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SELECTIVE N-DEALKYLATION OF TERTIARY AMINES WITH VINYL CHLOROFORMATE: AN IMPROVED SYNTHESIS OF NALOXONE†

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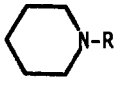
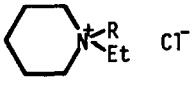
We introduce here a mild procedure for the selective N-dealkylation of aliphatic tertiary amines with the stable and potentially inexpensive reagent, vinyl chloroformate[1,2] (= VOCCl). While not different in concept from some earlier methods,[3] the new route has enough advantages to provide a tempting inducement to the synthetic chemist to consider the widespread use of certain simple alkyl groups as blocking agents (acid, base, redox stable) for secondary amines in complex syntheses. The potential of this new process in the chemical modification of alkaloid drugs is also outlined.

The method is exemplified by the conversion of N-ethylpiperidine (1a) with 1.3 eq VOCCl in 1,2-dichloroethane to N-VOC-piperidine[4] (1b, bp 63-65° at 0.4 torr) in 90% yield followed by quantitative VOC removal (→1c) under conditions (excess HCl or HBr or stoichiometric Br_2 in CH_2Cl_2 followed by warming with ROH) described in the preceding communication.[2]



1a: R = Ethyl
1b: R = VOC
1c: R = H HX
1d: R = CN
1e: R = CO_2Ph
1f: R = CO_2Et
1g: R = $CO_2CH_2CCl_3$
1h: R = CO_2CH_2Ph



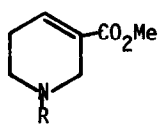
2a: R = VOC
2b: R = CO_2CH_2Ph
2c: R = CO_2CH_2Z

The unstable intermediate (2a), which immediately precipitates from solution while adding 1a to VOCCl at 0° or -35°, cleaves to 1b when the mixture is heated to reflux for a short period.[5] The only side product found was the trace moisture derived HCl salt of 1a,[6] a substance easily

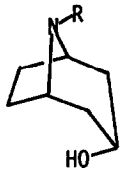
†Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

separated from the neutral 1b by extraction. In contrast, 1a is reported[7] to give a mixture of 1d (est 54%) and ε-bromopentylethylcyanamide (28%) on von Braun dealkylation[3] with BrCN. Under conditions comparable to those described for VOCCl, phenyl chloroformate (the best $ClCO_2R$ reagent previously recommended[8] for amine dealkylation) reacted with 1a to give 1e in only 34% yield and similar de-ethylation (→ 1f or 1g) with the sometimes used $ClCO_2Et$[3] or $ClCO_2CH_2CCl_3$[9] was even worse (10% or less). Only traces of 1h were obtained with $ClCO_2CH_2Ph$[10] and a major side product was $PhCH_2Cl$ produced by an alternative fragmentation of 2b, a process also responsible for the low yields of 1f and 1g. Similar S_N1 and S_N2 scissions of 2a are implausible. The increased reactivity of VOCCl vs. other chloroformates is attributed to steric factors and to enhanced electrophilicity at an acyl carbon attached to an electron withdrawing $OCH=CH_2$.

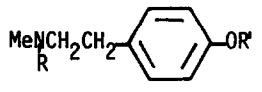
Other dealkylations accomplished with VOCCl include the cleavage of the alkaloid, arecoline (3a), to 3b (bp 104-106° at 0.2 torr) in 92% yield followed by hydrolysis to guvacoline hydrobromide[11] (3c) in 98% yield. When treated with 1 eq VOCCl in ether, tropine (4a) yielded 4b (76%, IR: OH stretch at 2.75, 2.86μ) uncontaminated by O-VOC material. Formation of nortropine hydrochloride[12] (4c) from 4a without isolation of 4b was achieved in 77% yield.



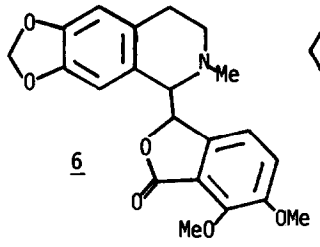
3a: R = Methyl
3b: R = VOC
3c: R = H·HBr



4a: R = Methyl
4b: R = VOC
4c: R = H·HCl



5a: R = Methyl, R' = H
5b: R = R' = VOC
5c: R = H·HCl, R' = H



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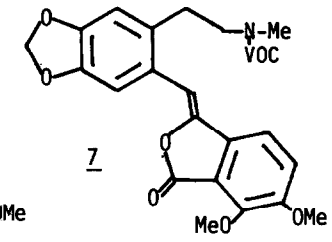

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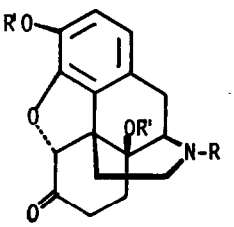
Similar reaction of 4a with $ClCO_2Et$ followed by acid hydrolysis of the intermediate urethancarbonate mixture is reported to afford 4c in 16% overall yield (a transformation even less satisfactory by the von Braun method).[12] In another experiment, hordenine (5a) has been converted to N-methyltyramine hydrochloride (5c) in 87% overall yield via the intermediate O,N-diVOC-N-methyltyramine (bp 162-164° at 0.3 torr).[13] Cleavage at benzylic and tertiary centers adjacent to the amine function is generally preferred. For example, $tBuNMe_2$ gives $VOC\text{-}NMe_2$ (bp 56° at 14 torr) exclusively while hydrastine (6) is converted in 88% yield to the enol lactone (7, mp 141° dec, IR: 5.62, 5.84, 6.07μ in CH_2Cl_2).[14] Further selectivity studies are

in progress. Very weakly basic tertiary amines such as N, N-dimethylaniline do not react with VOCCl even at reflux in dichloroethane.

We also report here the use of VOCCl as the key reagent in a much improved synthesis of the narcotic antagonist drug, naloxone[15] (8b) from its ordinary precursor, oxymorphone (8a). Only recently introduced commercially, naloxone is already generally considered the antidote of choice for the emergency treatment of heroin overdose victims and has largely replaced the classic narcotic antagonist, nalorphine,[15] for this purpose. Though its antagonist activity is 7-30 times greater, naloxone, unlike nalorphine, has little or no analgesic activity.



8a: R = Methyl, R' = H (oxymorphone)
8b: R = Allyl, R' = H (naloxone)
8c: R = Methyl, R' = Acetyl
8d: R = Cyano, R' = Acetyl
8e: R = R' = H (noroxymorphone)
8f: R = VOC, R' = Acetyl
8g: R = H·HCl, R' = Acetyl

Naloxone is presently made by diacetylation of 8a to give 8c which is then N-demethylated with BrCN to afford the N-cyano compound (8d). Strong acid hydrolysis of the latter yields noroxymorphone (8e) which is converted to naloxone on treatment with allyl bromide. The published overall yield of crude naloxone from oxymorphone is only 20%.[16]

When 3,14-diacetyloxymorphone (8c) was N-demethylated with VOCCl in dichloroethane at reflux, the N-VOC compound (8f, mp 210.5-211.5°, IR: 5.66, 5.73, 5.81[sh], 5.85, 6.08μ in CH_2Cl_2) was obtained in essentially quantitative crude yield (excluding the 3% of starting 8c recovered). The VOC and acetyl groups were most efficiently removed by a three step process in which anhydrous HCl was first bubbled through a CH_2Cl_2 solution of 8f to produce the normal adduct. Next, solvent evaporation followed by warming in methanol gave the salt (8g) which was dissolved in 25% sulfuric acid and refluxed for 5 hours. Neutralization of the reaction mixture precipitated noroxymorphone (8e). When the reaction sequence was performed without isolation of intermediates, crude noroxymorphone[17] was obtained in 98% overall yield from oxymorphone. Allylation of this material with 1.1 eq allyl bromide in ethanol gave naloxone in 71% recrystallized yield (70% from 8a). Another 5-8% of naloxone present in the filtrate was contaminated by O-allyl side products.

Acknowledgement. We thank the National Institutes of Health for a grant (GM 13980) which provided the major support for this investigation.

References

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

2) R.A. Olofson, Y.S. Yamamoto, and D.J. Wancowicz, Preceding communication.

3) G. Fodor, S. Abidi, and T.C. Carpenter, J.Org. Chem., 39, 1507 (1974); and refs. therein; F. Möller, Methoden Org. Chem. (Houben-Weyl), XI/1, 982-988 (1957).

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

5) N-Ethylpiperidine ranks with the most difficult aliphatic amines to dealkylate with VOCCl. Other adduct intermediates often cleave at 20-40°. In dichloroethane and in other solvents low temperature adduct formation followed by thermolysis usually gives the cleanest results. For isolation and characterization of $R_3\overset{+}{N}\text{-}\overset{-}{CN}\ X^-$, see ref. 3a. These investigators have obtained a similar intermediate in PhOCOCl induced dealkylation. For isolation of other N-acylammonium salts see: J.V.Paukstelis and M. Kim, J. Org. Chem., 39, 1499, 1503 (1974).

6) Since 1a HCl can be recycled in the reaction, the conversion of 1a to 1c in yields >90% is practical. Improvement in other yields reported here for VOCCl induced N-dealkylation can be achieved similarly if economically desirable.

7) J. von Braun, Chem. Ber., 42, 2035 (1909); also see ref. 3a. Reduced selectivity is not the only deficiency of von Braun dealkylation. Note that the process, $R_2N\text{-}CN \rightarrow R_2NH$, requires more vigorous conditions and usually is not as clean as VOC removal.

8) J.D. Hobson and J.G. McCluskey, J. Chem. Soc. (C), 2015 (1967). In less stringent test systems (e.g. processes involving N-methyl or N-benzyl scissions), the yield advantages of VOCCl over other chloroformates are not usually as dramatic.

9) T.A. Montzka, J.D. Matiskella, and R.A. Partyka, Tetrahedron Lett., 1325 (1974); M.G. Reinecke and R.G. Daubert, J. Org. Chem., 38, 3281 (1973).

10) E.H. Flynn, H.W. Murphy, and R.E. McMahon, J. Amer. Chem. Soc., 77, 3104 (1955).

11) K. Hess, Chem. Ber., 51, 1004 (1918); original isolation by E. Merck.

12) G. Kraiss and K. Nador, Tetrahedron Lett., 57 (1971).

13) For additional data see: R.A. Olofson and R.C. Schnur, following communication.

14) With narcotine (6-4-OMe) as the precursor, the first conversion of a phthalideisoquinoline alkaloid to a benzazepine alkaloid (an example is rhoeadine) has recently been published: W. Klotzer, S. Teitel, J.F. Blount, and A. Brossi, J. Amer. Chem. Soc., 93, 4321 (1971). In analogy with this work, the product expected from hydrolysis of 7 is a 7-membered ring enamine (by aminoketone cyclization) which should be similarly converted to a rheadan.

15) H.W. Kosterlitz, H.O.J. Collier, and J.E. Villarreal, Eds., Agonist and Antagonist Actions of Narcotic Analgesic Drugs, University Park Press, Baltimore, Md., 1973; see especially: H. Blumberg and H.B. Dayton, Naloxone and Related Compounds, pp 110-119.

16) M.J. Lewenstein, Brit. Patent 955,493, April 15, 1964.

17) Noroxymorphone generally is isolated by lowering the pH of an aqueous solution to 9 [I. Seki, Takamine Kenkyusho Nempo, 12, 56 (1960)] at which point the compound precipitates completely. This very polar substance darkens but does not melt below 300° and is essentially insoluble in common organic solvents. It has never been successfully recrystallized presumably because of the incompatibility of the ketone and secondary amine fuctions. No useful purification procedure is available and no simple assay of sample purity exists. For synthetic purposes, this intractable material ordinarily is assumed to be reasonably pure. The difficulty of imagining an equally insoluble reaction by-product or side product provides the main justification for this assumption. Thus the 98% yield reported here should be viewed with some skepticism.. However, it should be noted that the material obtained here is at least as pure as that isolated by other methods. For example, the best previous yield for the allylation step, noroxymorphone to naloxone was 72% crude: Sankyo Co., Belg. Patent 615,009, Mar. 30, 1962 [CA, 57, 15171c (1963)].