.38 (t, J=6.4 Hz, 2H), 3.62 (t, J=6.2 Hz, 2H), 2.43 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 148.7, 145.1, 136.1, 135.8, 129.9, 127.5, 100.1, 55.8, 41.1, 23.7, 21.8, 14.1; HRMS ($C_{15}H_{19}N_3O_3S$) calcd 322.1225 (MH^+), found 322.1207.

3.5.5. *N*-{5-(2-Pyridyl)-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-yl}-acetamide (15e). 78%. ^{1}H NMR, (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.56 (d, J=4.8 Hz, 1H), 7.67–7.61 (m, 4H), 7.24–7.15 (m, 3H), 6.74 (s, 1H), 4.47 (t, J=6.6 Hz, 2H), 3.72 (t, J=6.6 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 151.4, 150.6, 149.1, 145.1, 137.1, 136.5, 135.6, 129.9, 127.5, 122.6, 120.2, 99.1, 55.5, 41.9, 23.5, 21.7; HRMS ($C_{19}H_{20}N_4O_3S$) calcd 385.1334 (MH^+), found 385.1322.

3.6. Deprotection of 5-phenyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-ylamine (15b)

5-Phenyl-2-[2-(*p*-tosyl)-ethyl]-2*H*-pyrazol-3-ylamine (**15b**, 62 mg, 0.18 mmol) was dissolved in 5 mL of DMSO and 0.45 mL of a 1.0 M solution of NaOEt in EtOH was added at rt. The mixture was then heated at 45 °C for 30 min, cooled to rt, and quenched with 0.45 mL of 1.0 N aqueous HCl. The solvent was removed in vacuo, and the residue was subjected to silica gel flash chromatography (9:1 EtOAc/MeOH) to yield 17 mg (60%) of the known 5-phenyl-2*H*-pyrazol-3-ylamine (**16**).

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