Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5183-5186, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01031-3

Functionally Diverse Monofluorinated Vinylic Compounds from Trifluoroethanol.

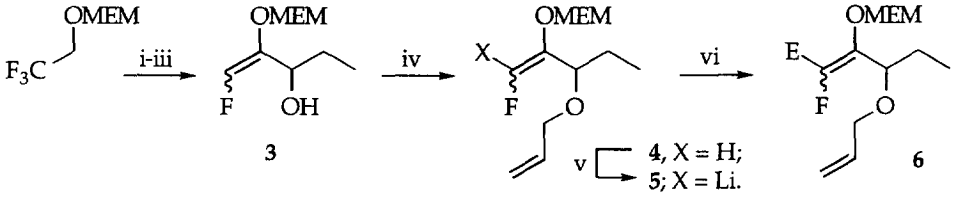
Sunita T. Patel, Jonathan M. Percy* and Robin D. Wilkes

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT (UK).

Abstract: Monofluorinated allylic ether **4** was synthesised in 4 steps from trifluoroethanol. Formation of the monofluoro vinyllithium **5** which was stable at up to –50 °C, and subsequent reaction with a wide range of electrophiles gave access to a series of highly functionalised monofluorinated allylic ethers. Effective electrophiles included Group (IV) halides, methyl iodide and benzaldehyde, whilst aliphatic aldehydes proved to be less efficient electrophiles. Use of a monofluoro vinylzinc reagent, prepared by transmetallation of **5**, allowed efficient access to the monofluorovinyl iodide **6e**.

Approaches to selectively fluorinated compounds include both the more traditional use of fluorinating reagents,[1] and increasingly, alternative, convergent building block strategies.[2] Recently, we described general and efficient routes to highly functionalised difluorinated compounds from trifluoroethanol which used a metallated enol acetal[3] as a key intermediate. Further elaboration was achieved by [3,3]-Claisen[4] and [2,3]-Wittig rearrangements.[5] The elaboration of monofluoroallylic alcohols *via* the [2,3]-Wittig rearrangement interested us because it offered the prospect of the highly stereocontrolled[6] synthesis of densely-functionalised monofluoro-compounds.[7]

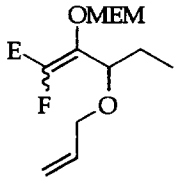
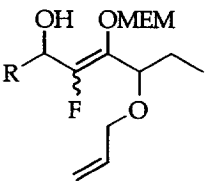
We have shown[4,8] that stereoselective reduction of difluoroallylic alcohols[9] occurs under mild conditions to afford the corresponding monofluoro-species. Subsequent β-metallation followed by electrophilic trapping would allow entry into a series of diversely functionalised monofluorinated compounds. **Scheme 1** outlines the synthetic sequence from published alcohol **3**,[4] which was obtained as a (9:1 *E*:*Z*) mixture of stereoisomers.



Scheme 1. Reagents and Conditions: i, 2.0 LDA, THF, -78 °C, inverse addition; ii, EtCHO, warm to -30 °C then NH_4Cl, MeOH; iii, 3.8 Red-Al, pentane, reflux, 3 hours; iv, 1.3 $H_2C{=}CHCH_2Br$, 50% aq. NaOH, Bu_4NHSO_4 (cat.), 0 °C to r.t., overnight (74%); v, LDA or n-BuLi (see text), THF, -78 °C; vi, electrophile, warm to r.t. overnight, then NH_4Cl(aq).

The alcohol **3** was converted to the corresponding ether **4**, (in which the 9:1 *E*:*Z* ratio of isomers was retained), in 74% yield using the phase transfer catalytic conditions developed by Schlosser.[10] Treatment of monofluoroallylic ether **4** with either *n*-butyllithium or LDA failed to result in the anticipated [2,3]-Wittig rearrangement.[5] Instead, **4** underwent metallation α-to the fluorine atom to afford the corresponding mixture of stereoisomeric organometallic species **5**, which were then trapped with a range of electrophiles (**Table 1**).

Table 1

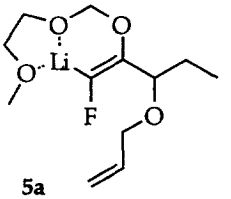
Electrophile	Product		E *or* R	% Yield
MeOD		**6a**	D	89
Me_3SiCl		**6b**	Me_3Si	71
Et_3SiCl		**6c**	Et_3Si	60
Bu_3SnCl		**6d**	Bu_3Sn	90
$ZnCl_2$.TMEDA, I_2[a]		**6e**	I	63
CH_3I[b]		**6f**	CH_3	57
Benzaldehyde		**6g**	Ph	60[c,f]
Propenal		**6h**	Et	23[d,f]
Propanal		**6i**	$CH{=}CH_2$	21[e,f]

[a]Zinc salt added at -78 °C, then warmed to 0°C; iodine added then warm to r.t.. [b]Iodomethane (10 equivalents) added at -50 °C. [c]Isolated as a 3:1 mixture of diastereoisomers. [d]Isolated as a 2:1 mixture of diastereoisomers. [e]Isolated as a 3:2 mixture of diastereoisomers. [f]For the *E* alkene diastereoisomer.

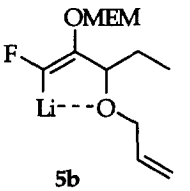
Silicon, tin and deuterium electrophiles gave good to excellent yields of products. Vinyl iodide **6e** was prepared in moderate (37%) yield initially by the reaction of **5** with zinc bromide (as a freshly prepared 1M solution in THF) at –78 °C. Warming to 0 °C resulted (presumably) in formation of the vinylzinc species, which was quenched subsequently with a solution of iodine in THF.[11] An improved yield (63%) of **6e** was achieved upon use of non-hygroscopic zinc chloride/TMEDA complex in the transmetallation step.[12] Methylation of **5** proved to be more problematic; all attempts to alkylate **5** at –78 °C were unsuccessful, even in the presence of a large excess of methyl iodide. However, upon allowing the vinyllithium species **5** to reach –50 °C, subsequent addition of ten equivalents of methyl iodide yielded **6f** in 57% yield. In all cases, separation of the major (*E*) and minor (*Z*) isomeric products of **6**, still present in the original 9:1 ratio established in the stereoselective reduction of **2**, could be

achieved by chromatography of the products. Earlier in the synthetic sequence, separation of the stereoisomers of **3** or **4** proved less convenient.

The alkylation reaction is particularly interesting because it implies that the both metallated fluoroalkenes have a useful lifetime at this temperature. We were unable to find any direct precedent for simple intermediates of this type, for example, 1-lithio-1-fluoroethene, in the literature.[13] Recent NMR studies by Pelter and co-workers[14] showed that certain sterically-hindered 2,2-diaryl congeners were stable up to -30 °C, but that the 2,2-dialkyl species could not be generated and observed in the NMR probe, even at very low temperature (-100 °C). We propose that chelation fulfills a key role in the generation and subsequent chemistry of **5**. In the *E*-stereoisomer, the part polyether structure of the MEMO group can enclose the lithium atom (**5a**), whereas in the *Z*-congener, coordination to the oxygen atom of the allyloxy group (**5b**) offers the prospect of stabilisation against the potential Fritsch-Buttenberg-Wieckell rearrangement and carbene formation.



5a



5b

Metallated intermediate **5** was also trapped with a variety of aldehydes. Yields proved to be relatively poor for aliphatic aldehydes; however, with benzaldehyde, diastereoisomeric alcohols were isolated in 60% yield. In each case the major (*E*-fluoroalkene) isomer of the alcohol product could be isolated cleanly, and a diastereoisomeric ratio determined, though the 1,4-relationship cannot be assigned from the data available to us.

We are exploring further [2,3]-Wittig rearrangements of the β-silyl species **6b** and **6c**, and the palladium-catalysed coupling reactions of stannyl- **6d** and iodo- **6e** derivatives. These results will be reported at a later date.

Acknowledgements

The authors wish to thank the EPSRC (Fellowship to RDW).

Typical Experimental Procedure:-

Preparation of 3-(Allyloxy)-1-fluoro-1-tributylstannyl-2-([methoxyethoxy]methoxy)pent-1-ene **6d**. n-Butyllithium (4.03 mL of a 2.0 M solution in hexanes, 8.06 mmol) was added slowly to a solution of 3-(allyloxy)-1-fluoro-2-([methoxyethoxy]methoxy)pent-1-ene **4a** (1.00g, 4.03 mmol) ((*E*) : (*Z*) = 9 : 1) in THF (50 mL) at –78 °C. The resultant yellow solution was stirred at –78 °C for 30 minutes, then a solution of tributyltin chloride (1.31 mL, 4.83 mmol) in THF (10 mL) was added; upon addition, the yellow colour of the solution faded. The solution was then allowed to warm to room temperature overnight. Saturated ammonium chloride solution (20 mL) was added, and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **6d** as

a pale yellow oil (1.93 g, 90% overall yield), (R_f 0.64) (both major (*E*) and minor (*Z*) isomers were separated cleanly); major (*E*) isomer (Found: C, 53.39; H, 8.87. $C_{24}H_{47}FO_4Sn$ requires C, 53.65; H, 8.82%); IR (neat) 2926, 1646, 1629 and 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 12H, $^3J_{H\text{-}H}$ = 7.2 Hz, -Sn($(CH_2)_3CH_3)_3$ and -$CHCH_2CH_3$), 1.04 (t, 6H, $^3J_{H\text{-}H}$ = 8.0 Hz, -Sn($CH_2CH_2CH_2CH_3)_3$, 1.32 (sextet, 6H, $^3J_{H\text{-}H}$ = 7.2 Hz, -Sn($CH_2CH_2CH_2CH_3)_3$, 1.52 (q, 6H, $^3J_{H\text{-}H}$ = 8.0 Hz, -Sn($CH_2CH_2CH_2CH_3)_3$, 1.58-1.82 (m, 2H, -$CHCH_2CH_3$), 3.37 (s, 3H, -OCH_3), 3.54 (t, 2H, $^3J_{H\text{-}H}$ = 4.7 Hz, -$OCH_2CH_2OCH_3$), 3.70-3.92 (m, 3H, -$OCH_2CH_2OCH_3$ and -$OCH_aH_bCH{=}CH_2$), 4.04 (dd, 1H, $^2J_{H\text{-}H}$ = 12.8 Hz, $^3J_{H\text{-}H}$ = 5.1 Hz, -$OCH_aH_bCH{=}CH_2$), 4.34 (dt, 1H, $^2J_{H\text{-}H}$ = 12.8 Hz, $^3J_{H\text{-}H}$ = 5.1 Hz, -$CHCH_2CH_3$), 4.79 (d, 1H, $^2J_{H\text{-}H}$ = 5.0 Hz, -OCH_aH_bO), 5.01 (d, 1H, $^2J_{H\text{-}H}$ = 5.0 Hz, -OCH_aH_bO), 5.13 (dd, 1H, $^3J_{H\text{-}H(cis)}$ = 10.2 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, -$CH{=}CH_aH_b$), 5.24 (d, 1H, $^3J_{H\text{-}H(trans)}$ = 17.2 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, -$CH{=}CH_aH_b$), 5.81-6.00 (m, 1H, -$CH{=}CH_aH_b$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.1, 10.2, 13.7, 25.1, 27.2, 29.0, 59.0, 68.6, 69.4, 71.7, 74.7, 98.2, 116.7, 134.9, 151.8 (d, $^2J_{C\text{-}F}$ = 18.6 Hz), 167.2 (d, $^1J_{C\text{-}F}$ = 309.5 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –138.4 (t, $^2J_{Sn\text{-}F}$ = 104.3 Hz); m/z (CI, NH_3) 481 (32%) ([M-$CH_2CH_2CH_2CH_3]^+$), 291 (100), 89 (84), 44 (89).

REFERENCES AND NOTES

1. Wilkinson, J. A. *Chem. Rev.*, **1992**, *92*, 505; Mascaretti, O. A. *Aldrichimica Acta*, **1993**, *26*, 4758; Mann, J. S. *Chem. Soc. Rev.*, **1987**, *16*, 381.
2. See Percy, J. M. *Contemp. Org. Synth.*, **1995**, *4*, 251 for a recent survey.
3. Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201.
4. Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 11327.
5. Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.*, **1996**, *61*, 166.
6. Nakai, T.; Mikami, K. *Org. React.*, **1994**, *46*, 105.
7. For alternative approaches, see; Bessière, Y.; Savary, D. N-H.; Schlosser, M. *Helv. Chim. Acta*, **1977**, *60* (173), 1739; Arai, K.; Welch, J. T. *Tetrahedron Lett.*, **1993**, *34*, 2251; Arai, K.; Yun, W. Q.; O'Toole, J.; Toscano, P. J.; Welch, J. T. Carbohydr. Res., **1993**, *249*, 139; Allmendinger, T.; Angst, C.; Karfunkel, H. *J. Fluorine Chem.*, **1995**, *72*, 247; McCarthy, J. R.; Huber, E. W.; Le, T-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron*, **1996**, *52*, 45; Fish, P. V.; Johnson, W. S. *J. Org. Chem.*, **1994**, *59*, 2324.
8. Hayashi, S.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.*, **1979**, 983.
9. Difluoroallyic alcohols can be prepared by synthetic manipulation of a range of fluorinated starting materials, including chlorodifluoromethyl ketones (Bégué, J-P.; Bonnet-Delpon, D.; Percy, J. M.; Rock, M. H.; Wilkes, R. D. *J. Chem. Soc., Chem. Commun.*, **1995**, 1857); dibromodifluoroethane (Burton, D. J.; Kesling, H. S.; Naae, D. G. *J. Fluorine Chem.*, **1981**, *18*, 293) and ethyl trifluoropyruvate (Shi, G.; Cai, W. *Synlett*, **1996**, 371) though the latter route is long and costly in comparison to all the others.
10. Schlosser, M.; Strunk, S. *Tetrahedron*, **1989**, *45*, 2649.
11. Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron*, **1995**, *51*, 10289 and references therein.
12. Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.*, **1977**, 679.
13. The observation has been made before in the literature; see Matthews, D. P.; Gross, R. S.; McCarthy, J. R. *Tetrahedron Lett.*, **1994**, *35*, 1027. Other fluorinated vinyl organometallic reagents form the subject of extensive reviews; see Normant, J-F. *J. Organometal. Chem.*, **1990**, *400*, 19; Burton, D. J.; Yang, Z-Y.; Morken, P. A. *Tetrahedron*, **1994**, *50*, 2993.
14. Pelter, A.; Kvicala, J.; Parry, D.E.; *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2681.

(*Received in UK* 7 *May* 1996; *revised* 20 *May* 1996; *accepted* 24 *May* 1996)