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(20) Compound **4d** had a lower R_f value than compound **3d** (GLC). Benzoyl derivative **3d** showed a carbonyl stretching vibration at 1701 cm^{-1}, while isomer **4d** exhibited a much higher value at 1733 cm^{-1}. The NMR data of **3d** and **4d** supported the respective structural assignment. NMR (CCl_4) of compound **3d:** δ 0.83 (t, 3, J = 6 Hz, CH_3), 1.2 (m, 2, CH_2Me), 1.9 (t, 2, J = 7 Hz, $CH_2CC{=}O$), 3.25 (s, 6, $(OMe)_2$), 7.8–8.2 (m, 2, ortho aromatic protons), 7.2–7.5 (m, 3, meta and para aromatic protons). NMR (CCl_4) of compound **4d:** δ 0.76 (t, 3, J = 6.5 Hz), 1.30 (sextet, 2, CH_2Me), 2.40 (t, 2, $CH_2C{=}O$), 3.18 (s, 6, $(OMe)_2$), 7.2–7.6 (m, 5, C_6H_5). The mass spectral fragmentation further established the identity of acetals **3d** and **4d.** Mass spectrum of **3d**: *m/e* (rel abundance) no M^+, 117 (100), 105 (21), 77 (18), 71 (18), 57 (9), 43 (42). Mass spectrum of **4d:** *m/e* (rel abundance) no M^+, 151 (100), 105 (36), 91 (12), 77 (24), 59 (12), 51 (8), 43 (8).

Oxygen-18 Exchange between $[^{18}O]H_2O$ and H_2O_2 in the Presence of FSO_3H

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A peroxide molecule may undergo a variety of chemical reactions. The chemical versatility of peroxides is due to the fundamentally different cleavage modes available to the peroxide structure. While the free-radical chemistry of peroxide involving the homolytic cleavage of the weak O–O bond under a variety of conditions is well documented, the heterolytic cleavage of the O–O bond of peroxide is poorly understood in the mechanistic level.[1-3]

The unimolecular heterolytic cleavage of a peroxide molecule would generate RO^+ (oxenium ion) species, which is expected to be extremely reactive and for whose existence in solution there is no convincing evidence.[4] The bimolecular nucleophilic substitutions of peroxides with carbon, nitrogen, sulfur, phosphorus, and halide nucleophiles are well-known, and acid catalysis in these reactions has been observed.[2,3]

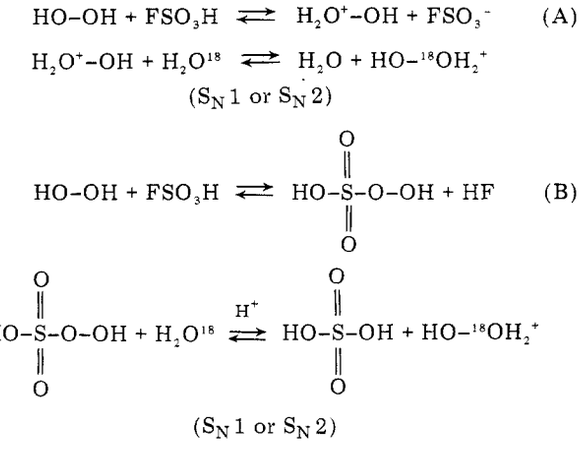
Although water is a reasonably good nucleophile in its attack on sp^3 carbon, its nucleophilic reaction with peroxides is not yet known. The lack of reactivity is normally explained in terms of the repulsion between the electrons on the incoming oxygen nucleophile and those on the peroxide oxygen.[2] Thus it was reported that no exchange occurs under acidic conditions between $[^{18}O]H_2O$ and either hydrogen peroxide,[5] alkyl hydroperoxides,[5] or peroxy acids[6] or between $[^{18}O]$ alcohols and hydrogen peroxide.[7] Similarly, hydrogen peroxide and alkyl hydroperoxides do not undergo oxygen isotope exchange with $^{18}OH^-$.[3]

Table I. $[^{18}O]$ Exchange of H_2O_2[f] with $[^{18}O]H_2O$[a]

run	H_2O_2, μL[b]	FSO_3H,[h] μL	$[^{18}O]H_2O$, μL[c]	Time, days	% exchange[d]
1	140	290	90	1.5	3.7
2	100	260	100	3.5	16.3
3	160	260	100	3.5	33.0
4	70	460[e]	50	3.0	<2.0

[a] Experiments were run by mixing the components in a Pyrex glass vessel under N_2 atmosphere at room temperature in the dark for the indicated time and by successively evacuating the system and treating with solid $KMnO_4$. O_2 evolved was trapped and analyzed for the ratio of *m/e* 34/32 by a mass spectrometer (Hitachi RMU-6 at 25 eV). Runs showing the presence of appreciable N_2 in the sample were discarded. [b] 90% H_2O_2. [c] Atom enrichment was determined to be 78% by mass spectrometric analysis. [d] The ratio of *m/e* 34/32 after correcting for the initial enrichment. The error limit of the measurement is about 1%. [e] Concentrated H_2SO_4 was used instead of FSO_3H. [f] Registry no. 7722-84-1. [g] Registry no. 14314-42-2. [h] Registry no. 7789-21-1.

Scheme I



In connection with our interest in oxygenase-catalyzed reaction mechanisms, we had an opportunity to reexamine the possibility of oxygen isotope exchange between $[^{18}O]H_2O$ and H_2O_2 in the presence of fluorosulfonic acid,[8] the strongest of the simple protonic acids, and wish to report the results of our work.

The results indicated by Table I demonstrate clearly that under these conditions water is a good enough nucleophile to cleave the O–O bond of hydrogen peroxide or its derivative. There appear to be two possible mechanisms for the exchange (Scheme I). Control experiments in which aliquots of the total mixture were analyzed for $SO^{16}O^{18}/SO^{16}O^{16}$ (*m/e* 66/64) prior to oxidation with $KMnO_4$ indicated that both concentrated H_2SO_4 and FSO_3H readily exchange oxygen isotope with $[^{18}O]H_2O$. However, only in the presence of FSO_3H does H_2O_2 exchange oxygen isotope with $[^{18}O]H_2O$. Therefore, it may be concluded that if mechanism (A) is operating, hydrogen peroxide is not significantly protonated by concentrated H_2SO_4, while if mechanism (B) is operating,[9] H_2O_2 and concentrated H_2SO_4 do not generate a significant concentration of persulfuric acid. Furthermore, distinguishing between the S_N1 and S_N2 processes is not possible based on the currently available information.

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Communications

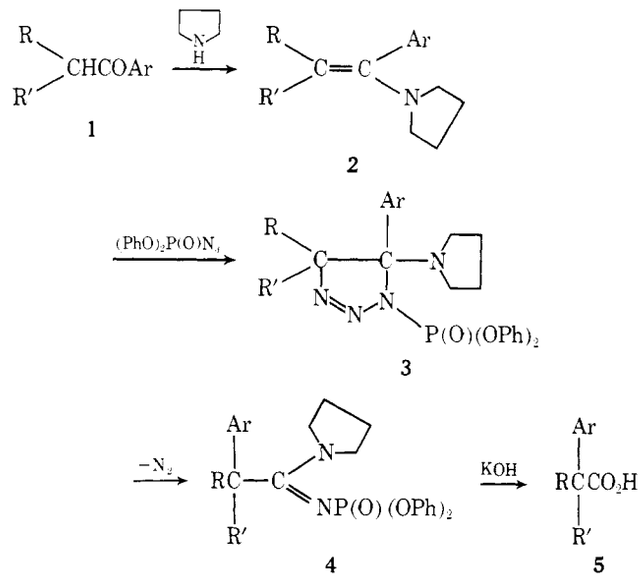
New Methods and Reagents in Organic Synthesis. 2.[1] A Facile Conversion of Alkyl Aryl Ketones to α-Arylalkanoic Acids Using Diphenyl Phosphorazidate. Its Application to a New Synthesis of Ibuprofen and Naproxen, Nonsteroidal Antiinflammatory Agents

Summary: α-Arylalkanoic acids are conveniently prepared from alkyl aryl ketones by the successive treatment with pyrrolidine, diphenyl phosphorazidate (DPPA), and potassium hydroxide; the method has been efficiently applied to a new synthesis of ibuprofen and naproxen, important nonsteroidal antiinflammatory agents.

Sir: Recent publications from these laboratories[1,2] and others[3,4] have revealed that diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$) may be used for various synthetic reactions. The 1,3-dipolar character of DPPA has been well demonstrated by its reaction with enamines of cyclic ketones, which has offered a new method of ring contraction.[2]

We now wish to report a convenient conversion of alkyl aryl ketones **1** to α-arylalkanoic acids **5** using DPPA as a 1,3-dipole in the key step. The new general method consists of three-step operations involving: (1) conversion of alkyl aryl ketones **1** to pyrrolidine enamines **2**; (2) 1,3-dipolar cycloaddition of DPPA to enamines **2** followed by aryl migration with concomitant evolution of nitrogen from labile triazoline intermediates **3**; and (3) hydrolysis of the resulting *N*-phosphorylated amidines **4**, as summarized in Scheme I.

Scheme I



Although similar conversion of alkyl aryl ketones to esters of α-arylalkanoic acids by oxidative rearrangements utilizing thallium(III) nitrate has been reported recently,[5] the present method possesses such advantages that: (1) the functional specificity of the reactions may be much superior; (2) nonoxidative and less toxic reagents[6] can be used; and (3) all the transformations may be readily carried out in multigram quantities using a single reaction vessel.

Condensation of alkyl aryl ketones **1** with pyrrolidine smoothly proceeded in refluxing benzene or toluene in the presence of boron trifluoride etherate[7] to give enamines **2**. Addition of DPPA to enamines **2** in tetrahydrofuran (or ethyl acetate), followed by refluxing the reaction mixture, generated nitrogen to yield *N*-phosphorylated amidines **4** by aryl migration. The intermediates of this transformation are obviously 1,3-dipolar cycloadducts **3**.[2] Although optimum conditions for the reaction have yet to be established,[8] the data in Table I[9] reveal that preparatively useful yields can be obtained under relatively mild conditions.

A typical procedure is as follows. To pyrrolidine enamine **2** (R = Me; R′ = H; Ar = Ph) (3.05 g) in tetrahydrofuran (45 mL) was added with stirring DPPA (4.95 g). The mixture was stirred at room temperature for 1 h, at 40 °C for 1 h, and then refluxed for 2 h. After dilution with ethyl acetate and benzene (1:1, 150 mL), the mixture was successively washed with 5% aqueous citric acid, water, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The dried solution was evaporated and the residue was purified by column chromatography on silica gel with ethyl acetate and benzene (1:5) to give the *N*-phosphorylated amidine **4** (5.68 g, 80%).

The one-flask procedure, in which the purification of the enamines by distillation was omitted,[10] as well as the use of an argon atmosphere afforded much better overall yields based on the ketones (compare entries 1 and 3). Morpholine and piperidine enamines gave lower yields (entries 4 and 5). Interestingly, neither the methyl enol ether **6**, the enol acetate **7**, nor the silyl enol ether **8** underwent the 1,3-dipolar cycloaddition reaction with DPPA.[2] Furthermore, 1-phenyl-1-propene (**9**) and ethyl 2-cyano-3-hydroxy-3-phenylacrylate (**10**) were also completely unreactive to DPPA. These results exhibit the prominent functional specificity of DPPA as a 1,3-dipole. This specific nature of the process is highlighted