

SYNTHESIS OF *trans*-3-CHLORO-4,4,5-TRIMETHYL-3,5-DIPHENYL-4,5-DIHYDRO-3*H*-PYRAZOLE

John Szwec, Pedro C. Vásquez, Paul J. Franklin, G. Davon Kennedy* and A.L. Baumstark*
Department of Chemistry, Center for Biotech and Drug Design
Georgia State University, Atlanta, Georgia 30303-3083, USA
e-mail: chealb@panther.gsu.edu; fax number: 404-651-1416

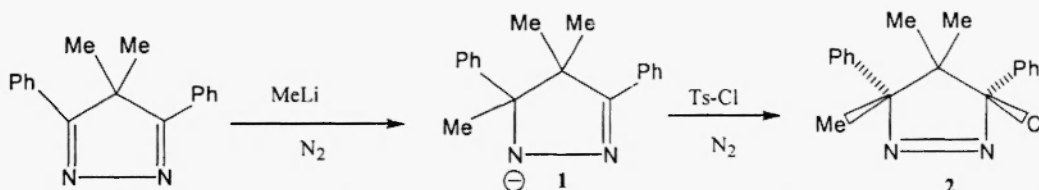
Abstract. The reaction of the lithium salt of 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2*H*-pyrazole, **1**, with tosyl chloride unexpectedly produced the C-chlorinated pyrazoline, **2**, in high yield.

Introduction

Previously we developed¹ a route for the synthesis of 5-acetoxy penta-substituted pyrazolines (4,5-dihydro-3*H*-pyrazoles) as part of an approach for the synthesis of highly substituted cyclopropanes. Specifically, addition of methyl lithium to cyclic azines produced² cyclic hydrazone anionic intermediates. In earlier work, benzoylation was carried out³ to stabilize these air-sensitive compounds. Recently, N-tosyl derivatives of penta substituted 3,4-dihydro-2*H*-pyrazoles were wanted as intermediates for additional studies. We report here the synthesis of *trans*-3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3*H*-pyrazole by C-chlorination of lithio 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2*H*-pyrazole with tosyl chloride.

Results and Discussion

The reaction of methyl lithium with 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole² produced intermediate **1** which upon addition of an equivalent of *p*-toluenesulfonyl chloride produced compound **2** in excellent yield. No evidence for N-tosylation was found. Compound **2** was identified initially by its unique ¹H NMR characteristic spectrum in which one of the 4,4-dimethyl groups gives a signal upfield of that of TMS. This is diagnostic^{2,4} of



the presence of *cis*-3,5-diphenyl groups in this type of pyrazoline (4,5-dihydro-3*H*-pyrazoles). The structural assignment was proven by x-ray crystallography.

Arylsulfonyl chlorides have been documented to yield C-chlorination upon reaction with enolates⁵ and phosphoylides.⁶ The reaction of structurally similar cyclic hydrazones with either tosyl chloride or arylsulfonyl chloride under neutral conditions has been reported to produce N-arylsulfonated compounds⁷. To the best of our knowledge, this is the first report of C-chlorination of this type of system by an arylsulfonyl chloride. This route represents a convenient, new approach for the synthesis of chlorinated pyrazolines.

Experimental

***trans*-3-Chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3*H*-pyrazole (2):** To a three-neck round bottom flask equipped with a pressure equalizing addition funnel was added 1.0 g (4.0

mmoles) of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole² dissolved in 50 mL of dry THF, under a nitrogen atmosphere. The system was cooled to 0 °C while stirring with the help of a magnetic stirrer, and then 1.1 eq. of methyllithium in THF was added dropwise via syringe. The resulting dark solution was allowed to warm up to room temperature, stirred for one hour, and cooled to 0 °C, after which 0.9 g of p-toluenesulfonyl chloride (1.1 eq.) in 20 mL of dry THF (N₂) was added dropwise via a pressure equalizing funnel. The solution was allowed to warm up to room temperature and stirred for one hour. After cooling to 0 °C, a solution of degassed saturated aqueous ammonium chloride was added. The reaction mixture was extracted with diethyl ether. The organic phase was washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed using a rotary evaporator. The crude product was purified using a chromatatron (petroleum ether-dichloromethane gradients as eluants). The final product was obtained as a white solid (1.1 g, 92% yield⁸): M.p. 123.5-124.5 °C, ¹H NMR (CDCl₃): δ -0.16 (s, 3H), 1.57 (s, 3H), 1.81 (s, 3H), 7.30-7.40 (m, 8H), 7.45-7.61 (m, 2H). ¹³C NMR (CDCl₃): δ 20.4, 22.1, 46.1, 97.8, 108.4, 125.2, 125.8, 127.4, 128.2, 128.4, 128.8, 139.5, 142.3; ms: M⁺/e 298. Anal. Calcd. For C₁₈H₁₉ClN₂: C, 72.35; H, 6.41; Cl, 11.86; N, 9.37. Found: C, 72.50, H, 6.50; Cl, 11.79; N, 9.27.⁹ Recrystallization from petroleum ether-diethyl ether yielded crystals suitable for x-ray analysis.¹⁰

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8. Lower yields were obtained if oxygen was not carefully excluded from the reaction mixture due to competing hydroperoxide formation (see A.L. Baumstark and P.C. Vasquez, *J. Heterocycl. Chem.* **28**, 113 (1991))
9. Elemental analysis was performed at Atlantic Microlabs, Atlanta, GA
10. X-ray analysis was performed at the X-Ray Cryst. Lab. of Emory Univ., Atlanta, GA

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