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

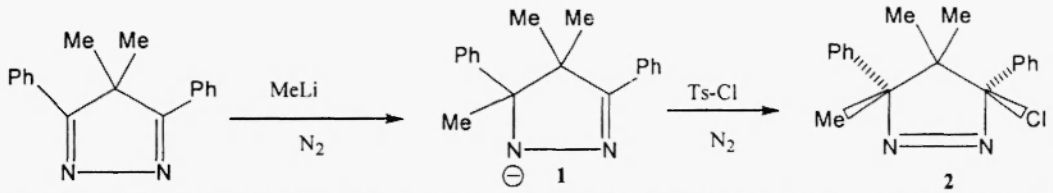
Abstract. The reaction of the lithium salt of 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2*H*-pyrazole, **1**, with tosyl chloride unexpectedly produced the C-chlorinated pyrazoline, **2**, in high yield.

Introduction

Previously we developed[1] 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 produced[2] cyclic hydrazone anionic intermediates. In earlier work, benzoylation was carried out[3] 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*-pyrazole[2] 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 ^{1}H 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 enolates[5] 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 compounds[7]. 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-4*H*-pyrazole[2] 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 (N_2) 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% yield[8]): M.p. 123.5-124 5 °C, ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{18}H_{19}ClN_2$: 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]

Acknowledgment. Acknowledgment is made to the Georgia State University Research Foundation for support of this work.

References and Notes

1. G.D. Kennedy, A.L. Baumstark, M. Dotrong, T. Thomas and N. Narayanan, *J. Heterocycl. Chem.* **28**, 1773 (1991)

2. A.L. Baumstark, M. Dotrong and P.C. Vasquez, *Tetrahedron Lett.* **28**, 1963 (1987)

3. A.L. Baumstark, A. Choudhary, P.C. Vasquez and M. Dotrong, *J. Heterocycl. Chem.* **27**, 291 (1990)

4. M.E. Landis, R.L. Lindsay, W.H. Watson and V. Zabel, *J. Org. Chem.* **45**, 525 (1980)

5. F. Hirsch, S. Honig and H.-M. Reissig, *Chem. Berichte* **115**, 399 (1982)

6. K. Lee, W.S. Shin and D.Y. Oh, *Synth. Commun.* **21**, 1657 (1991)

7. Selected references. a) P.S. Engel, R.A. Hayes, L. Keifer, S. Szilagyi and J.W. Timberlake, *J. Am. Chem. Soc* **100**, 1876 (1978); b) J. Figola, A. Colombo, J. Pares, L. Martinez, R. Sagarra and R. Rosen, *Eur. J. Med. Chem.* **24**, 435 (1989); c) G.L. Closs and H. Heyn, *Tetrahedron* **22**, 463 (1966)

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

Received on November 21, 2003.