Pergamon

Tetrahedron Letters 42 (2001) 5793–5796

TETRAHEDRON
LETTERS

Boron trihalide-promoted addition of aryl aldehydes to styrenes. A new convenient and highly efficient synthesis of 1,3-dihalo-1,3-diarylpropanes

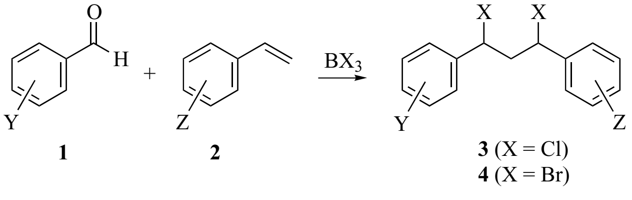
George W. Kabalka,* Zhongzhi Wu and Yuhong Ju

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

Received 3 May 2001; accepted 19 June 2001

Abstract—Reactions of aryl aldehydes with styrenes in the presence of boron trichloride in CH_2Cl_2 at 0°C produce 1,3-dichloro-1,3-diarylpropanes in excellent yields. Reactions carried out using boron tribromide generate the corresponding 1,3-dibromo-1,3-diarylpropane in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

The addition reaction of aldehydes with alkenes is a very important method for the formation of new carbon–carbon bonds in synthetic organic chemistry.[1] This reaction has been widely used in natural product syntheses because the products have an array of functional groups which can be subjected to further transformations.[2,3] The reactions of carbonyl compounds with alkenes are generally catalyzed by Lewis acids such as BF_3,[3a,b,f,4] $AlCl_3$,[5] $FeCl_3$,[6] $SnCl_4$,[5b,7] $TiCl_4$,[8] $BiCl_3$,[9] and alkylaluminum chlorides.[3g,4c,10] Boron trihalides have also been extensively used for C–O bond cleavage,[11] halogenation of aldehydes,[12,13] haloboration of alkynes[14] and enolization of carbonyl compounds.[15] However, boron trichloride and triboromide promoted addition reactions of aldehydes with alkenes have not been explored. In fact, BCl_3 has been reported to be an ineffective promoter for ene reactions of aldehydes with alkenes, low yields of the desired products (homoallylic alcohols) are obtained.[5b]



Scheme 1.

In our continuing efforts to explore boron halide chemistry,[13,16] we discovered that BCl_3 and BBr_3 are very effective in promoting the addition of aryl aldehydes to styrenes. The reactions produce diastereomeric mixtures of 1,3-dihalo-1,3-diarylpropanes (Scheme 1). 1,3-Dihalopropanes are important building blocks in organic synthesis due to their bifunctionality.[17] For example, they have been used to prepare arylcyclopropanes,[18] centrohexaindane,[19] and pyrazolidine.[20] They are usually prepared by halogenation of cyclopropanes[21] or 1,3-propanediols[22] but the regiochemistry of these reactions can be difficult to control, side reactions are abundant, and there is limited availability of substrates. We wish to present a preliminary report on a new, convenient, and highly efficient method for synthesizing of 1,3-dihalo-1,3-diarylpropanes via the reaction of aryl adehydes with styrenes in the presence of boron trihalides.

Initially, we examined the reaction of benzaldehyde with freshly distilled styrene. When a mixture of benzaldehyde and styrene (1:1 ratio in CH_2Cl_2) was treated with 1 equiv. of boron trichlorde at 0°C, only polymerization was observed. We then utilized commercially available styrene, which contained 4-*tert*-butycatechol as a stabilizer. The reaction produced diastereomeric mixtures of 1,3-dichloro-1,3-diphenylpropane in excellent yields.[23] When reactions were carried out at room temperature, chlorination of benzaldehyde occurred as noted in our earlier reports.[13,16c]

Since 1,3-dibromopropanes are synthetically more valuable than the corresponding chlorides, we examined the reaction of aryl aldehydes with styrenes in the presence

---

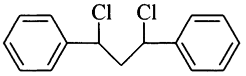
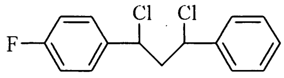
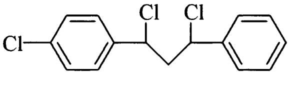
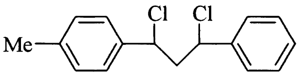
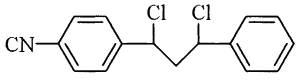
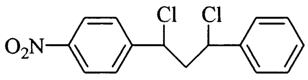
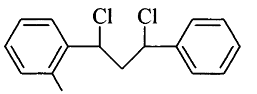
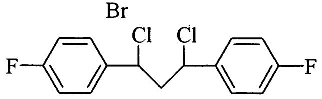
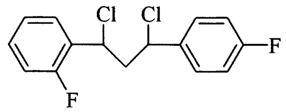
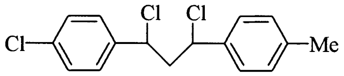
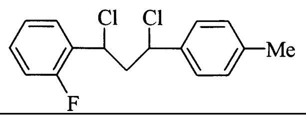
* Corrresponding author.

PII: S0040-4039(01)01125-X

of boron tribromide. The bromination of aryl aldehydes by boron tribromide is extremely fast,[12] consequently we carried out the reactions by slowly adding BBr_3 to mixtures of aryl aldehyde and styrene (1:1 ratio) at −40°C. Diastereomeric mixtures of 1,3-dibromo-1,3-diarylpropanes were formed rapidly and in excellent yields. A series of aryl aldehydes was then subjected to the new reaction. Essentially, all aldehydes generated 1,3-dichloro-1,3-diarylpropanes in excellent yields (Table 1) and 1,3-dibromo-1,3-diarylpropanes in good yields (Table 2). Aldehydes containing electron-withdrawing substituents reacted at a slower rate. In addition, it was observed that the products with electron-donating substituents tend to decompose during chromatography on silica gel, resulting in relatively low isolated yields. 1,3-Dibromo-1,3-diarylpropanes were found to be especially susceptible to decomposition.

Although a detailed mechanistic study has not been carried out, the reaction of aryl aldehydes with styrenes presumably proceeds through coordination of the carbonyl group to the boron trihalide followed by addition of the carbonyl carbon to the alkene to form a carbocation which then adds halide to form **5**. Loss of an oxyboron moiety from **5** would then generate another cation as a precursor to either **3** or **4**. (Scheme 2). A similar intermediate has been observed in the $AlCl_3$-catalyzed ene reactions of aldehydes with aliphatic alkenes.[4c,5a] NMR analyses of the reaction mixtures reveal a nearly statistical distribution of the diastereoisomers. The ^{1}H NMR resonances of the methine protons in the *R*,*R* and *S*,*S*-isomers appear at lower field than those in the *R*,*S* and *S*,*R*-isomers. The *R*,*R* and *S*,*S* racemate of 1,3-dibromo-1,3-di(4-fluorophenyl)propane has been isolated and characterized by NMR and X-ray crystallography.

Table 1. Synthesis of 1,3-dichloro-diarylpropanes via reaction of aryl aldehydes with styrenes

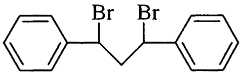
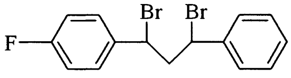
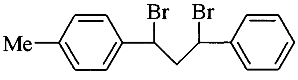
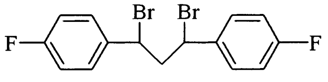
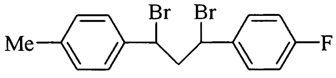
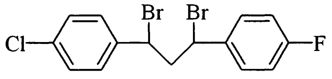
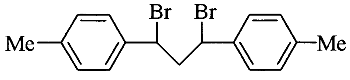
1 (Y=)	2 (Z=)	Time (hr)	3	R,R,(S,S)/ R,S (S,R)	Yield%[a,b]
H	H	10		53/47	90
p-F	H	18		55/45	98
p-Cl	H	12		30/50	97
p-Me	H	5		40/60	70[c]
p-CN	H	24		60/40	80
p-NO_2	H	48		52/48	99
o-Br	H	10		60/40	96
p-F	*p*-F	48		54/48	98
o-F	*p*-F	48		60/40	99
p-Cl	*p*-Me	6		52/48	83[c]
o-F	*p*-Me	10		56/44	85[c]

[a] Isolated yields based on starting aldehyde.

[b] All products characterized by elemental analyses and NMR spectroscopy.

[c] Product partially decomposed during silica gel chromatography.

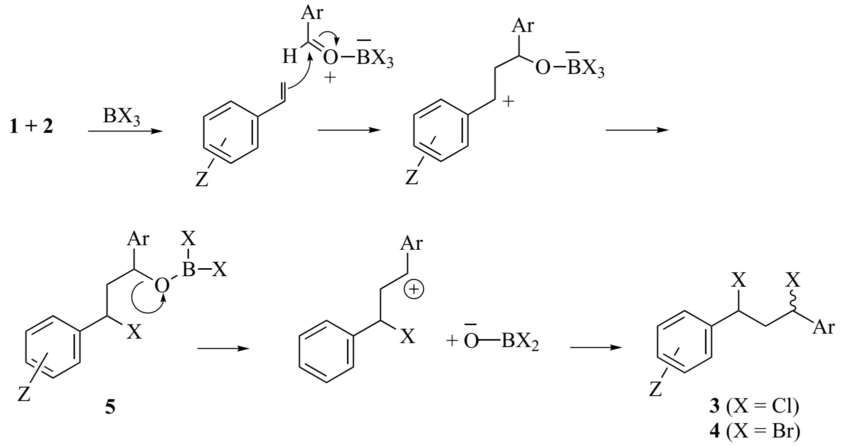
Table 2. Synthesis of 1,3-dibromo-diarylpropanes via reaction of aryl aldehydes with styrenes

1 (Y=)	2 (Z=)	Time (hr)	4	R,R(S,S)/ R,S (S,R)	Yield%^{a,b}
H	H	3		56/45	75^c
p-F	H	6		52/48	98
p-Me	H	2		50/50	60^c
p-F	*p*-F	10		51/49	96
p-Me	*p*-F	4		46/54	76^c
p-Cl	*p*-Me	4		45/55	73^c
p-Me	*p*-Me	1		48/52	57^c

[a] Isolated yields based on starting aldehyde.

[b] All products characterized by elemental analyses and NMR spectroscopy.

[c] Product partially decomposed during silica gel chromatography.



Scheme 2.

In an effort to verify the intermediacy of **5**, we allowed 4-chlorobenzaldehyde to react with styrene in the presence of dicyclohexylboron chloride. Since only one chloride is available for migration, we reasoned that 3-chloro-1-(4-chlorophenyl)-3-phenylpropan-1-ol would be obtained after hydrolysis. However, only reduction of the aldehyde was observed via β-hydride transfer. Phenylboron dichloride was then used to promote the reaction since it contains no enolizable β-hydrogens, 3-chloro-1-(4-chlorophenyl)-3-phenylpropan-1-ol was isolated in 79% yield.

In conclusion, we report a new, highly efficient method for preparing 1,3-dihalo-1,3-diarylpropanes via the reaction of aryl aldehydes with styrenes promoted by boron halides. We are planning to extend the reaction to 1,2-disubstituted, trisubstituted and tetrasubstituted styrenes as well as heterocyclic aromatic aldehydes utilizing BCl_3, BBr_3 and BI_3.

Acknowledgements

We wish to thank the US Department of Energy and the Robert H. Cole Foundation for their support of this research.

References

1. (a) Mikami, K.; Shimizhu, M. *Chem. Rev.* **1992**, *92*, 1021; (b) Evans, D. A.; Bargey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824; (c) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
2. (a) Whitesell, J. K.; Bhattacharya, A.; Buchananan, C. M.; Chen, H. H.; Deyo, C.; James, D.; Liu, C. L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993; (b) Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron: Asymmetry* **1990**, *1*, 13.
3. (a) Wovkulich, P. M.; Uskokovich, M. R. *J. Org. Chem.* **1982**, *47*, 1600; (b) Wovkulick, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovich, M. R. *Tetrahedron* **1984**, *40*, 2283; (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; (d) Ciufolini, M. A.; Zhu, S.; Deaton, M. V. *J. Org. Chem.* **1997**, *62*, 7806; (e) Ciufolini, M. A.; Chen, M.; Lovett, D. D.; Deaton, M. V. *Tetrahedron Lett.* **1997**, *38*, 4355; (f) D'Aniello, F.; Mann, A.; Mattii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762; (g) Houston, T. A.; Tanaka, Y.; Koreeda, M. *J. Org. Chem.* **1993**, *58*, 4287.
4. (a) Blomquist, A. T.; Himies, R. J. *J. Org. Chem.* **1968**, *33*, 1156; (b) Blomquist, A. T.; Himies, R. J.; Meador, J. D. *J. Org. Chem.* **1968**, *33*, 2462; (c) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555; (d) Malladi, R. R.; Li, N.-S.; Tejedor, D.; Kabalka, G. W. *Synth. Commun.* **2000**, *30*, 3163.
5. (a) Gill, G. B.; Parrot, S. J.; Wallace, B. *J. Chem. Soc., Chem. Commun.* **1978**, 655; (b) Gill, G. B.; Wallace, B. *J. Chem. Soc., Chem. Commun.* **1977**, 380; **1977**, 382; (c) Benner, J. P.; Gill, G. B.; Parrot, S. J. Wallace, B. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 291; **1984**, 331; (d) Benner, J. P.; Gill, G. B.; Parrot, S. J.; Wallace, B.; Begley, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 315; (e) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280; (f) Colonge, J.; Perrot, A. *Bull. Soc. Chim. Fr.* **1957**, 204; (g) Colonge, J.; Perrot, A. *Bull. Soc. Chim. Fr.* **1957**, 658.
6. Snider, B. B.; van Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.
7. Behr, A.; Fiere, M. *Eur. J. Lipid Sci. Technol.* **2000**, *102*, 212.
8. Vidari, G.; Bonicelli, M. P.; Anastasia, L.; Zanoni, G. *Tetrahedron Lett.* **2000**, *41*, 3471.
9. Peidro, L.; Le Roux, C.; Laporterie, A.; Dubac, J. *J. Organomet. Chem.* **1996**, *521*, 397.
10. Cartaya-Marin, C. P.; Jackson, A. C.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 2443.
11. Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
12. Lndinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
13. Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579.
14. Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629.
15. (a) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013; (b) Pelter, K.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988.
16. (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2000**, *41*, 5156; (b) Kabalka, G. W.; Wu, Z.; Trotman, S.; Gao, X. *Org. Lett.* **2000**, *2*, 255; (c) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron* **2001**, *57*, 1663.
17. (a) Mizuno, A.; Miya, M.; Kamei, T.; Shibata, M.; Tatsuoba, T.; Nakanishi, K.; Takiguchi, C.; Hadaka, T.; Yamaki, A.; Inomata, N. *Chem. Pharm. Bull.* **2000**, *48*, 1129; (b) Ocal, N.; Turgut, Z.; Kaban, S. *J. Heterocyclic Chem.* **1998**, *35*, 1349; (c) Yoshida, N.; Osuka, A. *Org. Lett.* **2000**, *2*, 2963; (d) Rooke, N.; Li, D.-J.; Keung, W. M. *J. Med. Chem.* **2000**, *43*, 4169; (e) Grimm, F. W.; Hafner, K. *Tetrahedron* **2000**, *56*, 4239; (f) Wang, Y.; Kurchan, A. N.; Barnhurst, L. A.; Kutataladze, A. G. *Org. Lett.* **2000**, *2*, 1133; (g) Singh, M. S.; Singh, K. K. *Heterocycles* **2000**, *53*, 851.
18. (a) Leonel, E.; Dolhem, E.; Devaud, M.; Paugam, J. P.; Nedelec, J. Y. *Electrochim. Acta* **1997**, *42*, 23125; (b) Miranda, M. A.; Perez-Prieto, J.; Font-Scenchis, E.; Konya, K.; Scaiao, J. C. *J. Org. Chem.* **1997**, *62*, 5713.
19. Kuck, D.; Schuster, A.; Paisdor, B.; Gestmann, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 721.
20. Buhle, E. L.; Moore, A. M.; Wiselogle, F. Y. *J. Am. Chem. Soc.* **1943**, *65*, 29.
21. (a) Lambert, J. B.; Chelius, E. C.; Schulz, Jr., W. J.; Carpenter, N. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156; (b) Hoffman, J. M.; Graham, K. J.; Rowell, C. F. *J. Org. Chem.* **1975**, *40*, 3005.
22. Jones, A. R. *J. Labelled Comp.* **1975**, *11*, 77.
23. Representative procedure for the synthesis of 1,3-dihalo-1,3-diarylpropanes: benzaldehyde (4.0 mmol, 0.41 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0°C in an ice bath, and boron trichloride (4.3 mmol, 4.3 mL of a 1.0 M hexane solution) was then added via syringe. The reaction was first allowed to stir at 0°C for 2 h and then at room temperature for 8 h, during which time the reaction solution turned purple. The reaction mixture was hydrolyzed, the organic layer separated, dried over anhydrous magnesium sulfate, and the product isolated by column chromatography (hexane, silica gel) to yield 0.95 g (90%) of the desired product.