Tetrahedron Letters 49 (2008) 4359–4361

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Convenient preparation of (*Z*)-α-halo-α,β-unsaturated aldehydes: synthesis of a *Laurencia flexilis* toxin

Deb K. Barma [a], Biao Lu [a], Rachid Baati [b,*], Charles Mioskowski [b], J. R. Falck [a,*]

[a] *Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA*
[b] *Université Louis Pasteur de Strasbourg, Faculté de Pharmacie UMR 7175-LC1, Laboratoire de Synthèse Bio-Organique, 74 route du Rhin, 67 401 Illkirch-Graffenstaden, France*

ARTICLE INFO

Article history:
Received 3 April 2008
Revised 21 April 2008
Accepted 7 May 2008
Available online 10 May 2008

Dedicated to the memory of Charles Mioskowski who passed away on June 2, 2007

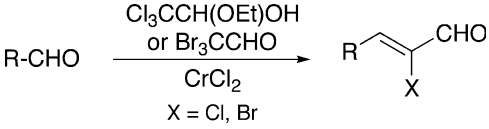
Keywords:
Homologation
Chromium
Aldehydes
Enals

ABSTRACT

The $CrCl_2$-mediated two-carbon halo-homologation of aryl, alkenyl, and aliphatic aldehydes with chloral ethyl hemiacetal or bromal affords (*Z*)-α-chloro- and (*Z*)-α-bromo-α,β-unsaturated aldehydes, respectively, in good to excellent yields and high stereoselectivity. The utility of this methodology was illustrated by a synthesis of 2-chloropentadec-2(*Z*)-enal, a toxin isolated from the marine red alga *Laurencia flexilis*.

1. Introduction

In many instances, organochromium intermediates offer chemo-, regio-, and/or stereoselectivities not achievable with traditional organometallic reagents.[1] For example, our laboratories have reported efficient, stereocontrolled condensations of α,α-di-[2]/α,α,α- trihalo-esters,[3] -amides, -ketones, -nitriles, and -methylbenzene with aldehydes and ketones[4] induced by Cr(II)-salts. Herein, we describe a convenient, stereoselective synthesis of (*Z*)-α-chloro- and (*Z*)-α-bromo-α,β-unsaturated aldehydes in good to excellent yields via the $CrCl_2$-mediated two-carbon halo-homologation of aldehydes with chloral ethyl hemiacetal or bromal (Eq. 1). α-Halo-α,β-unsaturated aldehydes are useful synthetic intermediates[5] as well as structural elements in natural products.[6] However, they are generally accessible only via multi-step sequences or using highly reactive reagents and are often obtained as *E*/*Z*-mixtures in reduced yields.[7]



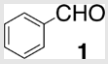
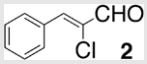
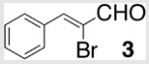
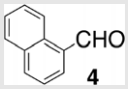
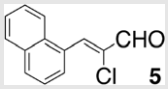
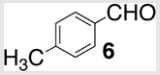
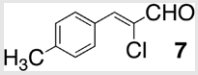
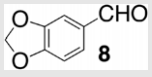
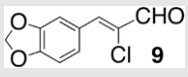
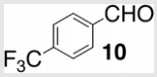
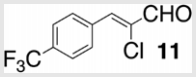
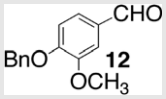
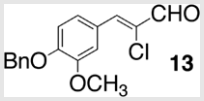
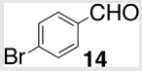
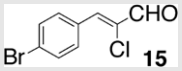
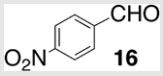
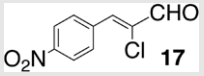
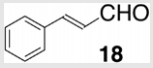
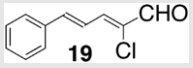
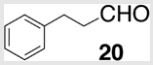
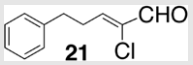
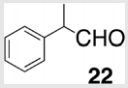
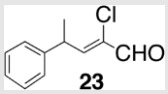
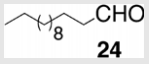
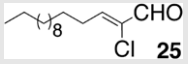
(1)

The scope and limitations of this facile transformation were explored using a panel of representative aldehydes as summarized in Table 1. The simplest aryl aldehyde, benzaldehyde (**1**), was readily converted into the corresponding (*Z*)-α-chlorocinnamaldehyde[8] (**2**) using chloral ethyl hemiacetal[9] and $CrCl_2$ under the standard reaction conditions, that is, THF at room temperature (entry 1).[10] Catalytic $CrCl_2$ regenerated in situ by Mn(0)[11] or Fe(0)[12] resulted in lower yields of **2** as did the use of solvents other than THF.[13] By conducting the reaction at 0 °C, the somewhat labile bromal gave rise to (*Z*)-α-bromocinnamaldehyde[7c] (**3**) from **1** in synthetically useful yield (entry 2). The halo-homologations were relatively insensitive to the nature of the aryl moiety. Electron-rich substrates, viz., 1-naphthaldehyde (**4**), *p*-tolualdehyde (**6**), and piperonal (**8**), and electron-poor 4-trifluoromethylbenzaldehyde (**10**) furnished adducts **5**[14] (entry 3), **7**[7b] (entry 4), **9** (entry 5), and **11** (entry 6), respectively, in comparable yields. Importantly, the reaction was compatible with a wide variety of functional groups. Benzyl/methyl bis-ether **12**, *p*-bromobenzaldehyde (**14**), and the reduction prone *p*-nitrobenzaldehyde (**16**) reacted smoothly and accordingly led to α-chloroenals **13** (entry 7), **15**[7b] (entry 8), and **17** (entry 9),

* Corresponding authors. Tel.: +33 (0)39 024 4301; fax: +33 (0)39 024 4306 (R.B.); tel.: +214 648 2406; fax: +214 648 6455 (J.R.F.).
E-mail addresses: baati@bioorga.u-strasbg.fr (R. Baati), j.falck@utsouthwestern.edu (J. R. Falck).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.026

Table 1
Synthesis of α-halo-α, β-unsaturated aldehydes

Entry	Aldehyde	Adduct	Yield(%)
1			91
2	**1**		69
3			81
4			91
5			82
6			89
7			85
8			77
9			71
10			87
11			71[a]
12			87
13			82

[a] 5–7% of the E-isomer was also obtained.

respectively, without complications. It was also gratifying to find conjugated (**18**→**19**, entry 10), aliphatic (**20**→**21**, entry 11), and α-branched aliphatic aldehydes (**22**→**23**, entry 12) behaved analogously. The utility of this methodology was further demonstrated using commercial tridecanal (**24**) for the one-step synthesis of 2-chloropentadec-2(*Z*)-enal (**25**, entry 13), a toxin isolated from the marine red alga *Laurencia flexilis*.[6]

In concert with earlier mechanistic proposals,[3] $CrCl_2$ likely acts as a multiple one-electron reductant generating chromium(III)-enolate **26** from chloral/bromal which is intercepted by aldehyde (Eq. 2). The resultant Reformatsky-type adduct **27** undergoes further reductive metallation with concomitant E2-elimination to give the final α-halo-α,β-enal adduct.

2. General procedure: α-chloro-α,β-unsaturated aldehydes

A mixture of aldehyde (1 mmol) and 2,2,2-trichloro-1-ethoxyethanol (chloral ethyl hemiacetal, 1 mmol) in anhydrous THF (1 mL) was added to a stirring, room temperature suspension of anhydrous $CrCl_2$[15] (4 mmol, Aldrich Chem. Co.) in anhydrous THF (10 mL) under an argon atmosphere. After 10 h, the reaction mixture was quenched with aqueous 5% HCl (10 mL), stirred for an additional 10 min and then extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to give α-chloro-α,β-unsaturated aldehyde in the indicated yields (Table 1).

2.1. α-Bromo-α,β-unsaturated aldehydes

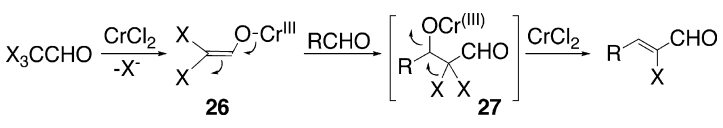
Same as above except a mixture of aldehyde (1 mmol) and bromal (2 mmol, Fluka Chem. Co.) was added to a 0 °C suspension of $CrCl_2$ and kept at this temperature for 1 h before quenching and purification as described above.

Acknowledgment

Financial support provided by the CNRS, the Robert A. Welch Foundation, and NIH (DK38226, GM31278) is gratefully acknowledged.

References and notes

1. Reviews (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045; (b) Hodgson, D. M. *J. Organomet. Chem.* **1994**, *476*, 1–5.
2. Barma, D. K.; Kundu, A.; Bandyopadhyay, A.; Kundu, A.; Sangras, B.; Briot, A.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2004**, *45*, 5917–5920.
3. Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218–3219.
4. Falck, J. R.; Bandyopadhyay, A.; Barma, D. K.; Shin, D.-S.; Kundu, A.; Kishore, R. V. K. *Tetrahedron Lett.* **2004**, *45*, 3039–3042.
5. (a) Nagamitsu, T.; Takano, D.; Marumoto, K.; Fukuda, T.; Furuya, K.; Otoguro, K.; Takeda, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *J. Org. Chem.* **2007**, *72*, 2744–2756; (b) Simpkins, S. M. E.; Weller, M. D.; Cox, L. R. *Chem. Commun.* **2007**, 4035–4037; (c) Timmons, C.; Chen, D.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 2075–2078.
6. de Nys, R.; König, G. M.; Wright, A. D.; Stricher, O. *Phytochem.* **1993**, *34*, 725–728.
7. Typical examples: (a) Chen, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 4993–4996; (b) Nenajdenko, V. G.; Reznichenko, A. L.; Lenkova, O. N.; Shastin, A. V.; Balenkova, E. S. *Synthesis* **2005**, 605–609; (c) Kim, K.-M.; Park, I.-H. *Synthesis* **2004**, 2641–2644; (d) Mitani, M.; Kobayashi, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 284–286; (e) Satoh, T.; Kitoh, Y.; Onda, K.-i.; Takano, K.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 4957–4972; (f) Ley, S.; Whittle, A. J. *Tetrahedron Lett.* **1981**, *22*, 3301–3304; (g) Masure, D.; Chuit, C.; Sauvêtre, R.; Normant, J. F. *Synthesis* **1978**, 458–460; (h) Poutsma, M. L.; Ibarbia, P. A. *J. Org. Chem.* **1970**, *35*, 4038–4054; (i) Jedlinski, Z.; Majnusz, J. *Tetrahedron* **1969**, *25*, 699–705; (j) Märkl, G. *Chem. Ber.* **1962**, *95*, 3003–3007.
8. Adduct **2** was identical in all respects with an authentic sample of (*Z*)-α-chlorocinnamaldehyde from Aldrich Chem. Co. and the spectral data of **25** corresponded closely with literature values (see Ref. 6). All other products were assigned (*Z*)-stereochemistry in analogy.
9. Anhydrous chloral, prepared by distillation of chloral hydrate from P_2O_5 under reduced pressure, gave **2** in only 56% yield. The superior yields obtained with chloral ethyl hemiacetal may result from the slow release of free chloral. A low steady state concentration of free chloral would minimize side reactions, thus improving overall halo-homologation yields.
10. Organochromium intermediates of the type described here belong to a small but growing class of organometallics, for example, indium reagents, that are tolerant of water, alcohols and hydroxylic solvents, yet are still capable of reaction with organic electrophiles such as aldehydes.



(2)

11. Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.
12. Falck, J. R.; Bejot, R.; Barma, D. K.; Bandyopadhyay, A.; Joseph, S.; Mioskowski, C. *J. Org. Chem.* **2006**, *71*, 8178–8182.
13. When 1 equiv of $CrCl_2$ was used along with 5 equiv of Mn(0) or 5 equiv of Fe(0), only 10% and 21% of **2** were obtained, respectively, at room temperature after 24 h. Increasing the temperature to 45 °C did not improve the yields. The use of other solvents such as DMF (no formation of **2**), EtOAc (5–10% of **2**), or DME (less than 10% of **2**) was also disappointing.
14. Spectral/physical data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.62 (m, 3H). 7.92–8.01 (m, 3H), 8.17– 8.19 (d, 1H, J = 8.0 Hz), 8.30 (s, 1H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.6, 142.9, 134.6, 133.7, 131.6, 131.5, 129.3, 128.8, 128.6, 127.5, 126.7, 125.3, 123.3. **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (s, 2H), 6.90–6.92 (d, 1H, J = 8.0 Hz), 7.36–7.39 (dd, 1H, J = 1.6, 8.4 Hz), 7.43 (s, 1H), 7.70 (s, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.9, 108.7, 109.9, 126.7, 128.2, 129.9, 145.2, 148.2, 150.5, 186.5; IR: 3002, 1684, 1611, 1593, 1504, 1455, 1271, 1128, 1038 cm^{-1}; MS (DCI/NH_3) m/z $(M+NH_4)^+$ 218; mp 87–89 °C. **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 7.72–7.75 (d, 1H, J = 12.0 Hz), 8.02–8.05 (d, 1H, J = 12.0 Hz), 9.54 (s, 1H). **13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 5.24 (s, 2H), 6.94–6.97 (d, 1H, J = 12.0 Hz), 7.30–7.74 (m, 7H), 7.74 (s, 1H), 9.45 (s, 1H). **19**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10–7.25 (m, 1H), 7.29–7.49 (m, 5H), 7.53–7.64 (m, 2H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 122.9, 128.4, 129.5, 130.7, 132.9, 135.9, 144.9, 145.9, 185.9; IR: 3012, 1685, 1613, 1584, 1546, 1263, 1166 cm^{-1}; MS (DCI/NH_3) m/z $(M+NH_4)^+$ 210; mp 64–66 °C. **21**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86–2.88 (m, 4H), 6.87 (t, 1H, J = 6.4 Hz), 7.20–7.26 (m, 3H), 7.30–7.34 (m, 2H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.9, 33.5, 126.6, 128.3, 128.7, 139.9, 185.6; IR: 3027, 1701, 1624, 1496, 1454, 1123 cm^{-1}; MS (DCI/NH_3) m/z $(M+NH_4)^+$ 212. **23**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.53 (d, 1H, J = 9.0 Hz), 4.22–4.32 (m, 4H), 6.90–6.93 (d, 1H, J = 9.0 Hz), 7.25–7.35 (m, 5H), 9.35 (s, 1H).
15. Commercial, anhydrous $CrCl_2$ was transferred to a tared flask under an argon atmosphere and dried in vacuo with a heat-gun or low flame for 3–5 min, then cooled to room temperature prior to weighing and use.