Gallium(III)-Promoted Halocyclizations of 1,6-Diynes

Org. Lett., 2015, 17, 2126-2129
https://hdl.handle.net/2144/12968

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Gallium(III)-Promoted Halocyclizations of 1,6-Diyynes

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ABSTRACT: Cyclization of 1,6-diyynes promoted by stoichiometric Ga(III) halides produces vinyl halides in good to excellent yields. Under acidic conditions, initially formed iodocyclization products undergo in situ Friedel–Crafts cyclizations, giving access to iodoindenopyridines. Application of the vinyl halides in cross-coupling reactions has been explored, and mechanistic aspects of the cyclization are discussed.

Scheme 1. Divergent Cyclization Catalyzed by In(III)

1. $\text{InX}_3$ (1 equiv) $\rightarrow$ Ph

2. H$_2$O (0.5 equiv) $\rightarrow$ Me

3. DCM, rt

4. n = 2, X = I

5. n = 1, X = Br

6. X = Cl, Br, I

7. 3-53%

8. 4a-24%

$\xi$-Lewis acid promoted cyclizations have become a highly productive field of research in the development of new synthetic methodologies. In an earlier investigation, we reported the use of stoichiometric In(III) as a $\xi$-Lewis acid catalyst to promote cyclization of 1,7-bisalkynyl ethers to tetrahydrofuranyl enones (Scheme 1, top). We noted at the time that decreasing the tether length between the two alkynes by a single methylene to 1,6-bisalkynyl ether 2a resulted in a modest conversion to dihydropropynyl vinyl bromide 4a in low isolated yield (Scheme 1, bottom). Given the broad utility of vinyl halides in natural product synthesis and drug development, we began developing this chemistry as a route to new scaffolds for the production of small-molecule libraries. Herein we report a method to construct several vinyl halide scaffolds in moderate to excellent yields from simple starting materials, using readily available Ga(III) halides as reagents.

In comparison to the considerable effort directed toward exploiting the $\xi$- acidity of the noble metals in the past several decades, the catalytic applications of In(III) and Ga(III) have only recently begun to garner interest. Perhaps this is due, in part, to the fact that they do not have an obvious catalytic niche, being both competent $\sigma$- and $\xi$-acids. As the former, they have both been shown to be potent oxophiles activating ketones and aldehydes, carboxylic acids, amides, epoxides, and ethers to a range of nucleophilic additions. As the latter, they have been used as competent ynoaphiles activating alkynes in hydroaminations, hydroarylations, and enyne reactions. Of particular relevance to this work, In$_3$ and GaCl$_3$ have recently been reported as effective catalysts for cationic polycyclizations initiated by alkynes. Despite these substantial efforts, yno-yne cyclizations have remained unexplored, and to the best of our knowledge, this is the first report of a halogenative cyclization involving GaX$_3$ or InX$_3$. Work by Yu reported a related oxocarbenium ion-initiated bisalkyne halocyclization triggered by Fe(III) halides.

Initial efforts to increase the yield of the In(III)-catalyzed halogenative cyclization (Scheme 1) were met with limited success. Attempts at optimization, including changes in solvent, temperature, and concentration proved fruitless in increasing the yield beyond 30%. The persistently low yields were found to be primarily attributable to the instability of vinyl bromide 4a, with decomposition occurring during the relatively long reaction times required for conversion (>12 h) and subsequent purification. Given the ability of Ga(III) to promote ring-opening polymerization reactions of cyclic ethers, N-tosylate (NTs)-tethered diyynes were examined as potentially more stable substrates. The NTs-linked substrates proved fruitful, and bisalkyne 2b was converted to vinyl bromide 4b with an 80% isolated yield (Table 1, entry 1). Screening related $\xi$- acids revealed In(III) chloride and iodide to be suitable catalysts, and the corresponding vinyl chloride 5b and iodide 6b were isolated in good to excellent yields (Table 1, entries 2 and 3). The reaction times increased in the series In$_3$ < InBr$_3$ < InCl$_3$, with the chloride requiring refluxing in dichloroethane (DCE) to complete the reaction in 12 h. Both In(III) triflate with added bromide and In(1) bromide were ineffective at promoting any reaction. In an effort to accelerate the reaction, Ga(III) was then examined as a promoter.

Gallium(III) was found to promote the reaction at a faster rate, and with GaBr$_3$, vinyl bromide 4b could be isolated nearly...
quantitatively in 30 min. Conversion to the vinyl chloride 5b and vinyl iodide 6b also proceeded smoothly, with Ga3 affording complete conversion to the corresponding vinyl iodide in less than 10 min (Table 1, entries 7–9). As with In(III) promoters, the rate of the reactions increased in the series I > Br > Cl.

A variety of halide sources and conditions were screened in an attempt to render the Ga(III) catalyst stoichiometric. These included additives such as halide salts (TBAB, NaBr, KI), acid halides (HBr, HI, pyridinium hydrobromide), and halosilanes (TMSBr, TM Silva), as well as Ga(O-Tol)3 and In(O-Tol)3 with added bromide or other nucleophile traps. Only the halosilanes gave any catalyst turnover, and vinyl bromide 4b or iodide 6b could be isolated in 76 and 56% yield, respectively, with 20 mol % catalyst and stoichiometric halosilane (Table 1, entries 8 and 9). Given the decrease in yield, more difficult purification, comparable cost of the gallium salts relative to the halosilanes, and a turnover number of only 3, stoichiometric Ga(III) halides were used in subsequent studies.

The range of dinyes amenable to this chemistry was then explored using Ga3 (Table 2). Consistent with previous observations, etherate 2a (Table 2, entry 1) gave a lower yield of vinyl iodide 6a in comparison to the N-tosylate 2b. Accordingly, we focused our efforts on N-tosylates. Terminal alkyne (Table 2, entry 2), a wide range of arylalkynyl substrates proved amenable to the reaction, and smooth conversion to the desired products was observed for most (Table 2, entries 3–10). Despite excellent conversions (80–99%), some of the products were unstable to silica gel chromatography, resulting in significant loss of material (Table 2, entries 2, 8, 9, and 10). Fortunately, basic extractive workup was effective at purifying the vinyl halides to >91% purity, and these products could be used in further cross-coupling chemistry as the near pure material (vida infra). The relative rate of the cyclizations showed a dependence on the electron-richness of the aryalkyne. Electron-rich substrates (Table 2, entries 4 and 5) gave near immediate conversion to product, while electron-withdrawing groups slowed the reaction considerably (Table 2, entries 7–10). In the case of benzene 2i and nitrobenzene 2j, mild heating was effective in decreasing the reaction time. β-Trimethylsilyl-substituted alkyne 2m gave only the desilylated allene 8 on treatment with catalyst (Table 2, entry 12).

Diphenyl dinyne 2i (Table 2, entry 11) gave the expected product 6i only in relatively low yield (41%), the major product being tricyclic scaffold 7, isolated in 46% yield. The use of GaCl3 was effective in increasing the yield of 7 to 82%, requiring only 10 mol % catalyst (Scheme 2).

The pathway to products 6 may follow an initial 6-exo-dig cyclization promoted by Ga(III) activation of dinyne A, giving vinyl carbenium intermediate B (Scheme 3). Trapping of this vinyl carbenium ion by a halide from the Ga(III) promoter to vinyl gallate C, followed by protodegallation from adventitious water or during aqeous quench, delivers vinyl iodides 6. Products were observed with the halide incorporated adjacent to the arenne as the sole regioisomers. Given that both allynes are potential π-bases, it is likely that this regioselectivity is driven by the stability of the vinyl cation B, favoring halogenation at the benzylic position. The increase in the reaction time observed with more electron-deficient arenes is thus rationalized by the
slower rate of formation of the higher energy vinyl carbenium intermediate due to increased electron withdrawal on the aryl ring.

Satisfyingly, this mechanism also anticipates the formation of 7 from 21 as the diphenyl system contains an arene nucleophile capable of trapping the vinyl cation via an intramolecular Friedel-Crafts reaction. The increase in the yield of 7 with 10 mol % of GaCl₃ is likely a consequence of the slower rate of chloride trapping of the vinyl carbenium, in comparison to iodide, allowing greater internal arene addition. Products such as 7 have also been observed with Au(I) catalysis. We are currently further exploring this bicsyclization with diaryl bisalkynes.

During optimization efforts for the formation of 6, several additives were examined as proton sources to quench the vinyl gallate intermediate C. While not significant to the formation 6, the addition of acid (TFA, HBr, and Ga(OtBu)₃) gave small amounts of indenopyridine 9b (Table 3, entry 2). This product was presumed to be the result of a Bronsted acid catalyzed intramolecular Friedel-Crafts alkylation of the carbenium ion formed upon protonation of the endoalkene of the vinyl iodide 6. Attempts to favor this process by the addition of TFA to the halocyclization products formed in situ were unsuccessful. N-Tosyl diyne 2b could be converted to indenopyridine 9b in a two-step, one-pot procedure with a 91% overall yield by adding TFA to the reaction mixture once thin-layer chromatography analysis had determined that all of the starting diyne 2b had been converted to 6b (Table 3, entry 2). This procedure was effective at further cyclizing several of the N-tosylate diynes to 9 (Table 2, entries 5 and 7). However, some of the substrates decomposed under these reaction conditions at rates comparable to the formation of the desired product. Surprisingly, a two-step procedure where the vinyl iodide 6 was isolated and then subjected to TFA without Ga₃, present afforded no reaction. Presumably, TFA was acting to liberate HI from Ga₃, and the stronger acid was necessary for protonation. Triflic acid provided a convenient solution, and the crude vinyl iodides 6 could be converted to 9 with superior yields by treatment with this acid after removal of Ga₃ via basic workup in a two-step sequence (Table 3, entries 3, 4, 6, 8, and 9). Dipropargyl ether 2a gave only a trace conversion to the desired indenopyrano, decomposing under all conditions. In addition, 2k failed to react even at high temperatures, stopping at the vinyl bromide 6k likely due to the low nucleophilicity of the nitroarene.

The vinyl halides 9 were more stable than their enoxoylic vinyl halide counterparts 6 and could be chromatographed in silica gel and stored for months without noticeable decomposition.

With access to a range of vinyl iodides 6 and 9, the utility of these structures in selected cross-couplings was then examined (Figure 1). Under standard unoptimized conditions, Suzuki and Sonagashira couplings produced the corresponding arylated and alkynyl products, respectively, in fair to excellent yields. Despite the relatively short shelf life of the vinyl halides 6, these cyclization products proved to be useful in Suzuki cross-couplings without the need to purify the vinyl halides, as evidenced by compounds 10c and 10i. The two-step isolated

#### Table 3. Tandem Iodocyclization/Friedel–Crafts Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>dyne</th>
<th>A</th>
<th>R₁</th>
<th>R₂</th>
<th>product (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>O</td>
<td>Me</td>
<td>H</td>
<td>N/A (0.6, 0.6)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>NTs</td>
<td>Me</td>
<td>H</td>
<td>96 (91+)</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>NTs</td>
<td>Et</td>
<td>H</td>
<td>94 (66, 53')</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>NTs</td>
<td>Me</td>
<td>p-OMe</td>
<td>9e (69, 58')</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>NTs</td>
<td>Me</td>
<td>3,5-Me</td>
<td>9f (91+)</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>NTs</td>
<td>Me</td>
<td>m-OMe</td>
<td>9g (29, 52')</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>NTs</td>
<td>Me</td>
<td>p-Cl</td>
<td>9h (977)</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>NTs</td>
<td>Me</td>
<td>p-CO₂Me</td>
<td>9i (20, 33')</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>NTs</td>
<td>Me</td>
<td>p-Cl</td>
<td>9j (25, 48')</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>NTs</td>
<td>Me</td>
<td>p-NO₂</td>
<td>N/A (0.6, 0.6)</td>
</tr>
</tbody>
</table>

*Isolated yield. †One-pot procedure with TFA. ‡Two-step procedure with TFOH.

#### Figure 1. Cross-coupling products of vinyl iodides.
yield of the cross-coupled products prepared from the crude vinyl iodide far exceeded the isolated yields of the first step. In conclusion, we have developed a simple method for the construction of iodotetralinhydroxypyridines and indenopyridines using Galj and have shown that these products are capable substrates in cross-coupling reactions. These reactions offer quick access to easily diversifiable scaffolds from simple starting materials via a previously unreported mechanism wherein GaxY acts to promote a dyne cyclization and is a halide source. We are now expanding on the cross-coupling reactions to produce a library for biological screening.

■ ASSOCIATED CONTENT

Supporting Information

General experimental protocols and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIGMS CMLD initiative (PS0 GM067041) for partial financial support, and the NSF for supporting the purchases of the NMR (CHE 0619339) and HRMS spectrometers (CHE 0443618). We also thank the NSF REU (CHE 1156666) for summer support for A.J.L., and the Boston University Undergraduate Research Opportunities Program (UROP) for support for A.C.I.

■ REFERENCES


(14) Coordinating solvents (ACN, THF, DMF) returned starting material, whereas noncoordinating solvents (DCE, chlorobenzene, CHCl3) behaved similarly. DCE was chosen out of convenience.


(17) Subjecting isolated 6 to the reaction conditions with both Gal1 and TFA did bring about conversion to 9.