ORGANIC LETTERS

2001
Vol. 3, No. 26
4237−4238

Chromium Vinylidene Carbenoids: Stereospecific Synthesis of (*Z*)-2-Chloroalk-2-en-1-ols

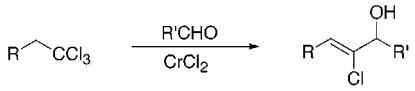
D. K. Barma,[†] Rachid Baati,[‡] Alain Valleix,[⊥] Charles Mioskowski,*[,‡,§] and J. R. Falck*[,†]

Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9038, Université Louis Pasteur, Faculté de Pharmacie, Laboratoire de Synthèse Bio-Organique associe au CNRS, 67401 Illkirch, France, and CEA de Saclay, Services des Molecules Marquees, Bat. 547, 91191 Gif-sur-Yvette, France

j.falck@utsouthwestern.edu

Received October 18, 2001

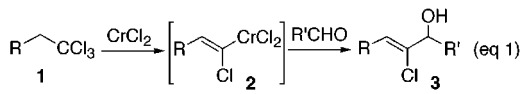
ABSTRACT



R, R' = aryl, alkyl, alkenyl

(*Z*)-2-Chloroalk-2-en-1-ols are obtained in excellent yields from a wide variety of aldehydes by addition of (*E*)-chromium vinylidene carbenoids, stereospecifically generated from trichloroalkanes using $CrCl_2$ in THF at room temperature.

Our laboratories recently described an efficient synthesis of terminal 2-chloropropenyl alcohols via in situ α-chlorovinylation of aldehydes using 1,1,1-trichloroethane and $CrCl_2$.[1,2] Subsequent mechanistic investigations identified a chromium vinylidene carbenoid as the penultimate intermediate.[3] Herein, we report that homologous trichloroalkanes **1** are stereoselectively transformed to (*E*)-chromium vinylidenes **2** which efficiently add to aldehydes affording (*Z*)-2-chloroalk-2-en-1-ols **3** (eq 1).[4] Halogenated alkenols such as **3** are versatile synthetic intermediates[5] as well as critical structural units in a variety of biologically active natural products of current interest.[6] However, their accessibility is often hampered by multistep routes and/or poor stereoselectivity.[7]



R, R' = aryl, alkyl, alkenyl

The results from a panel of representative substrates are summarized in Table 1.[8,9] For simple, unactivated trichlo-

[†] University of Texas.
[‡] Université Louis Pasteur.
[⊥] Services des Molecules Marquees.
[§] E-mail: mioskow@aspirine.u-strasbg.fr.

(1) Falck, J. R.; Barma, D. K.; Mioskowski, C.; Schlama, T. *Tetrahedron Lett.* **1999**, *40*, 2091−2094.

(2) For additional examples of recent $CrCl_2$-based methodology, see: (a) Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1281−1283. (b) Baati, R.; Valleix, A.; Mioskowski, C.; Barma, D. K.; Falck, J. R. *Org. Lett.* **2000**, *2*, 485−487.

(3) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196−9197.

(4) 2,2,2-Trichloroethanol derivatives also yield (*Z*)-2-chloroalk-2-en-1-ols accompanied by variable amounts of 1,1-dichloroalkene, (*E*/*Z*)-1-chloroalkene, and 1-alkoxy-1-chloroalkene: Takai, K.; Kokumai, R.; Nobunaka, T. *Chem. Commun.* **2001**, 1128−1129.

(5) (a) Taylor, R. E.; Ciavarri, J. P. *Org. Lett.* **2000**, *1*, 467−469. (b) Dai, W.-M.; Wu, A. *Tetrahedron Lett.* **2001**, *42*, 81−83.

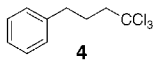
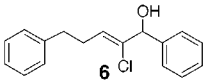
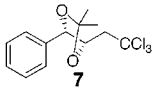
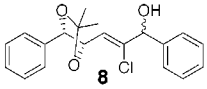
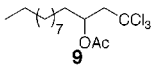
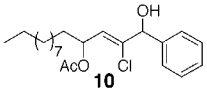
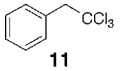
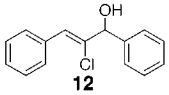
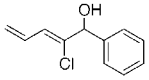
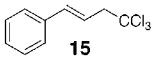
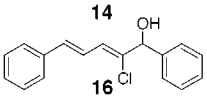
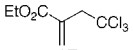
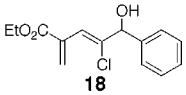
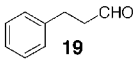
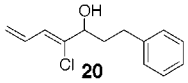
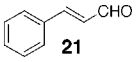
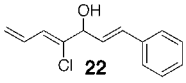
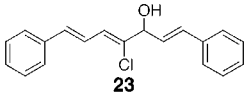
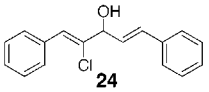
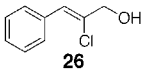
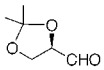
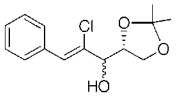
(6) For example: Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305−6308.

(7) (a) Kasatkin, A.; Whitby, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 7039−7049. (b) Kadota, J.; Komori, S.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1999**, *64*, 7523−7527. (c) Braun, M.; Mahler, H. *Liebigs Ann.* **1995**, 29−40. (c) Harre, M.; Nickisch, K. *Tetrahedron Lett.* **1993**, *34*, 3123−3126.

(8) **General procedure:** 1,1,1-Trichloroalkane (0.4 mmol) and aldehyde (0.4 mmol) in THF (1 mL) were added to a stirring, grayish suspension of anhydrous $CrCl_2$ (1.6 mmol) in THF (10 mL) under argon at ambient temperature. After 10−12 h, the resultant reddish reaction mixture was quenched with water and extracted thrice with ether, and the combined ethereal extracts were evaporated in vacuo. Chromatographic purification on SiO_2 gave the (Z)-chloroalkenol adducts in the indicated yields (Table 1).

10.1021/ol016935h CCC: $20.00
Published on Web 12/06/2001

Table 1. Synthesis of (*Z*)-2-Chloroalk-2-en-1-ols

entry	trichloroalkane	aldehyde	adduct	yield (%)
1	 **4**	 **5**	 **6**	91
2	 **7**	**5**	 **8**	91
3	 **9**	**5**	 **10**	89
4	 **11**	**5**	 **12**	82
5	 **13**	**5**	 **14**	77
6	 **15**	**5**	 **16**	89
7	 **17**	**5**	 **18**	48
8	**13**	 **19**	 **20**	88
9	**13**	 **21**	 **22**	97
10	**15**	**21**	 **23**	79
11	**11**	**21**	 **24**	89
12	**11**	$(CH_2O)_n$ **25**	 **26**	95
13	**11**	 **27**	 **28** (syn/anti 2:1)	89

roalkanes, e.g., **4**, stirring with 4 equiv of commercial $CrCl_2$ at room temperature for several hours generated the corresponding (*E*)-vinylidene intermediate **2** (R = $PhCH_2CH_2$-) which gave rise to **6** in excellent yield (entry 1) upon addition of benzaldehyde (**5**). None of the (*E*)-isomer could be detected by NMR analysis, indicating >95% stereochemical purity. Alternatively and more conveniently, **6** could be obtained under Barbier-type conditions in the same yield and stereochemical purity by simultaneous addition of both **4** and **5** to a slurry of $CrCl_2$ at room temperature. A catalytic system,[10] utilizing Mn powder to recycle chromium(III) to chromium(II), proved disappointing, and only small amounts of the desired adducts could be isolated.

Under the standard stoichiometric conditions, oxygenated trichloroalkanes **7** and **9** behaved analogously with **5** furnishing acetonide **8** (entry 2) and acetate **10** (entry 3), respectively, as ~7:3 diastereomeric mixtures based on ^{1}H NMR analysis. Conjugated versions of **2**, derived from benzyl **11**, allyl **13**, and cinnamyl **15** trichloromethyls, added smoothly to benzaldehyde providing adducts **12**[7b] (entry 4), **14**[7a] (entry 5), and **16** (entry 6), respectively. Notably, even the redox sensitive α,*β*-unsaturated ester **17** could be induced to add to **5** leading to diene **18**, albeit in modest yield (entry 7).

A wide variety of aldehydes were suitable coupling partners, inter alia, aliphatic **19** (entry 8), cinnamaldehyde **21** (entries 9, 10, and 11), and paraformaldehyde **25** (entry 12) which gave their respective (*Z*)-chloroalkenols **20**, **22**, **23**, **24**, and **26** free of regio- or geometric isomers. Condensation of chiral carboxaldehyde **27** with the chromium vinylidene derived from **11** (entry 13) evolved **28** in good yield as a chromatographically separable ~2:1 mixture of syn/anti-isomers. This level of stereoinduction is typical of vinylchromium additions to aldehydes bearing chiral α-heteroatoms.[11]

In summary, we report a convergent, one-pot method for the creation of (*Z*)-2-chloroalk-2-en-1-ols under mild conditions from readily available trichloroalkanes and aldehydes. Modifications to achieve synthetically useful chiral induction are under active investigation.

Acknowledgment. The authors thank Dr. E. R. Fogel for helpful discussions. Financial support was provided by the Instituts de Recherche Pierre Fabre, CNRS (to R. B.), the Robert A. Welch Foundation, NIH (GM 31278, DK38226), and an unrestricted grant from Taisho Pharmaceutical Co., Ltd.

Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.asc.org.

OL016935H

(9) Additions to ketones were sluggish, even at 75−80 °C, and gave low yields (10−15%) of the chloroalkenol adducts under the standard reaction conditions.

(10) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.
(11) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.