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Convenient Synthesis of (*E*)-5-Aryl(halo)methylenebicyclo-[2.2.2]oct-2-enes and -[2.2.1]hept-2-enes *via* Lewis Acid-Promoted Carbohalogenation of Cyclic 2,6-Enynols

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Abstract: An efficient synthesis of (*E*)-5-aryl(halo)-methylenebicyclo[2.2.2]oct-2-enes is reported. Lewis acid-promoted carbohalogenation of 4-(3-arylprop-2-ynyl)-cyclohex-2-enols in dichloromethane proceeds rapidly to afford the *exo*-methylene-bridged bicycles in good yields. This method also provides an easy access to (*E*)-5-aryl(halo)methylenebicyclo[2.2.1]hept-2-enes from the five-membered ring 2,6-enynols. The reactions are procedurally simple and high yielding, producing the aryl(halo)methylene-bridged bicycles in minutes under air and mild conditions.

Keywords: carbocations; carbocycles; cyclization; enynes; halogenation; Lewis acids

Exomethylene cycles are found in many natural products of biological interest.[1] Several methods have been developed for the construction of *exo*-methylene cyclic skeletons, including Diels–Alder reactions of cyclic dienes with allenes[2a,b] and vinylallenes with olefins,[2c] the palladium-catalyzed coupling reaction of vinyl or aryl halides with alkenes,[3] cycloisomerization of enynes,[4] and the rhodium-catalyzed [4+2] cycloaddition of dienes with allenes.[5] Only limited examples have been reported for the construction of bridged bicyclic skeletons having an *exo*-methylene group. Among them, Diels–Alder reactions of cyclic dienes with allenes have been employed for the construction of such ring skeleton.[2a,6] Alternative methods involved an intermolecular Diels–Alder cycloaddition reaction of a cyclic diene with 1,3-butadienes followed by isomerization of the vinyl group to the *exo*-methylene moiety,[7a,b] a cyclohexa-1,3-diene derivative with a conjugated enone followed by transforming the keto to the *exo*-methylene group[7c] or a cyclic diene with 2-chloroacrylonitrile as the dienophile followed by conversion of the chlorocyano moiety into the *exo*-methylene group.[7d] However, elevated temperatures and long reaction times often required for the Diels–Alder cycloadditions of unactivated dienes with dienophiles. Another method involved a zinc halides-catalyzed cycloaddition of propargyl halides with cyclopentadiene, producing the 5-[aryl(halo)methylene]bicyclo[2.2.1]hept-2-enes in low yields.[8] Based upon our previous experience with Lewis acid-promoted carbohalogenations of C-2 and C-3 propargyl-tethered cyclic 2-enols providing fused[9a] and spiro bicycles,[9b] respectively, we anticipated that cyclic 2-enols bearing a 3-arylpropargyl tether at the C-4 position of the ring may alter the reaction path and lead to bridged bicyclic skeletons bearing an *exo*-methylene group. Herein, we describe a Lewis acid-promoted carbohalogenation of cyclic C-4-(3-aryl-prop-2-ynyl)-tethered 2-enols to generate bridged bicyclic compounds having an (*E*)-aryl(halo)-methylene group at the C-5 position. These reactions offer an efficient and simple access to 5-aryl(halo)methylenebicyclo[2.2.2]oct-2-ene and -[2.2.1]hept-2-ene derivatives in a highly stereoselective manner under mild reaction conditions.

The six-membered ring 2,6-enynol **1a** was obtained as a mixture of stereoisomers (*trans/cis* = 8:1) using the published method and used as such without further purification (see the Supporting Information for details).[10] Compound **1a** was subjected to $FeCl_3$ under various conditions (Table 1).[11] When exposed to 2.0 molar equiv. of $FeCl_3$ in dichloromethane (DCM) at room temperature under air for 2 min, **1a** gave (*E*)-5-chloro(phenyl)methylenebicyclo[2.2.2]oct-2-ene (**2a**) in 86% yield (entry 1) together with

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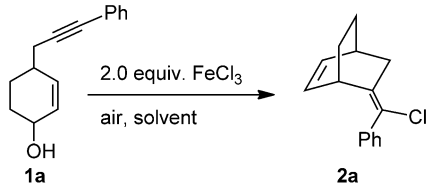
Table 1. Optimization of the reaction conditions.[a]



1a **2a**

Entry	Solvent	Temp. [°C]	Time	Yield [%][a]
1	DCM	24	2 min	86
2	DCM	40	3 min	78
3	DCM	0	4 min	86
4[b]	DCM	27	4 min	99
5	DCE	26	2 min	81
6	DBE	26	24 h	53
7	toluene	24	2 min	73
8	CH_3CN	24	24 h	0
9	ether	24	24 h	0
10	THF	26	24 h	0

[a] Reactions were carried out with 2.0 equiv. of $FeCl_3$ and **1a** in different solvents (0.1 M) at room temperature unless otherwise indicated. Yields were obtained after column chromatography over silica gel.

[b] The reaction was carried out with 0.01 M solution of **1a** in DCM.

a small amount of the *Z*-isomer (*E*/*Z* > 32:1). The (*E*)-configuration of **2a** is assigned by comparison of its ^{1}H NMR spectral data with the corresponding data of (*Z*)-5-chloro(phenyl)methylenebicyclo[2.2.1]hept-2-ene found in the literature.[8] The *E*-stereochemistry assignment for **2a** is in agreement with those obtained from X-ray structures of compounds **2d**, **2f**, **2j**, and **2p** (see below).[12] At a higher temperature (40 °C) in DCM, **1a** afforded a 78% yield of **2a** in 3 min (entry 2). Running the reaction at 0 °C in DCM did not slow the reaction and **1a** gave **2a** in 86% yield in 2 min (entry 3). On lowering the substrate concentration to 0.01 M in DCM at room temperature, the carbochlorination of **1a** finished within 4 min and provided **2a** in quantitative yield (Table 1, entry 4). Switching the reaction medium to dichloroethane (DCE) furnished **2a** in 2 min and in 81% yield (entry 5). The use of dibromoethane (DBE) prolonged the reaction time and afforded **2a** in only 53% yield (entry 6). Toluene is also efficient and **1a** gave **2a** in 2 min and in 73% yield (entry 7). The use of acetonitrile or ether as the solvent resulted in decomposition of the starting substrate **1a** (entries 8 and 9). Compound **1a** was recovered quantitatively when performing the reaction in THF (entry 10). As can be seen from Table 1, the best result was obtained with 2 equiv. of $FeCl_3$ at a lower DCM concentration (0.01 M) (entry 4). However, due to environmental concerns of DCM, the standard carbochlorination reaction condition was carried out with 0.3 mmol of **1a** and 0.6 mmol of $FeCl_3$ in 3.0 mL of DCM (0.1 M) under air at ambient temperature for subsequent studies, albeit in a slightly lower yield. Moreover, other Lewis acids such as $SnCl_4$, $TiCl_4$, $AlCl_3$, and BCl_3 were also tested for carbochlorination under the same reaction conditions. Among them, $SnCl_4$ showed a similar reactivity to $FeCl_3$ and afforded **2a** (*E*/*Z* = 20:1) in 84% yield. The use of $TiCl_4$ afforded **2a** in only 12% yield. On the other hand, $AlCl_3$ and BCl_3 resulted in the quantitative recovery of **1a** in each case.

Under the standard reaction conditions, we next explored the substrate scope of the carbochlorination by reacting a range of 6-membered ring 2,6-enynols **1** with 2.0 molar equiv. of $FeCl_3$ in DCM (0.1 M) (Table 2). It was found that substrates **1b** and **1c** bearing a methyl-substituted phenyl on the alkyne reacted instantaneously to afford **2b** and **2c**, respectively, in high yield (entries 2 and 3). Substrate **1d**, with a bulky naphthalenyl moiety at the alkyne terminus was also competent and provided a mixture of two atropisomers (entry 4, 69%). Notably, bromine-substituted phenyl moieties on the acetylene, **1e** and **1f**, were tolerated and provided the target products in 86 and 94% yield, respectively (Table 1, entries 5 and 6). Compounds **1g** and **1h** bearing an electron-donating methoxy substituent on the phenyl ring also reacted smoothly and afforded the desired products **2g** and **2h** in 70 and 58% yield, respectively (entries 7 and 8). In all these cases, higher *E*/*Z* ratios were obtained (Table 2, entries 1–8). An electron-withdrawing nitro or ester group on the phenyl ring (**1i–l**) was also efficient, yielding the corresponding *exo*-methylene-bridged bicycles **2i–l** in 83–97% yield, albeit with lower *E*/*Z* ratios (Table 2, entries 9–12). While the terminal alkyne **1m** (entry 13) gave an 84% yield of (*E*)-5-chloromethylenebicyclo[2.2.2]oct-2-ene (**2m**), the six-membered ring 7-alkyl-substituted 2,6-enynols **1n** and **1o**, provided the desired products **2n** and **2o**, respectively, in lower yields and *E*/*Z* ratios (Table 2, entries 14 and 15). Gratifyingly, the use of iron tribromide ($FeBr_3$) also generated the corresponding 5-aryl(bromo)methylenebicyclo[2.2.2]oct-2-enes **2p–u** with good yields and *E*/*Z* selectivities (Table 2, entries 16–21) under the standard reaction conditions (0.1 M in DCM, ambient temperature, air, 4–20 min). Next, the reactivity difference between isomers in the carbobromination of **1c** was studied. Treatment of **1c** (*trans*/*cis* = 4:1) with 2.0 equiv. of $FeBr_3$ for 2 min in DCM at room temperature followed by aqueous quenching gave a mixture of the cyclized product **2r** together with the starting material **1c** in a ratio of 1:1. ^{1}H NMR spectral analysis of the crude mixture revealed that the ratio of the remaining *trans*-**1c**/*cis*-**1c** is 8:1. Thus, the result indicated that *cis*-**1c** reacted with $FeBr_3$ faster than *trans*-**1c**. Moreover, **1m**, having a terminal alkyne gave a 45% yield of (*E*)-5-(bromomethylene)bicyclo[2.2.2]oct-2-ene (**2v**) (Table 1,

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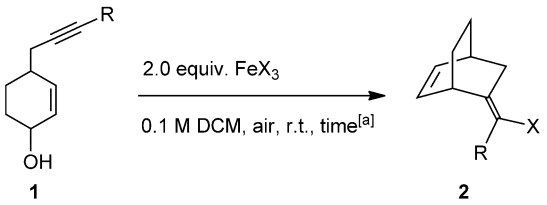
Table 2. Synthesis of (*E*)-5-*exo*-methylene-bridged bicycles (**2**).

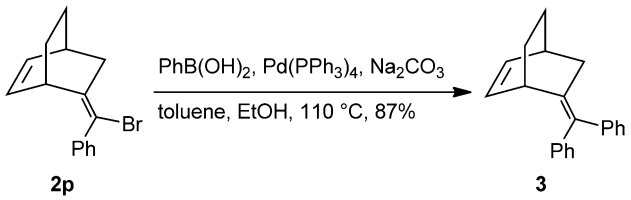


1 **2**

Entry	R	X	Product	Yield [%][b]	*E*/*Z*[c]
1	Ph (**1a**)	Cl	**2a**	86	32:1
2	3-MeC_6H_4 (**1b**)	Cl	**2b**	94	30:1
3	4-MeC_6H_4 (**1c**)	Cl	**2c**	90	18:1
4	1-naphthyl (**1d**)	Cl	**2d**[d,e]	69	>50:1
5	4-BrC_6H_4 (**1e**)	Cl	**2e**	86	>17:1
6	2-BrC_6H_4 (**1f**)	Cl	**2f**[e]	94	>50:1
7	3-MeOC_6H_4 (**1g**)	Cl	**2g**	70	>20:1
8	4-MeOC_6H_4 (**1h**)	Cl	**2h**	58	>13:1
9	3-$NO_2C_6H_4$ (**1i**)	Cl	**2i**	94	4:1
10	4-$NO_2C_6H_4$ (**1j**)	Cl	**2j**[e]	86	5:1
11	3-$CO_2EtC_6H_4$ (**1k**)	Cl	**2k**	97	5:1
12	4-$CO_2EtC_6H_4$ (**1l**)	Cl	**2l**	83	10:1
13	H (**1m**)	Cl	**2m**	84	>50:1
14	Me (**1n**)	Cl	**2n**	54	5:2
15	Bu (**1o**)	Cl	**2o**	39	5:2
16	Ph (**1a**)	Br	**2p**[e]	79	17:1
17	3-MeC_6H_4 (**1b**)	Br	**2q**	80	17:1
18	4-MeC_6H_4 (**1c**)	Br	**2r**	75	30:1
19	4-BrC_6H_4 (**1e**)	Br	**2s**	92	17:1
20	3-MeOC_6H_4 (**1g**)	Br	**2t**	82	15:1
21	4-MeOC_6H_4 (**1h**)	Br	**2u**	45	25:1
22	H (**1m**)	Br	**2v**	45	>50:1
23	Br (**1p**)	Br	**2w**	53	

[a] Typical reaction times for X = Cl, 1–3 min and X = Br, 4–19 min.
[b] Yields were obtained after column chromatography over silica gel.
[c] Determined by ^{1}H NMR spectroscopy analysis of the crude mixture.
[d] Isolated as a mixture of atropisomers.
[e] Structure is confirmed by X-ray diffraction analysis.

entry 22). Delightfully, a bromine atom at the alkyne terminus, **1p**, is not sensitive to the reaction conditions and **1p** furnished 5,5-dibromomethylenebicyclo[2.2.2]oct-2-ene (**2w**) in 53% isolated yield (Table 2, entry 23). It is important to note that the 1,1-dibromo-1-alkene moiety is known to serve as an important synthetic building block for the construction of various organic functional groups through metal-catalyzed coupling reactions.[13] Moreover, to demonstrate the use of the resulting aryl(bromo)-methylene bicyclic compounds, the transformation of **2p** was investigated. Thus, **2p** was treated with $PhB(OH)_2$ and $Pd(PPh_3)_4$ under the Suzuki–Miyaura coupling reaction conditions, affording 5,5-diphenylmethylenebicyclo[2.2.2]oct-2-ene (**3**) in 87% isolated yield (Scheme 1).[14]

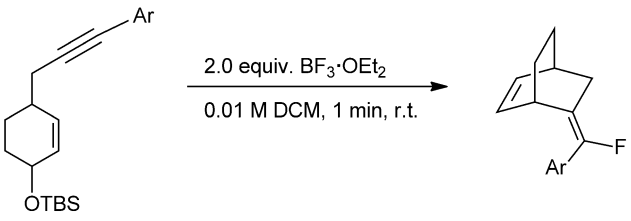


2p **3**

Scheme 1. Transformation of **2p** to **3**.

Next, we investigated the feasibility of carbofluorination of **1a** with $BF_3{\cdot}OEt_2$. Treatment of **1a** with 2 molar equiv. of $BF_3{\cdot}OEt_2$ at room temperature under air gave the desired (*E*)-5-fluorophenylmethylenebicyclo[2.2.2]oct-2-ene (**5a**) in only 45% isolated yield. Fortunately, TBS-protected 6-membered ring 2,6-enyn-1-ols, **4a**–**e**, reacted with $BF_3{\cdot}OEt_2$ (2.0 molar equiv.) instantaneously under air at ambient temperature to afford the desired carbofluorination products **5a**–**e** in good yields and with high *E*/*Z* selectivities (Scheme 2). The success of using the TBS-protected 2,6-enynols with $BF_3{\cdot}OEt_2$ for carbofluorination is consistent with our previous results.[9a]

We next turned our effort to apply this method toward the synthesis of (*E*)-5-[aryl(halo)methylene]-2-norbornenes. The 5-membered ring substrates **6a**–**d** were synthesized from 1,3-cyclopentadione using the same method as for the six-membered ring substrates **1**. To our delight, carbohalogenation of **6a**–**d** with 2.0 molar equiv- of FeX_3 (X = Cl or Br) proceeded efficiently to provide the corresponding (*E*)-5-[aryl(halo)methylene]bicycle[2.2.1]hept-2-enes **7** as the major



4 **5**

a: Ar = Ph, 75%, *E*/*Z* = 18:1
b: Ar = 4-MeC_6H_4, 60%, *E*/*Z* = 18:1
c: Ar = 2-BrC_6H_4, 73%, *E*/*Z* = 17:1
d: Ar = 3-MeOC_6H_4, 93%, *E*/*Z* = 50:1
e: Ar = 4-$CO_2EtC_6H_4$, 78%, *E*/*Z* = 20:1

Scheme 2. Synthesis of (*E*)-5-[(aryl)fluoromethylene]bicyclo[2.2.2]oct-2-enes **5**.

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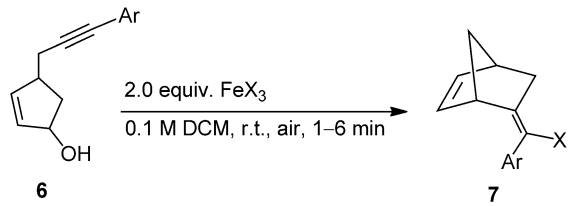
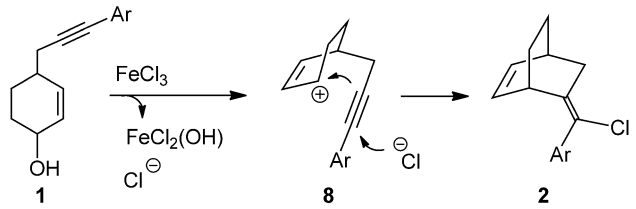


a: X = Cl, Ar = Ph, 85%, *E*/*Z* = 21:1
b: X = Cl, Ar = 4-BrC_6H_4, 72%, *E*/*Z* = 18:1
c: X = Br, Ar = Ph, 85%, *E*/*Z* = 14:1
d: X = Br, Ar = 4-BrC_6H_4, 81%, *E*/*Z* = 13:1

Scheme 3. Synthesis of (*E*)-5-[(aryl)halomethylene]bicyclo[2.2.1]hept-2-enes **7**.



Scheme 4. Plausible reaction path for the $FeCl_3$-promoted carbochlorination of **1** to **2**.

products in 72–85% yield (Scheme 3). In each case, only a small amount of the (*Z*)-isomer was isolated (*E*/*Z* > 13:1).

A reaction pathway for the proposed carbochlorination of the six-membered ring 2,6-enynols is suggested in Scheme 4. Detachment of the hydroxy moiety of **1** by $FeCl_3$ would transiently form the allylic carbonium **8**. Then, *anti*-addition of a chloride and the allylic carbonium across the acetylene furnished the *exo*-methylene-bridged bicycle **2** with the *E*-configuration as the major product.

In summary, an efficient and practical method for the construction of *exo*-methylene-bridged bicycles from cyclic 2,6-enynols and a Lewis acid has been developed. The desired products could be obtained with moderate to excellent yields and *E*/*Z* selectivities. The advantages of this procedure are its operational ease and the mild reaction conditions. Further studies on the synthesis of the bridged bicyclic diene-metal complexes and their synthetic applications are currently in progress.

Experimental Section

Typical Procedure

To a solution of 4-(3-phenylprop-2-yn-1-yl)cyclohex- 2-enol (**1a**) (64 mg, 0.30 mmol in 3.0 mL of dichloromethane (3.0 mL) was added $FeCl_3$ (97 mg, 0.60 mmol) at room temperature under air. The reaction mixture was stirred until no trace of **1a** was detected on TLC (*ca.* 2 min). The mixture was added 3.0 mL of water. The resulting mixture was extracted with diethyl ether (10 × 3 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give a crude oil. The resulting crude mixture was purified by flash column chromatography over silica gel (hexanes) to afford **2a** as a pale yellow oil; yield: 60 mg (0.26 mmol, 86%).

Supporting Information

Spectroscopic characterization and copies of $^1H/^{13}C$ NMR spectra of compounds **2a**–**w**, **3**, **4a**–**e**, **5a**–**e**, and **7a**–**d** and X-ray crystallographic information files for compounds **2d**, **2f**, **2j**, and **2p** are available in the Supporting Information.

Acknowledgements

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[11] $FeCl_3$ having a purity of >99% [impurities: sulfate <0.05%, ferrous iron (as $FeCl_2$) <0.1% and Fe_2O_3 <1%] was purchased from Showa Co. and used as received.
[12] Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1005786 (**2d**), CCDC 1005787 (**2f**), CCDC 1005789 (**2j**), and CCDC 1005789 (**2p**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, Union Road, Cambridge CB2 1EZ, U.K. [Fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].
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