Pergamon

Tetrahedron Letters 41 (2000) 2453–2455

TETRAHEDRON
LETTERS

Short, stereoselective syntheses of α-fluoroalkenoate derivatives, α-fluoroenones and α-fluoroenals from HFC-134a

M. Kanai [†] and J. M. Percy [*]

School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Received 7 December 1999; accepted 18 January 2000

Abstract

Readily-available 1,1,1,2-tetrafluoroethane (Klea HFC-134a) can be converted, via a two-pot sequence into a range of *Z*-α-fluoroalkenoyl derivatives following addition reactions to aldehydes. Reaction adducts can be processed into enals and enones upon hydride reduction or Grignard reagent addition in high yield. © 2000 Elsevier Science Ltd. All rights reserved.

Though they have little use directly as bioactive substances, *Z*-fluoroalkenoic acid derivatives have served as precursors to a range of interesting species such as fluoroanalogues of retinals.[1] Reduction affords valuable fluoroallylic alcohols which can be transformed via rearrangement[2] into fluoroapionucleosides[3] and peptide isosteres.[4] While a range of routes are available for the fluoroalkenoates, the one reported by Allmendinger is perhaps best known.[5] We were prompted to report our findings in this area by the appearance of a recent paper by Lequeux and co-workers[6] which described a novel synthesis of the target compounds (esters) from a derivative of thioacetic acid. In this paper, we wish to report access to related species from the new refridgerant and building block[7] 1,1,1,2-tetrafluoroethane (Klea HFC-134a) **1** which is available on a large scale. The groundwork was performed by Normant and co-workers, though the details and scope were neither explored fully nor applied extensively. Lithiotrifluoroethene was generated by direct deprotonation of trifluoroethylene at −135°C.[8] Trapping the alkenyllithium reagent with aldehydes and ketones, and subsequent hydrolysis afforded the reactive alkenoyl fluorides which could be hydrolysed or trapped with ethanol or diethylamine. The Gilman reagent dimethyllithiocuprate was also reported to intercept an acid fluoride cleanly at −80°C though this method does not appear to have been used since.

In an extension of our recent exploration of a route to α-fluoroenones,[9] we re-examined the Normant chemistry and now wish to report that a complementary range of derivatives with useful properties can indeed be prepared directly in two pots. Dehydrofluorination/metallation of HFC-134a occurred upon treatment with *n*-butyllithium in THF[10] and we prepared adducts with typical electrophiles, benzaldehyde

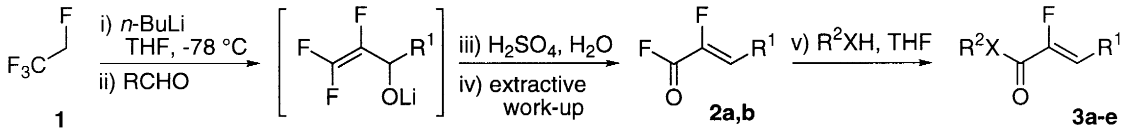
---

[*] Corresponding author.

[†] Permanent address: Chemical Research Centre, Central Glass Co., Ltd, Kawagoe-Shi, Saitama-Ken 350-11, Japan.

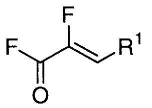
PII: S0040-4039(00)00154-4

and cinnamaldehyde. Hydrolysis with aqueous sulfuric acid followed by extractive work up afforded crude acid fluorides which were reacted further (Scheme 1), without characterisation or purification, with nucleophiles. Given the size of the $^3J_{H-F}$ coupling (typically >30 Hz), the alkene configuration seemed uncontroversial.

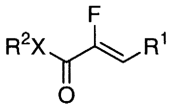


Scheme 1.

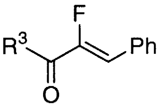
Adduct yields were effectively independent of the added nucleophile suggesting that the yield limiting factor is the stability of the intermediate acid fluoride; we continue to attempt to improve this aspect of the procedure in view of the high hydrolysis yields claimed in the original literature.[8]



2a, R^1= Ph;
2b, R^1= (*E*)-CH=CHPh.

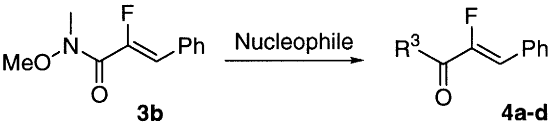


3a, R^1= Ph, R^2X = Et_2N;
3b, R^1= Ph, R^2X = MeONMe;
3c, R^1= (*E*)-CH=CHPh, R^2X = Et_2N;
3d, R^1= (*E*)-CH=CHPh, R^2X = MeONMe;
3e, R^1= (*E*)-CH=CHPh, R^2X = PhS.



4a, R^3 = Et;
4b, R^3 = Ph;
4c, R^3 = $CH_2CH{=}CH_2$;
4d, R^3 = H.

Weinreb amides **3b** and **3d** are of particular value given the transformations described in Scheme 2. Enones **4a**–**4c** and enal **4d**[11] were prepared in excellent yield upon treatment of **3b** with Grignard reagents or DIBAl-H, respectively.[12] Inexpensive thioesters are known to be of value, coupling with alkylzinc halides in a mild palladium-catalysed synthesis of ketones,[13] so the good yield of **3e** was satisfying.



Scheme 2. Reactions of Weinreb amide **3b** with nucleophiles in THF. For **4a**, EtMgI (4.0 equiv.), rt, (82%); **4b**, PhMgBr (3.0 equiv.), 0°C, (90%); **4c**, $H_2C{=}CHCH_2MgBr$ (3.0 equiv.), rt, (77%); **4d**, DIBAl-H (2.0 equiv.), 0°C, (80%). All reactions were run for 2 hours

Thioesters of this type can obviously be prepared from the corresponding acids, or via the route from fluoroacetonitrile described by Pirrung[14] which, while offering solutions to some special problems, is relatively long and uses some hazardous reagents (HMPA, CS_2, MeI, mercury(II) salts).

Given the generality of our recent route to α-fluoroenones,[9] we believe that the hydrolysis can be made to proceed smoothly given the correct selection of reaction conditions, allowing a wide range of aldehydes to be deployed in the synthesis. A general retrosynthetic route to α-fluoroenones and enals then becomes available, complementing existing routes and allowing an attractive starting material to be used in a unifying strategy, implemented in a most concise (two- or three-pot) sequence.

Acknowledgements

The authors wish to thank Central Glass Co. Ltd for a secondment to M.K. and ICI Klea for a generous donation of HFC-134a.

References

1. Shinada, T.; Sekiya, N.; Bojkova, N.; Yoshihara, K. *Tetrahedron* **1999**, *55*, 3675.
2. Percy, J. M.; Prime, M. E. *J. Fluorine Chem*. **1999**, *100*, 147.
3. Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett*. **1998**, *39*, 3443.
4. Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7927, *idem* 7301.
5. Allmendinger, T. *Tetrahedron* **1991**, *27*, 4905.
6. Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Org. Lett* **1999**, *1*, 1539.
7. For a full discussion of two-carbon fluorinated building blocks, see: Percy, J. M. *Top. Curr. Chem*. **1997**, *193*, 131. For the original report of dehydrofluorination/metallation of HFC-134a, see: Haslock, I. B.; Burdon, J.; Coe, P. L.; Powell, R. L. *Chem. Commun*. **1996**, 49.
8. Normant, J. F.; Foulon, J. P.; Masure, D.; Sauvêtre, R.; Villieras, J. *Synthesis* **1975**, 122.
9. Bainbridge, J. M.; Corr, S.; Kanai, M.; Percy, J. M. *Tetrahedron Lett*. **2000**, *41*, 971.
10. *n*-BuLi (2.8 ml of 2.12 M solution in hexane, 6 mmol) was added dropwise to a cold (−78°C) stirred solution of HFC-134a (134 ml, 6 mmol) in THF (10 ml). After 30 minutes, cinnamaldehyde (0.4 ml, 3 mmol) was added dropwise. After stirring for 1 hour at −78°C, the reaction was allowed to warm to −30°C then sulfuric acid solution (concentrated sulfuric acid:water=2 ml:0.1 ml) was added to the reaction mixture which was stirred for 20 minutes at 0°C. The reaction mixture was then poured onto ice (30 g) and extractive work-up afforded the crude acid fluoride which was taken up in THF (10 ml). *N*,*O*-Dimethylhydroxylamine in THF (3 ml) was cannulated into the solution at room temperature. After stirring for 2 hours, the reaction was quenched with the addition of saturated ammonium chloride. Extractive work-up, column chromatography and recrystallisation from Et_2O/petroleum ether afforded **3d** (208 mg, 31%, mp 122–124°C) as white needles. Selected data: found: C, 66.56%; H, 6.08%; N, 5.76%; calcd for $C_{13}H_{14}FNO_2$: C, 66.37%; H, 6.00%, N, 5.95%; δ_H (300 MHz, $CDCl_3$) 7.43–7.40 (2H, m), 7.32–7.23 (3H, m), 7.03 (1H, dd, J 15.8, 10.7 Hz), 6.74 (1H, d, J 15.8 Hz), 6.60 (1H, dd, J 32.1, 10.7 Hz), 3.72 (3H, s), 3.21 (3H, d, J 0.7 Hz) δ_F (282 MHz, $CDCl_3$) −123.00 (d, J 32.1 Hz). For details of gas handling, see: Bainbridge, J. M.; Brown, S. J.; Ewing, P. N.; Gibson, R. R.; Percy, J. M. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 2541.
11. Phenyl magnesium bromide (0.5 ml of 3 M solution, 1.5 mmol) was added to a solution of **3b** (105 mg, 0.5 mmol) in THF (5 ml) at 0°C. After stirring for 2 hours at room temperature, the reaction was quenched by the addition of saturated aqueous ammonium chloride (20 ml). Extractive work-up, chromatography and recrystallisation from Et_2O/petroleum ether afforded **4b** (102 mg, 90%) reported previously (Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; McCarthy, J. R. *J. Org. Chem*. **1999**, *64*, 3476) by a considerably less convenient route.
12. Funabiki has also described an attractive enal synthesis, see: Funabiki, K.; Murata, E.; Fukushima, Y.; Matsui, M.; Shibata, K. *Tetrahedron* **1999**, *55*, 4637.
13. Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett*. **1998**, *39*, 3189.
14. Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem*. **1993**, *58*, 5683.