Superbase-Promoted Acylation of Hindered Alcohols

Bosco A. D'Sa and John G. Verkade*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

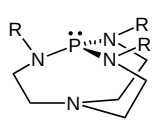
Received July 10, 1995[⊗]

The commercially available nonionic superbase $P(MeNCH_2CH_2)_3N$ (**1a**) is very useful for the acylation of unreactive hindered alcohols as well as acid-sensitive alcohols. The reactions proceed in high yields using an acid anhydride, and **1a** can be regenerated in a single step. The relative rates for benzoylation of (±)-menthol in C_6D_6 using conventional acylation reagents and strong nonionic bases are compared. In general, acetylation with **1a** is accelerated in the polar solvent CH_3CN whereas benzoylation is faster in the nonpolar solvent C_6H_6. The benzoylation intermediate $RC(O)P(MeNCH_2CH_2)_3N^+$ was found to be in equilibrium with **1a**, with lower temperatures favoring the intermediate. The relative stabilities of several known acylating intermediates are compared.

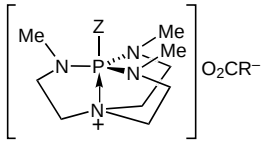
Introduction

High-yield acylations of hindered alcohols are functional group transformations of considerable current interest. Older methods for such reactions involve acetic anhydride,[1] acetyl chloride,[1] and the use of *n*-butyllithium in the presence of an acid chloride.[2] More contemporary approaches include catalysts such as DMAP,[3] Bu_3P,[4] and 4-pyrrolidinopyridine (PPY),[5] with DMAP being the most popular. Although both Bu_3P and DMAP provide good yields of acylated alcohols,[6,7] these catalysts have disadvantages. For example, Bu_3P has a flash point of 37 °C, allowing it to be easily oxidized in air. Moreover, DMAP is fairly toxic (rat LD_{50}, iv, 56 mg/kg[7]), although Bu_3P is not (rat LD_{50}, iv, 750 mg/kg[7]). Although toxicity data on **1a** and cations such as those in **2** and **3** are not available, it is of interest to note that the analogue of **3** (**4**) was found to be intermediate in toxicity (mouse, LD_{50}, ip, 270 mg/kg[8]).

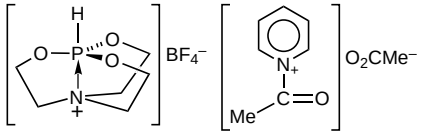
Herein we report the use of the strong nonionic Lewis base **1a** as an efficient acylation promoter for hindered alcohols, a transformation that easily allows **1a** to be recovered in high yield in a single-step reaction.[9] Evidence for the stability of the acylating intermediate **2a** and its equilibrium with **1a** is presented. The effect of solvent on the acylation of alcohols is also discussed.



1a, R = Me
1b, R = *i*-Pr



2a, Z = PhC(O); R = Ph
2b, Z = MeC(O); R = Me
3a, Z = H; R = Ph
3b, Z = H; R = Me



4

5

Results

According to ^1H NMR spectroscopy, benzoylation of 1.0 mmol of benzyl alcohol with 1.1 mmol of Bz_2O in the presence of 1.1 mmol of **1a** in C_6D_6 is >99% complete in 40 min. Using DMAP under identical conditions, this reaction is 91% complete in the same time period. This result prompted us to compare the percent conversion of (±)-menthol, a relatively hindered alcohol, using various acylation catalysts/promoters in similar NMR experiments. Thus benzoylation of 0.10 mmol of (±)-menthol with 0.11 mmol of Bz_2O in the presence of 0.11 mmol of acylation promoter in 0.6 mL of C_6D_6 at 24 °C under N_2 revealed the following percent conversions by ^1H NMR integration after 90 min: Bu_3P (74%), DMAP (76%), DBU (< 1%), the phosphazene base P_4-*t*-Bu (49%), and **1a** (99%). Our experiments reveal that, in addition to functioning as a superior benzoylation promoter, the benzoylation byproduct **3a** is quite insoluble in solvents such as ether, pentane, and toluene, thus allowing its facile separation for recycling back to **1a** in a single step with KO-*t*-Bu. Furthermore, only a 10% molar excess of Ac_2O or Bz_2O is needed in conjunction with **1a** whereas 50−100% molar excesses of Ac_2O or Bz_2O were employed in the presence of DMAP[5] or Bu_3P.[7]

The acylation promoter **1a** is 17 times more basic than DBU.[10] Although the phosphazene base P_4-*t*-Bu (pK_a of $[HPh\text{-}t\text{-}Bu]^+$, 42.6 in CH_3CN[10]) is slightly stronger than superbase **1a** (whose conjugate acid **3a** has a pK_a of 41.2 in CH_3CN[10]), P_4-*t*-Bu is a much slower promoter for benzoylating (±)-menthol than **1a**, possibly because of the relatively weaker P−C(O) bond in **2a** compared with the N−C(O) bond of the analogous intermediate for P_4-*t*-Bu. The superbase **1a** is capable of completely deprotonating protonated Proton sponge (pK_a = 12.3 in H_2O[11]).

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1996.

(1) Baker, R. H.; Bordwell, F. G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 141.
(2) McKaiser, E.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.
(3) Scriven, E. F. *Chem. Rev.* **1983**, *12*, 129.
(4) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358.
(5) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.
(6) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(7) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286.
(8) Casida, J. E.; Eto, M.; Mosconi, A. D.; Engle, J. L.; Milbrath, D. S.; Verkade, J. G. *Toxicol. Appl. Pharmacol.* **1976**, *36*, 261.
(9) Schmidt, H.; Lensink, C.; S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *75*, 578.
(10) Tang, J.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.
(11) Lensink, C.; Xi, S. K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478.

S0022-3263(95)01232-1 CCC: $12.00

Table 1. Alcohol Acylations using 1a

alcohol	solvent	acid anhydride	reactn time (h)	eluant ratio[a]	product (% yield)	
benzyl alcohol	pentane	Ac_2O	0.16	90:10	benzyl acetate	(67%)
	benzene					(57%)
	acetonitrile					(79%)
	pentane	Bz_2O		95:5	benzyl benzoate	(96%)
	benzene					(99%)
	acetonitrile					(98%)
7a	pentane	Ac_2O	0.25	80:20[b]	**7b**	(53%)
	benzene					(58%)
	acetonitrile					(89%)
	pentane	Bz_2O		91:9[b]	**7c**	(63%)
	benzene					(94%)
	acetonitrile					(85%)
(±)-menthol	pentane	Ac_2O	1.0	95:5	(±)-menthyl acetate	(96%)
	benzene					(95%)
	acetonitrile					(93%)
	pentane	Bz_2O	1.5	100:0	(±)-menthyl benzoate	(78%)
	benzene					(92%)
	acetonitrile					(58%)
6a	pentane	Ac_2O	1.0	90:10	**6b**	(48%)
	benzene					(51%)
	acetonitrile					(68%)
	pentane	Bz_2O		97:3	**6c**	(80%)
	benzene					(90%)
	acetonitrile					(48%)

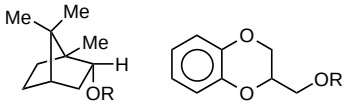
[a] Hexanes:ethyl acetate. [b] A neutralized silica gel column was used.

It is known that Ac_2O and pyridine react to produce a small amount of N-acylated **5** in an equilibrium reaction.[12] Because attempted acylation of **6a** in pentane using $P(NMe_2)_3$ or NEt_3 as an acylation promoter gave <1% of the acylation product, it seems unlikely that **1a** is N-acylated in our reactions. P-Acylation of **1a** to give intermediate **2a** is supported by NMR spectroscopy. A ^1H NMR spectrum of a mixture of 0.11 mmol of **1a** and 0.11 mmol of Bz_2O in 0.6 mL of C_6D_6 at 24 °C under N_2 revealed a doublet centered at 2.25 ppm with a P−H coupling constant J_{HP} of 13.8 Hz which we assign to a three-bond spin−spin interaction involving the methyl protons in **2a**. The ^{13}C NMR spectrum of this mixture shows a doublet for the carbonyl carbon peak centered at 209.0 ppm with a coupling constant of 135.7 Hz which is consistent with a one-bond C−P interaction. The ^{31}P NMR spectrum displays single peaks at −13.6 ppm (**2a**) and 119.7 ppm (**1a**) with or without proton decoupling. This substantiates the assignment of the −13.6 ppm ^{31}P NMR peak to the cation of **2a** rather than **3a** (−13.3 ppm) since the latter resonance without proton decoupling is a doublet owing to one-bond P−H coupling.

$$\mathbf{1a} + Bz_2O \rightleftarrows \mathbf{2a} \qquad (1)$$

Equilibrium 1 is shifted toward **2a** by lowering the temperature, as shown by variable temperature ^1H, ^{13}C, and ^{31}P NMR spectroscopy. It was determined by ^{31}P NMR integration that the ratio of **2a**:**1a** present at 10 °C was *ca.* 3:2 whereas at room temperature it fell to about 11:9. The percentage of **2a** decreased gradually as the temperature was increased until at 50 °C the peak for **2a** disappeared.

In view of the successful benzoylation of benzyl alcohol and (±)-menthol observed by NMR spectroscopy, we benzoylated and acetylated [(1*S*)-*endo*]-(−)-borneol (**6a**), 2-(hydroxymethyl)-1,4-benzodioxane (**7a**), benzyl alcohol, and (±)-menthol on a preparative scale in pentane, benzene, and acetonitrile. Table 1 contains the reaction and isolation conditions and the isolated yields of the acylated products.

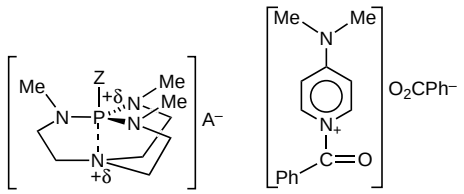


6a, R = H
6b, R = Ac
6c, R = Bz

7a, R = H
7b, R = Ac
7c, R = Bz

Discussion

The relatively high percentage of **2a** in equilibrium with **1a** at room temperature may be due to the stabilizing effect of at least partial transannular bond formation. The transannular distance in this type of molecule can vary from ~3.3 to ~2.1 Å, depending on the electron-withdrawing power of the phosphorus substituent.[13] This variability arises from resistance to transannular bonding stemming from the strain in the three five-membered rings that are formed.[14] Evidence for considerable transannulation in **2a** is its high-field ^{31}P NMR chemical shift (−13.6 ppm) which is indicative of phosphorus five-coordination. This shift is even more negative than that observed for the cation of **3a** (−13.3 ppm) which has nearly ideal trigonal bipyramidal symmetry and a transannular bond distance of 2.0778 Å.[13,14] The transannular distance in **1a** is likely to be close to that which we recently found in **1b** (3.29 Å) wherein the tertiary nitrogen is very nearly planar.[15] The ^{31}P NMR shift for **3a** coupled with transannular distances we have observed in cations similar to **2a**, such as **8** (2.190 Å)[14] and **9** (2.559 Å),[14] suggest considerable transannulation in cation **2a** (and by analogy in **2b**). Apparently the augmented

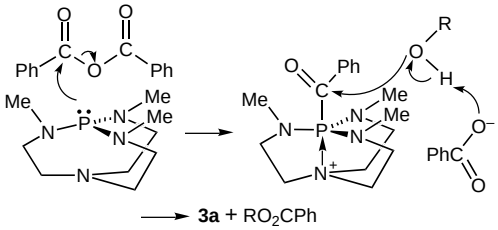


8, Z = MeSC(NPh); A = I
9, Z = HPhN; A = O_2CCF_3

10

nucleophilicity and basicity of phosphorus in **1a** stem-

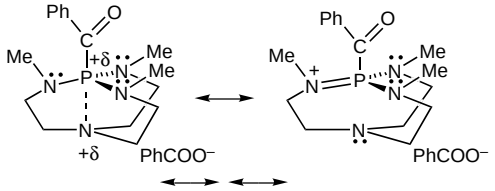
Scheme 1



ming from transannular bond formation (when Z is a sufficiently strong Lewis acid) play important roles in the rate of formation and stability, respectively, of cations of type **2**.

We believe that the extensive delocalization of positive charge in cations of **2a** and **2b** facilitated by transannular bond formation permits substantial separation of the ion pair, thereby making it more reactive. Thus loosely bound ion pairs of **2a** and **2b** facilitate the attack of a nucleophile on the activated acyl group which is then followed by general base catalysis by the corresponding anions as shown in Scheme 1. This mechanism is analogous to that proposed for acylations involving DMAP.[6]

The ^{31}P NMR spectrum of a mixture of 0.2 mmol of Bz_2O and 0.2 mmol of **1a** in 0.6 mL of C_6D_6 at 24 °C under N_2 revealed no change in its **2a**:**1a** ratio of 11:9 when 0.2 mmol of DMAP was subsequently added. The same observation was made when this solution was constituted by adding **1a** last, thus ruling out kinetically slow achievement of equilibrium. The observed thermodynamic stability of **2a** over the presumed DMAP benzoylation intermediate **10** may be rationalized by the disparate extents of positive charge delocalization in **2a** and **10**. The resonance structures for the cation of **2a** shown and implied below indicate the possibility of positive charge delocalization to all four nitrogens, whereas in DMAP only two nitrogens can be involved in such delocalization.



Although **1a** is a stronger base than DMAP and forms a thermodynamically more stable acylation intermediate (**2a**), this does not imply that **2a** is necessarily less reactive than the acylated intermediate **10** formed from the weaker base. The relatively high concentration of **2a** compared to **10** is undoubtedly also an important factor here.

From Table 1 it can be inferred that acetylation of a relatively hindered alcohol such as (±)-menthol and **6a** is faster than benzoylation in acetonitrile, whereas in general, benzoylation of an alcohol is faster than acetylation in benzene. These results can be rationalized from the observation that both acylation intermediates **2a** and **2b** are completely soluble in acetonitrile. The faster acetylation in acetonitrile is consistent with the basicity order $^{-}O_2CMe > {}^{-}O_2CPh$ for the counterions of **2a** and **2b**, respectively, and also with the proposed reaction pathway in Scheme 1. In benzene, the benzoylation intermediate **2a** is completely soluble whereas the acetylation intermediate **2b** is sparingly soluble, thus accounting for slower acetylation in the heterogeneous reaction mixture.

According to Table 1 the order of benzoylation of the relatively hindered alcohols (±)-menthol and **6a** in the solvents employed is acetonitrile < pentane < benzene. Here, solvation of the intermediate cation of **2a** and its anion in acetonitrile may interfere with nucleophilic attack on the cation by a bulky alcohol, and it may also inhibit the general base catalysis by the benzoate anion. Thus benzoylation of these hindered alcohols is faster in benzene than in acetonitrile, even though the benzoylation intermediates are soluble in both solvents. Although pentane and benzene are both nonpolar, the benzoylation intermediate **2a** is quite insoluble in pentane whereas it is completely soluble in benzene, thus accounting for the lower yields for all four benzoylated products in Table 1 obtained in pentane. The exceedingly low yield for the benzoylation of **7a** in pentane is undoubtedly due to the sparing solubility of **7a** and intermediate **2a** in this solvent. It is noteworthy that no acidic workup is required in our preparations as is the case with DMAP[6] or Bu_3P.[7] Hence acid-sensitive alcohols such as **7a** can also be successfully acylated with **1a**.

In the acylation of the alcohols in Table 1, 70−90% of **3b** and 94−98% of **3a** were isolated and converted back to **1a** generally in about 30 and 65% yields, respectively, using 1.1 equiv of KO-*t*-Bu. The higher solubility of **3b** in ether and the deprotonation of the acetate anion by KO-*t*-Bu (paralleling carboxylic acid dianion formation using LDA[16]) accounts for the generally lower yields of **1a**. Hence when 2.5 equiv of KO-*t*-Bu was used for the recycling of **3b**, the isolated yield of pure **1a** increased to 50%. When the acylations described here were carried out in the atmosphere, the yields of the esters were slightly lower. It should be noted that halogenated solvents react with **1a**[13] and must be avoided.

Conclusions

The exceedingly strong nonionic superbase **1a** is a superior acylation promoter, and it gives rise to the first detected P-acylation intermediate, namely, **2a**. Of the three solvents used in our acylation reactions, benzene seems to be optimum for benzoylating alcohols, whereas acetonitrile is the solvent of choice for acetylating them. The advantages of using **1a** as an acylation promoter are (1) the yields of acylated alcohols are high, (2) the byproducts **3a** and **3b** are easily isolated and recycled to **1a** in moderate to high yields, (3) only a slight excess of the acid anhydride is required, (4) compound **1a** is commercially available (Strem Chemical Co), and (5) because no acidic (or basic) workup is required, acid-sensitive alcohols can also be acylated. A minor drawback in using **1a** as an acylation promoter is that halogenated solvents cannot be employed.

(12) Fresht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.
(13) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233.
(14) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483 and references therein.
(15) Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1991**, *1*, 69.
(16) (a) Belletire, J. L.; Speltzer, E. G.; Pinkas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (b) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549. (c) Larock, R. C. *Comprehensive organic transformations; A guide to functional group preparations*, VCH Publishers Inc.: New York, 1989; p 869.

Experimental Section

Pentane, toluene, and benzene were distilled from Na−benzophenone under nitrogen. Acetonitrile was distilled from calcium hydride. The compounds [(1*S*)-*endo*]-(−)-borneol (98%), Ac_2O (99%), benzyl alcohol (99%), DMAP (99%), DBU (98%), 2-(hydroxymethyl)-1,4-benzodioxane (97%), and (±)-menthol (98%) were purchased from Aldrich Chemical Co. and were used as received. The phosphazene base P_4-*t*-Bu and Bz_2O (98%) were purchased from Fluka Chemical Co. and were used as received. Tributylphosphine (Aldrich) was purified from its CS_2 adduct.[17,18] All reactions were carried out at 24 °C under N_2. Although the superbase **1a** is commercially available (Strem Chemical Co.), we prepared it according to our previously published method[9] and stored it under N_2. The products were found to be >98% pure by ^{1}H NMR analysis.

General Preparative Procedure for Alcohol Acylations Promoted by 1a. After the superbase **1a** (1.1 g, 5.1 mmol) was dissolved in 30 mL of solvent at 24 °C under N_2, the appropriate acid anhydride (5.1 mmol) was added and the mixture was stirred for 5 min. Then 4.8 mmol of the alcohol was added with continued stirring. After the reaction time stated in Table 1, 0.05 mL of water was added with stirring. This was followed by the addition of 80 mL of ether, and stirring was continued for 5 min more. When acetonitrile or benzene was used as the solvent, ~95% of the solvent was evaporated before addition of the ether. The mixture was then filtered, and the residue was washed with 20 mL of ether. The organic layer was dried with anhydrous sodium sulfate, followed by concentration under vacuum, affording the crude ester which was purified by chromatography on silica gel using the eluant indicated in Table 1. The residue obtained from the reaction was treated with KO-*t*-Bu by our literature method[9] to recover **1a**.

Acknowledgment. The authors thank the Center for Advanced Technology Development of Iowa State University and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for grant support of this research.

Supporting Information Available: Compound characterization data, NMR peak assignments, and copies of ^{1}H NMR spectra (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951232X

(17) (a) Margulis, T. N.; Templeton, D. H. *J. Am. Chem. Soc.* **1961**, *83*, 995. (b) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; J. Wiley and Sons, Inc.: New York, 1976.

(18) Verkade, J. G.; Mohan, T.; in preparation.