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Access to benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety via a double decarboxylative formal ring-expansion process under palladium catalysis†

Pulakesh Das, Satoshi Gondo, Punna Nagender, Hiroto Uno, Etsuko Tokunaga and Norio Shibata

Direct access to pharmaceutically attractive benzo-fused nine-membered heterocyclic alkenes 3 with a trifluoromethyl carbinol moiety was achieved via a palladium-catalyzed double-decarboxylative formal ring-expansion process from six-membered trifluoromethyl benzo[\textit{d}][1,3]oxazinones 1 to nine-membered trifluoromethyl benzo[\textit{c}][1,5]oxazonines 2 in the presence of vinylene carbonates 2. Generation of a Pd-π-allyl zwitterionic intermediate was proposed in the catalytic cycle. The trifluoromethyl group in the benzooxazinanones 1 plays an important role throughout the transformation. Diastereoselective chemical transformations of products 3 were also demonstrated.

Introduction

Fluoro-functionalized heterocycles with diverse ring sizes and ring systems have been well studied in pharmaceuticals and agrochemicals. Thus, a remarkable number of publications have been dedicated to the development of efficient synthetic methods to construct fluoro-functionalized heterocycles. In particular, heterocyclic molecules with a trifluoromethyl carbinol moiety, \textit{i.e.}, CF_3C(OR_1)R_2R_3, have gathered much attention on account of their promising biological properties. Efavirenz (anti-HIV), trifluoromethylated artemisinins (antimalarial), and fluralaner (insecticide and acaricide) are representative examples (Fig. 1).

In this context, our group has been engaged in the development of novel synthetic methodologies for fluorine-containing heterocycles for decades. Including our reports, the present synthetic strategies for fluorinated heterocyclic molecules are mostly limited to the construction of five- and six-membered ring systems, while the synthesis of medium-to-large-sized fluoro-functionalized heterocycles such as derivatives of benzo-oxazepine and macrosphelide A (Fig. 1) is extremely rare, despite the pharmaceutical importance of medium-sized heterocyclic compounds (non-fluorinated) and biologically active natural products. Very recently, Liu and co-workers reported an elegant method for the construction of fluoroalkyl-functionalized medium-/large-sized carbocyclic alkenes via an intramolecular radical trifluoromethylation-cyclization process. Recently, Zhao and co-workers successfully reported the palladium-catalyzed [5 + 4] and [6 + 4] cyclo-addition reactions of azadienes with vinylene carbonates and vinyl oxetanes respectively in good yields and selectivities. We disclose herein the first synthesis of benzo-fused nine-membered heterocyclic alkenes 3 with a trifluoromethyl carbinol moiety and vinylene carbonates (Scheme 1).

Fig. 1 Biologically active heterocycles containing a trifluoromethyl carbinol moiety.
The resulting trifluoromethylated heterocycles 3 have a benzo[c][1,5]oxazinone skeleton, and are not only medicinally attractive fluorine-containing heterocycles,1 but also expanded variants of well-known [1,4]oxazepine pharmaceuticals.15 Synthesis of the titled nine-membered compounds 3 were achieved from previously unknown trifluoromethylbenzoxazinanones 1 (six-membered ring) via a formal ring-expansion pathway under palladium catalysis. The reaction proceeded via the double decarboxylation (DDC) of 1 and vinylethylene carbonates 2 followed by a [5 + 4] cycloaddition reaction. The formation of Pd-complex 1 as an intermediate was proposed by LC-MS spectrometric analysis. This method provides an expedient access to trifluoromethylated benzo[c][1,5]oxazinones 3 with diverse functional groups in the aromatic moiety, including electron-donating, electron-deficient, and halogenic groups. Moreover, the alkene moiety in products 3 was further functionalized by conventional chemical transformations such as epoxidation to 4 and reduction to 5 (Scheme 1) with high diastereoselectivities which make this novel trifluoromethylated nine-membered skeleton more attractive as a template for drug discovery research. The presence of a trifluoromethyl group on 1 plays a pivotal role for their successful transformation to 3 based on comparative studies using non-CF₃-variants of 1.

**Results and discussion**

We started a preliminary investigation with the reaction of trifluoromethyl (CF₃) benzoxazinanone 1a and phenyl vinylethylene carbonate 2a in the presence of suitable palladium precursors and/or phosphine ligands (Table 1). We first attempted our reaction of 1a using similar Pd₂(dba)₃·CHCl₃ conditions in the presence or absence of phosphine ligands, but the results were disappointing (entries 1–4). Moving on to Pd(PPh₃)₄ as a palladium precursor at 50 °C in THF furnished exclusively a nine-membered ring in good yield of 70% (entry 5). Motivated by this result, further optimization was carried out in different solvents. In toluene, a slight decrease in yield was observed, at 66% (entry 6), while in dichloroethane yield improved to 79% (entry 7). Lowering the temperature to room temperature (rt) furnished good yield (70%), but 40 hours were required to complete the reaction (entry 8). An excellent yield of 91% (89%) was observed by increasing the temperature to 80 °C (entry 9). Increasing the temperature further decreased yield dramatically (entry 10, see ESI for more details†).

Based on the optimized reaction conditions, the flexibility of the DDC reaction was scrutinized by using a broad array of vinylethylene carbonates (VECs) 2a–m with 1a. The results are summarized in Table 2. Both electron-withdrawing and electron-donating groups on the phenyl ring of 2 furnished

**Table 1 Optimization conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd catalyst (with or without ligand)</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>10 mol% Pd₂(dba)₃·CHCl₃</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>2a</td>
<td>5 mol% Pd₂(dba)₃·CHCl₃</td>
<td>THF</td>
<td>40</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>5 mol% Pd₂(dba)₃·CHCl₃/10 mol% PCy₃</td>
<td>THF</td>
<td>40</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>5 mol% Pd₂(dba)₃·CHCl₃/10 mol% dbpmb</td>
<td>THF</td>
<td>40</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>THF</td>
<td>50</td>
<td>7</td>
<td>75(70)</td>
</tr>
<tr>
<td>6</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>Toluene</td>
<td>50</td>
<td>36</td>
<td>68(66)</td>
</tr>
<tr>
<td>7</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>DCE</td>
<td>50</td>
<td>12</td>
<td>83(79)</td>
</tr>
<tr>
<td>8</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>DCE</td>
<td>rt</td>
<td>40</td>
<td>79(70)</td>
</tr>
<tr>
<td>9</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>DCE</td>
<td>80</td>
<td>12</td>
<td>91(89)</td>
</tr>
<tr>
<td>10</td>
<td>5 mol% Pd(PPh₃)₄</td>
<td>DCE</td>
<td>Reflux</td>
<td>12</td>
<td>40(34)</td>
</tr>
</tbody>
</table>

a Experiments were performed with 1a (0.1 mmol), 2a (0.15 mmol), 5 mol% Pd(PPh₃)₄ (0.05 mmol) in 1.0 mL solvent. b 2a (0.12 mmol) was used. c Yields are 19F NMR yields with internal standard PhCF₃ and yields (isolated) are also given in parentheses. dbpmb = 1,2-bis(di-tert-butylphosphinomethyl)benzene. DCE = 1,2-dichloroethane.
good to excellent yields. VECs 2b–c, which have electron-donating groups (Me and OMe) at the p-position, reacted efficiently to afford the desired products 3 in excellent yields (3ab: 83%; 3ac: 78%) whereas VEC 2g, which contains an electron-withdrawing group (CF₃) at the p-position, furnished moderate yield (3ag: 56%). Furthermore, halogen-substituted VECs (2d: F; 2e: Cl; 2f: Br) also underwent the DDC reaction very smoothly to furnish good to excellent yields (3ad: 69%; 3ae: 86%; 3af: 91%). Similarly, a highly electronegative atom (2h: F) and an electron-donating group (2i: OMe) at the o-position afforded excellent yields (3ah: 84% and 3ai: 88%). Noticeably, substrates bearing an electron-withdrawing group (F) and an electron-donating group (OMe) at the o-position furnished higher yields than p-substituted substrates. Moreover, the scope of VECs 2 was extended to heteroaryl systems (2j: 2-furyl; 2k: 2-thienophenyl) and the reaction proceeded smoothly to afford the desired products 3 in good yields (3aj: 76%; 3ak: 79%). Gratifyingly, non-aromatic substituent VEC 2l and extended π conjugate naphthalene-derived VEC 2m also underwent the cycloaddition reaction to furnish 3al and 3am in moderate to good yield (53% and 65%, respectively), thus significantly broadening the scope of substrate 2 of this DDC system (Table 2).

Spurred by this interesting result, a range of differently substituted CF₃-benzoxazinanones 1b–e were further examined to better understand the DDC reaction (Table 3). Substituents on 1 with electronically dissimilar properties at different positions on the benzene ring were well tolerated to provide 3 in moderate to good yields. The substrate-bearing electron-withdrawing methyl group on the benzene ring, 1b produced CF₃-tetrahydrobenzoxazoline 3ba in 81% yield. The halogen-substituted CF₃-benzoxazinanones 1c and 1e (F and Br) produced DDC products 3 in moderate to good yields (3ca: 69% and 3ea: 78%) (Table 3).

To ensure the effect of the CF₃ group at the C-4 position at the C-4 position instead, we examined the reaction of benzoxazinanones 6, which contain different substituents at the C-4 position, with 2a (Scheme 2). In recent years, palladium-catalyzed cyclization reactions using vinyl benzoxazinanone 6a with a variety of substrates have been actively investigated by several groups. We thus first attempted the reaction of 6a with 2a. Interestingly, substrate 6a with a vinyl at the C-4 position produced a very different result. Under our best conditions, a vinyl-substituted benzoxazinanone 6a was converted to an intramolecular cyclization product 7 in 29% yield but no desired nine-membered cyclized product was observed (Scheme 2a). We next examined the reaction using 6b with a methyl group at the C-4 position instead, but were unable to furnish the desired product and the starting material 6b remained (Scheme 2b). Similar no conversion was obtained when we carried out the reaction of 6c having protected N-benzyl group (Scheme 2c). Although the reasons for the high reactivity of 1a are not clear, it might be due to the higher electrophilicity value of 1a induced by the strong electronegativity of the CF₃ group (group electronegativity of CF₃ is 3.43). To ensure the effect of the CF₃ group at the C-4 position of 1a, we performed a DFT calculation. The electrophilic value of 1a having CF₃ at the C-4 position was estimated to be 3.67 (a)}
(eV)) while that of 5b containing CH₃ at the C-4 position (3.33) was lower (Table S6, Fig. S1 in ESI for details†).

Interestingly, the X-ray crystallographic analysis of starting substrate 1a revealed that 1a has a sterically unfavourable cis-configuration between CF₃ and tosyl groups (Fig. 2). Although the reasons for the stabilization of 1a in this configuration are not sure, the steric repulsion might be the additional factor for the high reactivity of 1a for decarboxylation reaction.

To demonstrate the synthetic applicability of CF₃-substituted tetrahydrobenzoxazines 3, epoxidation and hydrogenation reactions were carried out as displayed in Scheme 3 based on the classical work of Still and Hoveyda. By using the Zhao’s condition we performed the epoxidation of 3aa in the presence of m-CPBA at 0 °C to rt successfully transformed to epoxide 4 with 67% yield and >20 : 1 diastereoselectivity through the peripheral attack. The X-ray crystallographic structure of 4 (CCDC 1589030†) suggested that epoxidation proceeded via a less hindered convex approach. Hydrogenation of 3aa with H₂ in the presence of Pd-C at rt furnished the desired product 5 (5 : 1 dr) in 74% yield (isolated as a single isomer) (Scheme 3).

A plausible reaction mechanism of the palladium-catalyzed DDC reaction of 1a with 2a to 3aa is portrayed in Scheme 4. The catalytic cycle is first initiated by the oxidative addition of Pd(0) with 2 followed by decarboxylation, which generates the π-allyl-Pd(II) complex II. The extremely nucleophilic nature of the alkoxide oxygen of II attacks the most electrophilic carbon atom attached to the CF₃ group of 1a which triggers the opening of benzoxazinanone ring to generate reactive species III. Due to its highly reactive nature, species III immediately transforms into Pd-complex I via decarboxylation. Recently, Kleij et al. disclosed the similar kind of six membered Pd-complex with the support of DFT calculations. In our case, the formation of Pd-complex I was confirmed by LC-MS spectrometry (Fig. S2 in ESI for details†) but we could not detect it by NMR (Fig. S3, in ESI for detail†).

From complex I, there might be two possible pathways for the formation of two different cyclized products. Attack at the terminal position of the Pd-complex (path A) would generate the [5 + 4] cycloaddition product 3aa while internal attack (i.e., path B) of Pd-complex could result in [4 + 3] cycloaddition to furnish a seven-membered heterocycle 8. However, we did not obtain the [4 + 3] cycloaddition adduct 8. This may be attributed to steric hindrance of 8, i.e., the NTs group as well as the tetrafluoromethylated tertiary carbon center on 8.

Conclusions

In conclusion, we have established a novel and highly efficient methodology for the synthesis of benzo-fused nine-membered heterocyclic alkene with a trifluoromethyl carbino moiety through a palladium-catalyzed double decarboxylative formal ring expansion process. A combination of trifluoromethylated six-membered benzoxazinanones with vinylene ethylene carbonates resulted in direct access to previously unknown trifluoromethyl-functionalyzed nine-membered heterocycles. The trifluoromethyl substituent at the C-4 position of benzoxazinanones plays an important role in this transformation. Diastereoselective transformations of the benzo-fused nine-membered heterocyclic alkene were also achieved to demonstrate the synthetic utility of the products. Investigation of the formation of other medium-sized rings as well as enantioselective variants of the reaction are presently under way in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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References


