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4-Methoxybenzyl (PMB), A Versatile Protecting Group for the Regiospecific Lithiation and Functionalization of Pyrazoles

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4-METHOXYBENZYL (PMB), A VERSATILE PROTECTING GROUP FOR THE REGIOSPECIFIC LITHIATION AND FUNCTIONALIZATION OF PYRAZOLES

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Abstract: The use of 4-methoxybenzyl (PMB) protecting group for the regiospecific metallation/functionalisation of pyrazole is reported.

The regiospecific C-5 (C-3) metallation and functionalization of N-1 protected pyrazoles have attracted considerable attention over the last decade.[1] A number of protecting groups (eg: Me, Bn, Ph etc.) have been successfully employed for achieving this transformation. But many of these suffer from certain disadvantages such as ease of removal of the protecting group and competitive metallation of the protecting groups.[2] Although some of these limitations were overcome by the SEM[1] and the toluene sulfonyl (TS)[3] protecting groups, they were found to be unsuitable for our purposes (vide infra). Herein, we would like to report that the 4-methoxybenzyl (PMB) is a useful protecting group for the regiospecific lithiation and functionalization of the pyrazole nucleus.

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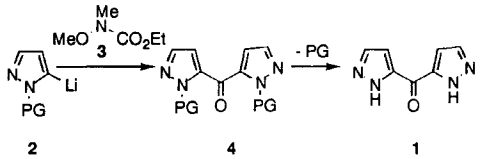
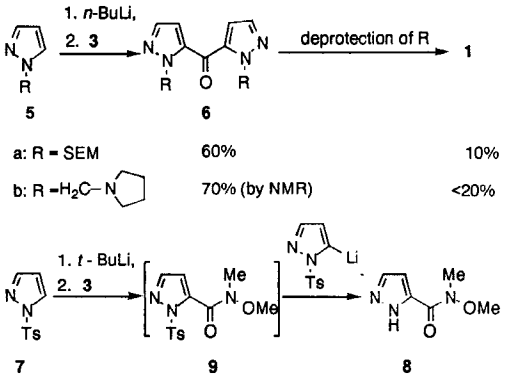
During the course of preparation of novel neuroprotective agents for the treatment of stroke,[4] we required large quantities of the bis-pyrazole ketone (**1**). Although this is a known[5] compound, its method of preparation involved use of the highly toxic agent diazomethane. Since it was not practical to use CH_2N_2 on a large scale, we looked for alternative methods for the synthesis of **1**. A route[6] that looked attractive was reaction of an anion such as **2** with the commercially available urethane **3**. The intermediate ketone **4** should after removal of the protecting group give the desired compound **1** (eq. 1).



(1)

As predicted, N-1 SEM pyrazole(**5a**)[1] was lithiated with *n*- BuLi and the resulting anion reacted with urethane **3** to give ketone **6a** in 60% yield (**Scheme I**). However, attempts to remove the SEM protecting group from **6a** under the reported conditions[1] gave little or none of the desired adduct **1**. Other conditions for the removal of the SEM group (CsF, CF_3CO_2H or KF) were also tried but with very little or no success (Scheme I). Although some of this problem could be overcome with the pyrrolidinomethyl protected pyrazole **5b** [7], the yield of **1** was still low (< 20%). We next attempted to prepare the ketone **1** by reaction of the anion generated from the tosyl pyrazole (**7**)[3] with **3**. However, the major product of the reaction was the amide **8**, which must have resulted from the attack of the 2nd equivalent of anion on the initially formed Weinreb-amide **9.**

Scheme 1



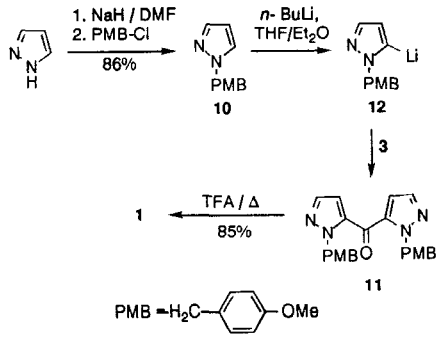
The problems encountered with the routes mentioned above, led us to look for an alternative protecting group that would fulfil the following requirements: 1) regiospecific lithiation at C-5 of pyrazole 2) show considerable reactivity towards urethane **3** or other electrophiles, and 3) be removed under resonably mild conditions. A survey of the literature showed that the 4-methoxybenzyl (PMB)[8] has been used with some success for the protection of sulfonamide nitrogen and also for the protection of N-1 of triazoles[9]. In both instances, the protecting group was removed efficiently using anhydrous CF_3CO_2H. There are however no reports of synthesis and reactions of N-1 PMB protected pyrazoles. At the outset, there was some concern in our part as to whether the PMB group would allow for regiospecific metallation of the pyrazole nucleus, because in the analogous 1-benzyl pyrazole, metallation was observed predominantly at the N-CH_2 group.[2] We predicted that the presence of electron donating 4-methoxyl group in the PMB protected pyrazole **10** should hinder metallation at the N-CH_2 group and because of the known propensity of pyrazoles to undergo metallation at C-5(C-3) the later should be the preferred site for lithiation. Also, competitive metallation (if any)

ortho to the methoxy group could be easily overcome by proper choice of reaction conditions.

The starting PMB-pyrazole **10** was easily prepared in 86% yield by reaction of pyrazole with NaH in DMF follwed by alkylation with PMB-Cl. Treatment of a cold solution (-78 °C) of **10** in ether:THF (3:2) with *n*-BuLi followed by quenching with MeOH-D4 resulted in >70% deuterium incorporation at C-5, as evidenced by ^{1}H NMR. None of the α-deuterated material could be detected either by ^{1}H NMR or mass spec.We then studied the stability of the anion at different temperatures. Quenching of aliquots of the reaction with MeOH-D4 at various temperatures upto -10 °C, indicated that the anion was not very stable at temperatures above -50 °C and at -10 °C, complete decomposition was observed. This is interesting because it has been reported[2] by Katritzky that in the case of 1-benzylpyrazole the initial metallation at -78 °C (kinetic control) occurs at α-position and on warming to room temperature, the α-lithio derivative rearranges to the thermodynamically more stable C-5 lithio derivative.

When urethane **3** was used as the electrophile, a 50% yield of ketone **11** was obtained as a colorless solid (mp: 83-84 °C) (**Scheme 2**). More importantly, the isolation of the desired product on a large scale, did not involve any

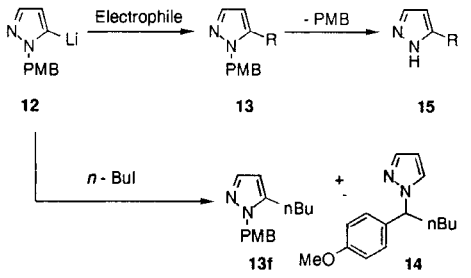
Scheme 2



chromatography . The regiochemistry of acylation was established by comparison of the chemical shift of N-CH_2 protons with that of **6a**.

Pleased by this out come, we next set out to evaluate the scope of the lithiation/funcctionalization of **10** for the synthesis of various C-5(C-3) substituted pyrazoles (**Scheme 3**).

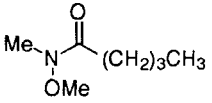
Scheme 3



As shown in **Table I**, reaction of anion **12** proceeds well with a number of carbonyl based electrophiles (entries a-e) yielding the desired adducts **13a-e** in good to excellent yields. Reaction with n-BuI (entry f) and benzyl bromide (entry g) were at best only modest and they required carefully optimised reaction conditions (see experimental) to achieve the observed results. Also, small amounts of the the α-alkylated isomer could be observed in crude reaction mixture of these later reactions. This α-alkylated material **14** was isolated and characterized by ^1H NMR in the reaction with n-BuI. Although the yields in the alkylation reactions were only moderate, even this level of reactivity was satisfactory when one considers that with SEM protecting group no reaction was observed either with DMF or benzyl bromide.

We next investigated the removal of the PMB protecting group from compounds **11** and **13a-g**. Although there are many methods that are avilable for

Table 1: Reaction of 1-(p-methoxybenzyl)pyrazol-5yllithium (**12**) with electrophiles.

Entry	Electrophile (E+)	Product **13** (R =)	Yield (%)
a	DMF	CHO	74
b	$CNCO_2Me$	CO_2Me	80
c	PhCOCl	COPh	70
d		$CO(CH_2)_3CH_3$	50
e	PhCHO	CH(OH)Ph	68
f	*n* - BuI	n - Bu	41
g	$PhCH_2Br$	CH_2Ph	30

the removal of PMB group from alcohols, none of those methods (DDQ or CAN or $Ph_3^+BF_4^-$)[10] were successful in our hands for the deprotection of **11**. Finally, we found that refluxing a solution of **11** in TFA led to smooth removal of the PMB groups, providing **1** in 85% yield. This procedure when applied to other compounds in Table 1 gave less than accepatable yields of the C-5(C-3) substituted pyrazoles **15a-g**. To circumvent this problem, we examined other (milder) deprotection conditions. After considerable investigation, we found that treatment of **13a-e** with TFA (5 eq) and anisole (10 eq) in refluxing dichloroethane resulted in cleavage of the PMB group, giving adducts 15a-e (**Table 2**) in good yields. The only exception to this was aldehyde **13a** which gave < 10% yield of **15a**. In the case of the alkyl substituted compounds **13f-g**, deprotection with TFA or TFA/Anisole was unsuccessful. Removal of the PMB group from these compounds could be acheived in excellent yields under reductive ($Na/liq.NH_3$) conditions.

In summary, we have demonstrated that PMB is a useful protecting group in lithiation reactions of pyrazole and that the anion generated from **10** reacts readily

Table 2: C-5(3) substituted pyrazoles **15** from PMB-pyrazoles **13**:

entry	Deprotection method[1]	product **15** (R =)	Yield (%)	mp (°C)	Lit. mp. (°C)[ref]
a	A	CHO	10	145-46	146-47[11]
b	A	CO2Me	76	140-41	140[12]
c	A	COPh	82	97-98	95-98[13]
d	A	$CO(CH_2)_3CH_3$	72	79-80	--
e	B	CH(OH)Ph	25	112-114	114[14]
f	B	*n*- Bu	85	oil	oil[15]
g	B	CH_2Ph	80	52-53	oil[16]

[1] see experimental section for the description of method A and B.

with a number of electrophiles. Finally, removal of the PMB protecting group (with either CF_3CO_2H or CF_3CO_2H/anisole or Na/liq. NH3) proceeds in good yield giving C-5(C-3) substituted pyrazoles **15a-g**. Application of this methodology for functionalization of other heterocycles (pyrole, indole, imidazole, indazole and triazole) are in progress and will be reported in due course.

Experimental Section:

General Methods. Melting points were determined on a Mel-Temp apparatus and are uncorrected. NMR spectra were acquired on a JEOL-FX270, General Electric QE-300 or Bruker-AC200 spectrometers in $CDCl_3$ solvent unless otherwise indicated. Chemical shifts are reported in parts per million downfield from tetramethysilane internal standard (δ sclae). Mass Spectra were recorded on a Nermag R10/10 coupled to a Varian 3400 Gas Chromatograph or on a JEOL JMS-01SC spectrometer. Thin layer chromatography (TLC) was performed on E. Merck

5x20, Kieselgel 60 F-254 plates. Flash chromatography was performed using Baker silcagel (25-40 μM). Anhydrous sodium sulfate was used to dry extracts unless otherwise noted.

Preparation of 1-(4-Methoxybenzyl)-1H-pyrazole (10): To a suspension of NaH (4.35 g, 0.17 mol) in anhydrous DMF (100 mL) at) oC was added dropwise a solution of pyrazole (10.3 g, 0.155 mol) in DMF (150 mL). After the addition was complete (1 h), the cooling bath was removed and the mixture stirred at rt for 1 h and a solution of 4-methoxybenzyl chloride (PMB-Cl) (25.0 g, 0.162 mol) in DMF (30 mL) was added. After stirring at rt under N_2 for 20 h, the reaction mixture was poured onto water (500 mL) and extracted with ether (3 X 200 mL). The organic phase was washed with water (2 X 100 mL), brine (1 X 100 mL), dried and concentrated in vacuo. The residue was purified by passing through a short plug of silica (2" X 6"), eluting with hexanes/ethyl acetate (3:1) to give 25.0 g (87%) of **10** as a colorless liquid which solidified upon storing in the refrigerator: ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 5.22 (s, 2H), 6.25 (m, 1H, pyrazole C4-H), 6.82 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 1.6 Hz, pyrazole C-5H), 7.55 (d, J = 1.6 Hz, pyrazole C-3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 139.8, 129.6, 129.3, 129.0, 114.6, 106.2, 55.8, 55.7; MS m/z $(M+H)^+$ calcd 189.1028, found 189.1024

Preparation of Ketone 11: To a solution of **10** (129 g, 0.69mole) in 3:2 ether:THF (2 L), at -78 °C was added 2.5 M *n* - BuLi (300 mL, 0.754 mol) at such a rate that the internal temperature was maintained below -70 °C. After stirring at -78 °C for 1.5 h, urethane **3** (43.7 g, 0.48 mol) was added neat and the cooling bath removed. After stirring at rt for 12 h, the reaction was quenched with satd. NH4Cl and extracted with ethylacetate (3 x 200 mL). The combined organic layer was dried and concentrated in vacuo. The residue was diluted with hexanes/ether

(1:1, 1L) and chilled in the refrigerator over night. The solids that crystallized was collected by filtration, washed with cold ether and air dried to give 66.0 g (50%) of ketone **11** as a colorless solid: mp 83-84 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 5.69 (s, 4H), 6.70 (d, J = 1.7 Hz, 2H), 6.81 (d, J = 8.5 Hz, 4H), 7.23 (d, J = 8.6 Hz, 4H), 7.55 (d, J = 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 175.5, 159.6, 138.6, 129.7, 129.4, 114.3, 114.0, 55.6, 55.0; MS m/z $(M+H)^+$ calcd 403.1770, found 403.1769

General Proceudure for the Synthesis of Compounds 13a-e: To a stirred, precooled (-78 °C) solution of 1-(4-methoxybenzyl)pyrazole (**10**) (1.88 g, 0.01 mol) in 3:2 THF:ether (50 mL) was added dropwise, 2.5 M *n*-BuLi (4.4 mL, 0.011 mol) at such a rate that the internal temperature was below -70 °C. The mixture was stirred at -78 °C for 1.5 h, during which time the anion (**12**) pptd. out as a yellow solid. The appropriate electrophile (**Table 1**) was added neat and the reaction stirred at -78 °C until TLC examination (EtOAc:Hexanes) indicated disapperance of **11** (2-3 h). After quenching with satd. NH_4Cl (5 mL),the reaction was warmed to room temperature. Ether (100 mL) and water (20 mL) were added and the layers seperated. Organic phase was washed with brine (1 x 20 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/ hexane) to give compounds **13a-e.**

1-(4-Methoxybenzyl)pyrazole-5-carboxaldehyde (13a): 74%; mp 42-43 °C; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 5.65 (s, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 1.7 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 1.9 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) d 180.1, 159.7, 139.5, 138.7, 129.7, 129.1, 115.9, 114.3, 55.6, 54.9; A satisfactory mass spectrum could not be obtained for this compound.

Methyl-1-(4-Methoxybenzyl)pyrazole-5-carboxylate (13b): 73%; mp 43-44 °C; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.85 (s, 3H), 5.75 (s, 2H), 6.82 (m,

3H), 7.25 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 1.8 Hz, 1H): MS m/z $(M+H)^+$ calcd 247.1083, found 247.1078

Phenyl 1-(4-Methoxybenzyl)-1H-pyrazol-5yl-Ketone (13c): 62%; mp 44-45 °C; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 5.75 (s, 2H), 6.63 (d, J = 1.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.45 (m, 2H), 7.65 (m, 2H), 7.81 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 186.4, 159.5, 138.6, 138.4, 138.2, 133.4, 129.9, 129.7, 128.8, 114.7, 114.3, 55.6, 54.9; MS m/z $(M+H)^+$ calcd 293.1290, found 293.1280

***n*-Butyl -1-(4-methoxybenzyl)-1H-pyrazol-5yl-Ketone (13d):** 50%; mp 27-28 °C; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3H), 1.31 (m, 2H), 1.59 (m, 2H), 2.79 (t, J = 7.4 Hz, 2H), 5.68 (s, 2H), 6.83 (m, 3H), 7.22 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 192.2, 159.5, 138.5, 138.3, 129.8, 129.7, 114.2, 112.2, 55.6, 55.2, 40.8, 26.8, 22.7, 14.3; MS m/z $(M+H)^+$ calcd 273.1603, found 273.1590

1-(4-Methoxybenzyl)-5-(1'-hydroxy-1'-phenylmethyl)pyrazole (13e): 68%; mp 95-96 °C; ^1H NMR ($CDCl_3$) δ 2.92 (br s, 1H), 3.76 (s, 3H), 5.14 (d, J = 15.4 Hz, 1H), 5.25 (d, J = 15.4 Hz, 1H), 5.75 (s, 1H), 6.02 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 1H), 7.25-7.38 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.5, 144.7, 141.3, 138.7, 129.4, 129.0, 128.9, 128.6, 126.9, 114.5, 106.6, 68.7, 59.4, 55.7, 53.5.

Synthesis of 1-(4-Methoxybenzyl)-5*n*-butylpyrazole (13f): To a stirred, precooled (-78 °C) solution of **10** (1.88 g, 0.01 mol) in THF(100 mL) was added dropwise, 2.5 M *n*-BuLi (4.4 mL, 0.011 mol) at such a rate that the internal temperature was below -70 °C. After stirring at -78 °C for 2 h, DMPU (2.56 g, 0.02 mol) was added and stirring continued at -78 °C for another 30 min. n-Butyl iodide (2.02 g, 0.011 mol) was added all at once, stirred for 8 h at -78 °C and

slowly warmed to rt over night. The resulting mixture was quenched with brine (5 mL), diluted with ether (100 mL), washed with water (3 x 20 mL) and brine (1 x 20 mL). The organic layer was dried and concentrated in vacuo. Purification by MPLC (6:1 hexane/ethyl acetate) gave 1.0 g (41%) of **13f** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.29 (m, 2H), 1.51 (m. 2H), 2.48 (t, J = 7.5 Hz, 2H), 3.72 (s, 3H), 5.19 (s, 2H), 6.02 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 159.4, 143.4, 138.9, 133.6, 132.4, 130.2, 129.8, 114.5, 104.8, 59.4, 55.65, 52.8, 30.9, 25.6, 22.7, 14.2; MS m/z $(M+H)^+$ calcd 245.1654, found 245.1664

Also isolated was 0.25 g (10%) of **14** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 6.2 Hz, 3H), 1.22 (m, 2H), 1.37 (m, 2H), 2.15 (m, 1H), 2.40 (m, 1H), 3.79 (s, 3H), 5.23 (t, J = 6.0 Hz, 1H), 6.22 (d, J = 1.6 Hz), 6.81 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H).

Preparation of 1-(4-Methoxybenzyl)-5-benzylpyrazole (13g): To a stirred, precooled (-78 °C) solution of 1-(4-methoxybenzyl)pyrazole (**10**) (1.88 g, 0.01 mol) in THF(100 mL) was added dropwise, 2.5 M *n*-BuLi (4.4 mL, 0.011 mol) at such a rate that the internal temperature was below -70 °C. After stirring at -78 °C for 1 h, benzyl bromide (1.3 mL, 0.011 mol) was added and the reaction slowly warmed to rt over night. The reaction was quenched with brine (5 mL) and filtered through a pad of florisil® and eluted with ethyl acetate (100 mL). The combined filtrate was concentrated in vacuo and the residue purified by MPLC (6:1 hexanes/ethyl acetate) to give 0.83 g (30%) of **13g** as a colorless solid: mp 41-42 °C; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.88 (s, 2H), 5.14 (s, 2H), 6.02 (d, J = 1.2 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 7.09 (m, 2H), 7.26 (m, 3H), 7.47 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 159.5, 141.5,

138.9, 137.9, 129.4, 129.1, 128.9, 128.6, 127.1, 114.5, 107.0, 55.7, 53.1, 32.2; MS m/z $(M+H)^+$ calcd 279.1497, found 279.1493

Synthesis of Bis-pyrazole ketone 1 from 11: A solution of ketone **11** (52.0 g, 0.129 mol) CF_3CO_2H (350 mL) was refluxed under nitrogen for 16 h and cooled to room temperature. The resulting dark mixture was concentrated to dryness in vacuo. To the residue was added 1:3 MeOH/EtOH (1.2 L) and the mixture heated on a steam bath for 15 min. The insolubles were filtered off and the filtrate concentrated in vacuo. The residue was triturated with CH_2Cl_2 (300 mL), the solids collected by filtration and dried to give 20.5 g (85%) of **1** as a colrless solid: mp 207-209 °C. (lit. [4] 207 °C); ^1H NMR (DMSO-d_6) δ 6.98 (s, 2H), 7.82 (s, 2H).

General Procedure for the removal of 4-methoxybenzyl (PMB) protecting group from compounds 13a-g:

Method A: A solution of the PMB potected pyrazole **13a-d** (1.0 eq.), anisole (10 eq.) and trifluroacetic acid (5 eq.) in dichloroethane (5 ml/mmol of compound) was refluxed under nitrogen until the TLC (ethylacetate/hexanes) indicated absence of starting material (12-24 h). The reaction mixture was cooled to room temperature and the volatiles removed in vacuo. The residue was purified by flash chromatography (ethylacetate/hexanes) to give the products which were identical to those reported in the literature by mp and ^1H NMR.

Data for compound 15d: mp 79-80 °C; 1H NMR ($CDCl_3$) δ 0.95 (t, J = 6.6 Hz, 3H), 1.42 (m, 2H), 1.68 (m, 2H), 2.98 (t, J = 6.7 Hz, 2H), 6.85 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H), 10.25 (br s, 1H).

Method B: To liquid NH_3 (20 mL) was added Na spheres until a deep blue color persisted. A solution of the pyrazole (**13e-13g**) in THF (2 mL/mmol) was added and the resulting solution stirred at -78 °C for 1 h (in some instances, more Na after the addition of the substrate was added in order to maintain the deep blue color).

Solid NH_4Cl was added and the ammonia evoporated. The resulting mixture was diluted with ethylacetate and filtered through a pad of silica, eluting with ethylacetate. The combined eluents were concentrated in vacuo and the residue purified by flash chromatography to give the desired products **15e-g**, which were identical by ^1H NMR to that reported in the literature.

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