Tetrahedron Letters 54 (2013) 1658–1660

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new approach to the synthesis of (*Z*)-2-fluoro-2-alkenals via Wittig-type carbonyl condensation reactions of 2-(fluoromethyl)-4,4,6-trimethyl-1,3-oxazine phosphonium bromide

Mohammed Kajjout [a], Michaël Smietana [b], Jacques Leroy [b], Christian Rolando [a,*]

[a] Université de Lille 1, Sciences et Technologies, USR CNRS 3290, Miniaturisation pour la synthèse, l'Analyse & la Protéomique, 59655 Villeneuve d'Ascq Cedex, France
[b] Ecole Normale Supérieure, UMR CNRS 8640, « PASTEUR », 24 rue Lhomond, 75231 Paris, France

ARTICLE INFO

Article history:
Received 4 August 2012
Revised 20 December 2012
Accepted 8 January 2013
Available online 16 January 2013

Keywords:
2-Fluoro-2-alkenals
Oxazine
Phosphonium salt

ABSTRACT

We report here the transformation of aldehydes to their (*Z*)-α-fluoro-α,β-unsaturated aldehyde homologs by condensation with the phosphonium salt of the Meyer's oxazine obtained from bromofluoroacetonitrile. After methylation with trimethyloxonium tetrafluoroborate the quaternized oxazine is cleanly reduced to mostly *Z* 2-fluoro-2-alkenals by sodium borohydride at room temperature. This methodology is compatible with usual protecting groups and affords an efficient access to functionalized mostly *Z* 2-fluoro-2-alkenals derived from natural products and their corresponding (*Z*)-2-fluoro-2-alkenols.

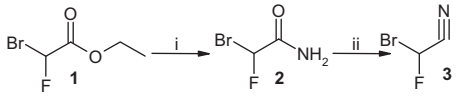
During the course of our studies devoted to the lignification process in plants, we were led to synthesize fluorinated analogs of some of the cinnamic glucoside monomers involved in lignin biosynthesis, such as β-fluoroconiferin. This compound was prepared via a Horner–Wadsworth–Emmons olefination reaction from tetra-*O*-acetylglucoside of vanillin and diethyl (fluorocarboethoxymethyl)phosphonate under phase transfer conditions, affording a *E*/*Z* mixture of isomeric α-fluoro-α,β-unsaturated esters which was isomerized into a pure (*Z*)-α-fluoro-α,β-unsaturated ester. The five ester groups were reduced by in situ generated lithium borohydride ($NaBH_4$, LiCl, glyme, 80 °C) to (*Z*)-β-fluoroconiferin whose isolation from glyme proved to be delicate.[1] So we looked for a more convenient route to such β-fluorocinnamyl alcohols which would proceed *via* the reduction of the corresponding aldehydes with $NaBH_4$. As a result, we are particularly interested in applying the same strategy we developed for the synthesis of the natural compound coniferin, which is based on the mild reduction of the corresponding aldehyde by $NaBH_4$.[2]

2-Fluoropropenal derivatives have attracted much attention and 2-fluoropropenals are key intermediates for the synthesis of biologically active compounds and complex structures.[3] (*Z*)-α-fluorocinnamic aldehydes have been used as precursors to obtain chiral 2-fluoro-3-phenylpropionic acid or have been transformed into an imine, which leads to chiral fluorinated allyl amines by addition of Grignard reagents. They also have been transformed into a conjugated chain by reaction with a Wittig–Horner reagent during the synthesis of retinoid X receptor agonists or RXR selective modulators.[4] α-Fluoro-α,β-unsaturated aldehydes are obtained by oxidation of the corresponding alcohol, using the Des-Martin reagent or tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) system. Only few syntheses lead directly to the aldehyde, and they use even harsher conditions, which are not compatible with functionalized molecules.[5] Indeed, aldehydes are easily reduced in mild conditions at room temperature by sodium borohydride to the corresponding alcohol.[6] We recently presented a strategy for the synthesis of (*Z*)-β-fluoroallyl alcohols based on the palladium-catalyzed formylation by carbon monoxide of α-bromo-α-fluoroolefins obtained by a Wittig–Burton reaction, to obtain α-fluoro conjugated aldehydes which were then reduced to the corresponding alcohols.[6a] We present here an alternate approach to 2-fluoro-2-alkenals based on the condensation of the anion of 2-(fluoromethyl)-4,4,6-trimethyl-1,3-oxazine phosphonium bromide **5** with the corresponding aldehydes.

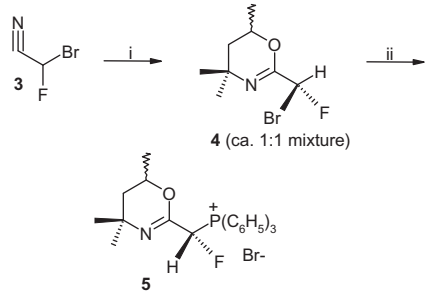
Oxazines are commonly prepared by the Ritter reaction of a nitrile with a diol in sulfuric acid and this method was used to prepare 2-(fluoromethyl)-4,4,6-trimethyl-1,3-oxazine from fluoroacetonitrile and 2-methyl-1,3-pentanediol.[7] Although bromofluoroacetonitrile **3** has been mentioned in the literature, neither preparation nor characterization data for this compound are available to the best of our knowledge.[8] We prepared it by dehydration over phosphorus pentoxide of bromofluoroacetamide

* Corresponding author. Tel.: +33 320434977; fax: +33 320336136.
E-mail address: Christian.rolando@univ-lille1.fr (C. Rolando).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.01.017



Scheme 1. Synthesis of bromofluoroacetonitrile **3**. Reagents: (i) aqueous ammonia, 0 °C; (ii) phosphorus pentoxide (1.25 equiv).



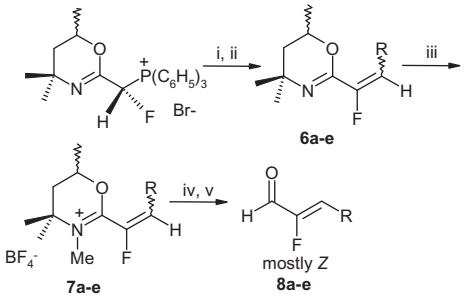
Scheme 2. Synthesis of **5**. Reagents and conditions: (i) 2-methyl-1,3-pentanediol, H_2SO_4, 0–5 °C; (ii) $(C_6H_5)_3P$ (1 equiv) 80 °C, overnight.

2 (76% yield) while the amide was obtained from ethyl bromofluoroacetate **1** and aqueous ammonia following the synthesis described by Young and Tarrant[9] for chlorofluoroacetonitrile (63% yield) (Scheme 1).[10]

Once the nitrile was synthesized, 2-(bromofluoromethyl)-4,4,6-trimethyl-1,3-oxazine **4** was obtained using the Meyers procedure[11] as a ca. 1:1 inseparable mixture of diastereomers (Scheme 2).[12] The bromofluoro oxazines, though moderately stable, were not distilled but were used as such (50% yield unoptimized). Treatment of the mixture with 1 equivalent of triphenylphosphine without a solvent at 80 °C, afforded a ca. 54:46 mixture of the diastereomeric phosphonium salts **5** which were identified by mass spectrometry and NMR (82% yield).

Wittig condensation of the anions of the diastereoisomeric mixture **5** generated with *n*-butyllithium in THF at −78 °C, with some representative carbonyl compounds, was checked. While the unsaturated ketone 6-methyl-5-hepten-2-one was found to be unreactive in these conditions, aldehydes reacted easily. For example, with benzaldehyde, a 60:40 mixture of *Z* and *E* alkenes **6a** was obtained in a 50% overall yield (preparative thin layer chromatography). Comparable results were obtained with some other aromatic aldehydes such as vanillin tetra-*O*-acetylglucoside or aliphatic aldehydes (Table 1).

Attempted direct reduction of the oxazine moiety with sodium borohydride at controlled pH (7.0) and low temperature (ca. −40 °C) failed.[10] On the other hand, catalytic reduction with hydrogen over $Pd/BaSO_4$ led to the selective reduction of the C–C double bond. Fortunately, the reduction of the carbon–nitrogen double bond of such conjugated systems could be more easily achieved after prior quaternization of the nitrogen atom.[13] While methyl iodide was found to be unreactive, trimethyloxonium tetrafluoroborate led to the *N*-methyl quaternary salt **7** (^{19}F NMR monitoring) which was subsequently reduced with sodium borohydride then hydrolyzed without further purification with aqueous oxalic acid to give α-fluoro-α,β-unsaturated aldehydes **8** (Scheme 3). Starting from benzaldehyde (entry **a**) and dodecanal (entry **e**) only *Z* alkenals were obtained whereas for the other substituted aromatic aldehydes examined (entries **b**–**d**), mixtures of *Z* and *E* alkenes were formed in which the Z isomer is more abundant (Table 1). During the reduction of (*E*,*Z*)-α-fluorocinnamic thioester mixtures by $NaBH_4$ at room temperature we obtained previously pure (*Z*)-β-fluoroallyl alcohols with double bond isomerization.[6i] A similar



Scheme 3. Synthesis of **8a**–**e**. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 30 min; (ii) RCHO, −78 °C to rt, 3 h, dil HCl; (iii) $Me_3O^+BF_4^-$, CH_2Cl_2, 2 h; (iv) $NaBH_4$, pH = 7.0, −35 to −40 °C; (v) $(CO_2H)_2$, H_2O, reflux, 2 h.

Table 1
Synthesis of aldehydes **8a**–**e** via the oxazines **6a**–**e**

Entry	Carbonyl compound	Alkene **6**		Alkenal **8**	
		Z/*E* ratio[a]	Yield[b,c] (%)	*Z*/*E* ratio[a]	Yield[b,d] (%)
a	C_6H_5CHO	60:40	50	100:0	56
b	*p*-$NO_2C_6H_4CHO$	60:40	63	86:14	40
c	*p*-$CH_3OC_6H_4CHO$	65:35	70	94:6	64
d	*o*-CH_3O*p*-(OGlu)C_6H_4CHO[e]	55:45	30	94:6	32
e	*n*-$C_{11}H_{23}CHO$	84:16	77	100:0	51

[a] Ratios determined on the crudes by ^{19}F NMR.
[b] Isolated, preparative TLC.
[c] Yields from **5**.
[d] Yields from **6**.
[e] OGlu = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl.

isomerization presumably took place during the reduction of oxazines **6** mixtures.

In conclusion, we have shown that α-fluoro-α,β-unsaturated aldehydes may be advantageously obtained using the oxazine derived from bromofluoroacetonitrile. These aldehydes can be smoothly reduced to the corresponding alcohols by sodium borohydride. This methodology is applied to access highly functionalized aldehydes as **8d** used as precursor for (*Z*)-β-fluoroconiferin, a strong inhibitor of lignin polymerization, for example.[6a] Other applications of the reactivity of this new reagent are currently under investigation. The obtained 2-fluoroalkenals may also be reduced with a deuterated chiral reagent to afford prochiral 2-fluroalkenols for biosynthetic studies.[14]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.017. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Daubresse, N.; Chupeau, Y.; Francesch, C.; Lapierre, C.; Pollet, B.; Rolando, C. *Chem. Commun.* **1997**, 1489–1490.
2. Daubresse, N.; Francesch, C.; Mhamdi, F.; Rolando, C. *Synthesis* **1998**, 157–161.
3. (a) Lamy, C.; Hofmann, J.; Parrot-Lopez, H.; Goekjian, P. *Tetrahedron Lett.* **2007**, *48*, 6177–6180; (b) Tsuchikawa, H.; Matsushita, N.; Matsumori, N.; Murata, M.; Oishi, T. *Tetrahedron Lett.* **2006**, *47*, 6187–6191; (c) Fishkin, N.; Yefidoff, R.; Gollipalli, D. R.; Rando, R. R. *Bioorg. Med. Chem. Lett.* **2005**, *13*, 5189–5194; (d) Michellys, P.-Y.; Boehm, M. F.; Chen, J.-H.; Grese, T. A.; Karanewsky, D. S.; Leibowitz, M. D.; Liu, S.; Mais, D. A.; Mapes, C. M.; Reifel-Miller, A.; Ogilvie, K. M.; Rungta, D.; Thompson, A. W.; Tyhonas, J. S.; Yumibe, N.; Ardecky, R. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4071–4075.

4. (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860–2861; (b) Pierry, C.; Zoute, L.; Jubault, P.; Pfund, E.; Lequeux, T.; Cahard, D.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron Lett.* **2009**, *50*, 264–266; (c) Noguchi, T.; Tanaka, N.; Nishimata, T.; Goto, R.; Hayakawa, M.; Sugidachi, A.; Ogawa, T.; Niitsu, Y.; Asai, F.; Ishizuka, T.; Fujimoto, K. *Chem. Pharm. Bull.* **2009**, *57*, 22–33; (d) Hibi, S.; Kikuchi, K.; Yoshimura, H.; Nagai, M.; Tai, K.; Hida, T. *J. Med. Chem.* **1998**, *41*, 3245–3252.
5. (a) Funabiki, K.; Murata, E.; Fukushima, Y.; Matsui, M.; Shibata, K. *Tetrahedron* **1999**, *55*, 4637–4642; (b) Hatanaka, F.; Tsuchiya, M.; Yoshimatsu, M. *Synlett* **2005**, 2191–2194; (c) Sauvetre, R.; Masure, D.; Chuit, C.; Normant, J. F. *Synthesis* **1978**, 128–130.
6. (a) Zemmouri, R.; Kajjout, M.; Castanet, Y.; Eddarir, S.; Rolando, C. *J. Org. Chem.* **2011**, *76*, 7691–7698; (b) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58–68; (c) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8878–8891; (d) Hackett, A. G.; Kotyk, J. J.; Fujiwara, H.; Logusch, E. W. *J. Am. Chem. Soc.* **1990**, *112*, 3669–3671; (e) Jaeger, B.; Lay, H.; Lehmann, J.; Ziser, L. *Carbohydr. Res.* **1991**, *217*, 99–106; (f) Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442–444; (g) Yang, J.; Rallapalli, S. K.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 815–817; (h) Yin, W.; Kabir, M. S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3339–3349; (i) Kajjout, M.; Zemmouri, R.; Eddarir, S.; Rolando, C. *Tetrahedron* **2012**, *68*, 3225–3230.
7. Patrick, T. B.; Hosseini, S.; Bains, S. *Tetrahedron Lett.* **1990**, *31*, 179–182.
8. Pews, R. G.; Lysenko, Z. *J. Org. Chem.* **1985**, *50*, 5115–5119.
9. Young, J. A.; Tarrant, P. *J. Am. Chem. Soc.* **1949**, *71*, 2432–2433.
10. *Selected data for bromofluoroacetonitrile* ***3***: bp 90 °C; ν_{max} (CCl_4)/cm^{-1} 3002, 2252; ^1H NMR (250 MHz, $CDCl_3$, δ_H) 6.70 (d, J = 48.8 Hz); ^{19}F NMR (235 MHz, $CDCl_3$, δ_F) −148.1 (d, J = 48.8 Hz); ^{13}C NMR (62 MHz, $CDCl_3$, δ_c) 66.7 (d, J = 255.5 Hz), 112.3 (d, J = 32.8 Hz).
11. Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36–56.
12. *Selected data for oxazine* ***4*** (ca. 1:1 mixture of diastereomers) ^1H NMR (400 MHz, $CDCl_3$, δ_H) 1.23 (d, 3H, J = 6.2 Hz), 1.42 (br s, 3H), 1.45 (dd, ½H, J ~10.0, 1.6 Hz), 1.46(6) (s, 1.5H), s 1.46(9) (s, 1.5H), 1.49 (dd, ½H, J = 10.2, 1.5 Hz), 1.75 (dd, ½H, J = 9.8, 9.2 Hz), 1.79 (dd, ½H, J = 9.9, 9.1 Hz), 4.17 (m, 1H), 6.41 (d, ½H, J = 51.0 Hz), 6.42 (d, ½H, J = 51.0 Hz); ^{19}F NMR (235 MHz, $CDCl_3$, δ_F) −145.1 (dd, J = 51.5, 2.1 Hz), −145.9 (dd, J = 51.2, 2.2 Hz); ^{13}C NMR (62 MHz, $CDCl_3$, δ_c) 24.2, 24.5, 25.49, 25.53, 27.6, 28.0, 49.63, 49.73, 54.1 (unresolved), 65.40, 65.45, 85.3 (d, J = 269.6 Hz), 85.4 (d, J = 270.1 Hz), 163.91 (d, J = 19.1 Hz), 163.99 (d, J = 19.5 Hz).
13. Malone, G. R.; Meyers, A. I. J. *Org. Chem.* **1974**, *39*, 623–628.
14. Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355.