Synthesis of Hexa(methyl/phenyl) Substituted Pyrazolines and Thermolysis to Hexasubstituted Cyclopropanes

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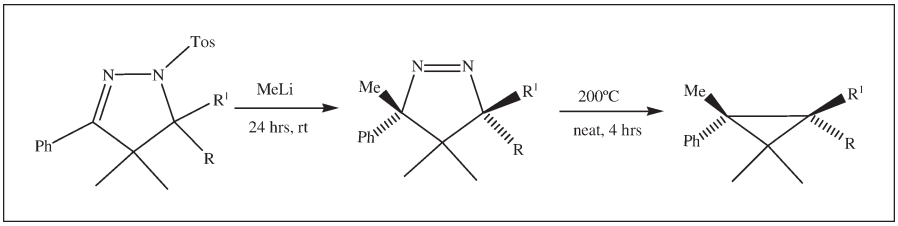

Addition of methyllithium to the 3-position of 4,5-dihydro-3,4,4,5,5-pentasubstituted-*N*-tosyl-1H-pyrazoles [**1a** 4,4,5,5-tetramethyl-3-phenyl; **1b** 4,4,5-trimethyl-3,5-diphenyl; **1c** 4,4-dimethyl-3,5,5-triphenyl] produced the corresponding hexasubstituted pyrazolines, **2a-c**, as the only isolable products. For **2b**, the 3,5-phenyl groups were found to be exclusively *cis*, indicative of facial specificity for the addition reaction. The reaction of phenyllithium with **1b** yielded **2c** as the minor product. For phenyllithium addition, direct attack on sulfur of the tosyl group with subsequent loss of phenyl *p*-tolylsulfone was the major pathway *vs*. the S_N2i attack at carbon-3. Thermolysis of pyrazolines **2a-c**, at 200°C, smoothly produced the hexasubstituted cyclopropanes [**3a** 1,1,2,2,3-pentamethyl-3-phenylcyclopropane; **3b** cis-1,1,2,3-tetramethyl-2,3-diphenylcyclopropane; **3c** 1,1,2-trimethyl-2,3,3-triphenylcyclopropane] in excellent yield.

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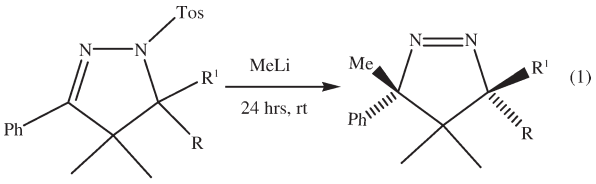
INTRODUCTION

We have an ongoing interest in the development of general methods for the synthesis of highly substituted cyclopropanes, particularly hexasubstituted systems. Historically, preferred methods for cyclopropane synthesis include pyrazoline thermolysis [For a review and recent articles see ref 1] and carbene/carbenoid addition [2] to alkenes. However, the latter method generally does not work well for the preparation of hexasubstituted compounds. Our approach has focused on synthesis and subsequent thermolysis of highly substituted pyrazolines. We have developed a methodology for the efficient synthesis of a series of 1-alkoxy and 1-acetoxy-1,2,2,3,3-pentasubstituted cyclopropanes [3]. However, routes to hexa(alkyl/aryl) substituted cyclopropanes are scarce and often highly specialized. [For cyclopropanation with dimethylcarbene, From photolysis of hexaalkylcyclohexane-1,3,5-trione, From reduction of α,γ-dibromides see ref. 4]. We report here a route to hexa(methyl/phenyl) substituted cyclopropanes *via* the synthesis and subsequent thermolysis of hexasubstituted pyrazolines.

RESULTS AND DISCUSSION

Addition of methylithium to 4,5-dihydro-3,4,4,5,5-pentasubstituted-N-tosyl-1H-pyrazoles, **1a-c**, under argon (rxn 1) yielded the hexasubstituted pyrazolines, **2a-c**, respectively, as the only isolated products, in variable yields. Recovered (unreacted) starting materials accounted for the remaining product balance. The 3,5-phenyl groups in



1a R = R¹ = Me
b R = Ph; R¹ = Me
c R = R¹ = Ph

2a R = R¹ = Me (87%)
b R = Ph; R¹ = Me (59%)
c R = R¹ = Ph (55%)

2b were found to be exclusively cis based on NMR data, indicating preferential reaction of the methyllithium with only one face of **1b**. Compounds **2a-c** were characterized by spectra and physical data.

The synthesis of **2c** was also accomplished in 25% yield by the reaction of phenyllithium with **1b**. The remaining products were indicative of the formation of 4,5-dihydro-4,4,5,5-tetramethyl-3-phenyl-1H-pyrazole [with subsequent air oxidation and decomposition] and phenyl tolylsulfone. Unlike the reaction with methyllithium, that with phenyllithium yielded products

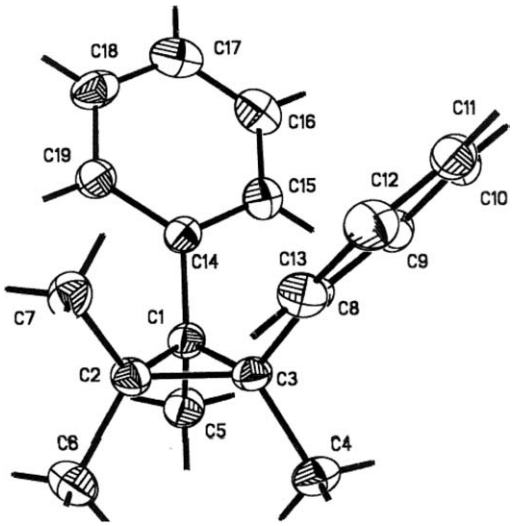
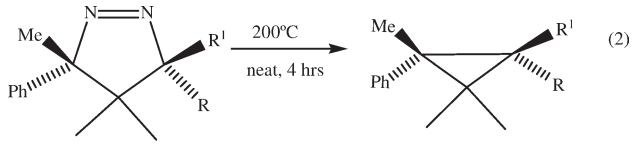


Figure 1. X-ray structure of **3b**.

indicative of preferential attack of phenyllithium on the tosyl group.

Thermolysis of pyrazolines **2a-c**, neat, at 200°C, produced the hexasubstituted cyclopropanes in excellent yield (rxn 2). The thermolysis of *cis* **2b** yielded *cis* **3b** in



(2)

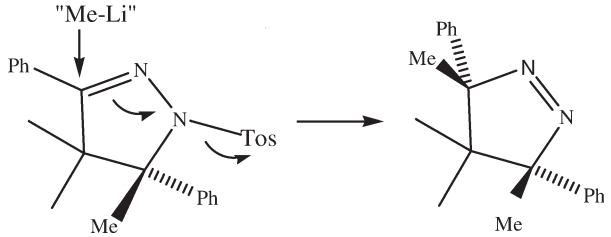
2a-c

3a R = R^1 = Me
b R = Ph; R^1 = Me (major)
c R = R^1 = Ph

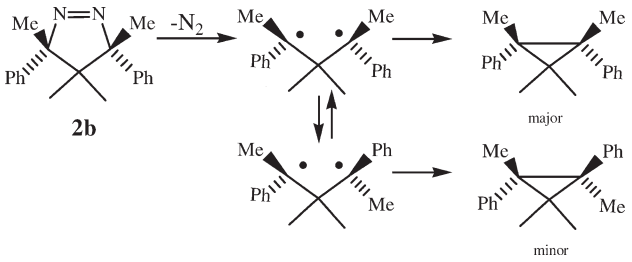
84% isolated yield. Analysis of the reaction mixture indicated that the product was a 95%/5% mixture of the *cis*/*trans* cyclopropane. Retention of configuration occurred with 95% efficiency. The cyclopropanes were characterized by spectra and physical data. The structure of **3b**, the major product, was confirmed by X-ray crystallography (Fig. 1) to have the *cis*-2,3-diphenyl configuration.

The addition of methyllithium to the 3-position of N-tosylated 4,5-dihydro-1H-pyrazoles to yield a tetrasubsti-

Scheme 1. Proposed pathway for methyl addition to position-3 for **1b**.



Scheme 2. Proposed mechanism for the thermolysis of **2b**.



tuted pyrazoline (4H-pyrazole) had been documented, but there appear to be no additional reports since that early work [5]. This is likely due to the inherent properties (air sensitivity, etc.) of selected 4,5-dihydro-1H-pyrazoles [6]. In addition, attempted N-tosylation of 4,5-dihydro-1H-pyrazoles with tosyl chloride, surprisingly, can yield unexpected products, 3-chloro pyrazolines [7] rather than the expected N-tosylated compounds. Recent development of synthetic methodology for the synthesis of 4,5-dihydro, *N*-tosyl-1H-pyrazoles was the key for the preparation of the required starting materials [8]. The addition of methyllithium to the *N*-tosyl 4,5-dihydro-1H-pyrazoles proceeded smoothly to generate the highly substituted pyrazolines. Interestingly, the results for conversion of **1b** to **2b** indicate a facial specificity of the attack of the methyllithium by an S_N2i mechanism as shown in Scheme 1 below.

For methyllithium, this route appears to be the favored mode of attack. Results with phenyllithium showed this route to be the minor pathway with direct reaction of phenyllithium with the sulfur of the tosyl group being the major pathway that appears to limit the scope of reaction 1.

Thermolysis of pyrazolines to cyclopropanes, in high yield, is a well established route [1]. Thermal decomposition of pyrazolines to cyclopropanes generally is thought to occur *via* a diradical mechanism that favors retention of configuration [1,9]. The present results are consistent with the diradical mechanism shown below in Scheme 2 for thermolysis of **2b**.

In conclusion, the addition of methyllithium to *N*-tosyl-4,5-dihydro-1H-pyrazoles and subsequent thermolysis of the pyrazolines is a useful method for the synthesis of highly substituted cyclopropanes. The method has obvious limitations in that the substituents must be stable to organolithium reagents but appears to provide a more general route to this type of highly substituted strained ring compound. Work is in progress to explore the scope of this route.

EXPERIMENTAL

The *N*-tosylated-4,5-dihydro-1H-pyrazoles, **1a-c**, were prepared according to published results [8]. Methyllithium (1.6*M*)

in diethyl ether and phenyl lithium (1.8*M*) in cyclohexane-ether were purchased from Sigma–Aldrich Company and used without further purification. All solvents were commercially available. Anhydrous toluene, anhydrous ether, and methanol were purchased from Aldrich Company and used without further purification. Tetrahydrofuran (Aldrich) was distilled from sodium and benzophenone before use. Acetone, ethanol, and hexane were purchased from Fisher Scientific Company. All ^{1}H and ^{13}C NMR spectra were obtained from a Varian Unity Plus 300 MHz instrument. Mass spectra were obtained from a Shimadzu GP-5000 Mass Spectrometer. 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. Exact mass analyses were performed at the Georgia Institute of Technology. X-ray crystallography was performed at Emory University.

Synthesis of 3,3,4,4,5-pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (2a). 4,4,5,5-Tetramethyl-3-phenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1a**) (0.30 g, 0.8415 mmol) was dissolved in anhydrous toluene (25 mL) under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (2 mL, 3.2 mmol, 3.8 mole equiv) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 24 h at room temperature. Then, the reaction was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the mixture before washing with saturated sodium bicarbonate (2 × 20 mL) solution and deionized water (30 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [95:5]) to give **2a** in an isolated yield of 87% (0.158 g, 0.732 mmol) as a clear and viscous liquid; ^{1}H NMR ($CDCl_3$) 300 MHz: δ 0.34 (s, 3H), δ 1.07 (s, 3H), δ 1.30 (s, 3H), δ 1.35 (s, 3H), δ 1.60 (s, 3H), δ 7.25–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) 300 MHz: 20.5, 23.9, 23.9, 24.1, 25.1, 41.8, 91.7, 96.0, 125.5, 126.8, 128.0, 143.8; Exact Mass Anal. Calcd. for $C_{14}H_{21}N_2$ = 217.17047. Found: 217.17060.

Synthesis of *cis*-3,4,4,5-tetramethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (2b). 4,4,5-Trimethyl-3,5-diphenyl-1(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1b**) (1.0 g, 2.389 mmol) was dissolved in 50 mL of anhydrous THF under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (4.48 mL, 7.17 mmol, 3 equiv) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 24 additional hours at room temperature. The mixture was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the mixture before washing with saturated sodium bicarbonate (2 × 20 mL) solution and deionized water (40 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [97:3]) to give **2b** in an isolated yield of 59% (0.391 g, 1.409 mmol) mp = 144–145°C; ^{1}H NMR ($CDCl_3$) 300 MHz: δ 0.26 (s, 3H), δ 1.34 (s, 3H), δ 1.68 (s, 6H), δ 7.25–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) 300 MHz: 20.2, 23.9, 28.5, 42.9, 96.7, 125.3, 126.9, 128.1, 143.6; IR peaks: 3064 cm^{-1}, 2990 cm^{-1}, 1599 cm^{-1}, 703 cm^{-1}; Anal. Calcd. for $C_{19}H_{22}N_2$ = C, 81.97, H, 7.97, N, 10.06% Found: C, 81.79, H, 8.19, N, 9.66%.

Synthesis of 3,4,4-trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (2c). 4,4-Dimethyl-3,5,5-triphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1c**) (0.5 g, 1.040 mmol) was dissolved in anhydrous THF (50 mL) under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (2.6 mL, 4.16 mmol, 4 Eq.) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 36 additional hours at room temperature. The mixture was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the reaction before washing with saturated sodium bicarbonate (2 × 40 mL) solution and deionized water (40 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by chromatatron (hexane/ethyl acetate) to give **2c** in an isolated yield of 55% (0.19 g, 0.558 mmol) mp = 117–118°C; ^{1}H NMR $CDCl_3$) 300 MHz: δ 0.15 (s, 3H), δ 1.16 (s, 3H), δ 1.56 (s, 3H), δ 7.16–7.97 (m, 15H); ^{13}C NMR ($CDCl_3$) 300 MHz: 20.7, 21.8, 27.3, 46.6, 96.6, 97.6, 125.7, 126.5, 126.7, 127.0, 127.2, 128.0, 128.1, 142.6, 143.5, 143.9; Anal. Calcd. for $C_{24}H_{24}N_2$: C, 84.67, H, 7.11, N, 8.23% Found: C, 84.73, H, 7.19, N, 8.26%.

Synthesis of 1,1,2,2,3-pentamethyl-3-phenylcyclopropane (3a). 3,3,4,4,5-Pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (**2a**) (0.100 g, 0.462 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When the viscous liquid was heated, evolution of gas (nitrogen) was observed. The NMR tube was removed from the oil bath after 4 h of heating and hexane was added to dissolve the products. The crude product was purified by chromatatron (hexanes) to yield 93% of **3a** (0.081 g, 0.429 mmol) as a clear viscous liquid. ^{1}H NMR ($CDCl_3$) 300 MHz: δ 0.92 (s, 6H), δ 1.16 (s, 6H), δ 1.23 (s, 3H), δ 7.1–7.3 (m, 5H); lit. ^{1}H NMR δ 0.91 (s, 6H), δ 1.15 (s, 6H), δ 1.23 (s, 3H), δ 7.12 (m, 5H) (Gloss *et al*., 1966; ^{13}C NMR ($CDCl_3$) 300 MHz: 18.5, 21.70, 21.74, 23.9, 29.7, 33.6, 125.0, 127.9, 130.7, 146.0.

Synthesis of *cis*-1,1,2,3-tetramethyl-2,3-diphenylcyclopropane (3b). 3,4,4,5-Tetramethyl-3,5-diphenyl-3H-pyrazole (**2b**) (0.1 g, 0.359 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When heated, the crystals melted and evolution of nitrogen gas was observed. The NMR tube was removed from the oil bath after 4 h of heating and hexane was added to dissolve the product. The crude product was purified by chromatatron (hexanes) and recrystallized from methanol to give **2b** in 84% yield (0.075 g, 0.301 mmol) as colorless crystals, mp = 79–81°C. ^{1}H NMR ($CDCl_3$) 300 MHz: δ 1.12 (s, 3H), δ 1.37 (s, 3H), δ 1.47 (s, 6H), δ 7–7.4 (m, 10H); ^{13}C NMR ($CDCl_3$) 300 MHz: 18.7, 23.2, 25.4, 27.0, 35.5, 125.3, 127.4, 131.1, 145.6; X-ray structure was obtained at Emory University; IR peaks: 3083–2927 cm^{-1}, 1599 cm^{-1}, 1577 cm^{-1}, 699 cm^{-1}. Anal. Calcd. for $C_{19}H_{22}$: C, 91.14, H, 8.86; found: C, 90.93, H, 9.04%.

Synthesis of 1,1,2-trimethyl-2,2,3-triphenylcyclopropane (3c). 3,4,4-Trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (**2c**) (0.1 g, 0.2937 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When heated, the crystals

melted and evolution of nitrogen gas was observed. The NMR tube was removed from the oil bath after 4 h of heating, and hexane was added to dissolve the products. The crude product was purified by chromatatron (hexanes) to give **2c** in 91% yield (0.83 g, 0.267 mmol) as a colorless viscous liquid. ^{1}H NMR ($CDCl_3$) 300 MHz: δ 1.32 (s, 3H), δ 1.33 (s, 3H), δ 1.38 (s, 3H), δ 6.9–7.6 (m, 15H); ^{13}C NMR ($CDCl_3$) 300 MHz: 22.2, 26.8, 27.2, 28.1, 37.9, 46.2, 125.0, 125.3, 125.5, 127.5, 127.9, 128.1, 131.0, 131.3, 143.9, 144.3, 144.4. MS Molecular Ion – 312. Anal. Calcd. for $C_{24}H_{24}$: C, 92.24, H, 7.74%; Found: C, 92.39, H, 7.60%.

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