Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3039–3042
Tetrahedron Letters

Stereoselective $CrCl_2$-mediated condensation of aldehydes with functionalized 1,1,1-trichlorides: synthesis of trisubstituted (*Z*)-chloroolefins

J. R. Falck,* Anish Bandyopadhyay, D. K. Barma, Dong-Soo Shin, Abhijit Kundu and R. V. Krishna Kishore

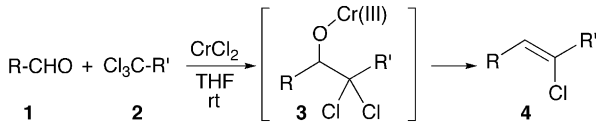
Department of Biochemistry, University of Texas, Southwestern Medical Center, Dallas, TX 75390, USA

Received 10 February 2004; accepted 19 February 2004

Abstract—The $CrCl_2$-mediated condensation of aldehydes **1** with a variety of functionalized 1,1,1-trichlorides **2** affords trisubstituted chloroolefins **4** in excellent yields and generally high *Z*-stereoselectivity. The intermediate dichlorohydrin adducts **3** can be isolated in good yields under conditions of limited reagent and reduced temperature.

1. Introduction

Recently, our laboratories described the efficient, stereoselective Cr(II)-mediated addition of 2,2,2-trihaloacetates to carbonyls.[1] The broad synthetic utility of the resultant (*Z*)-α-haloacrylates[2] prompted us to examine the scope of this condensation using aldehydes **1** and a panel of representative 1,1,1-trichlorides **2**[3] for the preparation of trisubstituted chloroolefins **4** (Eq. 1).[4]



1 2 3 4 (1)

The results are summarized in Table 1. For typical aryl and aliphatic aldehydes, exemplified by benzaldehyde (**5**) and hydrocinnamaldehyde (**8**), respectively, stirring with 1,1,1-trichloroacetone (**6**) and 5 equiv of commercial[5] $CrCl_2$ at room temperature for 0.5 h generated (*Z*)-3-chloroenones **7**[6] (entry a) and **9**[7] (entry b) in nearly quantitative yields. None of the (*E*)-isomer[8] could be detected by NMR analysis of the crude reaction mixtures, indicating >99% stereochemical purity. While catalytic $CrCl_2$ coupled to a Mn/TMSCl regeneration system[9] was also highly stereoselective, yields were reduced (65–80%) and reaction times were significantly longer (~16–24 h).

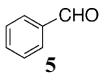
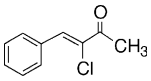
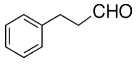
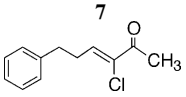
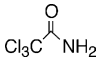
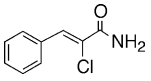
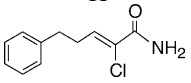
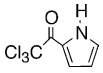
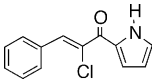
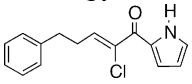
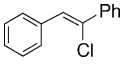
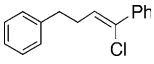
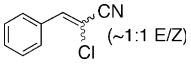
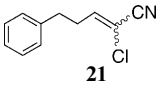
Despite the presence of easily exchangeable protons, both 2,2,2-trichloroacetamide (**10**) and 2-(trichloroacetyl)pyrrole (**13**) smoothly condensed with **5** and **8** giving rise to all-*Z* **11**[10] (entry c), **12** (entry d), **14** (entry e), and **15** (entry f), correspondingly. α,α,α-Trichlorotoluene (**16**) behaved analogously and stereoselectively generated **17**[11] (entry g) and **18**[12] (entry h) from **5** and **8**, respectively. In contrast, **20**[13] (entry i) was obtained in good yield, but as an ~1:1 mixture of *E*/*Z*-isomers, via union of trichloroacetonitrile (**19**) with **5**. The divergent reactivity of **19** was even more apparent with aldehyde **8**. The anticipated adduct, chloroolefin **21**, could be isolated in low yield only under a variety of reaction conditions.

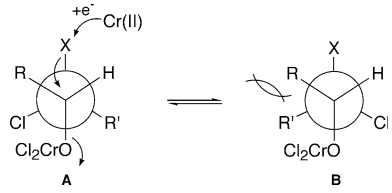
By analogy with earlier studies,[1] the preceding olefinations most likely involve initial metalation of **2** and addition of the nascent chromate anion to the aldehyde carbonyl yielding Reformatsky-type adduct **3** (Eq. 1). Reduction of a residual chloride and subsequent E2-elimination evolves chloroolefin **4**. Of the possible antiperiplanar conformations, conformer A (Scheme 1) is favored because it minimizes the steric interactions between the trichloride R′ and aldehyde R groups. Selective metalation of the chloride furthest from the chromate ester ensures the observed *Z*-stereochemistry.

Keywords: Chromium; Condensations; Stereocontrol; Olefination.
* Corresponding author. Tel.: +1-214-648-2406; fax: +1-214-648-6455; e-mail: j.falck@utsouthwestern.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.101

Table 1. (*Z*)-Chloroolefination of aldehydes

Entry	Aldehyde	Trichloride	Adduct	Yield (%)
a	 **5**	 **6**	 **7**	99
b	 **8**	**6**	 **9**	99
c	**5**	 **10**	 **11**	95
d	**8**	**10**	 **12**	92
e	**5**	 **13**	 **14**	89
f	**8**	**13**	 **15**	91
g	**5**	Cl_3C–Ph **16**	 **17**	95
h	**8**	**16**	 **18**	93
i	**5**	Cl_3C–CN **19**	 **20**	90
j	**8**	**19**	 **21**	<10



Scheme 1.

When R′=CN, this interaction is negligible and both conformers are equally populated.

Consistent with the proposed mechanism, the corresponding dihalohydrins **22**–**27** could be isolated in good yield under conditions of limiting chromium and low temperature (Table 2). Exposure of the dichlorohydrins

Table 2. Synthesis of Dichlorohydrins

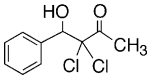
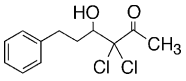
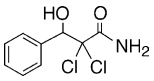
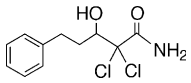
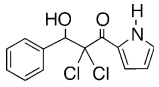
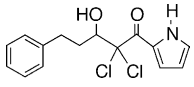
Entry	Aldehyde	Trichloride	Adduct	Yield (%)
a	**5**	**6**	 **22**	87
b	**8**	**6**	 **23**	82
c	**5**	**10**	 **24**	82

Table 2 (*continued*)

Entry	Aldehyde	Trichloride	Adduct	Yield (%)
d	**8**	**10**	 **25**	75
e	**5**	**13**	 **26**	75
f	**8**	**13**	 **27**	79

to the original reaction conditions led exclusively to (*Z*)-chloroolefins in yields comparable to those in Table 1.

2. General procedures

2.1. Stoichiometric $CrCl_2$

A mixture of trichloride (1 mmol) and aldehyde (1 mmol) in dry THF (2 mL) was added to a stirring, room temperature suspension of anhydrous $CrCl_2$[5] (5.0 mmol) in THF (8 mL) under an argon atmosphere. After 0.5–2 h, the resultant reddish reaction mixture was quenched with water, extracted thrice with ether, and the combined ethereal extracts were evaporated in vacuo. Chromatographic purification of the residue on silica gel furnished pure chloroolefin in the indicated yields (Table 1).

2.2. Catalytic $CrCl_2$

A mixture of trichloride (1 mmol) and aldehyde (1 mmol) in dry THF (3 mL) was added to a stirring, room temperature suspension of anhydrous $CrCl_2$[5] (0.5 mmol), Mn powder (4 mmol), and freshly distilled TMS–Cl (4 mmol) in THF (7 mL) under an argon atmosphere. After 16–24 h, the reaction was quenched and the product was purified as described above to give chloroolefin in the indicated yields (Table 1).

2.3. Dichlorohydrins

A mixture of trichloride (1 mmol) and aldehyde (1 mmol) in dry THF (2 mL) was added to a stirring, 0 °C suspension of anhydrous $CrCl_2$[5] (2.5 mmol) in THF (8 mL) under an argon atmosphere. After 12 h, the reaction was quenched and the product was purified as described above to give dichlorohydrin in the indicated yields (Table 1).

Acknowledgements

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

References and notes

1. Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218.
2. (a) Kakehi, A.; Ito, S. *J. Org. Chem.* **1974**, *39*, 1542; (b) Dollt, H.; Zabel, V. *Aust. J. Chem.* **1999**, *52*, 259; (c) Mironiuk-Puchalska, E.; Kolaczkowska, E.; Sas, W. *Tetrahedron Lett.* **2002**, *43*, 8351; (d) Tanaka, K.; Katsumura, S. *Org. Lett.* **2000**, *2*, 373; (e) Dai, W.-M.; Wu, J.; Fong, K. C.; Lee, M. Y. H.; Lau, C. W. *J. Org. Chem.* **1999**, *64*, 5062; (f) Qing, F.-L.; Zhang, X. *Tetrahedron Lett.* **2001**, *42*, 5929.
3. Poor yields of olefin and/or complex product mixtures were observed using trichloronitromethane, hexachloroacetone, and 1,1,1-trichlorotrifluoroethane.
4. For additional examples of recent $CrCl_2$-based methodology see: (a) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196; (b) Barma, D. K.; Baati, R.; Valleix, A.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2001**, *3*, 4237; (c) Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1281; (d) Barma, D. K.; Kundu, A.; Baati, R.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2002**, *4*, 1387; (e) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2179.
5. Available from Omm Scientific, Inc. (www.ommscientific.com).
6. Depres, J. P.; Navarro, B.; Greene, A. E. *Tetrahedron* **1989**, *45*, 2989.
7. Spectral data for **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.38 (s, 3H), 2.68–2.76 (m, 2H), 2.79–2.86 (m, 2H), 6.95 (t, 1H, $J = 6.9$ Hz), 7.91–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.66, 31.45, 33.89, 126.60, 128.50, 128.80, 134.38, 140.58, 140.67, 192.21; MS *m*/*z* 208 (M^+), 210 (M^++2). **12**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.58 (q, 2H, $J = 7.3$ Hz), 2.81 (q, 2H, $J = 7.3$ Hz), 5.63 (b s, 1H), 6.46 (b s, 1H), 7.16–7.33 (m, 6H). **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.41–6.50 (m, 1H), 7.03–7.12 (m, 2H), 7.31–7.42 (m, 3H), 7.64 (s, 1H), 7.75–7.81 (m, 2H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 111.26, 119.38, 126.10, 128.54, 128.95, 129.66, 129.91, 130.46, 133.24, 135.84, 179.01; MS *m*/*z* 231 (M^+), 233 (M^++2). **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.67–2.83 (m, 4H), 6.17–6.21 (m, 1H), 6.73–6.80 (m, 2H), 7.01–7.03 (m, 1H), 7.16–7.27 (m, 5H), 9.71 (b s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.13, 34.11, 77.47, 111.39, 119.15, 125.87, 126.61, 128.63, 128.85, 129.92, 132.02, 139.50, 140.84, 178.91; MS *m*/*z* 259 (M^+), 261 (M^++2). **21**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.61–2.70 (m, 2H), 2.80 (t, 2H, $J = 3.5$ Hz), 6.50 (t, 1H, $J = 4.5$ Hz), 7.36–7.40 (m, 3H), 7.51–7.56 (m, 2H). **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (s, 3H), 3.39 (d, 1H, $J = 4.2$ Hz), 5.38 (d, 1H, $J = 4.5$ Hz), 7.36–7.42 (m, 3H),

7.52–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.89, 77.68, 89.19, 127.94, 129.21, 129.38, 135.91, 198.74. **23**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.95–2.07 (m, 1H), 2.18–2.29 (m, 1H), 2.54 (s, 3H), 2.70–2.81 (m, 1H), 2.92–3.01 (m, 2H), 4.19–4.26 (m, 1H), 7.20–7.36 (m, 5H). **24**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.38 (d, 1H, $J = 5.4$ Hz), 4.25–4.32 (br s, 1H), 5.89 (br s, 1H), 6.69 (br s, 1H), 7.17–7.33 (m, 5H). **25**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90–2.02 (m, 1H), 2.15–2.27 (m, 1H), 2.68–2.79 (m, 1H), 2.94–3.04 (m, 1H), 3.38 (d, 1H, $J = 5.4$ Hz), 4.25–4.32 (m, 1H), 5.89 (br s, 1H), 6.69 (br s, 1H), 7.17–7.33 (m, 5H). **26**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.99 (d, 1H, $J = 3.9$ Hz), 5.54 (d, 1H, $J = 3.6$ Hz), 6.38–6.40 (m, 1H), 7.11–7.15 (m, 1H), 7.36–7.42 (m, 3H), 7.45–7.49 (m, 1H), 7.58–7.63 (m, 2H), 9.42 (br s, 1H). **27**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01–2.19 (m, 1H), 2.25–2.37 (m, 1H), 2.71–2.82 (m, 1H), 2.98–3.09 (m, 1H), 3.44–3.48 (m, 1H), 4.33–4.39 (m, 1H), 6.34–6.39 (m, 1H), 7.18–7.34 (m, 6H), 7.42–7.46 (m, 1H), 9.36 (br s, 1H).

8. Kim, K. M.; Chung, K. H.; Kim, J. N.; Ryu, E. K. *Synthesis* **1993**, 283.
9. Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.
10. Berkovitch-Yellin, Z.; Van Mil, J.; Addadi, L.; Idelson, M.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3111.
11. Kodomari, M.; Nagaoka, T.; Furusawa, Y. *Tetrahedron Lett.* **2001**, *42*, 3105.
12. Reich, I. L.; Haile, C. L.; Reich, H. J. *J. Org. Chem.* **1978**, *43*, 2402.
13. Kim, J. N.; Son, J. S.; Kim, H. R.; Ryu, E. K. *Bull. Korean Chem. Soc.* **1998**, *19*, 812.