Remote functionalization of (−)-menthol—synthesis of 4a,5,6,7,8,8a-hexahydro-4*H*-benzo[1,3]oxazine derivatives with the Selectfluor™ reagent F–TEDA–BF_4

R. Eric Banks, Nicholas J. Lawrence,* Mohammed K. Besheesh, Allan L. Popplewell and Robin G. Pritchard

Chemistry Department, University of Manchester Institute of Science and Technology, Manchester, UK M60 1QD

An unprecedented synthesis of 4a,5,6,7,8,8a-hexahydro-4*H*- benzo[1,3]oxazine derivatives involving the remote functionalization of alcohols using the Selectfluor™ reagent F–TEDA–BF_4 and an organonitrile is disclosed; X-ray crystallographic data for the oxazinium tetrafluoroborate derived from (−)-menthol and acetonitrile is presented.

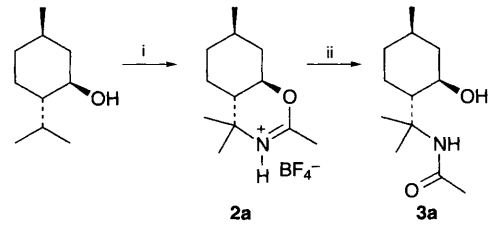
Many new reagents for the site-selective fluorination of organic compounds have recently been developed.[1] Of these, the Selectfluor™ reagent F–TEDA–BF_4 **1**† is one of the foremost, and since its introduction in 1992[2,3] has been used to fluorinate in electrophilic mode a wide variety of organic substrates.

As part of a programme to discover new uses for F–TEDA–BF_4 **1**, we are actively seeking one-pot transformation leading to non-fluorinated final products. The present report concerns a chance discovery—a novel synthesis of benzo[1,3]oxazine derivatives—made whilst extending work on the oxidation of benzylic alcohols to benzaldehydes and hence (*via* benzoyl fluorides) benzoic acid esters and amides.[4]

Treatment of (−)-menthol with 2 equiv. of F–TEDA–BF_4 **1** in refluxing acetonitrile did not result in its oxidation to (−)-menthone, as expected, but gave a crystalline salt of composition $C_{12}H_{21}NO{\cdot}HBF_4$ (50% yield), formation of which clearly had involved the incorporation of the reaction solvent.‡,§ ^{1}H NMR ($CDCl_3$) analysis revealed that the menthol cyclohexyl ring had remained intact, with a triple doublet at δ 4.31 (1 H, td, *J* 11.0 and 4.5 Hz) indicating no change in the relative stereochemistry at the Pr^{i}C–COH moiety.¶ A new signal was present at δ 2.42 (3 H, s) corresponding to a methyl group of an imidate moiety. The ^{19}F NMR spectrum ($CDCl_3$) of the product comprised a singlet at δ_{TFA} −71·8, characteristic of a tetrafluoroborate group. Clinching evidence that the product was the oxazinium tetrafluoroborate **2a** was provided by X-ray crystallographic analysis (Fig. 1).‖ This is the first reported crystal structure of a *trans*-4a,5,6,7,8,8a-hezahydro-4*H*-benzo[1,3]oxazine ring nucleus. The *cis* ring system[5] has a short C=N bond of 1.238(4) Å compared to 1.259(8) Å in **2a** in which the nitrogen atom is protonated. Although the BF_4^- anion is disordered two short non-bonded contacts to the proton reveal the presence of hydrogen bonding [F···H 1.85(2) and 1.96(2) Å]. This new salt is remarkably stable in air, and shows little to no signs of decomposition when stored in dry Pyrex for several weeks. The reaction is a remarkable example of remote functionalisation, a particularly difficult process to effect.

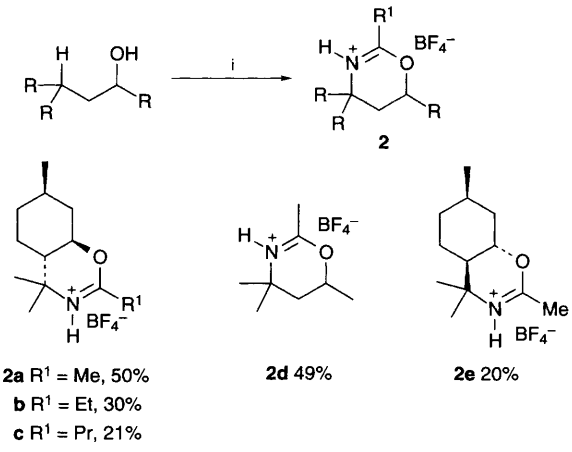
Preliminary results indicate that the reaction is not restricted to that between (−)-menthol and acetonitrile. The acetonitrile can be replaced by propionitrile or butyronitrile, leading to progressively lower yields of the homologous 1,3-oxazine salts **2b** (30%) and **2c** (21%), respectively. Use of 4-methylpentan-2-ol instead of (−)-menthol gives the monocyclic adduct **2d** in 49% yield, while (+)-isomenthol, under standard reaction conditions in acetonitrile, gives the 1,3-oxazine salt **2e** in 20% yield. Poor yields are believed to stem, in part, from ready hydrolysis of the oxazinium salts and incomplete conversion of the alcohols. In the case of **2e** the NMR spectrum of the crude product indicated a yield of 62%.** Also, when the crude

1



2a **3a**

Scheme 1 *Reagents and conditions*: i, Selectfluor™ **1** (2.2 equiv.), MeCN, 16 h, reflux; ii, NaOH, H_2O–CH_2Cl_2, 16 h room temp.

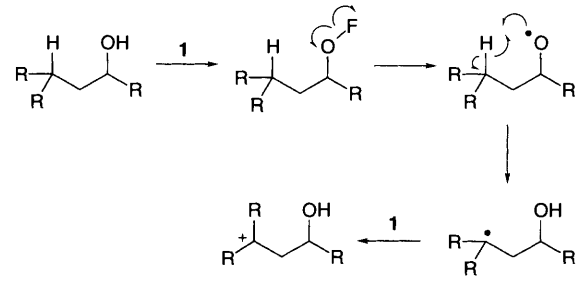


2a R^1 = Me, 50%
b R^1 = Et, 30%
c R^1 = Pr, 21%

2d 49%

2e 20%

Scheme 2 *Reagents and conditions*: i, Selectfluor™ **1** (2.2 equiv.), R^{1}CN, 16 h, reflux



Scheme 3 Possible mechanism for the formation of a γ-hydroxy carbenium ion

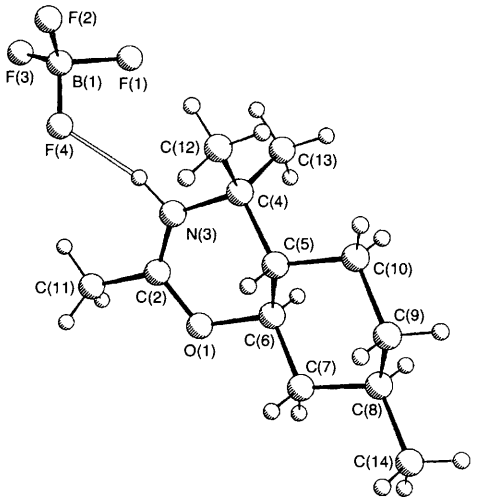


Fig. 1 X-Ray crystal structure of oxazinium tetrafluoroborate **2a**

reaction product from (−)-menthol, F–TEDA–BF_4 and acetonitrile was treated directly with aq. sodium hydroxide [NaOH (10%), room temp., 16 h], the hydroxy amide **3** was isolated in 83% yield, a clear improvement over the yield of isolated **2a** (50%). The amide was further hydrolysed to the hydroxyamine **4** (51%, isolated as the maleate salt) by more rigorous treatment with aq. sodium hydroxide [NaOH (10%), reflux, 15 h].

No reaction of the type alcohol → **2** was evident with 2-methylbutan-1-ol, pentan-2-ol and 4-phenylbutan-2-ol. This supports a reaction pathway involving formation of a tertiary carbenium ion at the position to the hydroxy function of the substrate. Generation of a tertiary carbenium ion would provide a route to the oxazinium salt *via* Ritter-like involvement of the organonitrile solvent.[6] The origin of such a carbenium ion is currently under investigation, two possibilities being solvolysis of the tertiary alkyl fluoride $R_2CFCH_2CH(OH)R$ formed first or SET conversion of a tertiary alkyl radical *via* decomposition of a hypofluorite produced initially (see Scheme 3).

We thank Dr Ray Fisher (Peakdale Fine Chemicals, Glossop) for financial support and Air Products and Chemicals, Inc., for samples of Selectfluor™.

Footnotes

† An MSDS (Material Safety Data Sheet) is available from Dr Helen M. Marsden, Air Products PLC, European Technology Group, Chineham, Basingstoke, Hampshire RG24 0FE, UK or Dr G. P. Pez, Air Products and Chemicals Inc., 7201 Hamilton Boulevard, Allentown, PA 18195-1501, USA.

‡ All compounds were fully characterised and gave the expected spectral and analytical data.

§ *Preparation of* **2a**: A stirred solution of the alcohol **2** (5.0 mmol) and F–TEDA–BF_4 **1** (11.0 mmol) in dry nitrile (50 cm^3) was refluxed under nitrogen. After the alcohol had been consumed (as judged by TLC in ethyl acetate–hexane with ammonium molybdate stain) the reaction was allowed to cool to room temp. The mixture was concentrated *in vacuo* to give a semi-solid which was triturated three times into dichloromethane (40 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude material which was recrystallised from ethyl acetate–hexane to give **2a** as a solid.

¶ *Selected physical and spectroscopic data* for **2a**: R_f = 0.06 (67% ethyl acetate in hexane); mp 176–177 °C; ν_{max}(KBr disk)/cm^{-1} 3260(m), 3180(w), 3085(w), 2940(s), 2870(m), 2785(m), 2730(m), 1660(s), 1550(m), 1465(m), 1440(m), 1400(m), 1380(m), 1365(m), 1320(m), 1295(m), 1230(m), 1205(m), 1175(m), 1080 (s, br), 920(m), 840(m), 615(w), 535(w) and 520(w); δ_H(300 MHz, $CDCl_3$) 1.02 (3 H, d, *J* 6.5 Hz, 6-CHCH_3), 1.07–2.17 (7 H, m, 5-,6-,7-,8-C*H* and CH_2), 1.34 (3 H, s, 10-CH_{3ax}), 1.48 (3 H, s, 10-CH_{3eq}), 2.28–2.38 (1 H, m, *ca.* dt, 9-CH), 2.42 (3 H, s, 2-CH_3), 4.31 (1 H, td, *J* 11.0, 4.5 Hz, 4-CH) and 10.05 (1 H, br s, 1-NH); δ_C (75.5 MHz, $CDCl_3$) 19.9 (10-CH_{3ax}), 21.5 (10-CH_{3eq}), 23.3, 30.7 (6-*C*H and 6-CHCH_3), 23.6, 33.0, 38.6 (5-,7-,8-CH_2), 25.5 (2-CH_3), 44.0 (9-CH), 55.8 [10-*C*$(CH_3)_2$], 79.5 (4-CH) and 172.7 [2-(C=N)O]; δ_F (188 MHz, $CDCl_3$) −71.8 (s, BF_4^-); *m/z* (Ar FAB$^+$) 479 (2M − BF_4^-, 10%), 196 (M − BF_4^-, 100%).

‖ *Crystal data* for **2a**. A colourless plate shaped crystal of **2a** having approximate dimensions of 0.30 × 0.30 × 0.20 mm was mounted on a glass fibre. All measurements were made on a Siemens R3m/v diffractometer with graphite-monochromated Mo-Kα X-radiation. The data were collected at a temperature of −40 ± 1 °C using the ω/2Θ scanning technique to a maximum 2Θ value of 52.1°. The structure was solved by direct methods using SHELXS-86[7] and DIRDIF.[8] Full-matrix least-squares refinement using TEXSAN,[9] in which each of the disordered F atoms occupied two semi-occupied sites, yielded final residuals of R = 0.087 and R' = 0.084 with w = $1/[\sigma^2(F_o) + 0.03F_o^2]$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/129.

** Based on diagnostic oxazine and alcohol NMR signals ($CDCl_3$, 200 MHz) present of the crude reaction mixture.

References

1 T. Umemoto, *Rev. Heteroatom Chem.*, 1994, **10**, 123; J. A. Wilkinson, *Chem. Rev.*, 1992, **92**, 505.
2 R. E. Banks, US Pat. 5 086 178, 1992 (to Air Products and Chemicals, Inc.)
3 R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif and R. G. Syvret, *J. Chem. Soc., Chem. Commun.*, 1992, 595; R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf and I. Sharif, *J. Chem. Soc., Perkin Trans. 1*, in the press.
4 R. E. Banks, N. J. Lawrence and A. L. Popplewell, *Synlett*, 1994, 831.
5 G. Bernárth, F. Fülöp, L. Gera, L. Hackler, A. Kálmán, G. Argay and P. Sohár, *Tetrahedron*, 1979, **35**, 799.
6 R. Bishop, *Ritter-type reactions*, in *Comprehensive Organic Synthesis*, ed. C. H. Heathcock, Pergamon, 1991, vol. 6, pp. 261–300.
7 G. M. Sheldrick, in *Crystallographic Computing 3*, ed. G. M. Sheldrick, C. Kruger and R. Goddard, Oxford University Press, pp. 175–189.
8 P. T. Beurskens, DIRDIF: Direct methods for Difference Structures—an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.
9 Molecular Structure Corporation TEXSAN, TEXRAY Structure Analysis Package. MSC, 3200A Research Forest Drive, The Woodlands, TX 77381, USA, 1985.

Received, 27th March 1996; Com. 6/02137I