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VALUE OF THE VINYLOXYCARBONYL UNIT IN HYDROXYL PROTECTION: APPLICATION TO THE SYNTHESIS OF NALORPHINE†

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The reactivity of vinyloxycarbonyl (VOC) esters of phenols and alcohols toward acid and base hydrolysis is sufficiently different from the lability of the analogous VOC derivatives of amines in the same media[1,2] that the disparities can be used to unique advantage in some complex syntheses involving the application of protecting group strategies.

Standard methods suffice for the preparation of VOC esters. For example, treatment of VOCCl[3] (1) with β-naphthol in aqueous dioxane maintained at pH 7 (pH stat) gave O-VOC-β-naphthol[4] (2, mp 48-49°) in 81% yield and O-VOC-phenol (3, bp 56° at 0.4 torr) was easily obtained in 94% yield from reaction of phenol with 1 and pyridine in 1,2-dichloroethane. The latter procedure also afforded 2 in 95% yield and O-VOC-cholesterol (4, mp 90.5-91.5°) from cholesterol in 93% yield.

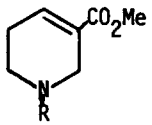
Hydrolysis of 2 to β-naphthol (96% after sublimation) and 4 to cholesterol (97% after recrystallization) was readily accomplished with Na_2CO_3 in warm aqueous dioxane. When the second experiment was repeated in the presence of 1 eq N-VOC-guvacoline[2] (5a) for comparison purposes, the N-VOC group of 5a was not affected but methyl ester hydrolysis was a significant side reaction. In contrast, both 2 and 4 could be recovered quantitatively from CH_2Cl_2 solutions to which one eq 5a and two eq HBr in methanol had also been added -- conditions under which 5a is deprotected (→5b) in 98% yield. The reisolation of 3 in 90% yield from a 2N anhydrous HCl in dioxane solution after 3 hr. and in 70% yield from a 50% aqueous HBF_4 solution after 12 hr. (both at 25°) further demonstrates the acid stability of the VOC-OAr unit.

†Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

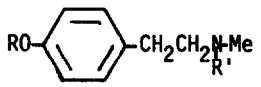
Complete acid hydrolysis of 3 to phenol required 8 hr. with 2N HCl in MeOH-water (4:1) at 60°.

The direction and magnitude of the acid-base reactivity differences between VOC esters and amides are not unexpected: for H_2C=CHOCOX, C=O attack by nucleophiles should be facilitated and H_2C attack by electrophiles (the first step in acid deprotection[1]) repressed as the electron withdrawing effect of X is increased (OR or OAr >> NR_2). Competition experiments also indicate that VOC esters of alcohols are less susceptible to both acid and base hydrolysis than VOC-OAr, though the differences are usually too small to be synthetically useful. The base order, VOC-OAr > VOC-OR, is in accord with the rationalization above, but the observation of the same trend in acid suggests that a complete explanation of the data is more complex.

The following transformations of hordenine (6a) (which also incorporate the dealkylation method already outlined[2]) provide another test of the hydrolytic selectivity introduced above.



5a: R = VOC
5b: R = H·HBr



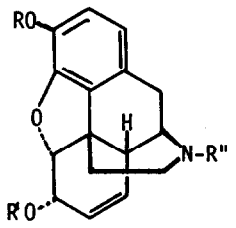
6a: R = H, R' = Me
6b: R = VOC, R' = Me
6c: R = R' = VOC
6d: R = H, R' = VOC
6e: R = VOC, R' = H·HBr
6f: R = H, R' = H·HCl

Reaction of 6a with 1 eq VOCCl in dichloroethane at 25° gave 6b (87%, bp 85° at 0.2 torr; anal. as HCl salt: mp 158-159°) after base neutralization. The N-demethylated product (6c, bp 162-164° at 0.3 torr)could be obtained from 6b after further treatment with VOCCl or in one step from 6a in 83% yield under the same conditions using 2.3 eq VOCCl with 1 eq 1,8-bis-(dimethylamino)-naphthalene (7) present to neutralize the HCl liberated in the phenol acylation. Selective hydrolysis of 6c to 6d (oil, anal. as α-naphthylurethan: mp 109-110.5°) was accomplished (75%) with 1.1 eq NaOH in dioxane-water (3:1), and the conversion, 6c → 6e (mp 121-122°), proceeded in 90% yield in CH_2Cl_2 with 1.1 eq 10% HBr in ethanol. One step diVOC removal to give N-methyltyramine hydrochloride[6] (6f) was most easily achieved by refluxing 6c in 5% methanolic HCl overnight (96%). The process, 6a → 6f, was performed in 87% overall yield without isolation of 6c.

The preparative advantage of being able to block both hydroxyl (particularly phenols) and amine functions simultaneously with a single acyl moiety is often lost if later elaboration at one of these sites is required. This is especially true if the amine group is to be the position of initial modification, since esters are generally more easily hydrolyzed than the analogous amides in both acid and base. The superiority of VOC protection in this area becomes

even more evident when illustrated by the synthesis of nalorphine which follows.

Nalorphine (8a ≡ Nalline, Norfin, Anarcon, NANM, Lethidrone, etc.) is the classic narcotic antagonist used in the emergency treatment of heroin overdose victims and in inducing respiration and thus the survival of infants born to narcotic addicted mothers.[7]



8a: R = R' = H, R" = Allyl
8b: R = R' = H, R" = Methyl
8c: R = R' = Acyl, R" = Methyl
8d: R = R' = Acyl, R" = CN
8e: R = R' = R" = H
8f: R = R' = R" = VOC
8g: R = R' = VOC, R" = H
8h: R = R' = VOC, R" = Allyl

The best published syntheses[8] of nalorphine from morphine (8b) involve initial conversion to an O,O-diacyl intermediate (8c) followed by von Braun N-demethylation (→8d), then vigorous hydrolysis to normorphine (8e), and finally N-allylation. In the final step, phenol O- and C-allylation are competitive side reactions which can be minimized but not avoided entirely. Because removal of the cyano residue in 8d (or its surrogate from another dealkylation method) has never been achieved without simultaneous loss of the O-acyl groups, potentially superior nalorphine syntheses in which the phenolic hydroxyl remains protected during the N-allylation step have never previously been designed or tested. The first such route is recorded below.

Treatment of morphine with 5 eq VOCCl and 2.4 eq of the base (7) in dichloroethane gave the di-O-protected N-demethylated compound (8f) in one step in 91% yield (mp 65-70° amorph, anal pure, IR: C=O stretch at 5.59, 5.66, 5.81, O-C=C at 6.05μ in CCl_4). Selective N-VOC removal was achieved (90%) with 2 eq anhydrous HBr in ethanol-ether at 25° (→8g·HBr, mp 228-229° dec). Alkylation of 8g·HBr (2.03 mmol) with allyl bromide (2.07 mmol) and Na_2CO_3 (2.2 mmol) in ethanol (10 ml) at 70° for 6 hr. afforded the allylamine (8h, IR: 5.60, 5.66, 6.05μ) which was not purified. Instead, 18 ml (30 mmol) of 1.7 N aq HCl was added to the reaction mixture, the ethanol distilled off, and the remaining solution heated at 100° until hydrolysis to 8a·HCl was complete (8 hr., followed by tlc). Nalorphine (8a) was separated from the neutralized mixture by standard methods and recrystallized from methyl acetate (yield: 83%). Because of the oxidation sensitivity of 8, base conversion of 8h to 8a was less satisfactory than acid treatment. Without purification of any intermediates, the complete synthesis of recrystallized nalorphine from morphine (20 mmol scale) was accomplished in 77% overall yield.[9] A comparison

sample of nalorphine was also made from normorphine (8e) which could be obtained by mild base or strong acid hydrolysis of 8g.

The further application of the procedures outlined here for the replacement of N-methyl by other biological activity potentiating N-substituents in pharmaceutically important alkaloids and derivatives is easily imagined as are practical advantages in the broad spectrum N-substituent modification of even completely synthetic tertiary amine drugs. A related investigation is described in the following communication.[10]

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References

1) R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, First of preceding communications.

2) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, Preceding communication.

3) F. E. Küng, U. S. Patent 2,377,085, May 29, 1945; see also footnote 1 in ref. 1.

4) Satisfactory combustion analyses and confirmatory IR, UV, NMR, and mass spectral data have been obtained for all new compounds.

5) R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, Chem. Commun., 723 (1968). Other potentially more economical proton selective bases which can be substituted for 8 in this reaction have also been developed; unpublished results.

6) G. Goldschmiedt, Monatsh. für Chemie, 34, 659 (1913); and refs. therein.

7) Medicinal Chemistry, 3rd Ed., Edited by A. Burger, Wiley-Interscience, New York, N. Y., 1970: see especially A. E. Jacobson, E. L. May, and L. J. Sargent, Analgetics Ch 49, P. W. Collins, Antitussives Ch 50, and L. M. Rice and E. C. Dobbs, Analeptics Ch 53; Agonist and Antagonist Actions of Narcotic Analgesic Drugs, Edited by H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, University Park Press, Baltimore, Md., 1973.

8) K. W. Bentley, The Chemistry of the Morphine Alkaloids, Oxford Press, London, 1954; G. Stork, The Morphine Alkaloids, Ch 7 in the Alkaloids, Vol VI, Edited by R. H. F. Manske, Academic Press, New York, N. Y., 1960; and refs. therein. For studies of the conversion, 8b to 8e using chloroformates see: M. M. Abdel-Monem and P. S. Portoghese, J. Med. Chem., 15, 208 (1972), and refs. therein; K. C. Rice, J. Org. Chem., 40, 1850 (1975); T. A. Montzka, J. D. Matiskella, and R. A. Partyka, Tetrahedron Lett., 1325 (1974).

9) A small amount of additional product along with some recoverable precursor are present in the recrystallization filtrate.

10) R. A. Olofson and J. P. Pepe, Following communication.