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Straightforward Synthesis of Dihydrobenzofurans and Benzofurans from Arynes

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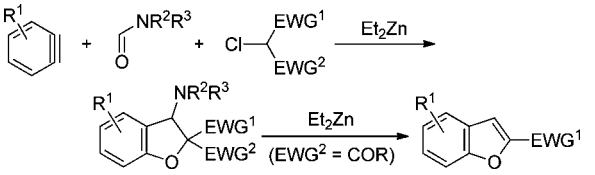
ABSTRACT



Synthesis of dihydrobenzofurans was achieved by a route involving the insertion of arynes into formamides followed by trapping with zinc enolates of α-chlorinated methines. Benzofurans were generated from dihydrobenzofurans having a ketone group *via* the addition of an ethyl anion, the retro-aldol type reaction, and the elimination of an amino group.

2,3-Dihydrobenzofurans and benzofurans are useful building blocks as well as core structures in biologically active natural products.[1] Most of the reported synthetic approaches have involved the use of the oxygen-atom-containing arenes such as *ortho*-functionalized phenols or other phenol derivatives.[2] Few methods are based on the aromatic C−O bond formation;[3] thus, we felt attracted to the possibility of a new aromatic C−O bond-forming route starting from arynes.

In recent years, aryne chemistry has made great advances in synthetic chemistry.[4,5] We have developed the efficient insertion of arynes, *in situ* generated from *ortho*-(trimethylsilyl)aryl triflates[6] and the fluoride ion, into the C═O π-bond of formamides (Figure 1).[7,8]

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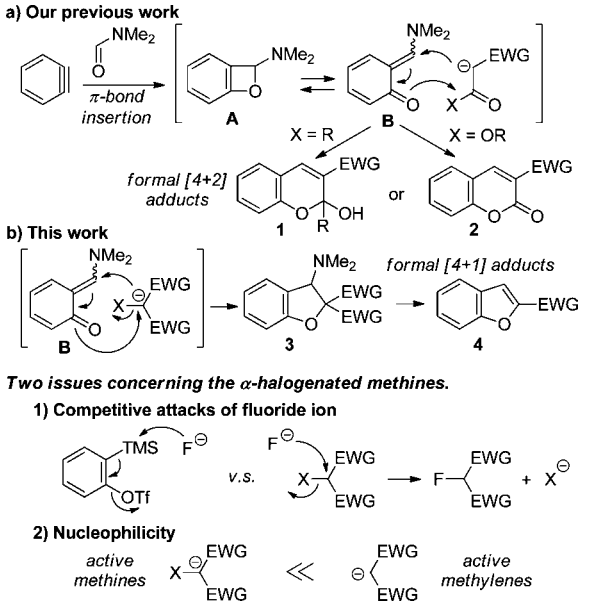

Figure 1. New synthetic methods using arynes.

This process provides a valuable method for introducing a pair of oxygen and carbon atoms into the aromatic ring, as benzoxetene **A** or *ortho*-quinone methide **B**. When the active methylenes are coexisting as nucleophiles, these intermediates are readily converted into the formal [4 + 2] adduct **1** or **2**.[9] In this communication, we report a three-component coupling reaction leading to the formal [4 + 1] adducts, 2,3-dihydrobenzofuran **3** and benzofuran **4**, *via* the trapping reaction of transient intermediate **B** with the methine compounds. In this manner, the α-halogenated active methines must be employed as second nucleophiles. However, there are two troublesome issues to notice. The competitive attack of the fluoride ion on the α-halogenated methines[10] might impede the generation of arynes from *ortho*-(trimethylsilyl)aryl triflates. Another problem is the insufficient nucleophilicity of anions generated from the active methines, as compared with those of the active methylenes.[11]

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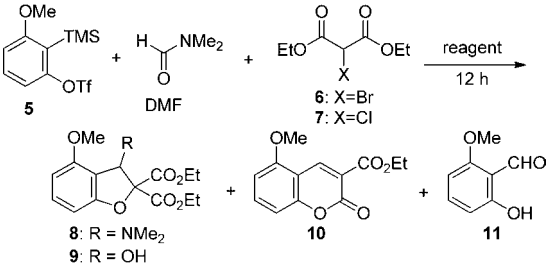
(11) In our calculation studies, the α-halogenated active methines are evidently made ca. 7 kcal mol^{-1} more stable than active methylenes.

Table 1. Reaction of Precursor **5**, DMF, and Methine **6** or **7**



				yield (%)[a]		
entry	methine	reagent	additive	**8**	**9**	**10**
1[b]	**6**	CsF	none	5	52[c]	–
2[b]	**6**	CsF	Me_3Al	–	–	34[d]
3[b]	**6**	CsF	Et_2Zn	–	–	11[e]
4[f]	**7**	CsF	Et_2Zn	63	–	–
5[g]	**7**	CsF	Et_2Zn	86	–	–
6[f]	**7**	TBAF	Et_2Zn	66	24	–

[a] Isolated yield. [b] Reactions were carried out with **5** (1.0 equiv), **6** (2.0 equiv), CsF (5.0 equiv), and additive (2.0 equiv) in DMF (0.1 M solution of **5**) at rt. [c] **11** was obtained in 15% yield. [d] **5** was recovered in 12% yield. [e] **5** was recovered in 64% yield. [f] Reactions were carried out with **5** (1.0 equiv), **7** (2.0 equiv), reagent (5.0 equiv), and Et_2Zn (2.0 equiv) in DMF (0.1 M solution of **5**) at −40 °C to rt. [g] Reaction was carried out with **5** (1.2 equiv), **7** (1.0 equiv), CsF (6.0 equiv), and Et_2Zn (1.0 equiv) in DMF (0.1 M solution of **7**) at −40 °C to rt.

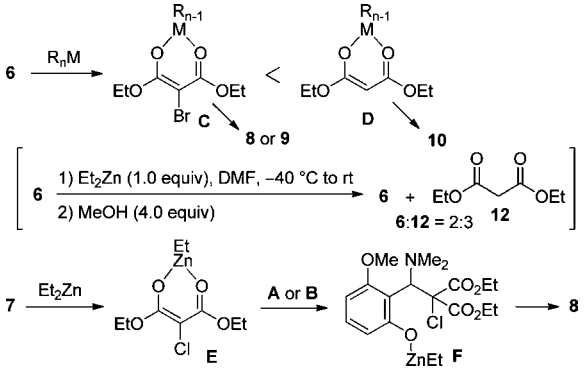
To test the viability of α-bromomalonate **6** as a nucleophile, our experiment began with the investigation of the reaction of an aryne precursor **5**, *N*,*N*-dimethylformamide (DMF), and **6** (Table 1). DMF was employed as a solvent to suppress the direct reaction of aryne with **6**.[12] The competitive attack of the fluoride ion on α-bromomethine **6** was mostly suppressed by using CsF as the fluoride ion source, whereas TBAF possessing good solubility toward DMF induced the undesirable reaction between **6** and the fluoride ion. In the presence of CsF, the reaction proceeded at room tempareture to give the formal [4 + 1] adducts **8** and **9** in 5% and 52% yields, respectively, accompanied by a 15% yield of salicylaldehyde derivative **11** (entry 1). Dihydrobenzofuran **9** and salicylaldehyde derivative **11** were formed as a result of hydrolysis of intermediate **A** or **B**; thus, it is assumed that the insufficient nucleophilicity of α-bromomalonate **6** caused the hydrolysis by contaminated water. Therefore, organometallic reagents such as Me_3Al or Et_2Zn were next employed, in expectation of both the dehydration and the activation of **6** as a metal enolate (entries 2 and 3). However, the desired adduct **8** was not obtained, but coumarin **10** was newly isolated. These results indicate that the debrominated enolate **D** was formed instead of α-bromoenolate **C** (Scheme 1). In fact, treatment of **6** with Et_2Zn gave the debrominated malonate **12**.[13] Next, we focused our attention toward less reactive α-chloromalonate **7**. As expected, the use of

(12) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

(13) The recovered α-bromomalonate **6** and malonate **12** were observed in a 2:3 ratio on ^1H NMR.

α-chloromalonate **7** led to drastic improvement (entries 4−6). Initially, we allowed 1 equiv of triflate **5** to react with 2 equiv of **7** in DMF from −40 °C to rt for 12 h in the presence of Et_2Zn (entry 4). The desired dihydrobenzofuran **8** was obtained in 63% yield without the formation of undesired coumarin **10**. Improvement in the chemical yield of **8** was observed, when 1.2 equiv of triflate **5** was reacted with 1 equiv of **7** in DMF (entry 5). The reasonable chemical yield was also obtained even when anhydrous TBAF was employed (entry 6).[14] Consequently, a suitable combination of α-chloromalonate **7** and Et_2Zn led to the selective generation of zinc α-chloroenolate **E**,[15] which reacted with intermediate **A** or **B** to give dihydrobenzofuran **8** *via* an intermediate **F** (Scheme 1).

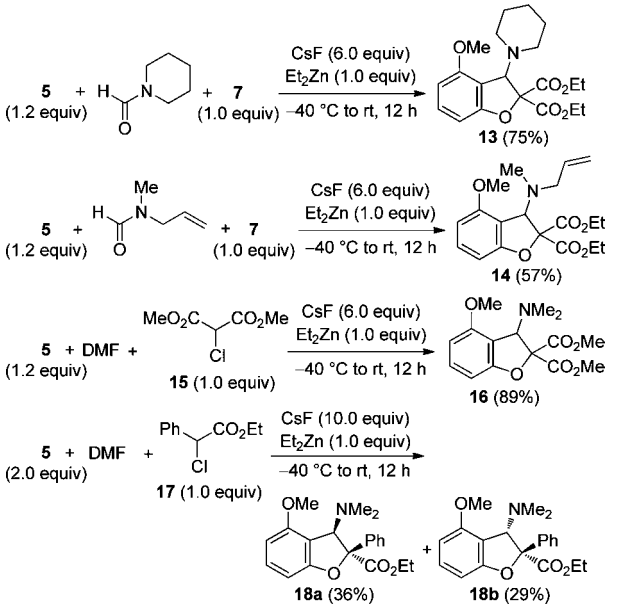
Scheme 1. Reaction Pathway *via* the Generation of Enolates



Further investigations using other formamides and active methines were performed (Scheme 2). Under the optimized conditions, the bulky 1-formylpiperidine worked well to give dihydrobenzofuran **13** in 75% yield without the insertion into the N−C σ-bond of amide[16] or α-arylation of **7**.[17] Dihydrobenzofuran **14** having *N*-allyl and *N*-methyl groups was formed from unsymmetrical formamide. As expected, a high chemical yield was observed in the reaction with dimethyl α-chloromalonate **15**. Interestingly, the sequential transformation took place, even when ethyl α-chlorophenylacetate **17** was employed. Although the increasing amounts of aryne precursor **5** and CsF were needed, two diastereomers **18a** and **18b** were obtained in acceptable yields.

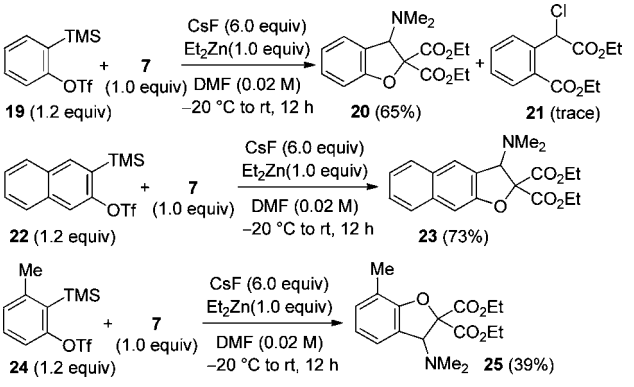
Aryne precursors **19**, **22**, and **24** were next tested (Scheme 3). Decreasing the steric hindrance around the

Scheme 2. Three-Component Coupling Reaction



triple bond of aryne induced the direct reaction of aryne with enolate **E**.[18] In contrast to bulky triflate **5**, the insertion of aryne, generated from sterically less hindered triflate **19**, into the σ-bond of α-chloromalonate **7** occurred to give arene **21** under the optimized conditions described in entry 5 of Table 1. Improvement in the chemical yield of dihydrobenzofuran **20** was observed by changing the concentration. Under the highly diluted concentration (0.02 M solution of **7** in DMF), the σ-bond insertion was mostly suppressed to afford **20** in 65% yield. The similar trend was observed in the reaction of triflate **22**. In the case of triflate **24**, dihydrobenzofuran **25** was isolated in 39% yield, accompanied by other byproducts.[19]

Scheme 3. Reaction of Aryne Precursors **19**, **22**, and **24**



We next applied the present three-component coupling reaction into the synthesis of benzofuran derivatives. A careful reaction analysis showed that the desired benzofuran **28** was obtained when the active methine **26** having

(14) When α-chloromalonate **7** was employed, TBAF did not induce the competitive attack of fluoride ion on **7**.

(15) In contrast to α-bromomalonate **6**, treatment of α-chloromalonate **7** with Et_2Zn did not give the dechlorinated malonate **12**, but **7** was quantitatively recovered. This result supports the formation of zinc enolate **E** without the generation of carbene species.

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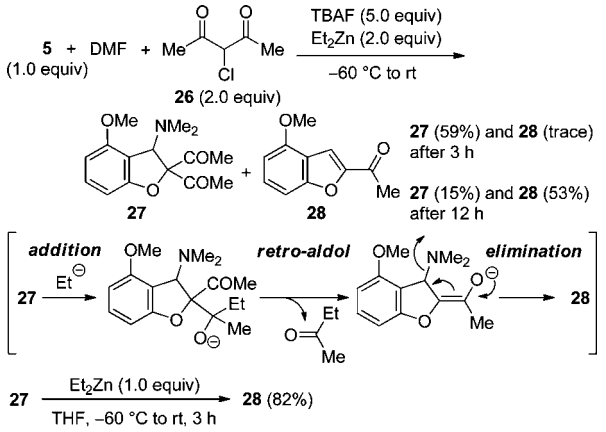
two ketone groups and an excess amount of Et_2Zn were used (Scheme 4).

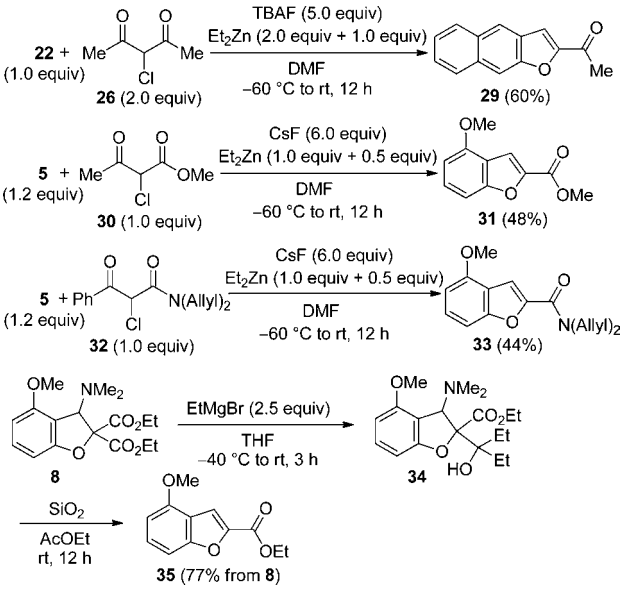
Scheme 4. Reaction with 3-Chloroacetylacetone **26**



In the presence of anhydrous TBAF (5.0 equiv), the reaction of triflate **5** with 3-chloroacetylacetone **26** (2.0 equiv) and Et_2Zn (2.0 equiv) in DMF gave the dihydrobenzofuran **27** in 59% yield after being stirred for 3 h. The formation of benzofuran **28** increased by simply changing the reaction time from 3 to 12 h. These observations show that benzofuran **28** was generated from dihydrobenzofuran **27** *via* the addition of an ethyl anion to a ketone group, the retro-aldol type reaction, and the elimination of a dimethylamino group. Indeed, treatment of **27** with Et_2Zn (1.0 equiv) gave benzofuran **28** in 82% yield.

Naphthofuran **29** was also obtained from triflate **22** by using TBAF and an excess amount of Et_2Zn (Scheme 5). Particularly, this benzofuran synthesis agrees with the use of methines **30** and **32** having a monoketone group. The reaction of **5** with methine **30** having ketone and ester groups gave benzofuran **31** having an ester group in 48% yield. In this case, CsF was employed as the fluoride ion source. The unsymmetrical methine **32** having a bulky phenyl ketone group worked well to give benzofuran **33** in moderate yield. Finally, we directed our attention into the conversion of dihydrobenzofuran having two ester groups into benzofuran *via* the retro-aldol type process. As expected, treatment of dihydrobenzofuran **8** with 2.5 equiv of EtMgBr gave benzofuran **35** in 77% yield without the isolation of adduct **34**.

Scheme 5. Synthesis of Benzofuran Derivatives



In conclusion, we have developed a new synthetic approach for the synthesis of dihydrobenzofurans and benzofurans. This approach is characterized by the use of arynes, is straightforward, and allows for the construction of two C–O bonds and two C–C bonds.

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Supporting Information Available. Experimental procedure, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(19) Regioselectivity could not determined by the competitive formation of a mixture of regioisomers of dihydrobenzofurans having a hydroxyl group similar to **9**.