Monofluorinated di- and tetrahydropyrans *via* Prins-type cyclisations

Adrian P. Dobbs,*[a] Levan Pivnevi,[b] Mark J. Penny,[a] Sǎsa Martinović,[c] James N. Iley[b] and Peter T. Stephenson[d]

Received (in Cambridge, UK) 2nd May 2006, Accepted 26th May 2006
First published as an Advance Article on the web 14th June 2006
DOI: 10.1039/b606121d

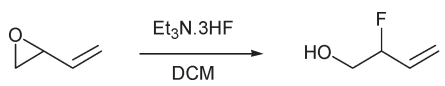
The synthesis of a range of fluorinated heterocycles is described *via* a Lewis acid-mediated Prins-type cyclisation.

Although naturally occurring fluorinated organic molecules are rare, the introduction of fluorine into natural products is currently the focus of much synthetic interest due to the profound effect that the fluorine atom may have on the properties of the compound. Strategically positioned fluorine atom(s) may greatly influence the biological properties of a compound.[1,2] For example, deoxyfluorosugars have been used to probe the mechanism of action of various enzymes.[1] Methods for the preparation of fluorinated sugars and related heterocycles are currently the focus for considerable synthetic effort. For example, Linclau *et al.* have recently reported the enantioselective synthesis of tetrafluoroethylene-containing monosaccharides[3] and Percy *et al.* have developed routes to a range of difluorinated sugar mimetics.[4] The search for a rapid and efficient method for the synthesis of simple monofluorinated compounds, however, is still ongoing.

The Prins cyclisation is a well-established method for the preparation of a range of heterocycles, most notably tetrahydropyrans[5] and more recently dihydropyrans.[6] A range of Lewis acids have been reported in recent years to promote the Prins reaction and indeed have been used to incorporate fluoride into the 4-position of tetrahydropyrans.[7] We have gained considerable experience of using indium trichloride[6] as a Lewis acid for Prins cyclisation reactions and embarked on a project to apply this methodology to the synthesis of fluorinated heterocycles.

Indium trichloride promotes the Prins cyclisation of various simple and complex homoallylic alcohols and homopropargylic alcohols to the corresponding pyran.[6,8] We reasoned that by incorporating fluorine into the homoallylic alcohol, it may be possible to build fluorinated pyrans using the Prins cyclisation.

The method of Hedhli and Baklouti[9] appeared ideal for the preparation of the desired fluorinated homoallylic alcohols. Reaction of triethylamine trihydrogen fluoride with various vinylepoxides (see Scheme 1) gave the desired homoallylic alcohols in good yield.

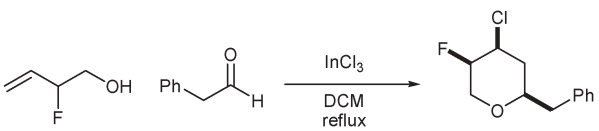


Scheme 1 Preparation of monofluorinated homoallylic alcohols.

Reaction of 2-fluoro-3-buten-1-ol with phenylacetaldehyde and indium trichloride in a 1 : 1 : 1 molar ratio (as we have previously reported[6]) in dichloromethane at room temperature only furnished a trace of the expected tetrahydropyran by GCMS. After investigating various molar ratios and the reaction temperature, it was found that using a molar ratio of alcohol : aldehyde : indium trichloride 1 : 1.5 : 2 and heating the reaction mixture at reflux temperature for between 2 and 12 h gave the desired tetrahydropyran in very good yield and as a single diastereoisomer (Scheme 2).

Further aldehydes were then investigated in the reaction and all gave good yields of the fluorinated tetrahydropyran, again as a single diastereomer in each case.

Entries 1–5 in Table 1 show that the cyclisation proceeds efficiently for most aldehydes, with the exception of aromatic aldehydes, where the yield is lower (entries 6 & 7). This observation is in keeping with previously reported findings on the Prins cyclisation using indium trichloride.[6] Entries 8–10[10] show that the reaction is not limited to using aldehydes as a substrate, and that epoxides and acetals may also be employed without compromising



Scheme 2 Synthesis of monofluorinated tetrahydropyrans.

Table 1 Synthesis of simple 2-alkyl-4-chloro-5-fluorotetrahydropyrans

Entry	Aldehyde	% Yield[a,b]	Control % yield (no fluorine)[c]
1	Phenylacetaldehyde	74	72
2	Hexanal	75	69
3	Cyclohexanecarboxaldehyde	80	79
4	2-Ethylbutyraldehyde	68	63
5	Diphenylacetaldehyde	57	64
6	Benzaldehyde	39	44
7	4-Nitrobenzaldehyde	54	66
	Alternative substrates		
8	Styrene oxide	49	55
9	*p*-Methylstyrene oxide	59	58
10	1,1-Dimethoxyhexane	63	58

[a] All are purified yields and all products gave satisfactory spectroscopic data. [b] Reaction performed at reflux temperature. [c] Reactions not performed at reflux temperature but at room temperature for the same period of time.

[a]*Department of Chemistry, Queen Mary, University of London, Mile End Road, London, UK E1 4NS. E-mail: A.Dobbs@qmul.ac.uk*
[b]*Department of Chemistry, The Open University, Walton Hall, Milton Keynes, UK MK7 6AA*
[c]*Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*
[d]*Discovery Chemistry, Pfizer Global R&D, Sandwich, Kent, UK CT13 9NJ*

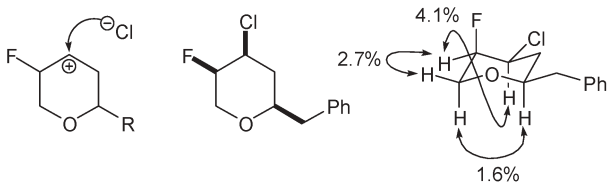
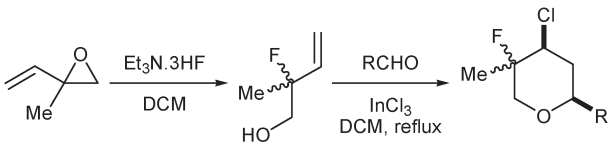


Fig. 1 Relative stereochemistry of the fluorinated tetrahydropyrans.



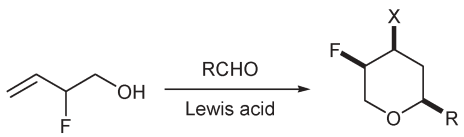
Cyclohexanecarboxaldehyde: 57%
Hexanal: 66%

Scheme 3

the yield significantly (there is literature precedent for epoxides generally being lower yielding in Prins reactions compared to aldehydes). Both epoxides and acetals gave single diastereomeric tetrahydropyran products.

The reaction is believed to proceed by the accepted Prins cyclisation mechanism, with the formation of a carbocation adjacent to the fluorine atom. It does not appear that the presence of the highly electronegative fluorine atom has any bearing on the outcome of the reaction, since yields are consistent (within experimental error) with those obtained in the absence of fluorine, as indicated by the control results in Table 1. Interesting, however, was the requirement to perform the reaction in dichloromethane at reflux temperature in order to obtain the fluorinated tetrahydropyrans, yet it would proceed rapidly at room temperature in the absence of fluorine.

The relative configuration of the substituents was obtained by nOe studies, which clearly showed that the product in each case was the all *cis* configuration, with the fluorine adopting an axial orientation at the C-5 position (see Fig. 1).[11] Similar diastereoselectivity was observed for each of the fluorinated products obtained.



Scheme 4 Alternative Lewis acid promoters.

The reaction similarly proceeded efficiently when employing 2-fluoro-2-methyl-3-buten-1-ol (prepared in an identical manner and in 63% yield from 2-methyl-2-vinyloxirane) and gave only a single diastereomeric product (see Scheme 3), although it has thus far been impossible to determine from NMR studies which conformation of the methyl group and fluorine atom has been obtained. All crystallisation attempts have failed.

Turning our attention to alternative Lewis acid promotors (Scheme 4 and Table 2), it was found that both trimethylsilyl triflate and indium tribromide were also efficient promotors for the reaction. Despite its wide use as a Lewis acid, including for Prins-type reactions, to the best of our knowledge, this is the first example of the triflate anion becoming trapped and isolated in the product of a Prins cyclisation reaction.† It is interesting to note that the reaction with indium tribromide required the use of dibromomethane as solvent, since employing dichloromethane led to a mixture of 4-chlorinated and brominated products, presumably by halogen exchange from the Lewis acid with the solvent.[12]

Interestingly, we observed a trace (*ca.* 5%) of what appeared to be a mixture of eliminated products as a minor product in entries 1–3 in Table 2. Therefore we decided to investigate further the possibility of eliminating the C(4) group to give a dihydropyran. No elimination products were observed when using either chloride or bromide at the C(4) position, irrespective of the base employed. When the triflate group was present, however, elimination occurred in reasonable to good yields, giving a mixture of the two possible dihydropyran products as an inseparable mixture.‡[13] Both sodium hydride and LHMDS showed a preference for forming **A** (Scheme 5 and Table 3), while potassium tert-butoxide showed a preference for forming the isomeric dihydropyran **B**, for reasons we are still examining.

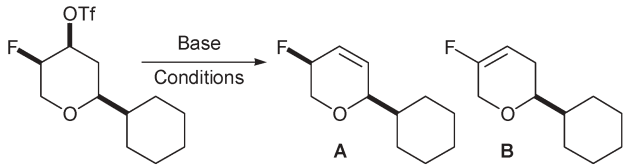
Given the success of the Prins reaction in the preparation of monofluorinated tetrahydropyrans, the formation of difluorinated tetrahydropyrans was examined. 3,3-Difluorononon-1-en-4-ol was prepared from 1-bromo-1,1-difluoroprop-3-ene in the presence of indium powder in almost quantitative yield. The Prins cyclisation was attempted using both cyclohexanecarboxaldehyde and the more reactive ethyl glyoxylate (Scheme 6). Unfortunately, no product was obtained, using either indium trichloride or trimethylsilyl triflate, presumably now because of the instability of the intermediate carbocation due to the presence of the two adjacent fluorine atoms. Work is currently directed at overcoming this problem and will be reported in due course.

In summary, we have reported the first example of a Prins cyclisation reaction incorporating fluorine at the position α to the intermediate carbocation generated and demonstrated this as a synthetically useful route to fluorinated tetrahydropyrans in good

Table 2 Effect of employing different Lewis acids in the Prins reaction of simple aldehydes with 2-fluoro-3-buten-1-ol

Entry	Aldehyde	Lewis acid/conditions	X in product	% Yield[a]
1	Phenylacetaldehyde	TMSOTf/−78 °C, DCM	OTf	36
2	Hexanal	TMSOTf/−78 °C, DCM	OTf	48
3	Cyclohexanecarboxaldehyde	TMSOTf/−78 °C, DCM	OTf	56
4	Hexanal	$InBr_3$/DCM, rt to reflux	Br : Cl[b] (1.2 : 1)	—
5	Hexanal	$InBr_3/CH_2Br_2$, rt to reflux	Br	63
6	Cyclohexanecarboxaldehyde	$InBr_3/CH_2Br_2$, rt to reflux	Br	66

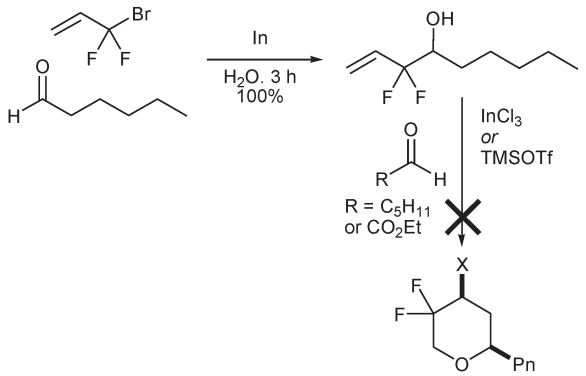
[a] All are purified yields and all products gave satisfactory spectroscopic data. [b] Two compounds inseparable by column chromatography, ratio obtained from GC-MS.



Scheme 5 Base-mediated triflate elimination from tetrahydropyrans.

Table 3 Bases and conditions used to promote triflate elimination from fluorinated tetrahydropyrans

Entry	Base and Conditions	% Yield	Ratio A : B
1	KO*t*Bu (3 eq.), rt, 3 h	45	1 : 2
2	NaH (5 eq.), 0 °C to rt, 18 h	63	9 : 1
3	LHMDS (3 eq.), THF, rt to reflux, 3 days	58	2.4 : 1



Scheme 6 Attempted preparation of difluorinated tetrahydropyrans.

yields. A range of anions may be incorporated during the cyclisation process, some of which may be subsequently eliminated to give fluorinated dihydropyrans. We are currently exploring this methodology for the preparation of more complex tetrahydropyrans in enantiopure form and their subsequent elaboration to fluorinated sugur analogues.

We thank The Open University (studentship to LP), Queen Mary, University of London and Pfizer (EPSRC DTA (originally held at University of Exeter, prior to closure of the Department of Chemistry, July 2005) and CASE awards to MJP) and Universities UK (ORS award to SM) for funding.

Notes and references

† *Representative procedure for the formation of 2-substituted-4-trifluoromethanesulfonyl-5-fluorotetrahydropyrans*: a solution of the aldehyde (2 eq., in range 5–10 mmol) in dry dichloromethane (15 ml) was cooled to −78 °C and treated with trimethylsilyl trifluoromethanesulfonate (2.5 eq.) and stirred for 30 mins at this temperature. 2-Fluorobut-3-en-1-ol (1 eq.) was added and the reaction stirred for 3–4 h at −78 °C. The reaction mixture was then warmed to room temperature over 16 h before adding water (20 ml). The two layers were separated and the aqueous layer extracted with dichloromethane. The combined dichloromethane layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography. The method to prepare 2-substituted-4-halo-5-fluorotetrahydropyrans involved identical molar ratio equivalents of reagents being added in the same order, but with the addition occurring at room temperature (rather than −78 °C) and the reaction subsequently being heated to reflux temperature for 5–15 h, as indicated by consumption of the starting material.

‡ *Representative procedure for the triflate elimination from substituted 4-trifluoromethanesulfonyl-5-fluorotetrahydropyrans*: to a solution of the 4-triflate-substituted tetrahydropyran (range 1–3 mmol, 1 eq.) in dry THF (5 ml) under a nitrogen atmosphere was added the base either at 0 °C (NaH) or at room temperature (KO*t*Bu and LHMDS, equivalents in Table 3). The reaction was stirred at room temperature for variable periods of time, until no further change was observed by t.l.c. (indicative times for each base given in Table 3). The reaction was quenched with water (10 ml) and stirred for a further 20 mins. The aqueous solution was extracted with diethyl ether (3 × 15 ml), the organic phases combined, dried (MgSO4), filtered and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (typically 10% ethyl acetate in petroleum ether (40–60 fraction)).

1 For an excellent recent treatment of the emerging role of fluorine in synthetic, medicinal, pharmaceutical and biological systems, see the Special Issue: Fluorine in the Life Sciences, *ChemBioChem*, 2004, **4**, 557–726.
2 C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303.
3 A. J. Boydell, V. Vinader and B. Linclau, *Angew. Chem., Int. Ed.*, 2004, **43**, 5677.
4 L. R. Cox, G. A. DeBoos, J. J. Fullbrook, J. M. Percy and N. Spencer, *Tetrahedron: Asymmetry*, 2005, **16**, 347; C. Audouard, J. Fawcett, G. A. Griffiths, J. M. Percy, S. Pintat and C. A. Smith, *Org. Biomol. Chem.*, 2004, **2**, 528; G. A. Griffith, J. M. Percy, S. Pintat, C. A. Smith, N. Spencer and E. Uneyama, *Org. Biomol. Chem.*, 2005, **3**, 2701.
5 For an excellent recent review on the formation of tetrahydropyrans *via* Prins and related reactions: P. A. Clarke and S. Santos, *Eur. J. Org. Chem.*, 2006, 2045.
6 A. P. Dobbs and S. Martinović, *Tetrahedron Lett.*, 2002, **43**, 7055.
7 L. D. M. Lolkema, H. Hiemstra, C. Semeyn and W. N. Speckamp, *Tetrahedron*, 1994, **50**, 7115; J.-I. Yoshida, M. Sugawara and N. Kise, *Tetrahedron Lett.*, 1996, **37**, 3157; J.-I. Yoshida, M. Sugawara, M. Tatsumi and N. Kise, *J. Org. Chem.*, 1998, **63**, 5950; J.-I. Yoshida and K. Nishiwaki, *J. Chem. Soc., Dalton Trans.*, 1998, 2589; E. H. Al-Mutairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith and C. L. Willis, *Chem. Commun.*, 2001, 835; J. J. Jaber, K. Mitsui and S. D. Rychnovsky, *J. Org. Chem.*, 2001, **66**, 4679.
8 Examples of the use of $InCl_3$ in Prins-type reactions: (*a*) J. Yang and C.-J. Li, *Synlett*, 1999, 717; (*b*) G. S. Viswanathan, J. Yang and C.-J. Li, *Org. Lett.*, 1999, **1**, 993; (*c*) Y. S. Cho, H. Y. Kim, J. H. Cha, A. N. Pae, H. Y. Koh, J. H. Choi and M. H. Chang, *Org. Lett.*, 2002, **4**, 2025; (*d*) X.-F. Yang, J. T. Mague and C.-J. Li, *J. Org. Chem.*, 2001, **66**, 739; (*e*) A. P. Dobbs, S. J. J. Guesné, S. Martinović, S. J. Coles and M. B. Hursthouse, *J. Org. Chem.*, 2003, **68**, 7880.
9 A. Hedhli and A. Baklouti, *J. Fluorine Chem.*, 1995, **70**, 141.
10 Previous use of epoxides: ref. 6, ref. 8*e* and J. Li and C.-J. Li, *Tetrahedron Lett.*, 2001, **42**, 793–796; previous use of acetals: unpublished results in our own work, S. J. J. Guesné, PhD Thesis, University of Exeter, 2005 and T. C. Gahman and L. E. Overman, *Tetrahedron*, 2002, **58**, 6473.
11 Precedent for fluorine demonstrating an axial preference at this position in related systems: D. O'Hagan and H. S. Rzepa, *Chem. Commun.*, 1997, 645; C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta and J. A. K. Howard, *Org. Biomol. Chem.*, 2004, **2**, 732; A. Sun, D. C. Lankin, K. Hardcastle and J. P. Snyder, *Chem.–Eur. J.*, 2005, **11**, 1579 and many examples in ref. 1.
12 Halogen exchange of this type is not unprecedented: P. O. Miranda, D. D. Díaz, J. I. Padrón, J. Barmejo and V. S. Martín, *Org. Lett.*, 2003, **5**, 1979.
13 Only previous example of triflate elimination from a glycoside: A. E. Nemr and T. Tsuchiya, *Carbohydr. Res.*, 1997, **303**, 267.

