These considerations led us to predict that the cycloadducts arising from the chair-like transition states **10a** and **16a** would be obtained preferentially upon thermolysis of the dienol ethers **2** and **3**.

Heating the cis dienol ether **2** at 170 °C (1.5 h, sealed tube) in decalin smoothly gave rise to the cycloadducts **13** and **11** with a high degree of stereoselectivity (ca. 60:1) in over 80% yield. However, unexpectedly, the major product proved to be **13** by comparison of the ^{1}H NMR spectra of the reduction products **12** and **14**[17] with that of authentic **12**.[18] The structure of **13** was further validated by a single-crystal X-ray analysis of the benzoate **15**.[19] Interestingly, the trans isomer **3** was found to be quite resistent to cyclization, even under much more drastic conditions (250 °C in decalin in a sealed tube for several hours).[20] The unexpected high stereoselectivity for the formation of **13** indicates a preference for the transition state possessing a boat conformation in the formation of the ring B. Efforts are currently underway in these laboratories to determine the factor(s) that favors this unusual boat transition state in the intramolecular Diels–Alder reaction.

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(16) Maier, W. F.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

(17) For **14**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.105 (ddd, 1 H, J = 2.2, 4.6, 12.7 Hz, 12β-H), 1.255 (t, 1 H, J = 4.3 Hz, OH), 1.42–1.67 (m, 5 H), 1.697 (s, 3 H, 16-H), 1.790 (m, 1 H, 3-H), 1.910 (m, 2 H, 8-H), 2.330 (d, 1 H, J = 12.7 Hz, 12α-H), 2.392 (dd, 1 H, J = 4.6, 6.5 Hz, 5-H), 3.357 (d, 2 H, J = 4.3 Hz, 15-H), 3.401 (d, 1H, J = 4.5 Hz, 11-H), 4.358 (s, 1 H, 2-H), 5.379 (dq, 1 H, J = 4.5 [d], 1.4 Hz [q], 10-H); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 22.71 (t), 23.19 (t), 23.61 (q), 27.65 (t), 30.20 (t), 34.32 (t), 38.00 (d), 42.36 (s), 64.18 (t), 65.64 (d), 75.45 (d), 120.65 (d), 138.80 (s).

(18) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(19) Performed by Dr. W. M. Butler (The University of Michigan).

(20) The fact that the cis dienol ether **2** is much more reactive than the trans isomer, contrary to the bimolecular case, is perhaps a reflection of the lower entropy of activation in the cycloaddition of **2** with respect to that of **3**, with higher population of conformers disposed for the cyclization.

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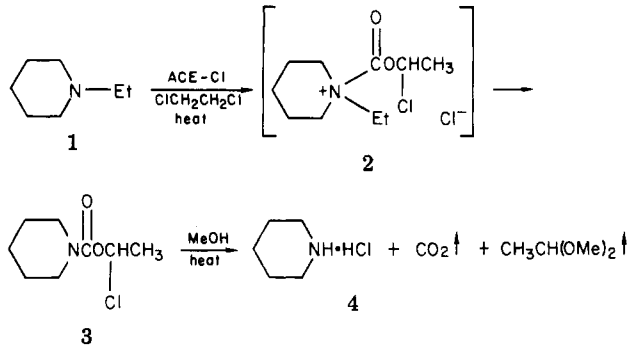
A New Reagent for the Selective, High-Yield N-Dealkylation of Tertiary Amines: Improved Syntheses of Naltrexone and Nalbuphine

Summary: Secondary amine hydrochlorides are obtained in high yield by reaction of tertiary amines with α-chloroethyl chloroformate followed by warming the intermediate carbamate in methanol.

Sir: We introduce here a new reagent, α-chloroethyl chloroformate (ACE-Cl), for the selective N-dealkylation of tertiary amines. While further development of the process is required (especially cleavage selectivity studies), we believe the initial results warrant bringing the new methodology to the early attention of synthetic chemists.

The new process is exemplified by the specific N-deethylation of *N*-ethylpiperidine (**1**) to give piperidine hydrochloride (**4**) in 99% yield. The reaction is performed



by adding ACE-Cl (1 equiv[1]) to **1** in $ClCH_2CH_2Cl$ at 0 °C (15 min) and then refluxing the mixture for 1 h. The intermediate ACE-piperidine **3** (bp 67–69 °C at 0.2 mm)[2] can be isolated but usually is de*ACE*ylated directly to **4** by evaporating the reaction mixture in vacuo and then heating the residue in MeOH (30–45 min at 50 °C to reflux).[1] Added H^+ is not needed to convert **3** to **4**. High-yield dealkylation with ACE-Cl is very surprising since other alkyl chloroformates (ROCOCl: R = Et, $PhCH_2$, Cl_3CCH_2) almost exclusively fragment to RCl + CO_2 in the presence of **1**.[3] Presumably the $CHClCH_3$ unit of **2** is too hindered to undergo competitive S_N2 attack by Cl^- and the related cation is too unstable to permit S_N1 substitution. In its reactivity toward **1**, ACE-Cl parallels the best previous chloroformate type N-dealkylation reagent, vinyl chloroformate (VOC-Cl).[3] However, ACE-Cl is much cheaper to make than VOC-Cl,[4] the yield of **4** is 99% (vs. 90% with VOC-Cl[3]), and in VOC removal,[3,5] HCl addition is required to convert VOC-piperidine to **3**. With ACE-Cl, this extra step is eliminated and the overall conditions are therefore much milder, thus expanding the list of functionalities permitted in the amine to be dealkylated.

With ACE-Cl (then MeOH), *N*-methylmorpholine is cleaved to morpholine·HCl in 96% yield and *N,N'*-dimethylpiperazine similarly is double N-demethylated to piperazine·2HCl in 96% overall yield. This selectivity is unexpected. In the mechanistically analogous von Braun dealkylation with BrCN, only ring scission products are obtained from both reactants.[6] However, as predicted benzyl cleavage is preferred over methyl loss: with ACE-Cl, glaucine (**5**) affords the ring-opened phenanthrene **6** (89% yield). Even dealkylation of aromatic amines occurs

(1) With complex amines, excess ACE-Cl is used. Reflux time is a function of amine complexity and difficulty of bond breaking; **1** is a simple amine with a very difficult bond to break. If the reaction medium is not dry, some starting amine is tied up as its HCl salt. If anhydrous conditions are unattainable, 0.05–0.2 equiv of H^+ scavenger (e.g., 1,8-bis(dimethylamino)naphthalene) can be included in the mixture. This should be protonated after reaction (with HCl gas) and removed from the reaction mixture (by filtration through silica) before methanolysis.

(2) Spectral and analytical data including high-resolution MS or combustion analyses are in accord with the structures proposed for all new compounds.

(3) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.

(4) Liquid phosgene (1.1 equiv) is added to a stirred mixture of acetaldehyde (1.0 equiv) and $PhCH_2N^+(n\text{-}Bu)_3Cl^-$ (0.05 equiv., reusable) (dry ice condenser to mediate exothermic process). After 1 h, excess phosgene is removed by aspiration (in hood! through traps!). The ACE-Cl is distilled at room temperature and 4 mm into a −60 °C trap and then purified by reduced pressure distillation (96% yield of bp 77 °C at 180 mm). **Note:** Review phosgene safety precautions before repeating! Cagnon, G.; Piteau, M.; Senet, J.-P.; Olofson, R. A.; Martz, J. T. Eur. Pat. Appl. EP 40 153 [*Chem. Abstr.* **1982**, *96*, 142281y].

(5) Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Tetrahedron Lett.* **1977**, 1563. Olofson, R. A.; Schnur, R. C. *Ibid.* **1977**, 1571.

(6) Hageman, H. A. *Org. React.* (*N.Y.*) **1953**, *7*, 198.

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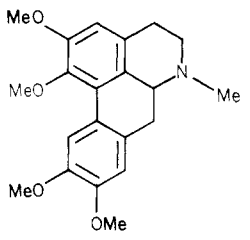

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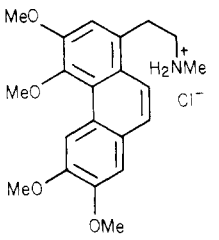
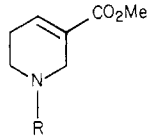


6 (mp 264-265.5 °C)

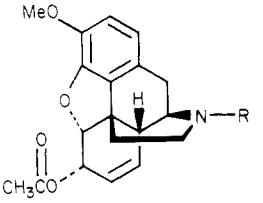
cleanly with ACE-Cl as is illustrated by the conversion in 87% yield of *N,N*-diethylaniline (**7**) to *N*-ethylaniline (**8**).[7] Such processes are unprecedented with other chloroformates including VOC-Cl and are only mediocre with the more activated BrCN.[6] As expected for a nucleophile as weak as **7**, reaction conditions are somewhat harsher (**7** heated neat with 2.5 equiv of ACE-Cl for 30 h at 130 °C).

In tests of the stability of other functionalities under the reaction conditions, arecoline (**9**) was cleaved to guvacoline·HCl (**10**, 95% yield), *O*-acetyltropine (**11**) afforded its



9, R = Me
10, R = H·HCl

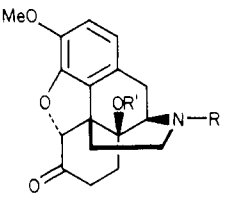
11, R = Me
12, R = H·HCl



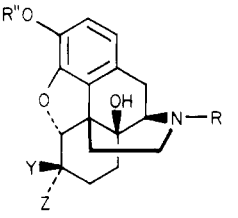
13, R = Me
14, R = H·HCl
15, R = H

nor-salt (**12**, mp 201-203 °C[8]) in 97% yield, and 6-acetylcodeine (**13**) was demethylated (→ **14**, mp 302.5–304 °C, ion exchange → **15**) in 97% recrystallized yield (significantly, both **14** and **15** are new compounds).

In another reaction sequence, acetylation[9] of commercial oxycodone[10] (**16**) produced crude 14-acetyloxycodone[9] (**17**), which upon ACE-Cl induced N-demethylation afforded **18**. Acid hydrolysis of **18** (homogeneous in hot 6 N HCl) and then neutralization gave noroxycodone (**19**, 86% overall from **16**). Amine **19** was converted to the narcotic antagonist naltrexone[12] (**23**, by alkylation with c-$C_3H_5CH_2Br$ and then O-demethylation with pyridine·HCl at 190 °C;[13] **16** → **23**; 58% overall).



16, R = Me; R′ = H (oxycodone)
17, R = Me, R′ = Ac
18, R = H·HCl, R′ = Ac
19, R = R′ = H (noroxycodone)
20, R = Me, R′ = $COcyC_4H_7$
21, R = H·HCl, R′ = $COcyC_4H_7$
22, R = $COcyC_4H_7$, R′ = H



23, R = $CH_2cyC_3H_5$, R″ = H, Y + Z = O (naltrexone)
24, R = $CH_2cyC_4H_7$, R″ = Me, Y = H, Z = OH
25, R = $CH_2cyC_4H_7$, R″ = Y = H, Z = OH (nalbuphine)

An ACE-Cl mediated synthesis of the analgesic nalbuphine[12] (**25**) based on the strategy of Olofson and Pepe[11,13] for the production of ENDO-1655 also is outlined here. Reaction of **16** with $(c\text{-}C_4H_7CO)_2O$ afforded crude **20**[11] which was demethylated by ACE-Cl to give **21**. Upon extraction with aqueous $NaHCO_3$, **21** quantitatively and spontaneously rearranged[11] to **22** (yield **16** → **22**; 96%). Simultaneous reduction of the amide and stereospecific reduction of the keto function (→ **24**) was accomplished with BH_3·THF,[14] and O-demethylation was cleanly achieved with BBr_3 as recommended by Rice[15] for codeine (69% overall yield from **16** to recrystallized **25**).

Acknowledgment. We thank the National Institutes of Health (U.S.) and SNPE (France) for supporting this research.

(7) This is a stringent test since Et is harder to split off than Me or *sec*- or *tert*-alkyl. Also see: Bachelet, J.-P.; Caubere, P. *J. Org. Chem.* **1982**, *47*, 234.
(8) Oxalate salt known: Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325.
(9) Freund, M.; Speyer, E. *J. Prakt. Chem.* **1916**, *94*, 135.
(10) Two steps from thebaine (from *Papaver brachteatum*): Seki, I. *Takamine Kenkusho Nempo* **1960**, *12*, 56. Lutz, R. E.; Small, L. *J. Org. Chem.* **1939**, *4*, 220.[11]
(11) Olofson, R. A.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1575, 2918.
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(14) Pachter, I. J.; Soloway, H. Canadian Patent 913 077; *Chem. Abstr.* **1972**, *77*, 105601*q*.
(15) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.

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