SYNTHESIS OF 3,3,4,4,5-PENTASUBSTITUTED-5-VINYL-4,5-DIHYDRO-3*H*-PYRAZOLES: ROUTE TO VINYLCYCLOPROPANES

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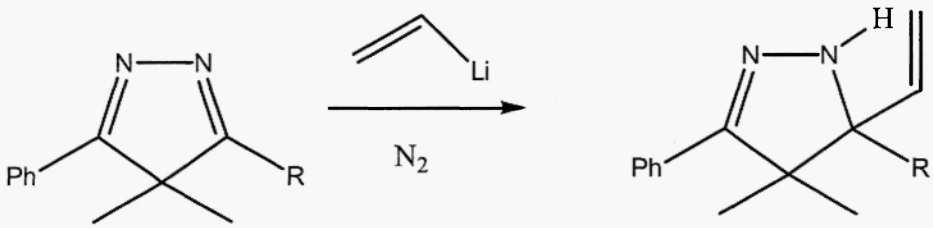
Abstract : The reaction of vinyl-substituted-3,4-dihydro-2H-pyrazoles, **1a** (R=Ph) and **b** (R=Me) [synthesized by reaction of vinyllithium with the corresponding cyclic azines], with iodobenzene diacetate produced the vinyl substituted-4,5-dihydro-3H-pyrazoles, pyrazolines **2a-b**, in fair yield. Thermal decomposition of **2a** yielded the highly substituted vinylcyclopropane, **3**, as the only observable product..

Introduction

Previously, we have reported methodology[1] for the synthesis of hexasubstituted 4,5-dihydro-3H-pyrazoles (pyrazolines) based on procedures developed for the synthesis of cyclic α-azohydroperoxides.[2] The new route to highly substituted pyrazolines involved two basic steps. The initial step was the addition of either methyllithium or phenyllilthium to a cyclic azine (4H-pyrazole) to produce 3,4-dihydro-2H-pyrazoles. The subsequent reaction of these reactive intermediates with lead tetraacetate in various solvents produced high yields of highly substituted acetoxy- or alkoxy-containing pyrazolines. Thermolytic decomposition of the highly substituted pyrazolines was shown[1,3,4] to be a useful route for the synthesis of selected hexasubstituted cyclopropanes. For mechanistic studies, vinyl-substituted compounds in this series were needed. However, there appear to be no reports in the literature of the addition of vinyllithium reagent to 4H-pyrazoles. We report here the synthesis of highly substituted vinyl-containing pyrazolines, the subsequent thermolysis of which is a route to highly substituted vinylcyclopropanes.

Results and Discussions

The reaction of vinyllithium with 4,4-dimethyl-3,5-diphenyl-4H-pyrazole or 3,4,4-trimethyl-5-phenyl-4H-pyrazole produced the corresponding vinyl-substituted 3,4-dihydro-2H-pyrazoles (**1a-b**) in very good to excellent yields (rxn 1). Compounds **1a-b** were, as expected,[2] very air-sensitive and difficult to handle.



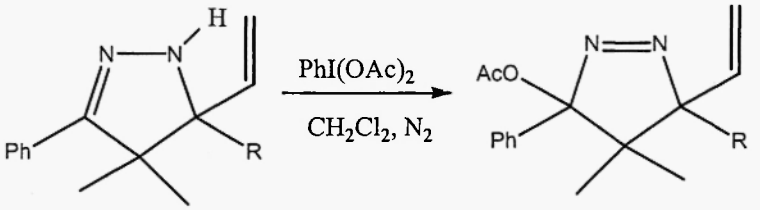
(1)

R=Ph or Me

1a R=Ph
b R=Me

Compounds **1a-b** were isolated as oils. Reaction of **1a-b** with lead tetraacetate led to the formation of vinyl-pyrazoles in very poor yields, presumably due to competing reaction of the reagent with the vinyl

moiety.[5] Substitution of iodobenzene diacetate for the lead reagent resulted in greatly improved yields (rxn 2) of vinyl-pyrazolines, **2a-b**. Compounds **2a-b** were purified with isolated yields ranging from 30-40%. The stereo-chemistry of the 3,5-diphenyl groups in **2a** was determined to be exclusively cis.

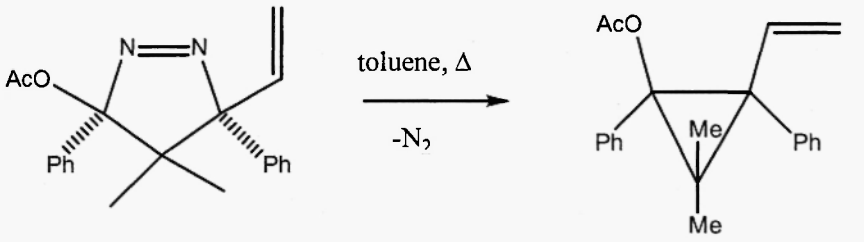


(2)

1a-b

2a R=Ph (cis to 3-Ph)
b R=Me (cis/trans)

Compound **2b** proved to be essentially a 50/50 mixture of the cis to trans 5-methyl-3-phenyl compounds. Rxn 2 could be carried out using purified **1a-b** or directly without purification of the 3,4-dihydro-2H-pyrazoles with little or no effect on the yield.



(3)

2a **3**

The thermolysis of pyrazoline **2a** produced the corresponding crude cyclopropane **3**, with the phenyl groups cis to one another, as the only product observable by NMR spectroscopy (rxn 3). The crude cyclopropane was purified via chromatatron followed by Kugelrohr distillation to produce an analytically pure sample of **3** (47% isolated yield). The thermolysis was carried out under relatively mild conditions (refluxing toluene for ~18 hrs) compared to that for similar non-vinyl containing pyrazolines.[1,3,4] The isomeric "trans" cyclopropane was not observed under these conditions. Based on earlier work,[6-8] the mechanism of pyrazoline decomposition is believed to involve the extrusion of nitrogen gas to yield a singlet 1,3-diradical. The retention of configuration in the product could be due to rapid closure of the singlet diradical or to the inherently greater stability of the cis-phenyl compound. In our earlier studies,[1] thermolysis of non-vinyl containing pyrazolines at much higher temperature yielded products with a very high degree of retention of stereochemistry. The present result is consistent with the earlier work and favors the rapid closure argument since, in addition, no ring expansion product (4-acetoxy-5,5-dimethyl-1,4-diphenylcyclopentane) was detected. The ring expansion product would arise from 1,5-coupling of the diradical (involving the distal position of the allylic radical). Furthermore, the lowered stability of the vinyl-containing pyrazolines suggests that scission of the bond between the nitrogen and C-5 is now leading step in 1,3-diradical formation in contrast to the earlier results.[5]

The current results show that the addition of the less-reactive vinyllithium to the 4H-pyrazoles is efficient and allows for the introduction of additional functionality into the ring system. For the vinyl-containing 3,4-dihydro-2H-pyrazoles, the use of the more environmentally friendly iodobenzene diacetate (instead of lead tetraacetate) resulted in better yields for the introduction of an acetoxy group. In conclusion, the overall methodology is useful for the synthesis of highly substituted vinylcyclopropanes.

Experimental

All solvents (HPLC grade) were commercially available (Aldrich). When needed, solvents were dried by the standard procedures before use. Vinyllithium was prepared in situ according to published procedures.[9] Alkyllithium reagents, lead tetraacetate, and iodobenzene diacetate, were commercially available (Aldrich) and were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 MHz spectrometer. The IR spectra were recorded on a Perkin-Elmer 1600-FTIR spectrometer. All MS were performed at the Georgia Institute of Technology, Atlanta, GA. Melting points were obtained with a Thomas Hoover Unimelt apparatus and are uncorrected. Elemental analyses (C, H, N), carried out by Atlantic Microlab, Inc., are in agreement ($\pm \leq 0.3\%$) with the calculated values.

4,4-Dimethyl-3,5-diphenyl-3-vinyl-3,4-dihydro-2H-pyrazole (**1a**) was prepared from 4,4-dimethyl-3,5-diphenyl-4H-pyrazole[2] by reaction with vinyllithium in anhydrous diethyl ether at 0°C, under nitrogen. Due to its instability, the crude oil (90% yield) was only characterized by its ^{1}H NMR ($CDCl_3$) [0.85 (s, 3H), 1.43 (s, 3H), 3.5 (b s, 1H), 5.1 (dd, J = 18 Hz, J = 1 Hz, 1H), 5.3 (dd, J = 11 Hz, J = 1 Hz, 1H), 6.6 (dd, J = 18 Hz, J = 11 Hz, 1H), 7.2-8.0 (m, 10H)].

3,4,4-trimethyl-5-phenyl-3-vinyl-3,4-dihydro-2H-pyrazole (**1b**) was prepared as above for **1a** from 3,4,4-trimethyl-5-phenyl-4H-pyrazole[2] (92% yield); ^{1}H NMR ($CDCl_3$): 1.15 (s, 3H), 1.22 (s, 3H), 1.42 (s, 3H), 3.2 (b s, 1H), 5.3 (dd, J = 18 Hz, J = 1 Hz, 1H), 5.6 (dd, J = 11 Hz, J = 1 Hz, 1H), 6.3 (dd, J = 18 Hz, J = 11 Hz, 1H), 7.2-8.0 (m, 5H).

3-Acetoxy-4,4-dimethyl-3,5-diphenyl-5-vinyl-4,5-dihydro-3H-pyrazole (**2a**, phenyl groups cis[10] to each other) was prepared from **1a** by treatment with 1.1 equivalents of either lead tetraacetate or iodobenzene diacetate in anhydrous methylene chloride, under nitrogen, at 0°C (8% and 42% isolated yields, respectively); mp 135-137°C; MS (CI) M+/e 335; IR (KBr) C=O, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$): -0.22 (s, 3H), 1.43 (s, 3H), 2.40 (s, 3H), 5.02 (dd, J = 1Hz, J = 18 Hz, 1H), 5.30 (dd, J = 11 Hz, J = 1 Hz, 1H), 6.36 (dd, J = 18 Hz, J = 11 Hz, 1H), 7.14-7.52 (m, 10H); ^{13}C NMR ($CDCl_3$): 8.9,17.0, 21.6, 25.1, 47.2, 117.9, 119.1, 124.7, 126.6, 127.6, 127.7, 128.4, 128.5, 128.7, 129.9, 132.7, 168.0.

3-Acetoxy-3,4,4-trimethyl-3-phenyl-5-vinyl-4,5-dihydro-3H-pyrazole (**2b**) was prepared from **1b** following the same procedure used for the preparation of **2a**, and it was obtained in an isolated yield of 30% (for iodobenzene diacetate) as a 51/49% mixture of isomers which was not resolved; mp 82-84°C; MS (CI) M+/e 335; IR (KBr) C=O, 1758 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.15 (s, 3H), 0.23 (s, 3H), 1.15 (s, 3H), 1.20 (s, 3H),1.41 (s, 3H), 1.59 (s, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 5.23 (dd, J = 1Hz, J = 18 Hz, 2H), 5.30 (dd, J = 11 Hz, J = 1 Hz, 2H), 6.36 (dd, J = 18 Hz, J = 11 Hz, 2H), 7.30-7.60 (m, 10H).

1-Acetoxy-2,2-dimethyl-1,3-diphenyl-3-vinylcyclopropane (**3**, phenyl groups cis to each other) was prepared from **2a** by heating a toluene solution (reflux) under nitrogen for ~18 hours. Cyclopropane **3** was the only product observed by ^{1}H NMR and this product was purified by Kugelrohr distillation to afford **3** (47% yield) as a solid; mp 57-59°C; MS (CI) M+/e 306; IR (KBr) C=O, 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.21 (s, 3H), 1.45 (s, 3H), 2.08 (s, 3H), 4.41 (dd, J = 1Hz, J = 18 Hz, 1H), 5.12 (dd, J = 11 Hz, J = 1 Hz, 1H), 6.15 (dd, J = 18 Hz, J = 11 Hz, 1H), 7.13-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$): 18.8, 21.4, 24.6, 31.6, 43.5, 72.4, 117.9, 119.1, 126.6, 127.0, 127.5, 129.9, 132.7, 137.6, 138.0, 139.3, 170.5.

Acknowledgments

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