Tributylphosphine: A Remarkable Acylation Catalyst

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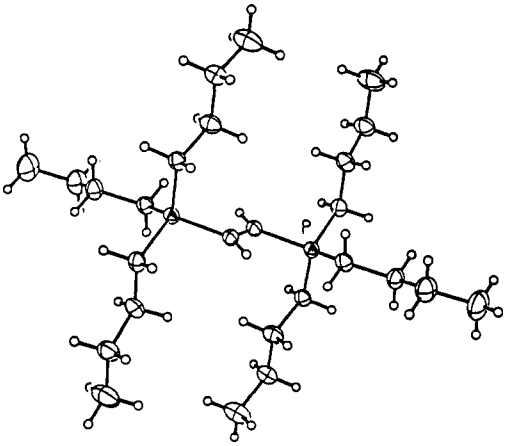
Nucleophiles as well as bases are known to catalyze the acylation of alcohols by anhydrides.[1,2] Significant catalysis was therefore anticipated with *n*-Bu_3P, a weak base in organic solvents (pK_a of $Et_3PH^+Cl^-$ = ca. 5.6 in methanol and 8.7 in nitromethane),[3] but a potent nucleophile. Nevertheless, it was a surprise to find that addition of 20 mol % of commercial *n*-Bu_3P to a 1 M solution of cyclohexanol in dichloromethane containing 3 equiv of acetic anhydride resulted in the formation of cyclohexyl acetate with an exotherm sufficient to boil the solvent. The corresponding benzoic anhydride reaction was also visibly exothermic. The same behavior is observed with 4-(dimethylamino)pyridine (DMAP), the widely-used acylation catalyst.[1] Since these observations suggested similar catalytic activity for the phosphine, both catalysts were compared for the benzoylation of menthol using identical conditions (0.25 M menthol, 0.75 M benzoic anhydride, CD_3CN at 23 °C, 0.1 equiv of catalyst). Remarkably, Bu_3P was *more* effective than DMAP in this experiment (88% conversion with Bu_3P[4] vs 23% with DMAP after 1 h). The difference was smaller when 3 equiv of Et_3N was added to the DMAP-catalyzed reaction (ca. 75% conversion in 1 h). Under the latter conditions, excess Et_3N prevents the deactivation of DMAP by the benzoic acid byproduct of benzoylation and the reaction proceeds to completion. However, in the absence of excess Et_3N, the DMAP rate levels off at 40–50% conversion, presumably due to catalyst inhibition by the products.

Similar behavior was observed in the reaction of menthol with acetic anhydride. Thus, an acetonitrile solution of menthol (0.17 M) containing 10 equiv of Ac_2O and 0.1 equiv of catalyst was monitored at 9 °C with or without 1.5 equiv Et_3N added. The acetylations followed pseudo-first-order kinetics if triethylamine was present, and the DMAP/Et_3N acetylation was ca. 10-fold faster compared to the Bu_3P/Et_3N reaction. In the absence of added amine, linear pseudo-first-order plots were not obtained because both Bu_3P and DMAP were subject to product inhibition or to partial decomposition. Both catalysts gave similar overall rates and conversions, and the acetylations were somewhat slower than with Et_3N present.

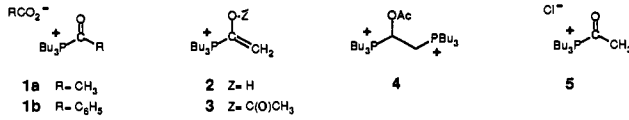
Several attempts were made to define the structure of the phosphine-activated acetylating agent, and to determine whether it might be destroyed under the acetylation conditions. No intermediates were detected in typical reactions, but evidence for two transient species A and B was obtained using higher concentrations of phosphine. When Bu_3P (50 μL) and acetic anhydride (50 μL) were combined in acetonitrile (0.4 mL) at −8 °C, complex signals were seen in the ^1H spectrum that



C

Figure 1. Crystal structure of C.

simplified over time. A 20.3-Hz triplet at δ 9.19 due to a relatively stable substance (C) slowly accumulated at the expense of a transient A having signals at δ 6.16 and 6.21 ppm. The latter signals are due to a P—C=CH_2 fragment,[6] consistent with either the enol **2** or, more likely, the enol acetate **3**.[7a] The structure of C became clear after it crystallized from a solution of Bu_3P in neat acetic anhydride (ca. 5 min at 0 °C). Initially, the ^1H NMR spectrum[8] was difficult to interpret, but X-ray analysis revealed that C has the composition $[(Bu_3PCH)(CH_3CO_2)(CH_3CO_2H)_2]_2$! The correct vinylenebis(phosphonium) structure is shown in Figure 1. There is some precedent for this transformation in the reaction of CH_3COBr with *P*-alkylphosphines, although the prior workers did not encounter the $[CH_3CO_2H]_2CH_3CO_2^-$ counterion.[7b]



1a R = CH_3
1b R = C_6H_5

2 Z = H
3 Z = C(O)CH_3

4

5

Further evidence regarding transient intermediates was obtained from the ^{31}P spectrum of a similar experiment[9] where 2-propanol was added *after* the phosphine. In addition to the signals of A (34.2 ppm) and C (32.9 ppm), transient doublets of B were observed at δ 36.1 and 43.9 ppm ($^3J_{P-P}$ = 42.7 Hz), characteristic of an unsymmetrical partial structure Bu_3P–C(X)–C–PBu_3. Since the signals of B also disappeared as C accumulated, B is tentatively assigned the structure **4**. No other data to confirm this structure was obtained, but **4** is a plausible precursor[7b] of C and can be formed from A (**3**) via the nucleophilic addition of tributylphosphine. The addition of 2-propanol did

(1) Reviews: (a) Höfle, G.; Steglich, V.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (c) Cherkasova, E. M.; Bogatkov, S. V.; Golovina, Z. P. *Russ. Chem. Rev.* **1977**, *46*, 246.

(2) Kinetics: (a) Connors, K. A.; Ebaka, C. J. *J. Pharm. Sci.* **1983**, *72*, 366. (b) Connors, K. A.; Lin, S.-F. *J. Pharm. Sci.* **1981**, *70*, 235.

(3) (a) Streuli, C. A. *Anal. Chem.* **1960**, *32*, 985. (b) Angelici, R. J.; Bush, R. C. *Inorg. Chem.* **1988**, *27*, 681.

(4) Unpurified commercial Bu_3P is an effective catalyst. For rate studies, Bu_3P from a freshly opened bottle was used, >95% pure by glpc analysis. Radical chain oxidation[5a] to Bu_2POBu, $Bu_2P(O)OBu$, and $Bu_3P{=}O$ is difficult to prevent, but this affects catalyst concentration, not reactivity. Bu_3P can be purified by distillation from the CuI complex,[5b] but contamination by Bu_2POBu[5a] occurs easily on small scale.

(5) (a) Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093. (b) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.

(6) Partial ^1H NMR (CD_3CN, ppm; methyl region obscured by Ac_2O signals): δ 6.21, dd, ^2J = 4.4 Hz, ^3J = 30.3 Hz; 6.16, dd, ^2J = 4.4 Hz, ^3J = 9.5 Hz; for an analogy, see p 49 in the following: Mavel, A. *Annu. Rep. NMR Spectrosc.* **1973**, *5B*, 1.

(7) (a) An analogous triphenylphosphine-derived enol propionate is known (ref 7b). (b) Christol, H.; Cristau, H.-J.; Joubert, J.-P. *Bull. Soc. Chim. Fr.* **1974**, 1421, 2263.

(8) C: mp 111–114 °C from CD_3CN; 270 MHz ^1H NMR (C_6D_6, ppm) δ 9.41 (4 H, br s), 8.90 (2 H, t, ^2J = 20.4 Hz, splitting by two identical ^{31}P nuclei), 2.47 (12 H, m), 2.06 (18 H, s), 1.42 (24 H, m), 0.94 (18 H, t, ^3J = 6.7 Hz); ^{31}P ($CDCl_3$, ppm) δ 32.0.

(9) A 10-mm NMR tube was charged with 1.0 mL of CD_3CN, 1.0 mL of Bu_3P, and 1.13 mL of Ac_2O at −4 °C. 2-Propanol (0.92 mL) was then added, and after 15 min, the reaction mixture was warmed to 27 °C and monitored by ^{31}P NMR.

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not destroy A, nor was the 2-propanol acetylated. Thus, A (**3**) cannot be the agent responsible for enhanced acetylation rates, nor can A readily equilibrate with the active catalyst. This evidence supports the structure assignment of A as **3**, not **2**. When 2-propanol was added *before* the Bu_3P, then neither A (**3**) nor B (**4**) was detected by ^{31}P NMR, and acetylation of the alcohol occurred normally. Evidently, the same reactive intermediate is responsible for rapid acetylation, and also for the formation of A (**3**) and B (**4**). Both A (**3**) and B (**4**) are irreversibly "downstream" of the reactive acetylating agent and are formed when the alcohol is not present in sufficient concentration to intercept the key intermediate.

From the analogy with DMAP,[1] the phosphonium salts **1a** and **1b** are logical choices for the reactive acetylation and benzoylation catalysts. However, no trace of the expected ^{13}C doublet near δ 200 ppm[10] nor other direct supporting evidence was ever found in our experiments. Furthermore, the adduct **5** obtained from Bu_3P and acetyl chloride[10,11] was unreactive with 2-propanol (<5% conversion after 30 min at −8 °C in CD_3CN). Since the analogous *N*-acetyl-*p*-(dimethylamino)pyridinium chloride is an active acetylating agent,[1a] these observations raised doubts regarding the role of **1**. On the other hand, addition of sodium acetate to **5** in the presence of 2-propanol resulted in the rapid (<10 min) formation of isopropyl acetate, presumably via anion exchange from **5** to **1a**. This evidence cannot prove that **1a** is the key intermediate, but it does provide support for that assumption. The experiment also indicates a crucial role for the carboxylate counterion in the mechanism of acylation. Removal of a proton from the alcohol substrate by basic carboxylate is one possibility.

Preliminary results indicate that Bu_3P is a broadly useful, relatively nonbasic alternative to DMAP in a variety of acylations involving anhydrides and related electrophiles.[12] The following Bu_3P-catalyzed gram-scale examples are representative (1.3–1.5 equiv of anhydride, 5–15 mol % catalyst, 1.5 equiv of Et_3N, room temperature; workup by dilute acid extraction to remove amine and phosphine): menthol (Bz_2O, CH_3CN, 2 h, 96% benzoate after chromatography); 1-ethynylcyclohexanol (Ac_2O, no solvent, 1 h, 65% yield of acetate, distilled); 2,4,6-trimethylphenol (Ac_2O, 2 h, 95% yield of acetate, distilled).

Since the phosphine catalyst appears capable of slow decomposition under typical acetylation conditions, simple kinetic comparisons are not possible at the present time. However, the qualitative rates of alcohol acetylation or benzoylation using Bu_3P are remarkably fast, similar to those observed with the DMAP catalyst. We are investigating other nucleophilic phosphine catalysts for related applications in synthesis.

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Supplementary Material Available: Structure determination summary and tables of atomic coordinates and equivalent isotropic displacement coefficients, bond lengths and angles, anisotropic displacement coefficients, and H atom coordinates and isotropic displacement coefficients for C (14 pages); listing of observed and calculated structure factors for C (12 pages). Ordering information is given on any current masthead page.

(10) The adduct **5** of $Bu_3P + CH_3C(O)Cl$ is reported,[11] but without decisive characterization. NMR data (CD_3CN, −8 °C, ppm), 500-MHz ^1H, δ 2.85 (3 H, d, ^3J = 5.0 Hz), 2.60 (6 H, m), 1.46–1.44 (12 H, m), 0.88 (9 H, m); 125.8-MHz ^{13}C, {H}, δ 204.5 (d, ^1J = 41.6 Hz), 33.9 (d, ^2J = 45.8 Hz), 24.5 (d, ^1J = 16.1 Hz), 24.0 (d, ^2J = 4.9 Hz), 18.5 (d, ^3J = 39.6 Hz), 13.5 (s); 202.5-MHz ^{31}P, {H}, δ 28.8 vs ext H_3PO_4. .

(11) Yakshih, V. V.; Sokul'skaya, L. I. *Zh. Obshch. Khim.* **1973**, *43*, 440 (English, p 438).

(12) Vedejs, E.; Bennett, N.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. Manuscript in preparation.