Gallium (III)-catalysed Bromocyanation of Alkynes: Regio- and Stereoselective Synthesis of β-Bromo-α,β-unsaturated Nitriles

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Treatment of arylacetylenes and cyanogen bromide in CICH₂CH₂Cl with a catalytic amount of GaCl₃ afforded (Z)-β-bromoacrylonitriles with high regio- and stereoselectivity.

The catalytic addition reactions of X-Y-type substrates to carbon-carbon multiple bonds are of continued interest due to the facile access to 1,2-difunctional units from simple alkenes or alkynes with ideal atom efficiency. Among these transformations, addition reactions of X-Y bonds to alkynes simultaneously form vinyl-X and vinyl-carbon bonds, both of which can be used to construct complex structures. Several notable examples of palladium- or nickel-catalysed regio- and stereoselective addition reactions to alkynes with several X-CN groups have been reported, such as X=H (hydrocyanation), X=C (carbocyanation), X=Si (cyanosilylation), X=Ge (cyanogermylation), X=Sn (cyanothannylation), X=B (cyanoboration), X=Si (cyanothiolation). However, much less attention has been paid to catalytic regio- and stereoselective halocyanation of alkynes or alkynes using cyanogen halides. Herein, we report on gallium-catalysed bromocyanation of alkynes with cyanogen bromide, providing an efficient route to (Z)-β-bromoacrylonitriles in a high regio- and stereoselective fashion (Scheme 1). Taking advantage of (Z)-β-bromoacrylonitriles, we can establish efficient routes to a wide range of α,β-unsaturated nitriles, which are of synthetic value.

Scheme 1 Catalytic Addition Reactions of X-CN to Alkynes.

When we examined the reaction of cyanogen bromide and phenylacetylene using palladium or nickel/phosphine complexes, which are effective catalysts in addition reactions of X-CN to acetylenes (vide supra), no adducts were generated. Next, Lewis acids were screened for bromocyanation of alkynes, because there is a precedent for the halocyanlation of alkynes in analogous reactions. Representative results of the reaction of cyanogen bromide with phenylacetylene are shown in Table 1. We found that phenylacetylene underwent bromocyanation in the presence of AlCl₃ (10 mol%) in 1,2-dichloroethane at 80 °C to give β-bromocyanammonitrile 1a in 42% yield as a mixture of Z- and E-isomers (Z:E = 89:11) (Table 1, entry 1). Interestingly, the use of GaCl₃ (10 mol%) instead of AlCl₃ led to 1a in a high yield and stereoselectivity (81% chemical yield, Z:E = 92:8) (entry 2). This is in sharp contrast with the non-catalysed bromocyanation of ynamines, which gave a low stereoselectivity of the adducts (Z:E = 50:50, ~60:40). The reaction using GaCl₃ at 70 °C led to a lower yield of 1a, but with similar stereoselectivity (entry 3). 1,2-Dichloroethane was the most suitable solvent for bromocyanation, while other solvents, e.g., CHCl₃, toluene, heptane, and 2-methyltetrahydrofuran gave a lower yield of the adducts (entries 4-6), or no adducts (entry 7). Using GaBr₃ as a catalyst afforded almost the same result as GaCl₃ (entry 8). Other Lewis acid catalysts, such as InCl₃ and InBr₃, showed marginal catalytic activity and gave lower yields of 1a (entries 9 and 10), while FeBr₃, CuBr₂, and ZnBr₂ exhibited no catalytic activity for bromocyanation (entries 11-13). It should be noted that

Table 1. Lewis Acid-catalysed Bromocyanation of Phenylacetylene Using BrCN

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield</th>
<th>Regio-</th>
<th>Stereo-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl₃</td>
<td>CICH₂CH₂Cl</td>
<td>42%</td>
<td>89 : 11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>GaCl₃</td>
<td>CICH₂CH₂Cl</td>
<td>81% (72%)</td>
<td>92 : 8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>GaCl₃</td>
<td>CHCl₃</td>
<td>41%</td>
<td>91 : 9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>GaCl₃</td>
<td>toluene</td>
<td>62%</td>
<td>90 : 10</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>GaCl₃</td>
<td>heptane</td>
<td>61%</td>
<td>90 : 10</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GaCl₃</td>
<td>2-MeTHF</td>
<td>25%</td>
<td>91 : 9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>GaCl₃</td>
<td>CICH₂CH₂Cl</td>
<td>75%</td>
<td>96 : 4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>InCl₃</td>
<td>CICH₂CH₂Cl</td>
<td>15%</td>
<td>93 : 7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>InBr₃</td>
<td>CICH₂CH₂Cl</td>
<td>32%</td>
<td>95 : 5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CuBr₂</td>
<td>CICH₂CH₂Cl</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>ZnBr₂</td>
<td>CICH₂CH₂Cl</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Reaction conditions: Pheny lacetylene (0.48 mmol) and BrCN (0.40 mmol) in solvent (1.6 mL) were heated in the presence of catalyst (10 mol%). b NMR yield (anisole as an internal standard). Isolated yield in parentheses. c Determined by NMR. d At 70 °C.
no chlorocyanation adducts were obtained even when Lewis acid catalysts bearing chloride ligands were used (entries 1-7 and 9).

With the optimized reaction conditions established (10 mol% GaCl3 in 1,2-dichloroethane at 80 °C), we then examined the substrate scope of alkynes (Table 2). Arylacetylenes having a range of aromatic rings underwent bromocyanation of the alkyne moieties to give the corresponding (Z)-adducts, 1b-h16 in good yields with high regio- and stereoselectivity (entries 1-7), while 1-octyne and 1-(trimethylsilyl)acetylene gave no adducts. Reactions with internal aliphatic or alicyclic alkynes, such as 4-octyne and cyclooctyne, gave complex mixtures, while internal alkynes substituted by a phenyl ring produced bromocyanation adducts 1i17 and 1j, having a cyano group at the β position to the phenyl group in good yields with high regio- and stereoselectivities (entries 8 and 9). Although the reaction of diphenylacetylene was sluggish, and required an elevated temperature (100 °C), the corresponding bromocyanation adduct 1k was obtained in a 56% yield with excellent stereoselectivity (entry 10).

**Table 2. GaCl3-catalysed Bromocyanation of Alkynes Using BrCN**

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>product</th>
<th>isolated yield</th>
<th>Z : E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CH3C6H4</td>
<td>H</td>
<td>1b</td>
<td>70%</td>
<td>95 : 5</td>
</tr>
<tr>
<td>2</td>
<td>2-CH3C6H4</td>
<td>H</td>
<td>1c</td>
<td>61%</td>
<td>98 : 2</td>
</tr>
<tr>
<td>3</td>
<td>2-naph</td>
<td>H</td>
<td>1d</td>
<td>55%</td>
<td>95 : 5</td>
</tr>
<tr>
<td>4</td>
<td>4-FC6H4</td>
<td>H</td>
<td>1e</td>
<td>71%</td>
<td>91 : 9</td>
</tr>
<tr>
<td>5</td>
<td>4-CIC6H4</td>
<td>H</td>
<td>1f</td>
<td>68%</td>
<td>90 : 10</td>
</tr>
<tr>
<td>6</td>
<td>4-BrC6H4</td>
<td>H</td>
<td>1g</td>
<td>68%</td>
<td>91 : 9</td>
</tr>
<tr>
<td>7</td>
<td>4-CF3C6H4</td>
<td>H</td>
<td>1h</td>
<td>92%</td>
<td>20 : 8</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>CH3</td>
<td>1i</td>
<td>70%</td>
<td>95 : 5</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>n-Bu</td>
<td>1j</td>
<td>72%</td>
<td>91 : 9</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>Ph</td>
<td>1k</td>
<td>56%</td>
<td>99 : 1</td>
</tr>
</tbody>
</table>

* Reaction conditions: Alkynes (0.48 mmol) and BrCN (0.40 mmol) in CICH2CH2Cl (1.6 mL) were heated in the presence of GaCl3 (10 mol%). * Determined by NMR. * Reaction carried out in toluene at 100 °C.

The alkenophility18 of trivalent GaX3 leading to the formation of cationic vinylgallium species is well known, and some notable synthetic applications have been demonstrated.19 To gain insight into the present bromocyanation of alkynes, we carried out an NMR study on a stoichiometric reaction. When GaCl3 was added to a solution of BrCN in CDCl3 at room temperature, the signal of CN (δ 76.1 ppm) in BrCN shifted to a new peak at δ 88.2 ppm. The downfield shift of the CN peak suggested the possibility of the formation of a complex between BrCN and GaCl3.20 When an equimolar amount of 1-phenyl-1-hexyne was added to a CDCl3 solution of this complex at room temperature, the quantitative formation of the bromocyanation product 1j (Z : E = 98:2) coordinated with GaCl3 was observed, with the signal of the CN moiety being observed at δ 149.5 ppm. This result clearly shows that electrophilic addition of the BrCN and GaCl3 complexes to alkynes21 occurs, even at room temperature, and a high temperature is required in the catalytic reaction conditions to release GaCl3 from cyano moieties of the adduct.

The synthetic utility of (Z)-β-bromo-α,β-unsaturated nitriles obtained from the bromocyanation of alkynes was demonstrated by the cross-coupling reactions of the representative product 1a (Scheme 2). The Stille coupling reactions of 1a with organostannanes afforded the stereo-defined structures 2 or 3 in good yields. The Sonogashira coupling reaction of 1a with phenylacetylene gave enyne 4 quantitatively, with complete stereoselectivity. The nickel-catalysed reductive homo-coupling of 1a produced 3,4-diphenyl-2,4-hexadiene-1,6-dinitrile 5.22 Moreover, we demonstrated the synthetic utility of 1a and its derivative 3 in the preparation of the biologically active heterocycles 623 and 7.11

**Scheme 2 Transformation of 1a.**

In summary, we developed gallium(III)-catalysed bromocyanation of alkynes using cyanogen bromide. This method enables the regio- and stereoselective introduction of the synthetically useful Br and cyano functionalities to carbon-carbon triple bonds in single operation. Further investigations into the reaction mechanism, substrate scope, and the synthetic application are currently underway in our laboratory.

**Acknowledgment.** This work is financially supported by a Grant-in-Aid for Scientific Research from MEXT. M. M. thanks the JSPS Research Fellowships for Young Scientists.

**Notes and references**


12 Cyanogen bromide (mp 52 °C) is a commercially available reagent and easy to handle. However, the handling of cyanogen bromide requires special care to avoid inhalation of hydrogen cyanide, and all operations should be carried out in a well-fumed hood.

13 (a) C. C. Price; J. A. Pappalardo, J. Am. Chem. Soc. 1950, 72, 2613; (b) H. Martens; F. Janssens; G. Hoornaar, Tetrahedron 1975, 31, 177; (c) H. Zhou; C. Zeng; L. Ren; W. Liao; X. Huang, Synlett 2006, 3504; For electrophilic cyanation of arenes with BrCN, see: (d) P. H. Gore; F. S. Kamounah; A. Y. Mira, Tetrahedron 1979, 35, 2927.

14 The cyano group was selectively introduced at the terminal position, with no regioisomers of 1a being detected.

15 The use of polar solvents, such as MeCN, dioxane, THF, and DMF resulted in complete recovery of phenylacetylene.

16 The structure of the major stereoisomer of 1a was unambiguously determined by X-ray crystallography. See electronic supplementary information for the detail of X-ray crystal analysis data. CCDC-796829 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

17 Determination of regio- and stereoselectivity of the major adduct was based on derivatization to a stereo-defined compound by reduction of 1H with Dibal-H and NaBH₄. (See electronic supplementary information.)


20 Although precise species are not clear at present, the formation of 15Br--[CN-GaCl] or [CN][GaClBr] is most likely.

21 We suppose that electrophilic addition of a positively charged CN followed by intramolecular nucleophilic attack of bromide in the intimate complex to the resulting vinyl cation center in syn fashion provides a Z-adduct. Precise mechanism awaits further investigation.
