3,3-Dibromo-2-trifluoromethyl Acrylic Acid Ethyl Ester: A Versatile Platform for the Stereoselective Preparation of Functionalized-α-Trifluoromethyl α,β-Unsaturated Lactones and Trifluoromethyl Pyrazolinones

Satoshi Mizuta,a Hiroki Otaki,a Kanami Kitamura,a Kodai Nishi,b Ken Watanabe,a Juliann Nzembi Makau,a Ryō Hashimoto,c Toshiya Usui,c and Kenya Chibac

We herein describe a method for the synthetic routes to multi-functionalized-α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones. This involves tandem stereoselective functionalization of 3,3-dibromo-2-trifluoromethyl acrylic acid ethyl ester and intramolecular cyclization reaction to afford precursors for a Suzuki-Miyaura cross-coupling reaction with arylboronic acids.

Introduction

Trifluoromethyl heterocycles have been an important motif of pharmaceutical drugs and agrochemicals because the presence of a CF3 group can cause the improved metabolic stability, lipophilicity and bioavailability.1 Nowadays, numerous CF3 substituted heterocycle-containing pharmaceuticals on the market can be witnessed,2 with examples such as trifluridine,3 efavirenz,4 celecoxib5 and mefloquin.6 Over the past decades, there has been an increasing interest in the development of method for the efficient synthesis of such fluorinated heterocyclic molecules as potential biological targets.7 Nevertheless, synthetic method accessing an array of CF3-containing heterocycles remains underdeveloped, in particular for nonaromatic heterocycles.8 Considering the difficulty of introducing CF3 moiety in nonaromatic ring systems,9 divergent synthesis using a simple and readily available CF3-containing precursor to convert into the diverse set of trifluoromethyl heterocyclic compounds may be one of the versatile and straightforward strategies for drug discovery.10 In the divergent synthesis, the designing building blocks to improve compound quality and accelerate drug discovery must be chosen carefully in an early stage. In a previous paper, we disclosed an efficient synthesis of α-hydroxy-α-trifluoromethyl γ-lactams using ethyl trifluoropyruvate and enamines via tandem aldol condensation and cyclization reaction.11 In addition, we developed an efficient synthesis of a series of bicycle trifluoromethyl pyrazolinone compounds using reactions of 2-aryl-3-chloro-3-trifluoromethyl acrylate.12 Meanwhile, gem-dibromoalkenes have been widely used as important building blocks for organic synthesis because they act as not only coupling partners in transition-metal catalysis and also precursors of metal carbeneid intermediate formed by...
monometalation with organo-lithium and magnesium.\textsuperscript{13} Consequently, we envisaged that trifluoropyruvate derived ethyl 3,3-dibromo-2-trifluoromethylacrylate (1) bearing multi-reaction sites toward regioselective functionalization (bromine-magnesium exchange and 1,4-addition reaction), cyclization and a Pd-catalyzed cross-coupling reaction might serve as a suitable precursor for the selective functionalization of fluorine-containing gem-dibromoalkanes. In 2004, Lu et al. reported that the Z-selective bromine-lithium exchange reaction of O-protected 2-trifluoromethyl-

To the best of our knowledge, there are few reports about the diverse synthesis of trifluoromethyl heterocycles (Fig. 2).

Herein, we would like to report our efforts by performing two new approaches involving an umpolung strategy, with gem-dibromoalkene 1 as a single precursor, leading to the multi-functionalized α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones. The synthetic routes are summarized in Fig. 3: (a) a regioselective magnesium-bromine exchange reaction of 1 with organometals generates the magnesium carbenoid intermediate 2. The intermediate 2 subsequently undergoes a tandem C-C bond formation and cyclization reaction with electrophiles such as aliphatic, aromatic and cyclic ketones, affording α-trifluoromethyl α,β-unsaturated lactones 5. The intermediate 2 can be proposed to be an equivalent to carbanion 3. Another way is a 1,4-addition reaction of hydrazine derivatives to gem-dibromoalkene 1 as Michael acceptor followed by the elimination of HBr and intramolecular cyclization to provide trifluoromethyl pyrazolinone derivatives 6 (Fig. 3:(b)). It may be said the precursor 1 is a carbocation synthon which is also in a relationship with umpolung of 3. (c) Further functionalization by a Pd-catalyzed auration of 5 and 6 affords the corresponding products 7 and 8, respectively.

**Results and discussion**

**Generation and reaction of magnesium carbenoids**

![Fig. 3. Approach for the diverse synthesis of multi-functionalized trifluoromethyl heterocycles.](image)

![Fig. 4. Examples of novel building blocks for the regioselective functionalization.](image)

**Table 1. Bromine-magnesium exchange reaction of 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1/R2 of 1</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>conv. (%)</th>
<th>11/12a%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i PrMgCl</td>
<td>THF</td>
<td>-20</td>
<td>40</td>
<td>60-40</td>
</tr>
<tr>
<td>2</td>
<td>i PrMgCl</td>
<td>THF</td>
<td>-60</td>
<td>59</td>
<td>58-42</td>
</tr>
<tr>
<td>3</td>
<td>i PrMgCl</td>
<td>i BuCl</td>
<td>-20</td>
<td>&lt;56</td>
<td>27-73</td>
</tr>
<tr>
<td>4</td>
<td>i PrMgCl</td>
<td>i BuCl</td>
<td>-60</td>
<td>&lt;56</td>
<td>20-80</td>
</tr>
<tr>
<td>5</td>
<td>i PrMgCl</td>
<td>THF</td>
<td>-60</td>
<td>&lt;56</td>
<td>40-80</td>
</tr>
<tr>
<td>6</td>
<td>MMgCl</td>
<td>i BuCl</td>
<td>-80</td>
<td>&lt;5%</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>i PrMgCl</td>
<td>i BuCl</td>
<td>-60</td>
<td>&lt;5%</td>
<td>ND</td>
</tr>
</tbody>
</table>

\(a\) The conversion was determined by \(^{19}F\) NMR. \(b\) The ratio was calculated by the relative integration ratios in \(^{19}F\) NMR spectra. **Note:** Numbers in parentheses represent the yield based on the internal standard of benzotrifluoride.

Fig. 4 Examples of novel building blocks for the regioselective functionalization.

![Fig. 4. Examples of novel building blocks for the regioselective functionalization.](image)
selective reaction of bromine trans to the trifluoromethyl group is still challenging. In our synthetic plans, the presence of the ester of 1 was needed to aid E selective metal-bromine exchange due to the electrostatic interaction between the cationic magnesium and the partially negatively charged carbonyl oxygen (Fig. 4: C). The carbenoid intermediate undergoes a nucleophilic addition to a variety of ketones, followed by intramolecular cyclization accessing β-bromo-α-trifluoromethyl α,β-unsaturated lactones.

To begin our study, gem-dibromoalkene 1 was prepared from the reaction of 2,2,2-trifluoromethylpyruvate with carbon tetrabromide and triphenyl phosphine according to a previous report. Next, some experiments were performed in order to examine the stereoselectivity and reactivity of the bromine-metal exchange reaction of 1. When i-PrMgCl (1.0 equiv, 2 M in Et2O) was added to a THF solution of 1 at –80 °C, after quenching methanol a mixture of 11 and 12 was obtained in a ratio of 1.5:1 (Entry 1, Table 1). The ratio of isomers was carefully determined using 1H and 19F NMR of the crude mixtures because it was difficult to isolate products due to their volatility. The stereochemistry for 11 is determined to be in (E)-configuration based on the H-F coupling constant. Next, we further investigated the impact of temperature, solvent and organometals concerning the reactivity and selectivity. The reaction with i-PrMgCl in THF was performed at –50 °C, and gave several unidentified by-products along with isomers 11 and 12 (E/Z = 58:42, Entry 2). When the reaction was performed at 0 °C, the decomposition of 1 was observed. It should be noted that the carbenoid intermediates 9 and 10 were quite unstable. Interestingly, use of Et2O solvent caused the opposite selectivity and improved decomposition of 1 (Entry 2). When the reaction was performed at 0°C, the selectivity was slightly increased to E/Z = 20:80 (Entries 3 and 4). When the reaction was conducted in hexane at –50 °C instead of Et2O, both the E/Z ratio and yield were decreased to 2:3 and 20%, respectively (Entry 5). In addition, the treatment of 1 with MeMgCl and n-BuLi at –80 °C in Et2O resulted in no conversion (Entries 6 and 7). Therefore, these results reveal that the combination of i-PrMgCl and Et2O are the good choice for the generation of carbenoid 10.

To elucidate this reaction process, we calculated the four initial geometries of the carbenoid intermediates and estimated the stability of 9 vs. 10 (Fig. 5). The relative energies show that the geometry of the 5-membered metallacycle 10b formed by the interaction between magnesium with carbonyl oxygen is most stable than the other geometries 9a, b and 10a. Relevant reports about the chelation of O with lithium or magnesium to control the selectivity of monometalation of dibromoalkane would support these calculated results. In contrast to 10b, their relative energies reveal that 9a, b are substantially less stable by ca.15 kcal mol−1. Therefore, the transformation of 1 to carbenoid intermediate 10b would be favorable, while the transformation to 9a, b would be unfavorable. Nevertheless, the experimentally observed ratio was moderate (E/Z = 1:4, Entries 4, Table 1). We deduced from the large differential relative energies between 9 and 10 that (E)-11 was the kinetic product, and no isomerisation occurred. In summary, the presence of a carbonyl group of ester was crucial for (E)-selectivity by the coordination with magnesium. Furthermore, we assumed that the bromine-magnesium exchange reaction in Et2O of 1 at low temperature (–80 or –50 °C) gave the thermodynamic product 12 as the major isomer and the minor isomer 11 spontaneously. The solvent effect in detail is currently under investigation.

We further investigated the bromine-magnesium exchange reaction of 3,3-dibromo-N-(tert-butyl)-2-(trifluoromethyl)acrylamide (13). As shown in Scheme 1, the treatment of 13 with 1.0 equiv of i-PrMgCl at –50 °C in Et2O by adding methanol after 15 min gave isomers 14 and 15 with moderate selectivity (E/Z = 21:79). The result was similar to those using 1 (Entry 4, Table 1). Thus, the amide group for 13 had a minor influence on the E/Z ratio. However, we could ascertain that the chelation between carbonyl oxygen and magnesium was supposed to be the significant factor to give the regioselectivity in the bromine-magnesium exchange reaction.

With the optimum conditions in hand, we explored the reactivity of intermediate 10b generated by the treatment of 1 with i-PrMgCl in Et2O at –50 °C for 15 minutes to carbonyl substrates (Fig. 6). In the case of benzaldehyde, the reaction gave benzylalcohol by the reduction by i-PrMgCl. The reaction with acetophenone provided β-bromo-α-trifluoromethyl α,β-unsaturated lactone 16a in 44% isolated yield without any the (Z)-bromine exchanged product, presumably due to concerns over the decomposition of carbenoid intermediate 9 prior to the reaction with electrophile. Therefore, we demonstrated that the carbenoid 10b could be trapped by a series of ketones like cyclic ketone, acetophenone, 1-indanone and 3-...
pentanone affording the corresponding lactones 16–20 in 30–44% yield. The transformation showed that some para-substituted groups of acetophenone were tolerated, including methyl, chloro and methoxy group furnishing the corresponding products 17a–d in 31–41%. By using 2.0 equiv of 1 and i-PrMgCl to acetophenone, the isolated yield for 17a was increased to 63% based on the carbonyl substrate. Otherwise, reactions with 3-acylpyridine and 2-acetyliophene gave trifluoromethyl α,β-unaturated lactones 21 and 22 in 33% and 35% yield, respectively.

**Tandem 1,4-addition-cyclization reaction of 1 with hydrazine derivatives**

Previously, we disclosed that reaction of gem-dihaloalkene with cyclic hydrazine derivatives in 1,4-dioxane in the presence of an organic base at raised temperature could provide a variety of bicyclic pyrazolinone compounds. According to the procedure, we demonstrated the further utility of 1 as novel building block for highly regioselective synthesis of 5-bromo-4-trifluoromethyl pyrazolinone derivatives. A plausible mechanism of the transformation to pyrazolinone is shown in Fig. 7. Initially, addition of either of two nitrogen atoms in hydrazine derivatives to the Michael acceptor 1 at the β position forms 1,4-adduct 28, which undergoes regioselective elimination of HBr in the presence of i-Pr2NEt, giving the corresponding acrylate intermediate 29. Finally, the intramolecular cyclization of 29 allows for the formation of pyrazolinone ring. This tandem 1,4-addition-cyclization reactions with some hydrazine derivative hydrobromide was amenable to give 5-bromo-4-trifluoromethyl pyrazolinones 23–27 in moderate yield with high regioselectivity. The reaction of 1 using monobenzyl hydrazine furnished the single isomer 23 in 68% isolated yield. The reaction of N,N-dimethyl hydrazine allowed for the product 24 in 63% yield. This approach allowed us to use cyclic pyrazolinone derivatives such as hexahydropyridazine and [1,3,5]oxadiazepane.

**Pd-catalyzed cross-coupling reactions of bromolactones and bromopyrazolinones**

Actually, these reactions successfully gave bicycle products 25 and 26 in 71% and 83% yield, respectively. Otherwise the reaction of 1,2,3,4-tetrahydrophthalazine provided tricyclic compound 27 in 58% yield.

To this end, we executed further transformation of bromolactones 16–19 and bromopyrazolinone 25 and 27 by using a Suzuki-Miyaura cross-coupling reaction with various arylboronic acids (Table 2). Bromolactone 16a was chosen as a model substrate for Pd-catalyzed cross-coupling reaction. Indeed, the reaction of 16a with phenylboronic acid in the presence of palladium (0) tetakis(triphenylphosphine) (5 mol%) and Na2CO3 (2.0 eq) at 90 °C for 10 hour in a mixture of toluene and H2O furnished the arylated product 30a in 92% yield. Without optimization of the reaction conditions, other substrates were subject to Suzuki coupling reactions under same conditions. As illustrated in Table 2, a wide range of functional group are tolerated, including methoxy, cyano, ester and nitro group. The cross-coupling reactions with such arylboronic acids involving (E)-styrilboronic acid were successful, and obtained the corresponding arylated products 30b,c,e–j (55–87% yield), but 3-pyridine boronic acid resulted in poor conversion to 30d (14% yield). Additionally, we also performed single-crystal X-ray diffraction analysis for 30c (Fig. 8). The structure of 30c in solid-state shows that the geometry of 4-CN phenyl group is unequivocally cis to CF3 group. In extensive experiments, we explored the reactions of bromopyrazolinones 25 and 27 with same
conditions. Four examples of arylboronic acid were performed, an aryalted pyrazolinone each 31a–e was obtained in up to 77% yield. Use of 27 also was successful, and the reaction of 27 with PhB(OH)₂ proceeded smoothly to furnish the polycyclic compound 31e in 56% yield. Consequently, we were pleased to find both of bromolactones 16–19 and bromopyrazolinones 25 and 27 to be facile coupling partners for the Pd-catalyzed cross coupling reaction with various arylboronic acids.

Conclusions
In summary, we have developed a novel synthetic method accessing various multi-functionalized-α,β-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones from 3,3-dibromo-2-trifluoromethyl-acrylic acid ethyl ester 1 as a single precursor. The significant feature of our method involves two approaches: one is that a carbenoid intermediate in situ-generated through bromine-magnesium exchange reaction of 1, another is a condensation of 1 with hydrazine derivatives with high stereoselectivity. Further modification of bromo-lactones and pyrazolinones by using Suzuki-coupling reactions with arylboronic acids led to a series of arylated trifluoromethyl compounds. Since α,β-unsaturated lactones and pyrazoline compounds are important part of the structure of the natural bioactive compounds, the potential importance of these synthetic entries have stimulated our interest to develop new drugs with medicinal and agricultural applicability. The further application to evaluate their biological activity is currently underway. The detailed outcome will be reported soon.

Acknowledgements
This study was supported financially by Grants-in-Aid for Scientific Research (No. 26713041) from Japan Society for Promotion of Science (JSPS). We thank Mrs. Junko Nagaoka, of Faculty of...
Engineering of Nagasaki University, for measurement of X-ray diffractometer measurements and analysis of the structure.

Notes and references
17. For details, see the Electronic Supporting Information (ESI).