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Supporting Information

ABSTRACT: FeCl₃- and FeBr₃-mediated tandem carboarylation/cyclization of propargylanilines with diethyl benzaldehyde acetals furnished the tetracyclic core of indeno[2,1-c]quinolines. 5-Tosyl-6,7-dihydro-5H-indeno[2,1-c]-quinoline and 7H-indeno[2,1-c]quinoline derivatives were obtained in good to excellent yields, respectively, by tuning the FeX₃ loadings and/or reaction temperatures.

Construction of functionalized carbo- and heteropolycyclic architectures with minimum operations from relatively simple building blocks has been a challenging task in organic synthesis.¹ Tetracyclic indenoquinoline fused with quinoline² and indene³ frameworks is a common structural unit in a number of biologically active natural products and pharmaceuticals such as DNA topoisomerase inhibitor TAS-103⁴ and its analogues I⁵ and II⁶,⁷ etc., for anticancer treatment. Time-consuming multistep procedures have usually been applied to access an indeno[2,1-c]quinoline core consisting of tetracycles A–D, involving Diels−Alder⁵ and Friedel−Crafts⁶ reactions, cyclization⁸ and addition to carbonyl compounds.⁹ Alkynes were documented to undergo versatile cycloaddition, carbocyclization, and/or cyclosomerization¹⁰,¹¹ to form quinolines,¹² indeno[1,2-b]quinolines,¹³ and indeno[1,2-c]quinolines,¹⁴ while indeno[2,1-c]quinolines have not yet been prepared by such methods.

Recently, iron salts have been paid much attention as promising alternatives to traditional transition-metal catalysts¹⁵ and also employed for the synthesis of polycyclic compounds.¹⁶ Fe(OTf)₃ catalyzed the intramolecular hydroarylation of alkynes with electron-deficient arenes, building 1,2-dihydroquinolines and phenanthrenes.¹² ² FeCl₃ mediated the intramolecular isomerization/cyclodehydration of substituted 2-[(indoline-3-ylidene)(methyl)]benzaldehydes to form benzo[b]carbazoles,¹⁶b which were used for the synthesis of indeno fused heterocycles.¹⁶c We recently reported FeX₃-promoted Prins-type cyclization of alkylnyl acetals¹⁷ and intermolecular cyclization of diynes with acetals to give tricyclic compounds.¹⁸ Herein, we report FeX₃-mediated carboarylation/cyclization/detosylation of propargylanilines with benzaldehyde acetals for the synthesis of indeno[2,1-c]quinolines.

Table 1. Screening of Reaction Conditions

<table>
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<tr>
<th>entry</th>
<th>[Fe] (equiv)</th>
<th>temp (°C)</th>
<th>3a yield (%)</th>
<th>4a yield (%)</th>
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<td>1</td>
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<tr>
<td>2</td>
<td>FeBr₃ (0.2)</td>
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<td>6</td>
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<td>17</td>
<td>FeCl₃ (3.0)</td>
<td>25</td>
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Initially, the reaction of propargylaniline (1a) with diethyl benzaldehyde acetal (2a) was performed to screen the reaction conditions (Table 1). With 20 mol % FeCl₃ as the catalyst at 80 °C, the reaction proceeded to form 5-tosyl-6,7-dihydro-5H-indeno[2,1-c]quinoline (3a, 73%) and 7H-indeno[2,1-c]-quinoline (4a, 9%), achieving 100% conversion for 1a (Table 1, entry 1). Increasing the FeX₃ loading rendered 1a to be completely converted (Table 1, entries 1–4), but use of 1 equiv of FeX₃ deteriorated the selectivity to yield 3a (56%) and 4a (<40%). Longer reaction time enhanced the yield of 4a to 42–47%. To our delight, the reaction afforded 3a in 72% yield at ambient temperature (Table 1, entries 7 and 8). At 80 °C, FeBr₃ (3 equiv) acted more efficiently than FeCl₃ and FeCl₃·6H₂O to generate 4a (82%) (Table 1, entries 9–13). Varying temperatures at 100 or 60 °C by using FeBr₃ as the promoter lowered the yield of 4a (69%), and ambient temperature led to indiscriminate formation of 3a (34%) and 4a (31%) (Table 1, entries 14–17). Thus, the optimal conditions for the preparation of 3a and 4a (Table 1, entries 3 and 11) were achieved. It is noted that other Lewis acids such as SnCl₄ could also promoted the reaction: under the conditions employed for entry 7 of Table 1, the reaction using 1 equiv of SnCl₄ afforded 3a in 54% yield.

Under the optimized conditions, the substrate scope for the synthesis of 3 was explored (Table 2). Propargylanilines 1a–g reacted with 2 to afford 3a–g in 71–90% yields, exhibiting no obvious substituent effect from the NAr moieties (Table 2, entries 1–7). o- or m-methyl on the aryl group of a propargyl moiety favored the formation of 3h (75%) and 3i (77%), while a p-methyl lowered the yield of 3j (64%) (Table 2, entries 8–10). A p-methyl on the aryl group of the NAr functional group facilitated the generation of 3k (Table 2, entry 11). 1,2-Dihydroquinolines 5a (53%) and 5b (46%) were isolated from the reactions of 1l and 1m, respectively (Table 2, entries 12 and 13). Substituted acetals 2b–k reacted to give diverse target products 3n–w (58–80%) (Table 2, entries 14–23). It should be noted that arylpropargylanilines of type 1 bearing a p-OMe substituent only reacted to give a product of type 3 in 33% yield. The acetals derived from heterocyclic aromatic aldehydes such as 2-furaldehyde and 2-thiophenaldehyde could not undergo the desired reactions. The acetals of the alkyl aldehydes are not very stable under the stated conditions and were not applied in the reactions.
Next, the protocol generality for the preparation of 4 was investigated under the optimal conditions (Table 3). Both FeBr₃ and FeCl₃ could promote the desired reactions. Substituents such as Me, OEt, Cl, F, and Ac were tolerated on the aryl groups of the NAr moieties (Table 3, entries 1–11). Unsubstituted 1a and 2-Me- and 2-Cl-substituted substrates 1n and 1p efficiently underwent the reactions with 2a, giving 4a (82%), 4d (88%), and 4i (88%), respectively (Table 3, entries 1, 4, and 9). The 4- and 3-electron-withdrawing substituents rendered low yields for 4g (67%), 4h (51%), and 4k (61%). A methyl or methoxy on the aryl group of a propargyl moiety of 1 did not exhibit obvious effect on the yields of 4l−n (75−84%), whereas 3,5-dimethyls remarkably improved the formation of 4o (96%) and 4p (98%) (Table 3, entries 12−16). An electron-withdrawing substituent such as chloro on the aryl functional unit of a propargyl moiety of 1 deteriorated the reaction efficiency to give 4q (61%) and 4r (67%). Compound 1a also reacted with other acetals to form the target products 4s−w in 53−74% yields (Table 3, entries 19−23).

To probe the reaction mechanism, control experiments were conducted (Scheme 1). Compound 1a reacted with 2a in the presence of 10 mol % of FeCl₃ or FeBr₃ to afford 1-tosyl-1,2-dihydroquinoline 5c (27−28%) via intermolecular carboxylation/cyclization, which further reacted under the stated conditions as shown in Tables 2 and 3 to give 3a and 4a in decent yields, respectively. Compound 3a could be converted into the target products in 45−65% yields.
to 4a with FeCl₃ or FeBr₃ as the promoter. These results have revealed that both 5 and 3 can act as the intermediates to form 4 in the catalytic cycle. 4-Phenyquinoline (6a) could also be utilized to access 4a, further suggesting that species of types 5 and 6 may be generated as the reaction intermediates. It is noteworthy that 3a, 4i, and 5c were structurally confirmed by X-ray crystallographic analysis (see the Supporting Information).

A plausible mechanism is proposed (Scheme 2). Acetal 2a initially reacts with FeX₃ (X = Cl or Br) to form FeX₃(OEt)₄ anion (A) and oxocarbonium cation PhCH=OEt⁺ (B). Cation B interacts with propargylaniline 1a to generate vinyl cation 20 via the possible cationic species stabilized by an aryl group, which undergoes intramolecular Friedel–Crafts reaction to yield D. Deprotonation of D by species A forms intermediate 5c and ethanol, regenerating FeX₃. Following path a, species 5c can be converted to product 3a via the possible cationic species 21 and 22 assisted by FeX₃. Compound 3a further reacts with FeX₃ to undergo detosylation/aromatization, forming 4a. Compound 5c may also react with FeX₃ to form 6a via species H by detosylation/aromatization (path b), which further undergoes carboarylation with FeX₃ to furnish 4a and ethanol and regenerate the catalyst.

In summary, FeX₃-mediated tandem reactions of propargylanilines with aromatic aldehyde acetals form indeno[2,1-c]quinolines in good to excellent yields through carboarylation/cyclization under mild conditions. The present synthetic method provides a concise and nontoxic metal-mediated route to highly functionalized heteropolycyclic architectures.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for the prepared compounds; X-ray crystallographic data for 3a, 4i, and 5c. 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.

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REFERENCES