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Mechanistic Study of the Mitsunobu Reaction

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The Mitsunobu reaction occurs typically with inversion of configuration in secondary alcohol derivatives. In this paper, a mechanistic explanation for lactonizations of hindered alcohols under Mitsunobu conditions with retention is proposed. This involves the intermediacy of an acyloxyphosphonium salt followed by acyl transfer to the alcohol.

Introduction

The Mitsunobu reaction is widely employed for the inversion of configuration in secondary alcohol derivatives.[1−5] Recently, we reported lactonizations under Mitsunobu conditions that afforded bicyclic lactones in which either inversion or retention of configuration was observed depending on the steric accessibility of the alcohol moiety as summarized in Scheme 1.[6] In that paper, it was proposed that the retention product, lactone **8**, resulted from direct acyl transfer from phosphonium ion **6**. The lactonization with retention proceeded in preference to formation of phosphonium salt **7**, the classical Mitsunobu intermediate (see Scheme 1). In this system, the hindered nature of the alcohol precluded formation of the Mitsunobu intermediate **7**. Previously, Hughes had proposed formation of acyloxyphosphonium ions (i.e., **2** and **6**) as intermediates in the Mitsunobu process.[7] However, direct evidence for their formation in the Mitsunobu reaction was not reported. In this paper, we report studies designed to prepare acyloxyphosphonium salts such as **2** and **6** by alternative methods and investigate the stereochemical consequences of their reactions with alcohols.

From the outset, the standard mechanism proposed for the Mitsunobu reaction (**9**−**13**, Scheme 2) was deemed incomplete.[7−14] For example, as noted by Hughes, anion **9** should preferentially undergo proton transfer with benzoic acid to give benzoate and phosphonium ion **10**.[9] However, at this juncture, it is unlikely that benzoate would serve as a base to assist in proton removal from alcohol **11** as indicated in Scheme 2. Hughes proposed that benzoate would displace hydrazide anion **15** to afford acyloxyphosphonium ion **14** instead.[7] Deprotonation of alcohol **11** by hydrazide anion **15** followed by phosphorus transfer would lead to formation of phosphonium salt **12** and, subsequently, the inverted product **13**. With unhindered alcohols, it is expected that conversion of **14** to **12** occurs readily and that attack at phosphorus is preferred to acyl transfer. Under these circumstances, the inverted product **13** is observed exclusively. However, in systems in which the alcohol is hindered (i.e., **5**, Scheme 1), we proposed that attack onto phosphorus by alkoxide to give the Mitsunobu intermediate **12** was precluded and that lactonization with *retention* was observed instead.[6] The central question posed by these results was whether acyl transfer was observed only because of the intramolecular nature of the reaction. In an effort to determine whether acyl transfer would be observed in intermolecular reactions, we investigated unambiguous methods for preparation of acyloxyphosphonium salts and determined their fate in esterification reactions.

Results and Discussion

As summarized in Scheme 3, treatment of benzoic acid under Mitsunobu conditions (PPh_3, DEAD)[15,16] in *the absence of an alcohol* gave benzoic anhydride (**19**) in high yield. The formation of the anhydride **19** was consistent with the intermediacy of acyloxyphosphonium salt **14**,[17,18] followed by benzoate attack on the acyl function. Also, benzoic anhydride (**19**) was obtained from the reaction of benzoyl peroxide (**18**) and triphenylphosphine (Scheme 3), presumably via intermediate **14**. Under these conditions, benzoate anion reacted with the in situ generated phosphonium salt **14** by acyl transfer to provide the anhydride **19**.

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[18] Burke and co-workers have also proposed that an acyloxyphosphonium salt intermediate is produced from the reaction of tribromo- and trichloroethyl esters with phosphines.[17] They demonstrated that amines and alcohols react rapidly with the acyloxyphosphonium salt with acyl transfer to afford amides and esters, respectively.

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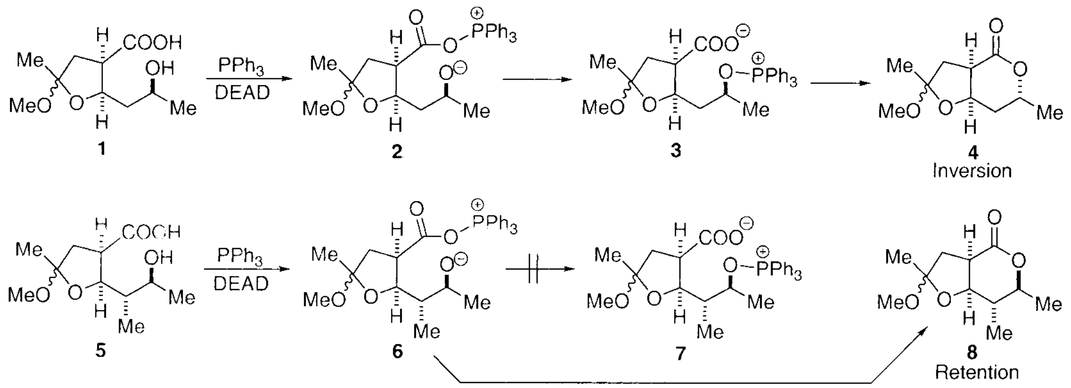
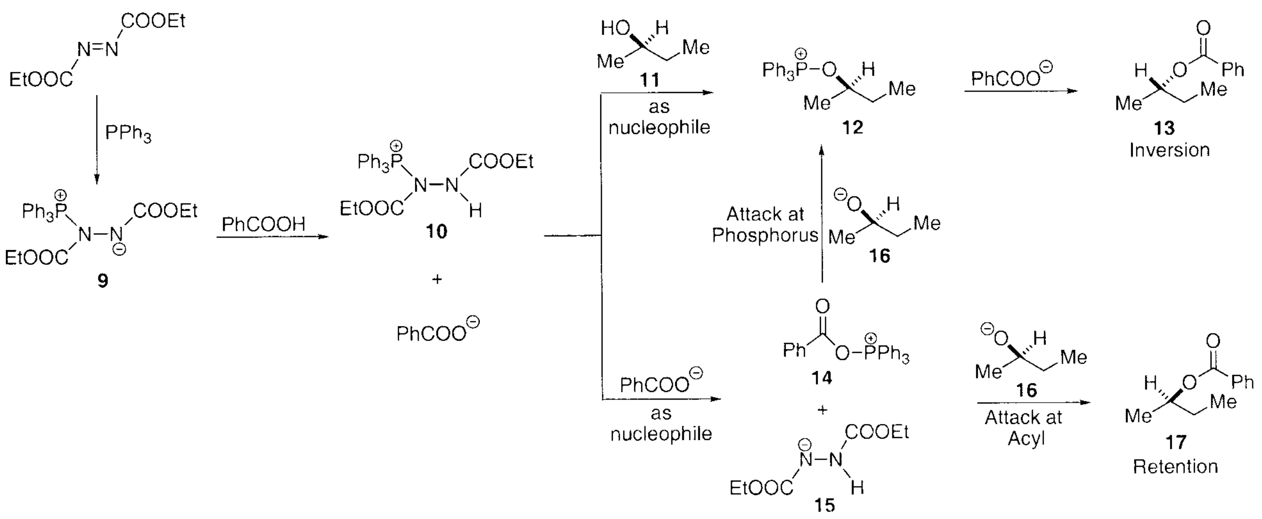
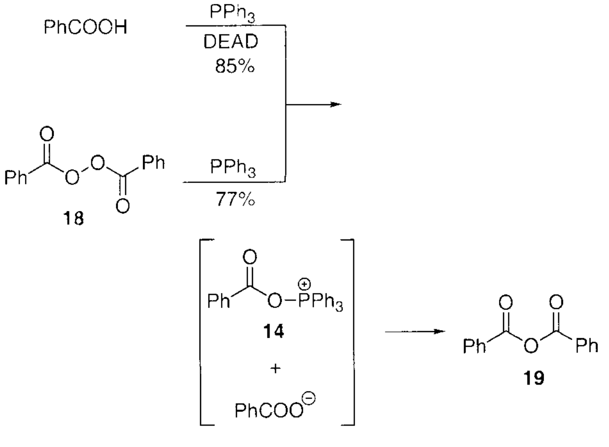
Scheme 1



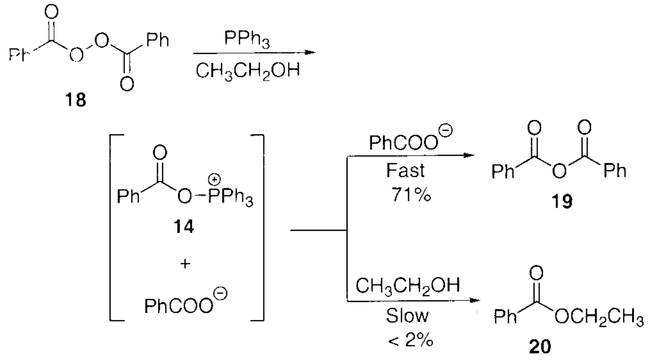
Scheme 2



Scheme 3



Scheme 4



Having demonstrated that acyloxyphosphonium ion **14** could be prepared in situ, we investigated the reaction of this intermediate with ethanol (Scheme 4). It was important to compare the reaction rate of benzoate anion and ethyl alcohol with acyloxyphosphonium ion **14**. Benzoyl peroxide (**18**) underwent reaction with triphenylphosphine *in ethanol* to provide benzoic anhydride (**19**); only traces of ethyl benzoate (**20**) were observed. This result was expected since benzoate is much more nucleophilic than ethanol[19] and should react preferentially with phosphonium salt **14** to give the anhydride **19**. The absence of ester **20** in this reaction is a clear indication that benzoate is unable to function as a base for proton transfer involving an alcohol. Compare this result with the mechanism of the Mitsunobu reaction shown in Scheme 2 (i.e., **9**−**13**).

Reaction of perester **21** with triphenylphosphine in dioxane at 70 °C gave *tert*-butyl benzoate (**23**), isobutylene, and benzoic acid (Scheme 5). Presumably, the perester **21** reacted with phosphine with cleavage of the peroxy bond to provide acyloxyphosphonium salt **14**/*tert*-butoxide and benzoate/phosphonium salt **22**. Nucleophilic attack of *tert*-butoxide at the acyl of phosphonium salt **14** resulted in the formation of ester **23**. It is noteworthy that this highly hindered alkoxide underwent acylation as was observed with salt **6** in Scheme 1. *tert*-Butoxide attack at the phosphorus of **14** gave phosphonium ion

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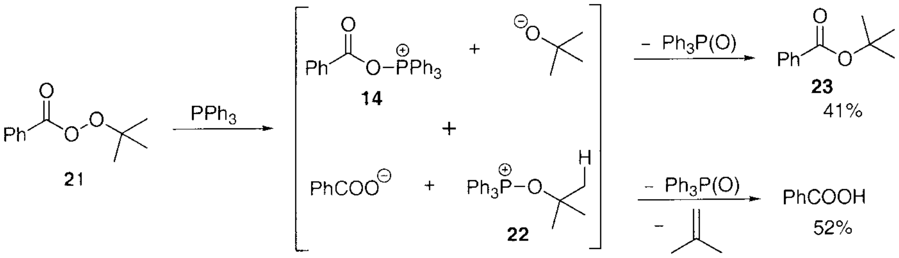
Scheme 5



22 and benzoate. Since this alcohol derivative **22** is unable to undergo substitution, benzoate promoted E1-like elimination to afford isobutylene. These results clearly demonstrate that acyloxyphosphonium ions such as **6** (Scheme 1) and **14** (Schemes 4 and 5) are competent acyl transfer reagents when the classical Mitsunobu process is unable to occur.

Conclusion

These studies have provided insight into the mechanism of the Mitsunobu reaction and can be employed in development of new methods for lactonization for medium and large ring systems with complete control of stereochemical integrity. Additional studies in this area will be forthcoming.

Experimental Section

General Methods. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded either on a 200 or 400 MHz spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (δ) relative to the nondeuterated solvent peak. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Infrared spectra were recorded as solutions in CCl_4. Band positions are given in reciprocal centimeters (cm^{-1}), and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or vanillin/sulfuric acid charring. Flash chromatography data are reported in the following manner: (column diameter in mm, column height in cm, solvent).

Tetrahydrofuran (THF) and 1,4-dioxane were distilled from sodium/benzophenone ketyl. Ethanol was stored over molecular sieves. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted. Glassware used in the reactions described below was dried for a minimum of 12 h in an oven at 120 °C. All reactions were run under an atmosphere of nitrogen unless otherwise noted. The starting materials and authentic samples, which include benzoic acid, benzoic anhydride, benzoyl peroxide, triphenylphosphine (PPh_3), triphenylphosphine oxide, diethyl azodicarboxylate (DEAD), and ethyl benzoate, were purchased from Aldrich. All reported compounds were >95% pure as determined by ^{1}H and ^{13}C NMR spectroscopy.

Benzoic Anhydride (19) Prepared from Benzoic Acid, PPh_3, and DEAD. A solution of 0.37 g (3.0 mmol) of benzoic acid in 10 mL of THF was treated at 0 °C with a preformed solution of PPh_3 and DEAD (formed by addition of 0.24 mL (1.5 mmol) of DEAD to a solution of 0.38 g (1.5 mmol) of PPh_3 in 10 mL of THF at 0 °C). The reaction was stirred at 25 °C for 24 h and neutralized with 5% $NaHCO_3$. The aqueous layer was extracted with 3 × 30 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (25 mm, 15 cm, 20% EtOAc/hexane) gave 0.29 g (85%) of benzoic anhydride (**19**) as a white solid. The melting point, IR, and ^{1}H and ^{13}C NMR data were identical to the data of an authentic sample.

Benzoic Anhydride (19) Prepared from Benzoyl Peroxide (18) and PPh_3. A solution of 2.1 g (8.7 mmol) of benzoyl peroxide (**18**) in 20 mL of THF was added to a solution of 2.3 g (8.7 mmol) of PPh_3 in 20 mL of THF at 25 °C. The reaction was stirred at 25 °C for 3 h and concentrated in vacuo. The crude mixture was partitioned between 20 mL of H_2O and 3 × 30 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (30 mm, 15 cm, 20% EtOAc/hexane) gave 1.5 g (77%) of benzoic anhydride (**19**) as a white solid. The melting point, IR, and ^{1}H and ^{13}C NMR data were identical to the data of an authentic sample.

Benzoic Anhydride (19) Prepared from Benzoyl Peroxide (18) and PPh_3 in the Presence of Ethanol. A solution of 2.1 g (8.7 mmol) of benzoyl peroxide (**18**) in 20 mL of THF was added to a solution of 2.3 g (8.7 mmol) of PPh_3 and 5.0 mL (85 mmol) of ethanol in 20 mL of THF at 25 °C. The reaction was stirred at 25 °C for 5 h and concentrated in vacuo. The crude mixture was partitioned between 20 mL of H_2O and 3 × 30 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (30 mm, 15 cm, 20% EtOAc/hexane) gave 1.4 g (71%) of benzoic anhydride (**19**) as a white solid. The melting point, IR, and ^{1}H and ^{13}C NMR data were identical to the data of an authentic sample. TLC and ^{1}H NMR analysis of the crude reaction mixture indicated the formation of traces (<2%) of ethyl benzoate (**20**) by comparison with an authentic sample.

***tert*-Butyl Perbenzoate (21).** The perbenzoate **21** was prepared according to the procedure of Surgenor:[20] IR (CCl_4) 2985 (m), 1763 (s), 1235 (s); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 7.42–7.62 (m, 3H), 7.96 (d, $J = 7.9$, 2H); ^{13}C NMR ($CDCl_3$) δ 26.2, 84.0, 127.7, 128.6, 129.1, 133.3, 164.4.

***tert*-Butyl Benzoate (23).** A solution of 0.50 g (2.6 mmol) of perbenzoate **21** and 1.3 g (5.0 mmol) of PPh_3 in 10 mL of dioxane was heated at 70 °C under a nitrogen atmosphere for 14 h and concentrated in vacuo. Purification of the residue by flash chromatography (25 mm, 15 cm, 20% CH_2Cl_2/hexane) gave 0.19 g (41%) of benzoate **23**. The IR, ^{1}H NMR, and ^{13}C NMR data were identical to the data reported by Burke.[17] Benzoic acid (0.16 g, 52%) was isolated and compared with an authentic sample by TLC and ^{1}H NMR spectroscopy. The ^{1}H NMR data of isobutylene collected from the reaction were identical to the data reported by Bianchini.[21] TLC and GC analysis of the crude reaction mixture indicated the formation of triphenylphosphine oxide by comparison with an authentic sample.

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