A New Convenient, Efficient, and Regioselective Synthesis of 1,3-Diaryl-1,3-dihalopropanes

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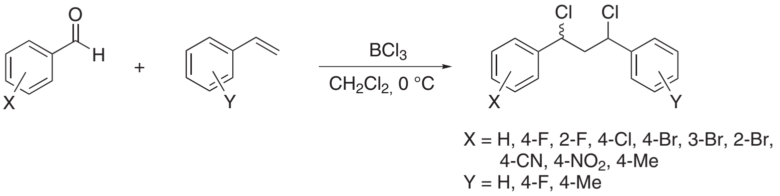
Abstract: Reactions of aryl aldehydes with styrenes in the presence of boron trihalides produce 1,3-diaryl-1,3-dihalopropanes in excellent yields.

Key words: Lewis acids, propanes, aldehydes, styrenes, boron halides



Scheme 1

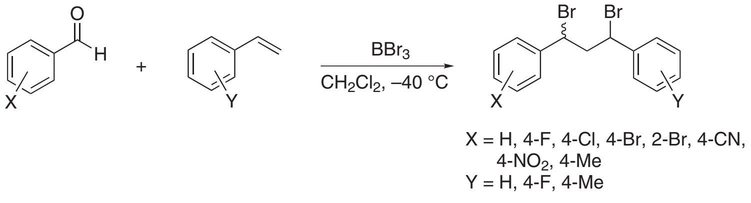
Introduction

The Lewis acid promoted addition of carbonyl compounds to alkenes is an important method for forming new carbon–carbon bonds in synthetic organic chemistry.[1] The reactions are usually catalyzed by Lewis acids such as BF_3,[2,3]$AlCl_3$,[4] $FeCl_3$,[5] $SnCl_4$,[6] $TiCl_4$,[7] $BiCl_3$,[8] and alkyl aluminum chlorides.[1,9] Interestingly, BCl_3 has been reported to be an ineffective promoter for ene reactions of aldehydes with alkenes.[4b,c] During our exploration of the organic chemistry of boron halides,[10,11] we discovered that BCl_3 and BBr_3 effectively promote the addition of aryl aldehydes to styrenes. The reactions produce diastereomeric mixtures of 1,3-diaryl-1,3-dihalopropanes in excellent yields (Schemes 1 and 2).

The dihalopropane products are useful intermediates in organic synthesis.[12] For example, they have been used to prepare arylcyclopropanes,[13] centrohexaindane,[14] and pyrazolidine.[15] Benzylic bromides can also undergo Suzuki coupling reactions.[16] 1,3-Diaryl-1,3-dihalopropanes are usually prepared by halogenation of cyclopropanes[17] or 1,3-propanediols[18] but the regiochemistry of these reactions can be difficult to control and there is limited availability of starting materials. The new method provides a simple and efficient and regioselective procedure for the preparation of a variety of 1,3-diaryl-1,3-dihalopropanes.

Scope and Limitations

The reactions of aryl aldehydes with styrenes in the presence of boron trichloride were carried out in dichloromethane at 0 °C. When freshly distilled styrenes were used, only polymerization was observed. However, the reactions produced excellent yields of 1,3-diaryl-1,3-dichloropropanes when commercially available styrenes (containing 4-*tert*-butylcatechol as a stabilizer) were utilized. If the reactions were carried out at room temperature, chlorination of the aryl aldehydes occurred.[10] The new reactions readily tolerate functional groups but aryl aldehydes containing electron-withdrawing groups tend



Scheme 2

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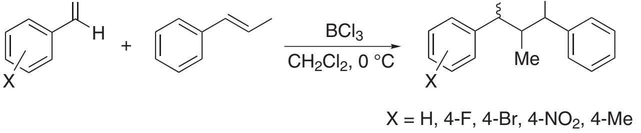
to react at a slower rate. They do, however, produce higher yields of the desired products.

Due to the facile bromination of aryl aldehydes by boron tribromide, reactions involving boron tribromide were carried out in dichloromethane at –40 °C. The corresponding 1,3-diaryl-1,3-dibromopropanes were obtained in good to excellent yields.

A series of aryl aldehydes containing a variety of functional groups were subjected to the reactions. Essentially, all aldehydes gave 1,3-diaryl-1,3-dichloropropanes in excellent yields and 1,3-diaryl-1,3-dibromopropanes in good yields. Reactions involving aldehydes containing phenoxy and methoxy groups were unsuccessful due to the well-known ether cleavage reactions. All products consist of a 1:1 ratio of diastereoisomers. Products containing electron-donating substituents tend to decompose on silica gel resulting in relatively low isolated yields. 1,3-Diaryl-1,3-dibromopropanes were found to be more susceptible to decomposition on silica gel than the corresponding dichlorides. Aldehydes and styrenes containing electron-withdrawing groups reacted more slowly than those containing electron-donating substituents. Solvents such as ethyl ether and THF interfered with the reaction due to cleavage of the ether linkage by the boron halides. The use of solvents such as hexanes, benzene and toluene enhanced competing reactions including the direct chlorination of the aldehydes.[10] Dichloromethane was found to be the most effective solvent for the reaction.

1-[(*E*)-Prop-1-enyl]benzene produced excellent yields of the corresponding 1,3-diaryl-1,3-dichloro-2-methylpropanes when allowed to react with aryl aldehydes in the presence of boron trichloride (Scheme 3). NMR data revealed that three pairs of diastereomers had been produced. Stilbene, 1,1-diphenylethylene, tetraphenylethene and triphenylethene failed to yield the desired products. Aliphatic alkenes produced only low yields of the corresponding ene products.



Scheme 3

In conclusion, we have discovered a new, highly efficient method for preparing 1,3-diaryl-1,3-dihalopropanes via reactions of aryl aldehydes with styrenes promoted by boron trihalides (BCl_3 and BBr_3). The product, 1,3-diarylpropanes are potential intermediates in a variety of synthetic transformations including the preparation of cyclopropane derivatives.

Representative Procedures

Herein, we describe the typical synthetic procedures for the synthesis of 1,3-diaryl-1,3-dichloropropanes, 1,3-diaryl-1,3-dibromopropanes, and 1,3-diaryl-1,3-dichloro-2-methylpropanes. The syntheses of 1,3-dichloro-1-(4-fluorophenyl)-3-phenylpropane, 1,3-dibromo-1-(4-fluorophenyl)-3-phenylpropane and 1,3-dichloro-1,3-diphenyl-2-methylpropane are representative.

All glassware was dried in an oven heated at 120 °C for at least 12 h and cooled under argon prior to use. CH_2Cl_2 was dried over CaH_2 and distilled prior to use. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography using silica gel (230–400 mesh, 60 Δ, ICN Biomedical GmbH, Eschwege, Germany) and hexanes as eluent.

BCl_3 (1 M in hexane) was purchased from Aldrich Chemical Co. and used as received. BBr_3 (Aldrich Chemical Co.) was diluted to 1 M in CH_2Cl_2. All aldehydes and styrenes (Aldrich Chemical Co.) were used as received.

NMR spectra were measured in $CDCl_3$ at 250 MHz (^{1}H) or at 62.9 MHz (^{13}C). In cases where more than one isomer are formed, the NMR shifts of all isomers are reported. Chemical shifts for ^{1}H and ^{13}C were referenced to TMS and $CDCl_3$.

1,3-Dichloro-1-(4-fluorophenyl)-3-phenylpropane; Typical Procedure

4-Fluorobenzaldehyde (4.0 mmol, 0.42 g) and styrene (4.0 mmol, 0.42 g) were dissolved in CH_2Cl_2 (20 mL) at r.t. in a dry 100 mL round-bottomed flask equipped with a magnetic stirring bar under N_2. The reaction mixture was stirred at 0 °C in an ice bath and BCl_3 (4.3 mmol, 4.3 mL of a 1.0 M hexane solution) was added via a syringe. The mixture was allowed to stir for 2 h and then for 16 h at r.t., during which time the solution turned purple. The mixture was hydrolyzed by adding H_2O (5 mL) and extracted into hexane (3 × 20 mL). The combined organic layers were separated, dried ($MgSO_4$), concentrated under reduced pressure and the product was isolated by column chromatography (hexanes, silica gel) to afford 0.95 g (99%) of the desired product as a colorless oil.

^{1}H NMR: δ = 7.36–7.28 (m, 7 H), 7.05–6.97 (m, 2 H), 5.20 (dd, 0.5 H, J = 6.5 Hz), 5.17 (dd, 0.5 H, J = 6.4 Hz), 4.80–4.71 (m, 1 H), 2.96–2.87 (m, 0.5 H), 2.68–2.56 (m, 1.5 H).

^{13}C NMR: δ = 164.5, 160.6, 140.6, 139.9, 136.6, 135.9, 128.8, 128.7, 128.6, 127.0, 126.9, 116.0, 115.9, 115.6, 115.5, 60.6, 59.9, 59.3, 49.6, 49.5.

Anal. Calcd. for $C_{15}H_{13}Cl_2F$: C, 63.62; H, 4.63. Found: C, 63.77, H, 4.73.

1,3-Bromo-1-(4-fluorophenyl)-3-phenylpropane; Typical Procedure

To a dry, N_2 flushed, 100 mL round-bottomed flask equipped with a magnetic stirring bar were added, 4-fluorobenzaldehyde (3.0 mmol, 0.32 g), styrene (3.0 mmol, 0.32 g) and CH_2Cl_2 (20 mL). The solution was cooled to –40 °C in a dry ice-acetone bath and BBr_3 (3.2 mmol, 3.2 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe with vigorous stirring. The reaction mixture was allowed to stir at –40 °C for 2 h and then at r.t. for 5 h. The mixture was hydrolyzed by adding H_2O (5 mL) and the product was extracted into hexanes (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the product was isolated by flash column chromatography (silica gel, hexanes) to give 0.80 g (98%) of the desired product as a colorless oil.

^{1}H NMR: δ = 7.34–7.25 (m, 7 H), 7.03–6.96 (m, 2 H), 5.16 (t, 1 H, J = 7.1 Hz), 4.83 (dd, 1 H, J = 14.9, 7.2 Hz), 3.24–3.11 (m, 0.5 H), 2.90–2.78 (m, 1.5 H).

^{13}C NMR: δ = 164.4, 160.5, 140.7, 140.1, 136.9, 136.2, 129.3, 129.1, 128.9, 128.7, 127.4, 116.0, 115.7, 52.8, 51.6, 50.6, 49.3, 49.1.

Anal. Calcd for $C_{15}H_{13}Br_2F$: C, 48.42; H, 3.52. Found: C, 48.48; H, 3.51.

1,3-Dichloro-1,3-diphenyl-2-methylpropane; Typical Procedure

Benzaldehyde (4.0 mmol, 0.42 g) and 1-[(*E*)-prop-1-enyl]benzene (4.0 mmol, 0.47 g) were dissolved in CH_2Cl_2 (20 mL) at r.t. in a dry 100 mL round-bottomed flask maintained under N_2. The solution was cooled to 0 °C in an ice bath and BCl_3 (4.3 mmol, 4.3 mL of a 1.0 M hexane solution) was added via a syringe. The reaction mixture was allowed to stir at 0 °C for 2 h and then at r.t. for 4 h during which time the solution turned purple. The mixture was hydrolyzed by adding H_2O (5 mL) and the product was extracted into hexane. The organic layer was separated, dried ($MgSO_4$), and the product isolated by column chromatography (hexane, silica gel) to give 1.12 g (95%) of the desired product; colorless crystals; mp 71–72 °C.

^1H NMR: δ (1*R*,3*R*; 1*S*,3*S*-isomers) = 7.37–7.28 (m, 10 H), 4.75 (d, 2 H, *J* = 6.3 Hz), 2.63–2.50 (m, 1 H), 1.22 (d, 3 H, *J* = 6.4 Hz).

^{13}C NMR: δ (1*R*,3*R*; 1*S*,3*S*-isomers) = 140.0, 128.6, 128.2, 127.2, 66.0, 49.9, 11.0.

^1H NMR: δ (other two pairs of diastereomers) = 7.48–7.23 (m, 10 H), 5.91 (s, 0.8 H), 5.01 (d, 0.4 H, *J* = 7.2 Hz), 4.95 (d, 0.8 H, *J* = 10.2 Hz), 2.89–2.81 (m, 0.2 H), 2.60–2.48 (m, 0.8 H), 0.74 (d, 0.6 H, *J* = 7.0 Hz), 0.64 (d, 2.4 H, *J* = 6.7 Hz).

^{13}C NMR: δ (other two pairs of diastereomers) = 140.0, 138.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.7, 127.2, 66.6, 65.4, 64.8, 49.3, 49.1, 10.8.

Anal. Calcd for $C_{16}H_{16}Cl_2$: C, 68.83; H, 5.78. Found: C, 68.70; H, 5.92.

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