SYNTHESIS OF 4,5-DIHYDRO-3,4,4,5,5-PENTASUBSTITUTED- N-TOSYL-1H-PYRAZOLES

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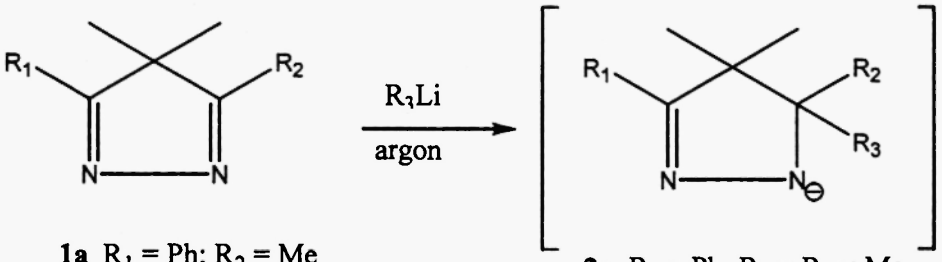
Abstract: Addition of methyl- or phenyllithium to 3,4,4,5-tetrasubstituted-4*H*-pyrazoles (**1a-b**) smoothly produced the extremely air-sensitive anions of 4,5-dihydro-3,4,4,5,5-pentasubstituted-1*H*-pyrazoles (**2a-c**) which were converted to the *N*-tosylated compounds **3a-c** in low to very good yields by reaction with tosyl fluoride. The two-step process is a convenient one-pot route to 4,5-dihydro-*N*-tosyl-1*H*-pyrazoles.

Introduction

Our interest in the synthesis of highly substituted pyrazolines as reagents[1] for oxidation (cyclic azohydroperoxides) or as precursors[2] to the synthesis of highly substituted cyclopropanes required the synthesis of 4,5-dihydro-3,4,4,5,5-pentasubstituted-1*H*-pyrazoles and various derivatives. These substituted 4,5-dihydro-1*H*-pyrazoles are generally extremely sensitive to air oxidation and are often difficult to handle.[1b] *N*-Tosylated derivatives were needed as precursors for the synthesis of hexasubstituted pyrazolines. Interestingly, there is surprisingly little literature available on *N*-tosylation of 4,5-dihydro-1*H*-pyrazoles. Engel reported[3a] the *N*-tosylation of 4,5-dihydro-3,5,5-trimethyl-1*H*-pyrazole with tosyl chloride in 61% yield. Arylhydrazones, the acyclic analogs of 4,5-dihydro-1*H*-pyrazoles, have also been reported[3b] to undergo *N*-tosylation with tosyl chloride. However, a relatively recent study[4] on the reaction of a 4,5-dihydro-3,4,4,5,5-pentasubstituted-1*H*-pyrazole with tosyl chloride under strong basic conditions did not yield the expected *N*-tosyl compounds. Surprisingly, the reaction yielded the pyrazoline chlorinated at carbon 3.[4] We report here a convenient two-step, one-pot route for the synthesis of a series of 4,5-dihydro-3,4,4,5,5-pentasubstituted-*N*-tosyl-1*H*-pyrazoles.

Results and Discussion

The reaction of methyl- or phenyllithium with 4,4-dimethyl-3,5-disubstituted-4*H*-pyrazoles **1a-b** produced the anions of 4,5-dihydro-3,4,4,5,5-pentasubstituted-1*H*-pyrazoles (**2a-c**) as intermediates (rxn 1).

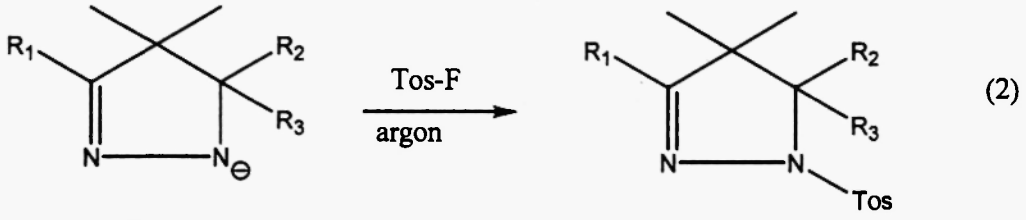


(1)

1a R_1 = Ph; R_2 = Me
1b R_1 = R_2 = Ph

2a R_1 = Ph; R_2 = R_3 = Me
2b R_1 = R_3 = Ph; R_2 = Me
2c R_1 = R_2 = R_3 = Ph

Due to their extreme reactivity with oxygen, intermediates **2a-c** were used without isolation. The reaction of **2a-c** with tosyl fluoride produced the 4,5-dihydro-3,4,4,5,5-pentasubstituted- *N*-tosyl-1*H*-pyrazoles (**3a-c**) in low to very good overall yields (rxn 2).[5] Compounds **3a-c** were isolated and characterized by spectra and physical data.

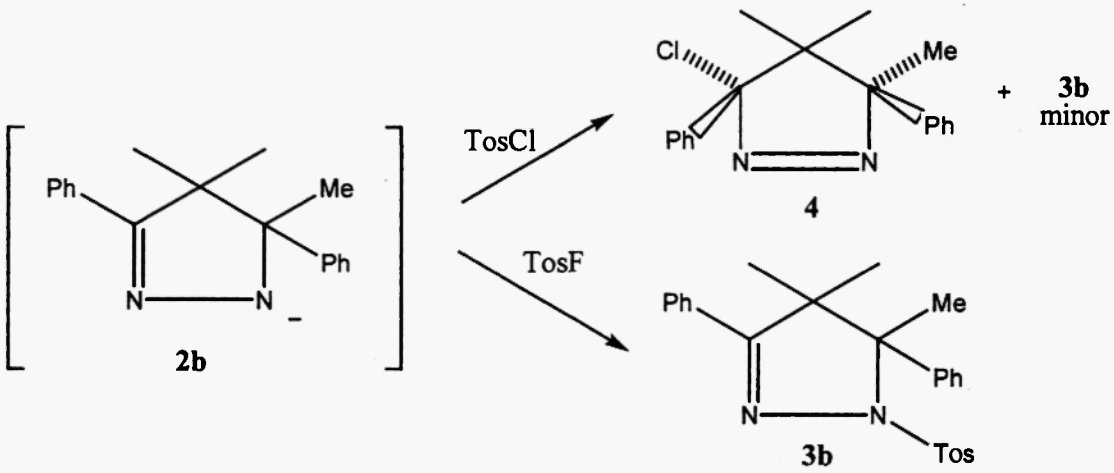


(2)

2a-c

3a R_1 = Ph; R_2 = R_3 = Me
3b R_1 = R_3 = Ph; R_2 = Me
3c R_1 = R_2 = R_3 = Ph

Previous results on **2a** had shown[4] that reaction with tosyl chloride produced 3-chloro-4,5-dihydro-3,4,4,5,5-pentasubstituted-1*H*-pyrazole (**4**) in excellent yield, formally via an apparent S_n2 attack on the chlorine (Scheme 1). Tosyl chloride has been reported[6] to preferentially C-chlorinate enolates with O-sulfonation as the minor pathway. Tosyl fluoride, in that study,[6] was found to yield primarily the O-sulfonation product. In agreement, the use of tosyl fluoride in the present study (Scheme 1) has also shifted the attack of the hydrazonyl anion from the halide to the sulfuryl group. The reaction of **2b** with tosyl chloride was checked for the presence of the *N*-tosylated compound **3b**. The 3-chloro-pyrazoline, **4**, was the major product



Scheme 1. Pathways for reaction of anion **2b** with tosyl chloride[4] and tosyl fluoride.

as previously reported,[4] but **3b** was found in approximately 5% yield. For the rxn. 2 above, a corresponding 3-fluoro-pyrazoline was not detected. In retrospect, the initial report[3a] by Engel of *N*-tosylation of 4,5-dihydro-1*H*-pyrazoles with tosyl chloride was carried out under relatively neutral conditions (triethylamine 1.2 equivalents). Clearly, the reaction conditions greatly affect the product distribution when tosyl chloride is employed as reactant. The combination of rxns. 1 and 2 is a convenient route to the one-pot synthesis of 4,5-dihydro-*N*-tosyl-1*H*-pyrazoles.

Experimental

The following reagents were purchased from Sigma-Aldrich Company and used without further purification: methyllithium (1.6 M) in diethyl ether, phenyl lithium (1.8 M) in cyclohexane-ether, and *p*- toluenesulfonyl fluoride (98%). All solvents were commercially available. Tetrahydrofuran (Aldrich) was distilled from over sodium and benzophenone before use. All ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity Plus 300 MHz instrument. Elemental analyses were performed at the Department of Chemistry at Georgia State University and at Atlantic Microlab, Atlanta, Georgia. Melting points were recorded in a calibrated Thomas Hoover Unimelt apparatus. The preparations of 3,4,-trimethyl-5-phenyl-4*H*-pyrazole (**1a**) and 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole (**1b**) were accomplished according to the reported procedure.[7]

4,5-Dihydro-4,4,5,5-tetramethyl-3-phenyl-1-tosyl-1*H*-pyrazole (3a). 4,4,5-Trimethyl-3-phenyl-4*H*-pyrazole (**1a**, 2.0 g, 10.7 mmol) was dissolved in anhydrous THF (120 ml) in a 250 ml three-neck round bottom flask with a magnetic stir bar. The solution was purged with argon gas and cooled to 0° C with an ice bath. Methyllithium (8.05 ml, 12.9 mmol, 1.2 mol. eq.) was added to the solution via syringe and the reaction mixture was stirred for 30 minutes at 0° C. The solution was removed from the ice bath and stirred for two additional hours at room temperature. A solution of p-toluenesulfonyl fluoride (3.74 g, 21.5 mmol, 1.2 mol. eq.) in dry THF (10 ml) was added to the reaction flask using a glass syringe and stirred for three hours at room temperature. The mixture was quenched with 15 ml of saturated, degassed ammonium chloride solution. Diethyl ether (30 ml) was added and the contents were washed with saturated sodium bicarbonate (2 x 50 ml) and with deionized water (30 ml). The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 90:10) with an isolated yield of 39% (1.49 g, 4.2 mmol, mp 113-114 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6H), δ 1.32 (s, 6H), δ 2.42 (s, 3H), δ 7.27-7.96 (m, 9H); ^{13}C NMR ($CDCl_3$) 20.2, 20.4, 21.5, 53.5, 75.1, 127.4, 128.2, 128.3, 129.2, 129.6, 131.5, 137.4, 143.4, 161.9.
Anal. Calcd. for $C_{26}H_{24}N_2O_2S$; C, 67.38; H, 6.79; N, 7.86%. Found: C, 67.33; H, 6.70; N, 7.78%.

4,5-Dihydro-4,4,5-trimethyl-3,5-diphenyl-1-tosyl-1*H*-pyrazole (3b). The procedure outlined for **3a** above was followed. Product **3b** was crystallized from ethanol with an isolated yield of 91% (3.05 g, 7.29 mmol, mp 169-170 °C; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H), δ 1.26 (s, 3H), δ 1.72 (s, 3H), δ 2.42 (s, 3H), δ 7.27-7.92 (m, 14H); ^{13}C NMR ($CDCl_3$) 19.2, 20.3, 21.6, 24.1, 55.5, 80.5, 126.8, 127.5, 127.6, 127.7, 128.4, 128.5, 129.1, 129.6, 131.5, 137.3, 139.4, 143.5, 161.2.
Anal. Calcd. for $C_{25}H_{26}N_2O_2S$; C, 71.74; H, 6.26; N, 6.69%. Found: C, 71.79; H, 6.44; N, 6.71%.

4,5-Dihydro-4,4-dimethyl-3,5,5-triphenyl-1-tosyl-1*H*-pyrazole (3c). The procedure as outlined above with the following modification was used for **3c**. 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole (**1b**, 1.0 g, 4.0 mmol) was dissolved in 100 ml anhydrous THF and phenyllithium (4 ml, 8.1 mmol, 2 mol. eq.) was added. The crude product **3c** was purified by crystallization from acetone and ethyl acetate to give an isolated yield of 51% (0.98 g, 2.1 mmol), mp 240-242 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 6H), δ 2.31 (s, 3H), δ 6.89-7.76 (m, 19H); ^{13}C NMR ($CDCl_3$) 21.4, 24.0, 56.5, 86.9, 127.0, 127.7,

127.8, 128.3, 128.6, 128.9, 129.8, 130.7, 130.8, 135.6, 136.8, 142.5, 161.4; *Anal.* Calcd. for $C_{30}H_{28}N_2O_2S$; C, 74.97; H, 5.87; N, 5.83%. Found: C, 75.05; H, 5.82; N, 5.58%.

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References and Notes

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