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Oxygen-Atom Transfer Reagents: New, Reactive α-Azohydroperoxides‡

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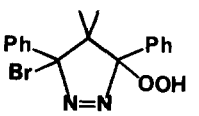
Summary: 3,4,4-Trimethyl-4,5-dihydro-5-hydroperoxy-3,5-diaryl-3H-pyrazoles, synthesized by autoxidation of the corresponding 3,4-dihydro-2H-pyrazoles, are a new type of cyclic α-azohydroperoxide which is of high reactivity in oxygen-atom transfer chemistry.

Organic hydroperoxides are important reagents for the oxidation of many classes of organic compounds.[1] In addition to free-radical pathways, organic hydroperoxides are able to transfer oxygen-atoms under mild conditions via concerted (electrophilic) mechanisms (reaction 1). We have recently shown[2] that a class of "alkyl" hydroperoxides, α-azohydroperoxides

$$ROOH + :X \rightarrow ROH + O{=}X \qquad (1)$$

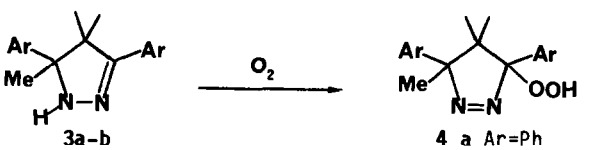
(α-peroxydiazatenes) are of high reactivity in ionic (electrophilic) oxygen-atom transfer reactions. Many acyclic α-azohydroperoxides (**1**) are known[3] but only one cyclic compound, **2** (cis-3-bromo-4,5-dihydro-5-hydroperoxy-3,5-diphenyl-3H-pyrazole),[4] has been reported. Cyclic α-azohydroperoxide **2** has been shown[5] to be of similar reactivity to that of flavin 4a-hydroperoxide model compounds[6] in heteroatom oxidations. Interestingly, **2** is approximately two orders of magnitude more reactive[7] than acyclic analogs (**1**). Unfortunately, the synthetic route[4] to **2** is highly specialized; of limited scope; and, thus, has not been successfully applied to even the synthesis of closely related compounds. Additional cyclic α-azohydroperoxides are needed to better understand the factors that determine the ease of oxygen-atom transfer. We wish to report the synthesis, via a new autoxidation route, of new cyclic α-azohydroperoxides that are of high reactivity in oxygen-atom transfer chemistry.

$R_1R_2C(OOH)\text{-}N{=}N\text{-}R_3$ **1**



2

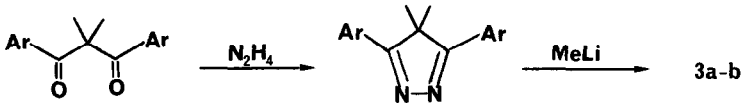
The autoxidation of 3,4,4-trimethyl-3,4-dihydro-3,5-diaryl-2H-pyrazoles **3** in acetone at low temperature produced the α-azohydroperoxides **4** (3,4,4-trimethyl-4,5-dihydro-5-hydroperoxy-3,5-diaryl-3H-pyrazoles, reaction 2) in good yield.



3a-b **4** a Ar=Ph; b Ar=p-$MeOC_6H_4$ (2)

‡This paper is dedicated to Professor P.D. Bartlett on the occasion of his 80th birthday.

The 3,4-dihydro-2H-pyrazoles **3** are new compounds and were synthesized by addition of methyllithium to cyclic azines prepared by addition of hydrazine to 1,3-diketones as shown below:



Compounds **3a-b** were extremely sensitive to oxygen and underwent complete autoxidation in solution in minutes at room temperature upon exposure to the atmosphere. Unlike compounds of the general type **1**, cyclic α-azohydroperoxides **4a-b** could not be isolated from autoxidations of **3** in benzene-d_6 despite the observation that the reaction was complete within minutes at low temperature; only decomposition products were obtained. However, the autoxidation of **3** could be controlled if carried out in acetone. In acetone-d_6, the α-azohydroperoxides **4** were formed in 76-82% yield and could be isolated (Caution!). Reaction times varied from 3 hrs at -20°C to one hour at 0°C. Due to the explosive properties of α-azohydroperoxides, the structures were established by analysis of spectral data (^1H and ^{13}C NMR spectra) and by characterization of the corresponding (stable) α-azohydroxides **5**. Treatment of acetone-d_6 solutions of **4a-b** with excess dimethylsulfide at 0°C resulted in the formation of the corresponding α-azohydroxides **5a-b** in essentially quantitative yield (80% isolated yield) with concomitant formation of dimethylsulfoxide (Reaction 3). The structures were proven by physical and spectral

(3)

methods. The ^1H NMR spectra of the cyclic α-azohydroperoxides showed the signal for one of the 4,4-dimethyl groups to be upfield of that of TMS (similar to that of **2**). This methyl group must lie between the faces of the two 3,5-diaryl groups indicating that the phenyls are in a cis configuration (confirmed by crystal structure determination of the acetyl derivative of **5a**). ^1H NMR data, obtained for the α-azohydroxides **5**, showed similar characteristics.

The oxygen-atom transfer capabilities of the new cyclic α-azohydroperoxides **4a-b** were determined relative to that of **2** and that of a typical acyclic compound **1a** [p-$MeOC_6H_4CH(OOH)$-N=NPh] for S-oxidation (BzSMe) in acetone -d_6 at 34°. All kinetic runs showed excellent second-order behavior (first order in substrate and α-azohydroperoxide). The cyclic compounds **4a-b** were of comparable reactivity to **2** and approximately 100 times more reactive than the acyclic compound **1a**. The S-oxidations in acetone-d_6 were found to be approximately 20 fold slower than the corresponding oxidations in aprotic nonpolar solvents (benzene-d_6).[7b,8] N-oxidation of triethylamine by **4a-b** or **2** in acetone-d_6 at 34° showed similar reactivity patterns for N- and S-oxidation (Table 1).

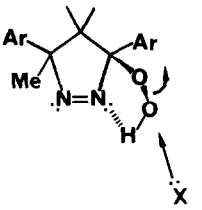
The relative reactivity of α-azohydroperoxides **4** toward oxygen-atom transfer reactions is high, similar to that of **2** and those of "intramolecularly catalyzed" compounds.[9] This suggests that the enhanced reactivity noted for **2** (compared to that of acyclic compounds) is an inherent property of the system and not due to the presence of a labile bromine and/or

Table 1. Product Yields and Rate Constants for Oxygen-Atom Transfer Reactions of α-Azohydroperoxides 1a, 2, 4a, 4b with Substrates in Acetone-d_6 at 34°C.

ROOH	Substrate	Product	Yield %	$k_2 M^{-1}sec^{-1}$	Rel React.
4a	BzSMe	BzS(O)Me	92	$4.0\pm0.5\times10^{-2}$	1.00
4b	BzSMe	BzS(O)Me	100	$1.8\pm0.2\times10^{-2}$	0.45
2	BzSMe	BzS(O)Me	100	$1.0\pm0.3\times10^{-1}$	2.5
1a	BzSMe	BzS(O)Me	81	$4.9\pm0.5\times10^{-4}$	0.012
4a	Et_3N	Et_3NO	74	$1.0\pm0.2\times10^{-2}$	1.00
4b	ET_3N	Et_3NO	86	$5.7\pm0.4\times10^{-3}$	0.57
2	Et_3N	Et_3NO	100	$2.3\pm0.2\times10^{-2}$	2.3

subsequent unusual reactions of **2**. The slight difference in reactivity between **4a** and **4b** is consistent with that expected[7b] based on the electronic effect of a methoxy group. The enhanced reactivity of cyclic α-azohydroperoxides is likely due to a combination of the increased basicity of the syn azo function and the presence of the five-membered intramolecular hydrogen bond. A representation of the transition state for electrophilic oxygen-atom transfer reactions of cyclic α-azohydroperoxides is shown in Scheme 1.

Scheme 1.



The synthesis of cyclic α-azohydroperoxides by autoxidation is a new, convenient route to reactive oxygen-atom transfer reagents. The synthetic route to cyclic compounds **4** is adaptable, allowing the variation of substituents as well as changes in ring size. Thus, this new approach is general and much more useful than that to **2**. The autoxidation of **3a-b** is extremely rapid and efficient. Good yields of reactive α-azohydroperoxides (**4**) can be obtained even if only one equivalent of molecular oxygen is employed. Thus, ^{17}O-enriched compounds can be made economically and rapidly for use as ^{17}O-labeling reagents. These labeling reagents can be used <u>in situ</u> safely without the need for unusual precautions. Further work is in progress.

<u>3,4,4-Trimethyl-3,4-dihydro-3,5-diaryl-2H-pyrazoles **3**.</u> The preparation, isolation, purification and storage of these new compounds were carried out under inert (nitrogen) atmosphere. The following <u>synthesis of **3a** is</u> representative. To a solution of 10.0 g (40 mmol) of 3,5-diphenyl-4,4-dimethyl-4H-pyrazole in 60 ml anhydrous ether, was added (slowly) 35 ml of a 1.4 <u>M</u> solution of methyllithium in ether (via syringe). The temperature of the reaction mixture was maintained at 0° for 1 hr (magnetic stirring) after which the reaction mixture was kept at ambient temperature for 16 hrs. After quenching, the ether layer was washed with a saturated NaCl solution and dried over Na_2SO_4. Removal of the solvent under reduced pressure left a solid residue which was recrystallized from methanol to yield 9.15 g of **3a** (86% yield; mp 79-81°d). Spectral data **3a**: IR (KBr), 3250 cm^{-1} NH, 1465 cm^{-1} C=N; ^1H NMR (acetone-d_6) δ 0.86 (s,3H), δ 1.46 (s,3H), δ 1.53 (s,3H); δ 6.4 (s,1H); δ 7.2-7.9 (m,10H); ^{13}C NMR ($CDCl_3$) 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-p^+/e at 264; Anal - theory 81.74% C, 7.62% H, 10.64% N, found 81.66% C, 7.64% H, 10.54% N. Data for **3b**: (76% yield; mp 97-102°d) IR (kBr), 3300 NH, 1470 C=N; ^1H NMR (acetone-d_6) δ 0.80 (s,3H), δ 1.50 (s,3H), δ 1.53 (s,3H); δ 3.90 (s,6H); δ 6.3 (s,1H), δ 6.9-7.8 (m,8H); ^{13}C NMR 19.7, 22.7, 23.3, 51.8, 44.9, 55.0, 73.6, 113.1, 113.4, 125.7, 127.1, 127.9, 134.0, 156.9, 158.1, 159.2; MS-p^+/e 324; Anal - theory 74.02% C, 7.45% H, 8.67% N, found 73.83% C, 7.50% H, 8.50% N.

3,4,4-Trimethyl-4,5-dihydro-5-hydroperoxy-3,5-diaryl-3H-pyrazoles **4.** The following procedure for the synthesis of **4a** is representative. A weighed sample of **3a** (usually 30 mg) was dissolved in 1.0 ml of acetone-d_6 (Aldrich-sealed ampule, no TMS) under N_2 in a Schlenk tube. The appropriate volume of O_2 was added via syringe to the magnetically stirred solution at -20°C/0°C (in the dark). After 3 hr/1 hr the reaction was complete as monitored by NMR spectroscopy. With larger amounts of **3a**, the α-azohydroperoxide crystallized from the reaction mixture at -20°. Due to the explosive properties of α-azohydroperoxides the structure was proven by spectroscopic techniques: ^{1}H NMR (acetone-d_6) δ -0.20 (s,3H), δ 1.33 (s,3H), δ 1.80 (s,3H); δ 7.2-7.8 (bm,10H), peroxy proton not seen; ^{13}C NMR 16.9, 24.5, 27.7, 46.8, 97.8, 119.3, 126.3, 127.0, 127.4, 127.9, 128.6, 128.9, 138.3, 143.2. Spectral data obtained for **4b**: ^{1}H NMR (acetone-d_6) δ -0.20 (s,3H), δ 1.30 (s,3H), δ 1.75 (s,3H); δ 3.81 (s,3H); δ 3.87 (s,3H), δ 6.7-7.5 (m,8H); ^{13}C NMR 16.9, 24.5, 27.8, 47.0, 55.5, 55.6, 97.5, 114.0, 114.2, 119.3, 127.3, 128.2, 130.4, 135.3, 159.3, 160.2.

3,4,4-Trimethyl-4,5-dihydro-5-hydroxy-3,5-diaryl-3H-pyrazoles **5.** A large excess (100 µl) of dimethylsulfide was added via syringe to a (stirred) solution of 100 mg of **4a** or **4b** in acetone-d_6 at 0° in the dark under N_2. The solvent and excess Me_2S were removed under reduced pressure. Work up and recrystallization from ether yielded 77 mg of **5a** (81% yield mp 152-4°C d): IR (KBr), 3300 OH, 1575 N=N; ^{1}H NMR (acetone-d_6) δ -0.23 (s,3H), δ 1.40 (s,3H), δ 1.76 (s,3H); δ 6.1 (s,1H), δ 7.2-7.7 (m,10H); ^{13}C NMR 17.8, 24.4, 27.2, 45.0, 97.3, 113.1, 126.3, 126.7, 127.6, 128.5, 128.8, 141.9, 144.1; MS-CI 281; Anal - theory 77.11% C, 7.19% H, 9.99% N, found 76.82% C, 7.29% H, 9.79% N. Data obtained for **5b**: (78% yield; mp 149-151°C d) IR (KBr), 3210 OH, 1570 N=N; ^{1}H NMR (acetone-d_6) δ -0.20 (s,3H), δ 1.40 (s,3H), δ 1.73 (s,3H); δ 3.85 (s,6H); δ 6.0 (s,1H), δ 6.8-7.6 (m,8H); ^{13}C NMR 17.0, 24.0, 26.5, 44.3, 55.0, 96.6, 111.8, 113.1, 126.1, 126.5, 132.5, 134.6, 158.0, 159.2.

Kinetics. The following procedure was employed for the oxygen-atom transfer reactions of **4a-b, 2,** and **1a.** To an internal standard (anisole or t-butylbenzene) was added a sample of α-azohydroperoxide usually 20-30 mg in acetone-d_6 and the ^{1}H NMR spectrum recorded and integrated. The desired quantity (1 to 10 fold excess) of sulfide or amine was added and the NMR signals recorded and integrated vs time. The rate of appearance of product and final product yields were determined relative to the internal standard. The kinetic data, obtained for at least two half-lives, were analyzed by standard procedures and yielded excellent correlations (r=0.99+ all cases).

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