Tributylphosphine-Catalyzed Acylations of Alcohols: Scope and Related Reactions

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Recent findings in our laboratory show that tributylphosphine is a potent catalyst for the acylation of representative alcohols by acetic or benzoic anhydrides.[1] Acylations using excess anhydride and 5-20 mol % of Bu_3P catalyst in benzene or acetonitrile are comparable in rate to the analogous reactions catalyzed by *p*-(dimethylamino)-pyridine (DMAP).[1,2a] In the case of benzoic anhydride, the Bu_3P-catalyzed reaction is faster than the DMAP analogue, partly because the weakly basic phosphine is less subject to protonation (and catalyst deactivation) by the benzoic acid byproduct. The mechanism of catalysis is not yet clear, but nucleophilic activation of the anhydride via an ion pair $R_3P^+C(O)CH_3,AcO^-$ appears most likely.[1] This mechanism is supported by the isolation of decomposition products derived from the ion pair and is reasonable in view of the DMAP analogy.[1,2] Recently, we have obtained additional supporting evidence from a qualitative comparison of phosphine reactivity in the acetylation of menthol by acetic anhydride. Acetylation rates decrease as the catalyst is varied according to the following order of reactivity: $Bu_3P > PhEt_2P > Ph_2PMe \sim Ph_2PEt > Bu_3P{=}O$ or $(MeO)_3P$ (unreactive). These results indicate that electron availability at phosphorus is a dominant variable, as expected in the nucleophilic catalysis mechanism. Furthermore, there is no significant difference in reactivity between Ph_2PEt and *P*-ethyldibenzophosphole (1) (Chart I). This result argues against substantial rehybridization at phosphorus in the rate-determining step and implicates tetrahedral phosphorus geometry in the reactive intermediate.

Among the phosphine catalysts tested for anhydride activation, Bu_3P is the cheapest, the most reactive, and the most easily removed from products (simple extraction with dilute mineral acid or filtration chromatography). Tributylphosphine is also inexpensive by comparison with DMAP, and it is somewhat less toxic (LD_{50} in the rat, intravenous: Bu_3P, 750 mg/kg; DMAP, 56 mg/kg).[3a] These advantages could be important in experiments conducted on large scale. In certain other specialized applications with base-sensitive substrates, the reduced basicity of Bu_3P compared to DMAP may also be useful. On the other hand, Bu_3P is flammable (flash point: 37 °C), and exposure to the air can result in radical chain oxidation to give $Bu_2P(O)OBu$, $Bu_3P{=}O$, and related byproducts.[3b] Furthermore, DMAP remains an eminently useful and extensively documented catalyst for many applications. In view of these considerations, we have briefly explored the Bu_3P activation of several types of electrophiles to learn whether the phosphine is comparable to DMAP in the scope of catalysis. As outlined below, the phosphine has good reactivity toward several different activated ester reagents and can be recommended for a variety of applications.

The Ac_2O/Bu_3P or Bz_2O/Bu_3P reagents acylate typical hydroxyl substrates, including menthol, hindered phenols, and tertiary alcohols, etc.[1] Mercaptans are also acetylated readily under similar conditions. Thus, *n*-dodecyl mercaptan gave $n\text{-}C_{12}H_{25}SC(O)CH_3$[4] in >90% yield after treatment with Ac_2O (2 equiv) and Bu_3P (0.1 equiv) in CH_2Cl_2 at rt, 2 h. As expected from these results, and from the DMAP precedent,[2b] the *in situ* diimide method for activating carboxylic acids can also be used. Thus, treatment of menthol with 2 equiv of benzoic acid, 1.1 equiv of diisopropylcarbodiimide, and 0.1 equiv of Bu_3P in CH_2Cl_2 (mixing at 0 °C, 11 h at room temperature) gave menthyl benzoate in 82% isolated yield. Less than 5% of the ester was formed in the absence of the phosphine catalyst.

Catalysis by Bu_3P was also observed with cyclic anhydrides, but the reactions were considerably slower than the Ac_2O experiments. Thus, **2** gave only ca. 30% conversion into **3** after 6 h with 1.5 equiv of benzyl alcohol and 10 mol % Bu_3P in CD_3CN at room temperature (NMR assay). Previous reports indicate that cyclic anhydrides are also relatively unreactive with the DMAP catalyst.[2b] Thus, a similar experiment using **2** with 10 mol % DMAP in place of the phosphine gave 35% conversion to **3** after 1 h and 83% conversion after 6 h at room temperature. Comparable rates were achieved with the phosphine when a full equivalent of Bu_3P was used, resulting in 78% conversion to **3** after 4 h or ca. 95% after 6 h.

In a related cyclic anhydride example, Heathcock and Theisen report that 3-methylglutaric anhydride reacts with the chiral alcohol **4** at −40 °C to give a 16:1 ratio of **5**:**6** (94% yield after 48 h).[5] We have repeated this reaction using racemic **4** with Bu_3P as the catalyst. The reaction was slower than the DMAP analogue (78% conversion after 48 h at rt) and gave an 8:1 diastereomer ratio of **5**:**6** (racemic products; one arbitrary enantiomer pair is illustrated to reflect relative stereochemistry). The product ratio was determined according to the published NMR assay after conversion into the methyl esters.[5]

The ability of Bu_3P to activate several other carboxylic acid derivatives was tested, following the DMAP precedents.[2] Diketene (2 equiv) and cinnamyl alcohol reacted within a few minutes upon addition of 0.1 equiv of Bu_3P (exotherm; CH_2Cl_2, rt) to afford cinnamyl acetoacetate (**7**) (89%).[6a,b] No conversion was observed on the same time scale in the absence of tributylphosphine. A slower reaction was seen with benzoyl cyanide (1.1 equiv) and cinnamyl alcohol under similar conditions (32 h at rt, 20 mol % of the phosphine catalyst) to give cinnamyl benzoate

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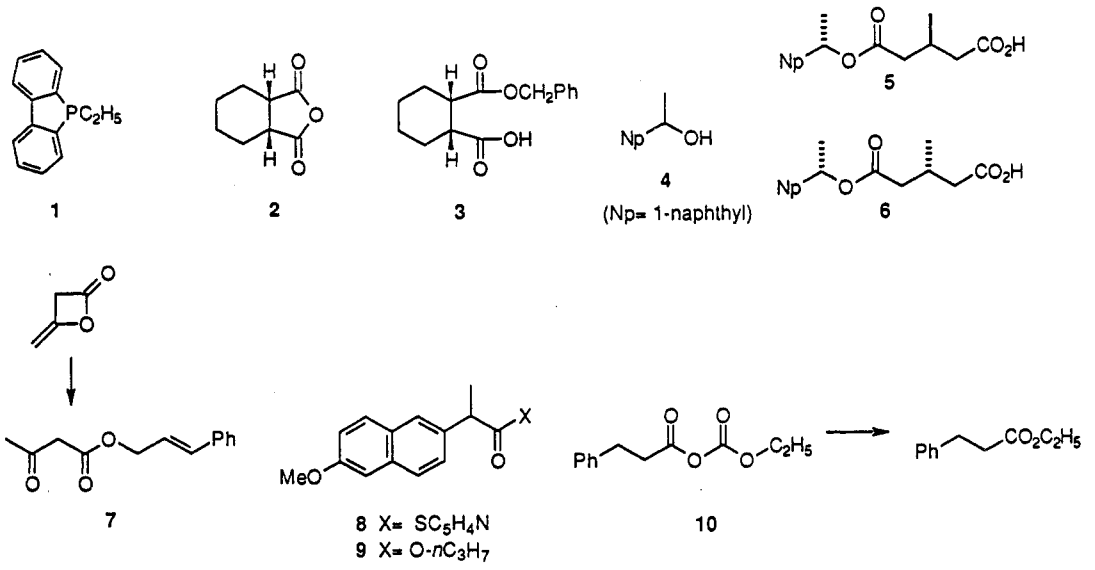
Chart I



(89%).[6c] Pyridylthioester 8[8] derived from naproxen was likewise activated by tributylphosphine in a relatively slow reaction. The *n*-propyl ester 9[7] was obtained in good yield (3 equiv of *n*-propanol, CH_2Cl_2; 6 h at rt; >90%). In the absence of tributylphosphine, ca. 10% conversion from 8 to 9 was observed in a similar experiment. No significant catalysis was detected in attempted acylations using several less activated carboxylic acid derivatives, including vinyl acetate and *p*-nitrophenyl acetate.

The conversion of mixed carbonic anhydrides into esters via CO_2 extrusion has recently been reported using DMAP catalysis.[9] We have observed the analogous reaction in the presence of Bu_3P. Thus, treatment of hydrocinnamic acid with ethyl chloroformate and triethylamine in CH_2Cl_2 at 0 °C afforded the mixed anhydride **10**, and addition of 0.2 equiv of tributylphosphine induced conversion into ethyl dihydrocinnamate (0 °C to room temperature; 63% isolated after distillation).

Phosphine catalysis does not facilitate the silylations of secondary alcohols using t-$C_4H_9(CH_3)_2SiCl$. Representative silylation conditions were studied with the Bu_3P catalyst and basic additives including DABCO, 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU), Et_3N, and potassium hydride. These experiments gave silyl ethers at the same approximate rates with or without the phosphine. On the other hand, silylation of a tertiary alcohol (2-methyl-3-buten-2-ol) using *N,O*-bis(trimethylsilyl)acetamide in refluxing dichloromethane was significantly accelerated by Bu_3P (complete conversion within 24 h; no silylation in the absence of catalyst under the same conditions).

The above results suggest that phosphine catalysis depends on the counterion in the potential phosphonium intermediate and also on the nature of the electrophilic reactant. Similar findings have been reported with DMAP,[2a] but the latter does catalyze silylations with t-$C_4H_9(CH_3)_2SiCl$[10] and can also be used to accelerate the formation of sulfonate esters from sulfonyl chlorides.[11] We have observed no significant rate acceleration in reactions of CH_3SO_2Cl, $CH_3C_6H_4SO_2Cl$, or $(CH_3SO_2)_2O$ with alcohols in the presence of the phosphine. In the specific case of mesylate formation, it is known that DMAP-mediated reactions occur via the sulfene mechanism.[12] Apparently, this pathway is not available using the weakly basic phosphine, while nucleophilic activation of the sulfonyl chloride is ineffective. The advantage of DMAP over Bu_3P in some of the other sulfonations and in the silylations may also be related to the need for base catalysis.

Substrates that lack a heteroatom X–H subunit are usually not reactive with the Ac_2O/Bu_3P reagent. No reaction was observed at room temperature with tetraallyltin, alkenes, nonactivated benzene derivatives, menthone, ethyl acetoacetate, or pentane-2,4-dione. Our tentative explanation is that the ion pair $Bu_3P^+C(O)CH_3$ AcO^- activates the substrate for acylation by internal proton transfer to basic acetate. It is reasonable to expect that the kinetics of proton transfer will depend on the pK_a of the substrate and also on the nature of the proton (C–H vs X–H) to be transferred.

In conclusion, tributylphosphine activates representative acylation agents for reaction with alcohols. The DMAP catalyst is more versatile since it shows catalytic activity in the reactions of alcohols with a larger variety of electrophiles compared to the Bu_3P catalyst. At least in part, this is because DMAP is better suited for the dual role of nucleophilic catalyst and base. The phosphine also appears to be somewhat more sensitive to counterion effects by comparison with DMAP. However, Bu_3P is not easily deactivated by carboxylic acids, does not require basic additives, and can be used under nearly neutral conditions for the acylation of sensitive substrates.

Experimental Section

General. Dodecyl thiolacetate,[4a] cinnamyl benzoate,[6b] cinnamyl acetoacetate,[6a] menthyl benzoate,[1] and the naproxen *n*-propyl ester[7] have been described previously. The Bu_3P catalyst (Aldrich) was used without purification, but opened bottles of the phosphine must be stored under nitrogen to prevent

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autoxidation. Improperly stored samples are slowly converted into $Bu_2P(O)OC_4H_9$,[3b] a potential source of butyl ester contaminants. This can be a problem with the relatively unreactive cyclic anhydrides or in experiments where large amounts of catalyst are used.

General Procedure for Bu_3P-Catalyzed Acylation of Alcohols Using Anhydrides, Benzoyl Cyanide, or Diketene. A solution of the alcohol reactant (1.5 mmol) and Bu_3P (0.15 mmol, Aldrich) in dry CH_2Cl_2 (distilled from P_2O_5) was prepared. The acylating agent (2 equiv; acetic anhydride, benzoic anhydride, benzoyl cyanide, diketene) was then added dropwise over 1–2 min. Exotherms were observed with the anhydrides and with diketene and were controlled where necessary using a water bath. The benzoyl cyanide reaction with cinnamyl alcohol required 32 h, but the other acylations were complete in 3 h or less (primary alcohol substrates). To decompose excess acylating agent, the product mixture was quenched with water (ca. 5 mL) and the two-phase mixture was stirred vigorously for 15 min. After separation of phases, the phosphine catalyst was removed by extraction with dilute H_2SO_4 (2 × 10 mL) and carboxylic byproducts were removed by extraction with 5% NaOH (10 mL). The aqueous layers were back-extracted with hexane (10 mL), the combined organics were dried ($MgSO_4$) and concentrated (aspirator), and the residual oils were further purified by filtration chromatography over silica gel using 10–20% ethyl acetate/hexane.

Preparation of Menthyl Benzoate Using the *In Situ* Diimide Method for Activation of Benzoic Acid. A solution of benzoic acid (2.44 g) and menthol (1.56 g) in CH_2Cl_2 (50 mL) was cooled to 0 °C. *N,N'*-Diisopropylcarbodiimide (Aldrich; 1.70 mL, 1.08 equiv) was added, followed by Bu_3P (0.25 mL, 0.1 equiv), and the mixture was stirred 15 min. The cooling bath was then removed, and the reaction was allowed to proceed at room temperature for 11 h. The dichloromethane was evaporated (aspirator), and the residue was stirred with ether (30 mL) and filtered to remove *N,N'*-diisopropylurea. The ether solution was then stirred with water and extracted with dilute H_2SO_4 and NaOH to remove phosphine and benzoic acid, respectively, as described above. Filtration chromatography over silica gel (5 × 2 cm; hexane) gave menthyl benzoate as an oil, 2.14 g (82%), >97% pure by NMR analysis.

***n*-Propyl 2-(6-Methoxy-2-naphthyl)propanoate (9).**[7] The pyridyl thioester 8 was prepared using the method of Mukaiyama *et al.*[8] To a solution of 8 (0.026 g, 0.080 mmol) and tributylphosphine (0.002 mL, 0.008 mmol) in 0.4 mL of CD_2Cl_2 was added 1-propanol (0.018 mL, 0.24 mmol) via syringe, and the solution was monitored by ^1H NMR over 7 h (>90% conversion). After removal of solvent (aspirator), the residue was purified by preparative layer chromatography on silica gel PF254 (20 × 20 × 0.1 cm) (1:5 EtOAc/hexane eluent), analytical TLC on silica gel (1:5 EtOAc/hexane, R_f = 0.47); and recrystallization from hexane to give 9 (0.016 g, 73%), mp 52–53 °C: molecular ion calcd for $C_{17}H_{20}O_3$ 272.14120, found *m/e* = 272.1405, error = 2 ppm; M − $C_4H_7O_2$, 185.0966, error = 0 ppm; base peak = 185 amu; IR (CD_2Cl_2, cm^{-1}) 1732, C=O; 1634, C=C; 1606, C=C; 270-MHz NMR ($CDCl_3$, ppm) 7.70 (2 H, d, *J* = 8.6 Hz), 7.68 (1 H, s), 7.41 (1 H, dd, *J* = 8.4, 1.8 Hz), 7.15–7.10 (2 H, m), 4.03 (2 H, t, *J* = 6.7 Hz), 3.89 (3 H, s), 3.84 (1 H, q, *J* = 7.2 Hz), 1.68–1.50 (2 H, m), 1.57 (3 H, d, *J* = 7.2 Hz), 0.84 (3 H, s).

***cis*-2-(Benzyloxycarbonyl)cyclohexanecarboxylic Acid (3).** Tributylphosphine (80 μL, 0.32 mmol) was added to a solution of *cis*-cyclohexanecarboxylic anhydride (2) (0.050 g, 0.32 mmol) and benzyl alcohol (17) (43 μL, 0.48 mmol) in 1.00 mL of CD_3CN which had been degassed by the freeze–pump–thaw method. After 24 h the solution was concentrated and filtered through a 2-in. plug of silica gel (100 mL of 1:4 EtOAc/hexane, followed by 50 mL of EtOAc). The ethyl acetate solution was concentrated and redissolved in CH_2Cl_2, and the acidic products were extracted into 5% $NaHCO_3$ (2 × 25 mL). The bicarbonate extract was washed with diethyl ether (2 × 25 mL). After acidification to pH = 3 (dilute H_2SO_4), the product 3 was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated (aspirator) to give a pale yellow oil, 0.060 g, 70% yield: *m/e*, 262.120 (3 ppm error); analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.45; IR (benzene-d_6, cm^{-1}) 3500–2600, O—H; 1734, C=O; 1706, C=O; 200-MHz NMR (C_6D_6, ppm) 7.3–7.1 (5 H, m), 5.0 (2 H, AB q, *J* = 12.4 Hz), 2.7–2.4 (2 H, m), 2.2–1.9 (2 H, m), 1.7–0.9 (6 H, m).

Reaction of 3-Methylglutaric Anhydride with 4. The procedure of Theisen and Heathcock[5] was modified by replacing DMAP by Bu_3P and by allowing the reaction to proceed at room temperature. Into a septum-capped 5-mm NMR tube under nitrogen were placed 11.6 mg (0.090 mmol) of 3-methylglutaric anhydride (Aldrich; 28 mg), racemic 1-(1'-naphthyl)ethanol (4, 0.162 mmol, 2.0 equiv),[5b] and 22.4 μL of Bu_3P (Aldrich; 0.090 mmol, 1 equiv) in 500 mL of CD_2Cl_2 at room temperature. The NMR tube was allowed to stand with periodic ^1H NMR monitoring of the methine resonances at δ 6.65 and 5.65 corresponding to the product ester and starting alcohol, respectively. The reaction was 51% complete after 23 h and 85% complete after 48 h. The mixture was diluted with 5 mL of Et_2O, washed twice with 1 M H_3PO_4, neutralized with saturated $NaHCO_3$, and then dried ($MgSO_4$) to afford 43 mg of colorless oil which proved to be a mixture of 1-(1'-naphthyl)ethanol (R_f 0.16 in 1:1 ethylacetate/hexane) and the esters 5 and 6 (R_f 0.50). These compounds were separated by preparative TLC on silica gel to give 17 mg of 5 + 6 (63% yield). The isomer ratio was assayed after conversion to the methyl esters using diazomethane as described by Theisen and Heathcock.[5a] According to the integral ratios of the methyl ester resonances at δ 3.66 and 3.64, the ratio of 5:6 was 8:1.

Preparation of Ethyl Dihydrocinnamate; Bu_3P-Catalyzed Decomposition of the Mixed Anhydride 10. The procedure of Kim *et al.*[9] was modified by replacing DMAP by Bu_3P. Thus, dihydrocinnamic acid (Aldrich; 110 mg, 0.73 mmol) and triethylamine (110 μL; 0.79 mmol) were dissolved in CH_2Cl_2 (2 mL) at 0 °C. Ethyl chloroformate (70 μL, 0.73 mmol) was then added to the stirred solution by syringe. After 5 min, this was followed by Bu_3P (19 μL, 0.076 mmol) and the mixture was stirred for 45 min at 0 °C. The cooling bath was removed and the mixture was stirred 1 h at rt. Another 10 μL of Bu_3P was then added, and the mixture was stirred 30 min and was then worked up as described above for the acylations. The crude liquid was purified by bulb-to-bulb distillation to give 82 mg (63%) of ethyl dihydrocinnamate, >97% pure by NMR analysis. A control experiment (no phosphine) was conducted side by side and gave <5% ethyl dihydrocinnamate.

Silylation of 2-Methyl-3-buten-2-ol. An authentic sample of the trimethylsilyl ether of the title alcohol was prepared as follows. To a stirred suspension of KH (3.85 g; washed with Et_2O to remove oil under N_2) in dry Et_2O at 0 °C was added the allylic alcohol (5 mL; Aldrich, distilled prior to use) dropwise via syringe over 10 min (bubbling occurred and a white precipitate formed). After 15 min of further stirring at 0 °C, the TMSCl (distilled from CaH_2; 7.3 mL) was added dropwise via syringe and the reaction stirred 1 h at 0 °C, warmed to room temperature overnight, and poured *slowly* onto *cold* saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated (aspirator) to yield a cloudy colorless oil. Kugelrohr distillation (1 mm; pot temperature 20 °C; receiver temperature −78 °C) gave a clear, colorless chromatographically pure oil, >97% pure according to NMR assay: 200-MHz NMR ($CDCl_3$, ppm) 5.95 (1 H, dd, *J* = 17.2, 10.6 Hz), 5.13 (1 H, dd, *J* = 17.2, 1.5 Hz), 4.93 (1 H, dd, *J* = 10.6, 1.5 Hz), 1.31 (6 H, s), 0.12 (9 H, s); *m/e* 158.1114 (error = 8 ppm); base peak = 143 amu.

The phosphine-catalyzed reaction was performed as follows. The title alcohol (10 μL) in CD_2Cl_2 (0.5 mL) was combined with Bu_3P (2 μL) and *N,O*-bis(trimethylsilyl)acetamide (30 μL). The solution was warmed to 35 °C and was periodically monitored by NMR. After 18 h, the starting alcohol was >95% converted into the silyl ether, identical with material prepared by the potassium hydride method as described above. A blank experiment was performed in the same way except that no phosphine was added. This reaction gave <5% conversion as judged by integration of the olefinic signals (δ 5.17 for the alcohol; δ 5.13 for the silyl ether).

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