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SYNTHESIS AND CHARACTERIZATION OF 4-DIMETHYLAMINO-N-TRIPHENYLMETHYLPYRIDINIUM CHLORIDE, A POSTULATED INTERMEDIATE IN THE TRITYLATION OF ALCOHOLS

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4-Dimethylamino-N-triphenylmethylpyridinium chloride (1) reacts with primary but not secondary alcohols to produce trityl ethers in good yield; in addition, amines may be selectively N-tritylated with 1 in the presence of alcohols.

Recently, we reported a simplified procedure for the preparation of triphenylmethyl ethers which involves the use of 4-dimethylaminopyridine (DAP) as a highly efficient and selective catalyst.[1] A mechanism was advanced which involved the formation of the N-tritylpyridinium salt of DAP. In this report, we describe the preparation and physical properties of this salt. Reaction of DAP with tritylchloride in dry methylene chloride at room temperature for 30 minutes under nitrogen provides, a powdery solid in 95% yield, m.p. 126-128° (1). ^{1}H and ^{13}C NMR spectra were fully consistent with alkylation of the heterocyclic nitrogen rather than the exocyclic dimethylamino group.[2] The ease of formation of this salt is remarkable when compared with the corresponding unsubstituted pyridinium salt,[1] the formation of which takes place by heating a dioxane solution of reactants at 60-70° for 10-15 hours under 4000-5000 atm.[3] The DAP salt of trityl chloride is considerably more stable towards hydrolysis than the corresponding N-trityl pyridinium chloride (2) and tetrafluoroborate salts.[4] A sample of 1 kept in a closed bottle for several months at room temperature showed no significant decomposition as evidenced by ^{1}H NMR.

Reaction of 1 with primary alcohols takes place at 25° in CH_2Cl_2 using a slight excess of reagent. Reaction of 1 with secondary alcohols was unsuccessful under several sets of conditions. Yields of primary trityl ethers obtained from reaction of 1 with alcohols are comparable to those obtained by the catalytic procedure.[1] A striking difference is the effect of solvents on the reactivity of 1. Uridine did not react with 1 in DMF solution at 25° (24 hr), however, upon addition of CH_2Cl_2 (2 volumes) a 60% yield of 6-O-trityl uridine was obtained overnight. This observation encouraged a search for solvents which could potentially alter the selectivity and reactivity of 1. Hence the reaction of 1,4-pentanediol with 1 to produce 3 was examined in different solvents (Table 1).

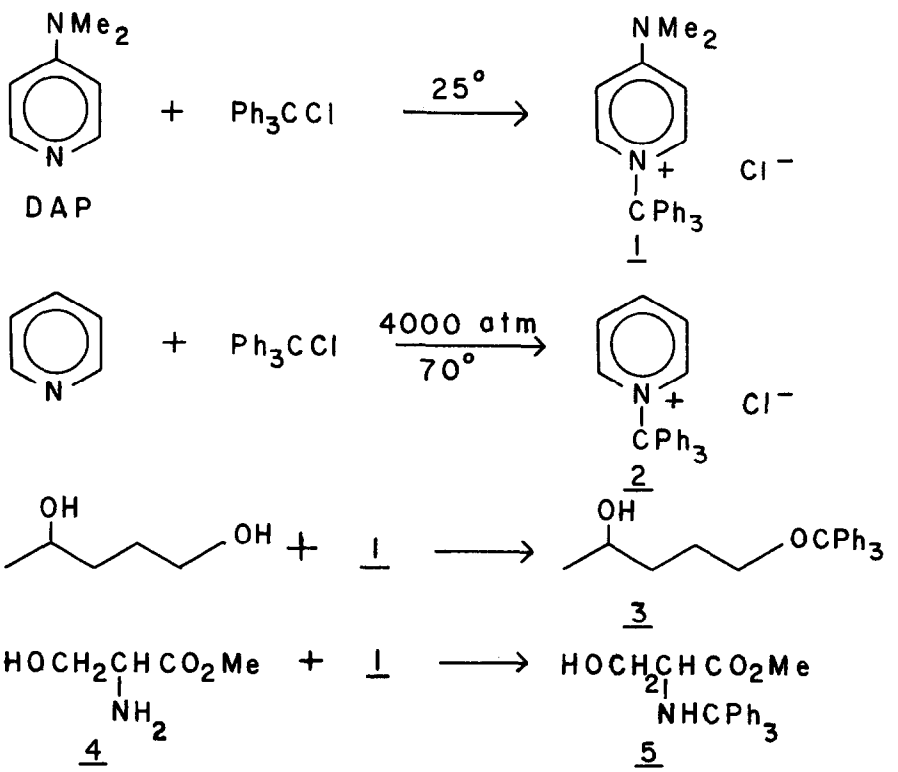
Examination of Table 1 shows that at 25° the reactivity of 1 is inversely related to the solvent polarity. This solvent effect is decreased and finally eliminated by gradual increases in temperature. The lack of reactivity in CCl_4 and THF is explained by the negligible solubility of 1 in these solvents. The ^{1}H and ^{13}C NMR spectra of 1 in CD_3CN were identical to the ones determined in CD_2Cl_2. An explanation of this solvent effect is not available at this time, however, acyl pyridinium salts are known to exhibit similar sensitivity towards solvent polarity.[5]

TABLE 1: The Effect of Solvent on the Reaction of 1 with 1,4-Pentanediol

Solvent	Yield of 3 (%) 25°, 16 hr[a]	45°, 5 hr[a]	90°, 5 hr[b]
CH_2Cl_2	100	100	-
CH_3CN	20	40	85
DMF	5	15	65
THF	No Rxn.	No Rxn.	-
CCl_4	No Rxn.	No Rxn.	-

[a]Relative to CH_2Cl_2 by HPLC - see experimental.

[b]Isolated yield.



The protection of amino groups by reaction with 1 was briefly explored. Reaction of glycine ethyl ester in DMF solution afforded the N-protected amino acid in 65% yield. By taking advantage of the solvent effect described above the reaction of serine methyl ester (4) with 1 in DMF gave product (60% yield) resulting exclusively from N-tritylation (5).

Both the selectivity shown by 1 in reactions with alcohols, and the preferential protection of amines in the presence of hydroxyl groups (e.g. 4) have a definite synthetic potential in nucleoside and amino-sugar chemistry. The scope of these transformations remains to be established. The application of 1 to the preparation of specific cyclodextrine derivatives will be described elsewhere.

A conclusive assessment of the prevailing mechanism in the DAP catalyzed reaction of alcohols with trityl chloride is not possible at this point. The data presented here rule out the participation of 1 in the tritylation of secondary alcohols, however, 1 is a likely intermediate in the formation of primary trityl ethers.

Preparation of 1. Freshly crystallized trityl chloride (11 mmol), and DAP (10 mmol) in 20 ml of dry CH_2Cl_2 were stirred for 30 min under nitrogen at room temperature. Addition of 100 ml of absolute diethyl ether precipitated 1 which was filtered and washed with ether to give 3.84 g (95%) of pure salt, mp 126-128°.[2] Further crystallizations failed to increase the mp.

1,4-Pentanediol monotrityl ether (3). A solution of 1,4-pentanediol (10 mmol) and 1 (12 mmol) in CH_2Cl_2 (30 ml) was stirred overnight at 25°. Conventional work-up followed by silica gel chromatography [(C_6H_{12}:EtOAc(7:1)] gave an oil (2.6 g, 75%) identified as 3. 6-O-Trityl uridine (60%) and benzyltriphenylmethylether (85%) were prepared by a similar procedure.

Solvent Effects. Solutions of 1 (1.2 mmol) and the diol (1 mmol) in the appropriate solvent (10 ml) were prepared and aliquots were taken as indicated in Table 1. Analysis was performed on a reversed-phase column (μ-Bondapak C18, 0.39 x 30 cm) eluted isocratically (15% H_2O/MeOH) at 0.8 ml/min. Peaks were detected at 254 nm and integrated using a Waters Data Module 730. Retention times for trityl alcohol and 3 were 6.1 and 8.3 min, respectively.

Preparation of 5. The hydrochloride of 4 (4 mmol), diisopropylethylamine (4 mmol), and 1 (5 mmol) were dissolved in DMF (25 ml) and stirred at 25° for 24 hr. Extraction with EtOAc followed by aqueous work-up gave an oil which was crystallized from C_6H_6-Et_2O to give 5 (450 mg, 35%) mp 145-146°; silica gel chromatography (50% hexane/Et_2O) of the mother liquor afforded 400 mg of 5 for a combined yield of 60%. ^{13}C NMR ($CDCl_3$), the methine carbon ($Ph_3\underline{C}$-) in 5 absorbs at 71.2 ppm which is similar to that for N-trityl glycine (70.9 ppm, $Ph_3\underline{C}$-N) and substantially different from benzyltriphenylmethylether ($Ph_3\underline{C}$-O, 87.2 ppm). By a similar procedure, N-trityl glycine ethyl ester was prepared in 65% yield, mp 98°.

REFERENCES AND FOOTNOTES

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2. ^{1}H NMR (60 MHz, CD_2Cl_2): 3.3 (s,6H,N-CH_3), 7.27 (m,17H,phenyl plus H_3 and H_5 of pyridine ring), and 7.95 (d,2H,H_2 and H_6 of pyridine ring) ppm; ^{13}C NMR (25.2 MHz,CD_2Cl_2): 41.1 (N-CH_3), 139.9 (C-2,-6). 107.9 (C-3,-5), and 156.4 (C-4) ppm for the pyridine ring. The shifts induced in the pyridine ring upon salt formation as well as lanthanide shift reagent experiments on 1 conclusively indicate alkylation of the pyridine nitrogen.
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