Synthesis of 4,4-Dimethyl-3,4-dihydro-3,3,5-trisubstituted-2*H*-pyrazoles and *N*-Benzoyl Derivatives: Method for "Hydrolysis" of Unreactive Amides and Carbamates

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Addition of organolithium reagents to 4,4-dimethyl-3,5-disubstituted-4*H*-pyrazoles produced a series of 4,4-dimethyl-3,4-dihydro-3,3,5-trisubstituted-2*H*-pyrazoles, **2-6**, in good yield. The reaction was stereoselective: addition of organolithium compounds occurred only to carbon-3 of 4,4-dimethyl-3-alkyl-5-aryl-4*H*-pyrazoles. The 3,4-dihydro-2*H*-pyrazoles were found to be of high sensitivity to oxygen. For long term storage and ease of handling, N-benzoyl derivatives were synthesized. Removal of the protecting group could not be accomplished by use of many standard sets of conditions. Deprotection was accomplished in high yield by reaction of the N-benzoyl-4,4-dimethyl-3,4-dihydro-3,3,5-trisubstituted-2*H*-pyrazoles with anhydrous potassium *t*-butoxide in toluene [heated under reflux (ultra-pure argon)] in the presence of a phase transfer catalyst (18-Crown-6). Cleavage of a N-carbamate derivative was also achieved by this phase transfer approach. This methodology should be applicable to the hydrolysis of unreactive amides and carbamates in general.

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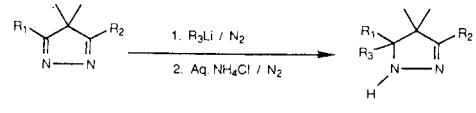
α-Azohydroperoxides are an extremely reactive class of organic hydroperoxides in electrophilic oxygen-atom transfer chemistry [1]. Cyclic α-azohydroperoxides, 5-hydroperoxy-4,5-dihydro-3*H*-pyrazoles, are of similar reactivity [2] to that of flavin-4a-hydroperoxides [3] in heteroatom oxidation and are approximately two orders of magnitude more reactive than electronically-similar acyclic analogs [4]. Prior to 1987, only one cyclic α-azohydroperoxide, *cis*-3-bromo-4,5-dihydro-5-hydroperoxy-3,5-diphenyl-3*H*-pyrazole, was known [5]. The synthetic approach [5] to this compound was found to be highly specialized and of limited scope. Recently, we have developed [6] a new synthetic route to cyclic α-azohydroperoxides *via* oxidation of 3,4-dihydro-2*H*-pyrazoles (reaction 1). We report here the synthesis of a series of 4,4-dimethyl-3,4-dihydro-3,3,5-trisubstituted-2*H*-pyrazoles by addition of organometallic reagents to the corresponding 4,4-dimethyl-3,5-disubstituted-4*H*-pyrazoles as well as methods for the protection/deprotection of these unstable (oxygen-sensitive) compounds.

(1)

Results and Discussion.

The addition of organometallic reagents to 4,4-dimethyl-3,5-disubstituted-4*H*-pyrazoles, cyclic azines **1a-c**, produced a series of 4,4-dimethyl-3,4-dihydro-3,4,5-trisubstituted-2*H*-pyrazoles, **2-6**, in good yield (reaction 2).

Reaction 2 worked well with methyl or phenyl lithium: addition of methyl lithium to **1a** or phenyl lithium to **1b** yielded **6** in essentially equivalent yields. In addition, the



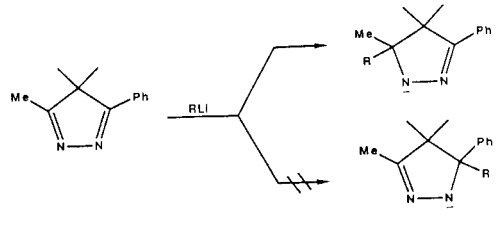
(2)

R_3=Ph;CH_3

1a	R_1=R_2=Ph	2	R_1=R_2=R_3=Ph	96%
1b	R_1=CH_3; R_2=Ph	3	R_1=R_3=CH_3 R_2=Ph	91%
1c	R_1=R_2=CH_3	4	R_1=R_2=R_3=CH_3	86%
		5	R_1=R_2=CH_3; R_3=Ph	90%
		6	R_1=CH_3; R_2=R_3=Ph	89%

corresponding Grignard reagents could be substituted for the organolithium compounds with little or no effect on the product yields. 3,5-Alkyl and/or aryl substituents on the 4*H*-pyrazoles, **1a-c**, yielded equivalent results. Reaction 2 was found to be stereoselective. Addition of the organometallic reagents to unsymmetric 4,4-dimethyl-3-alkyl-5-phenyl-4*H*-pyrazoles occurred exclusively at the 3-alkyl position (Scheme 1).

SCHEME 1

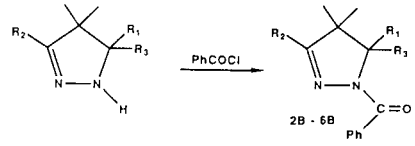


Consistent with these results, addition of the organolithium reagents to the 3,5-dimethyl compound **1c** was observed to be slower than the corresponding additions to **1a** and **1b**. With the exception of compound **2**, the 3,4-dihydro-2*H*-pyrazoles were found to be extremely oxygen sensitive. Pure samples or solutions in nonprotic solvents became discolored (dark red) and underwent complete decomposition (*via* the unstable α-azohydro-

peroxides) within minutes of exposure to the atmosphere. Compounds **3-6** had to be kept under inert atmosphere at all times. However, the compounds were much less sensitive to autoxidation in protic solvents and could be readily purified by recrystallization or precipitation from ethanol (under nitrogen) at low temperature. The 3,4-dihydro-2*H*-pyrazoles were characterized by spectroscopic and physical methods.

Addition of Grignard reagents has been shown to occur to the carbon-nitrogen double bond of acyclic azines to yield hydrazones [7]. The addition of organolithium compounds to azines has not been extensively investigated while that to imides may be hampered when α-hydrogens are present [8-9]. In the present cases, α-hydrogens did not affect the results; however, position-4 of the 4*H*-pyrazole starting materials was required to be blocked. The reaction of organolithium reagents with the imine of *N*-alkenylimines [10] to produce the enolates of the corresponding enamines is analogous to the behavior observed in reaction 2. A second addition of excess organolithium reagent to the anion of the 3,4-dihydro-2*H*-pyrazoles (reaction 2) was not observed.

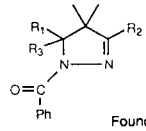
The extreme sensitivity (decomposition) of compounds **2-6** to the presence of even trace amounts of oxygen made long-term storage inconvenient and impractical. Protection of the N-H group was necessary to overcome this problem. Compounds **2-6** were found to undergo reaction with benzoyl chloride in pyridine to yield the stable *N*-benzoyl derivatives, **2B-6B**, in good yield (reaction 3).



(3)

The N-benzoyl derivatives **2B-6B** were easy to purify and handle (air-stable, crystalline solids). In addition, since 3,4-dihydro-2*H*-pyrazoles **3-5** were oils, the corresponding *N*-benzoyl derivatives were necessary for final structure proof. For convenience, the *N*-benzoyl derivatives could also be generated directly in good yield from the lithium salts produced in reaction 2 without isolation of the 3,4-dihydro-2*H*-pyrazoles. The results are summarized in Table 1.

Table 1. Physical Data on N-Benzoyl Compounds **2B-6B**.

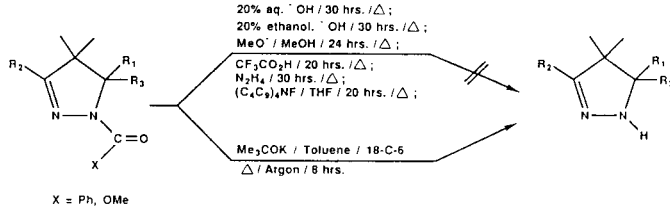


Compound	R_1	R_2	R_3	Yield [a]	mp (°C)	Formula	Found (%) (Calcd) (%) C	H	N
2B	Ph	Ph	Ph	95	219-220	$C_{30}H_{26}N_2O$ 1/2 H_2O	82.34 (82.16)	6.47 (6.20)	6.27 (6.38)
3B	CH_3	Ph	CH_3	84	111-112	$C_{20}H_{22}N_2O$	78.20 (78.40)	7.18 (7.23)	-- --
4B	CH_3	CH_3	CH_3	78	100-101	$C_{15}H_{20}N_2O$	73.77 (73.73)	8.20 (8.25)	-- --
5B	CH_3	CH_3	Ph	89	128-129	$C_{20}H_{22}N_2O$	78.31 (78.40)	7.25 (7.23)	-- --
6B	Ph	Ph	CH_3	93	144-145	$C_{25}H_{24}N_2O$	81.44 (81.49)	6.59 (6.56)	7.61 (7.60)

[a] % isolated; recrystallized from EtOH

Cleavage of the *N*-benzoyl derivatives **2B-6B** to regenerate the 3,4-dihydro-2*H*-pyrazoles was found to be more difficult than expected. Many standard sets of "hydrolysis" conditions [11] resulted in no net reaction: compound **6B** was inert to boiling 20% ethanolic potassium hydroxide even after 30 hours. Deprotection was achieved in good yield by heating the *N*-benzoyl compounds with potassium *t*-butoxide in toluene with a crown ether (18-Crown-6) as phase transfer catalyst [12] (Scheme 2) under inert atmosphere (ultra-pure argon). For example, isolated yields of **2**, **4** and **6** of 90%, 81% and 86%, respectively, were obtained for cleavage of **2B**, **4B** and **6B**.

SCHEME 2



To determine if this method was applicable to the cleavage of other "hydrolysis-resistent" systems, the carbamate derivative **7** of compound **6** was synthesized by reaction with methyl chloroformate. As expected this compound was inert to normal "hydrolysis" attempts [11]. However, this carbamate derivative underwent smooth cleavage to regenerate **6** in good yield under the phase transfer conditions developed for removal of the *N*-benzoyl protecting group (Scheme 2). This methodology should be applicable to the cleavage of unreactive amides and carbamates in general.

Summary.

Organometallic reagents undergo stereoselective addition to 4,4-dimethyl-3,5-disubstituted-4*H*-pyrazoles to produce the air-sensitive 3,4-dihydro-2*H*-pyrazoles in good yield. *N*-Protected derivatives are straightforward to prepare but are resistent to "hydrolysis" under standard conditions. The use of phase transfer catalysts allows the facile removal of the unreactive amides and carbamate groups. This methodology should be applicable to other hydrolysis-resistant systems.

EXPERIMENTAL

All solvents were of reagent grade (Aldrich). Tetrahydrofuran and diethyl ether were distilled from benzophenone/sodium metal before use. Toluene and benzene were distilled, from over calcium hydride, prior to use. Phenyl lithium, methyl lithium, potassium *t*-butoxide, phase-transfer catalyst (18-Crown-6), and benzoyl chloride were commercially available (Aldrich) and were used without further purification. The nmr spectra were recorded on a JEOL GX-270 and a Varian GX-400 NMR spectrometer. Melting points were taken in a Thomas Hoover Uni-melt apparatus and are uncorrected. Analyses were performed at Atlantic Microlabs, Atlantic, GA. The ms data were obtained at the Georgia Institute of Technology.

4,4-Dimethyl-3,5-disubstituted-4*H*-pyrazoles **1a-c**.

Compounds **1a-c** were prepared by the reaction of the corresponding 2,2-dimethyl-1,3-diketones with hydrazine. The following procedure [13] is representative: to a solution of 25.2 g (0.10 mole) of 2,2-dimethyl-1,3-diphenyl-1,3-propanedione [14] in 200 ml of dry benzene, 6.4 g (0.20 mole) of hydrazine was added, dropwise. The mixture was heated under reflux (under nitrogen) and water was removed by use of a Dean-Stark trap (total reaction time 6-8 hours). The volatile components were removed under reduced pressure. The residue was crystallized from benzene to yield 24.0 g (97%) of **1a**, mp 126-127° (lit mp 127-128° [13]). Compound **1c** was obtained in 93% yield, mp 94-95° (from benzene, lit value 94-95° [13]); **1c** 92% yield mp 43-44° (from hexane, lit mp = 44° [13]).

The 2,2-dimethyl-1,3-diketones (2,2-dimethyl-1,3-diphenyl-1,3-propanedione [14], 1-phenyl-2,2-dimethyl-1,3-butanedione [13], and 3,3-dimethyl-2,4-pentanedione [15]) were prepared in good yield by dimethylation of the corresponding 1,3-diketones in toluene (methyl iodide, potassium carbonate, phase-transfer catalyst [16]).

4,4-Dimethyl-3,4-Dihydro-3,3,5-trisubstituted-2*H*-pyrazoles **2-6**.

The synthesis, isolation, purification and storage of these compounds were carried out under inert (ultra-pure nitrogen) atmosphere. The synthesis of compound **6** has been previously reported [6]. The following synthesis of **2** is representative. A solution of 2.5 g (0.010 mole) of 3,5-diphenyl-4,4-dimethyl-4*H*-pyrazole **1a** in 20 ml of diethyl ether/tetrahydrofuran (1/1 by vol) was prepared under inert atmosphere and anhydrous conditions and cooled to 0°. A 1.2 fold excess of 2.0 *M* phenyl lithium (6.0 ml, 0.012 mole) in ether was added to the reaction mixture *via* syringe. The solution immediately became dark in color. The solution was allowed to warm to room temperature followed by heating under reflux for 16 hours (overnight). The solution was cooled to 0° and quenched with degassed, saturated, aqueous ammonium chloride solution. The organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to yield a crude solid. Pure **2**, mp 120-122° (3.1 g, 0.0096 mole), was obtained in 96% yield by recrystallization from ethanol at low temperature (under an inert atmosphere); ^{1}H nmr (deuteriochloroform): δ 1.28 (s, 6H), 5.95 (br s, 1H), 7.15-7.50 (m, 13H), 7.60-7.80 (m, 2H); ^{13}C nmr (deuteriochloroform): 23.1, 52.9, 81.1, 127.0, 127.1, 127.6, 127.7, 128.2, 128.3, 132.5, 142.1, 158.4; ms: M$^+$/e 326: ir (potassium bromide): 3320 cm^{-1} N-H.

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.62; H, 6.79; N, 8.58. Found: C, 84.45; H, 6.80; N, 8.53.

Compound **3** was obtained as an oil, 91%, high sensitivity to oxygen; ^{1}H nmr (deuteriochloroform): δ 1.15 (s, 6H), 1.19 (s, 6H), 5.1 (br s, 1H), 7.17-7.7 (m, 3H), 7.78-8.0 (m, 2H); ^{13}C nmr (deuteriochloroform): 20.1, 22.2, 50.5 (q), 68.5 (q), 126.8, 128.3, 128.8, 133.7, 158.7; ms: M$^+$/e 202.2 (39%). Compound **4** was obtained as an oil, 86%, extreme sensitivity to oxygen; ^{1}H nmr (deuteriochloroform): δ 0.95 (s, 6H), 1.08 (s, 6H), 1.85 (s, 3H), 4.83 (br s, 1H); ^{13}C nmr (deuteriochloroform): 12.4, 19.0, 22.7, 50.4 (q), 66.0 (q), 160.1.

Compound **5** was obtained as an oil, 90%, high sensitivity to oxygen; ^{1}H nmr (deuteriochloroform): δ 0.52 (s, 3H), 1.17 (s, 3H), 1.39 (s, 3H) 1.88 (s, 3H), 4.9 (br s, 1H), 7.06-7.70 (m, 5H); ^{13}C nmr (deuteriochloroform): 12.5, 18.7, 21.6, 24.1, 51.9 (q), 72.4 (q), 127.2, 128.2, 128.8, 143.3, 158.4. For Compound **6** mp 79.81°, 92%, high sensitivity to oxygen; ^{1}H nmr (acetone) δ 0.86 (s, 3H), 1.46 (s, 3H), 1.53 (s, 3H), 6.4 (br s, 1H), 7.2-7.9 (m, 10H); ^{13}C nmr (deuteriochloroform) 19.6, 22.7, 23.4, 51.9, 74.2, 126.0, 126.6, 126.7, 127.8, 127.9, 133.2, 142.0, 156.8; ms M$^+$/e 264; ir (potassium bromide): 3250 cm^{-1} NH.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.59. Found: C, 81.66; H, 7.64; N, 10.54.

N-Benzoyl-4,4-trimethyl-3,4-dihydro-3,3,5-trisubstituted-2*H*-pyrazole **2B-6B**.

The following procedure for the synthesis of **6B** is representative. A mixture (under an inert atmosphere) of 2.6 g (0.01 mole) of **6** and 1.5 g (0.011 mole) benzoyl chloride in 10 ml of pyridine was stirred at room temperature for 1 hour and then heated to 100° for 2 hours. The reaction mixture was cooled, quenched with 100 ml of 5% aqueous hydrochloric acid, and the organic materials extracted in 100 ml of benzene/ether (1:1 vol). The benzene/ether layer was washed with dilute aqueous hydrochloric acid followed by saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a crude solid. The product was recrystallized from ethanol to obtain 3.2 g (86%) of **6B**, mp 144-145°; ^{1}H nmr (deuteriochloroform): δ 0.82 (s, 3H), 1.41 (s, 3H), 1.90 (s, 3H), 7.18-7.39 (m, 11H), 7.60-7.62 (m, 2H), 7.86-7.88 (m, 2H); ^{13}C nmr (deuteriochloroform): 19.5, 22.1, 23.2, 55.0, 75.9, 126.2, 127.2, 127.6, 127.8, 128.2, 128.5, 129.6, 130.1, 130.9, 131.8, 135.7, 139.7, 161.0, 168.5; ms: M$^+$/e 368.

The physical and spectra data for the remaining *N*-benzoyl derivatives are reported below.

Compound **2B** had mp 219-220°, yield 95%; ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 6H), 7.29-7.51 (m, 18H), 7.78-7.81 (m, 2H); ^{13}C nmr (deuteriochloroform): 25.6, 52.9, 84.3, 126.4, 126.9, 127.0, 128.0, 128.2, 128.5, 129.6, 130.0, 130.9, 139.3, 163.5, 170.1; ms: 430 M$^+$/e.

Compound **3B** had mp 111-112°, 84%; ^{1}H nmr (deuteriochloroform): δ 1.29 (s, 6H), 1.53 (s, 6H), 7.35-7.43 (m, 6H), 7.65-7.69 (m, 2H), 7.79-7.82 (m, 2H); ^{13}C nmr (deuteriochloroform): 19.7, 20.5, 53.0, 70.6, 127.4, 128.4, 129.5, 129.8, 130.5, 131.9, 136.0, 161.3, 168.9; ms: M$^+$/e 306.

Compound **4B** had mp 100-101°, 78%; ^{1}H nmr (deuteriochloroform): δ 1.03 (s, 6H), 1.45 (s, 6H), 1.91 (s, 3H), 7.25-7.75 (m, 3H), 7.94-7.97 (m, 2H); ^{13}C nmr (deuteriochloroform): 12.2, 19.4, 20.1, 52.8, 68.8, 127.4, 129.4, 130.3, 136.3, 162.9, 168.4; ms: M$^+$/e

244.

Compound **5B** had mp 128-129°, 89%; ^{1}H nmr (deuteriochloroform): δ 1.28 (s, 6H), 1.61 (s, 3H), 1.96 (s, 3H), 7.35-7.52 (m, 8H), 7.76-7.81 (m, 2H); ^{13}C nmr (deuteriochloroform): 11.8, 26.4, 26.5, 26.9, 51.1, 76.5, 127.4, 128.9, 129.5, 130.0, 130.5, 131.6, 134.6, 136.2, 163.5, 167.6; ms: M$^+$/e 306.

The following modification can be employed for the direct synthesis of **2B-6B** without isolation of the 3,4-dihydro-2*H*-pyrazoles. For example, a solution (0.01 mole) of the anion of **6** in ether/-tetrahydrofuran (1:1 vol) taken directly from the organolithium addition without quenching or work-up, cooled to 0° was treated with 1.7 g (0.012 mole) of benzoyl chloride (inert atmosphere, magnetic stirring). The reaction mixture was allowed to warm to ambient temperature and then heated under reflux for 4 hours. Work-up as before yielded 3.5 g (93%) of **6B** after recrystallization.

The *N*-carbamate derivative **7** was synthesized by the above procedure by substitution of methyl chloroformate (Aldrich) for benzoyl chloride, 94%, mp 156-157°; ^{1}H nmr (deuteriochloroform): δ 0.76 (s, 3H) 1.35 (s, 3H), 1.89 (s, 3H), 3.81 (s, 3H), 7.20-7.38 (m, 8H), 7.61-7.64 (m, 2H); ^{13}C nmr (deuteriochloroform): 19.8, 21.9, 22.9, 52.8, 55.5, 75.1, 126.0, 127.2, 127.9, 128.1, 128.3, 129.4, 131.7, 140.4, 154.3, 161.2; ms: M$^+$/e 322.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.65; H, 6.89; N, 8.60.

Cleavage of the *N*-Benzoyl Derivatives.

The following procedure was used to cleave the *N*-benzoyl and *N*-carbamate derivatives to regenerate the 3,4-dihydro-2*H*-pyrazoles. A mixture of 0.01 mole of *N*-substituted derivative, 5.6 g (0.05 mole) of potassium *t*-butoxide and 0.050 g (0.0002 mole) of 18-Crown-6 in 30 ml of anhydrous toluene were heated under reflux in an inert atmosphere (ultra pure Argon) for 8 hours. Use of anhydrous benzene as the solvent required extended reaction times (15 hours). The reaction mixture was cooled and quenched with degassed, saturated, aqueous sodium chloride solution. Work-up as before and recrystallization from ethanol at -20° (inert atmosphere) afforded the desired compounds in 85-90% yields.

Acknowledgment.

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