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Halogenation of 1,1-diaryl alkenes

Meng-Yang Chang *, Ming-Fang Lee, Chung-Han Lin, Nein-Chia Lee

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

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ABSTRACT

A variety of vinyl halides were prepared from reaction of 1,1-diarylalkenes with different halogenating agents (e.g., Selectfluor and *N*-halosuccinimide) with good yields under mild and base-free conditions. Synthesis of these molecules has been reported in the literature for being not easy to conduct. Among all the existing preparations of vinyl halide procedures, this protocol has the most facile and practical process.

1. Introduction

Recent reports on new methods for the preparation of vinyl halides have reflected strong interests in the synthesis of these useful building blocks.[1] The halogen atom could also readily undergo metal–halogen exchange,[2] allowing homologation of the parent structure through C-alkylation. When an additional vinyl halogen atom is found at an α-position of the carbonyl, a more synthetic application of α-haloacrylate analogs has been found due to this added functional handle.[3] These vinyl halides are the key ingredients in many therapeutic agents,[4] as important bioactive components (e.g., chlorotrianisene,[4f] enclomiphene,[4g] and 5-fluorouracil[4h]) in pharmaceutical research. With the rapidly increasing applications of such coupling reactions in synthetic and medicinal chemistry,[5] alternative synthetic methods for these building blocks are under intense research. In the Letter, a mild and efficient halogenation of a series of 1,1-diaryl alkenes was being described, and many vinyl halides with a five-, six-, or seven-membered ring system have been provided.

More than a decade ago, Stavber et al. reported that in the presence of cesium fluoroxysulpham (CFS and $CsSO_4F$) in alcohols, the fluoride ion reacted with the five-, six-, and seven-membered rings of 1-phenylbenzocycloalkene to introduce a fluoride atom and an alkoxide component on adjacent positions.[6] 1-Alkoxy-2-fluoro-1-phenylbenzocycloalkanes are efficiently formed during a fluoroalkoxylation procedure. Similarly, in this research, when the structural framework of benzocycloalkene derivatives, with a 4-methoxyphenyl group at the 1-position, were treated with Selectfluor, 1-(4-methoxyphenyl)-2-fluoro-1-benzocycloalkenes with a five- or seven-membered ring system were isolated with high yields (Fig. 1). Selectfluor has been examined for reactions involving carbon–fluoride formation. Due to the numerous advantages associated with this mild, stable, and eco-friendly compound, recent investigations have explored its application as an effective reagent for reactions of interests.[7]

2. Results and discussion

During the synthesis of tetralin-containing heterocycles with Selectfluor,[8,9] the reaction of compound **1a** was studied via fluoronium intermediate **A** isomerization (pathway a) for the formation of 1-(4-methoxyphenyl)-2-fluoro-1-tetralin **2a** in 83% yield, as shown in Scheme 1. Furthermore, the scheme was simple; inexpensive reagents were utilized to result in the title compounds with a high yield, and the process could be done in just one step.

But, with the addition of compound **1b** (Ar = Ph) or **1c** (Ar = 4-FPh) in a reaction with Selectfluor, *trans*-fluorohydrins **3a** or **3b** was produced, respectively, as the sole isomer via pathway b with an 81% or 87% yield, respectively. It was believed that the differences among skeletons **1a**, **1b**, and **1c** should be a 4-methoxyphenyl group providing a stabilizing factor for the formation of

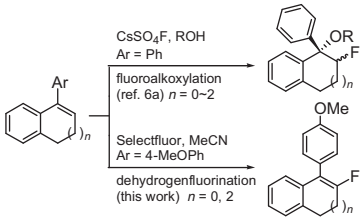

Figure 1. Reaction of benzo cycloalkene with fluoride ions.

* Corresponding author. Tel.: +886 7 3121101x2220.
E-mail address: mychang@kmu.edu.tw (M.-Y. Chang).

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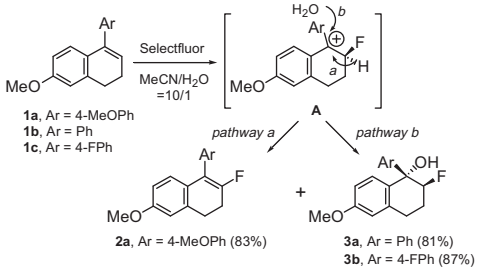
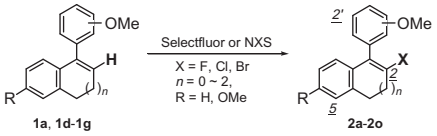


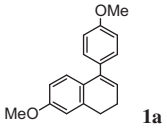
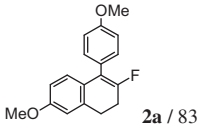
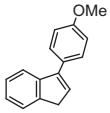
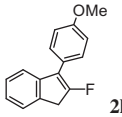
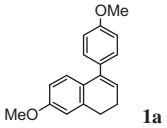
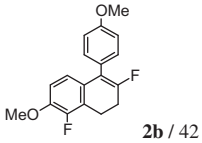
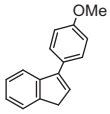
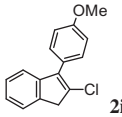
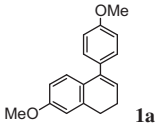
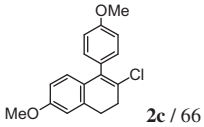
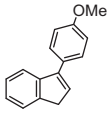
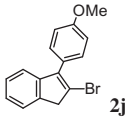
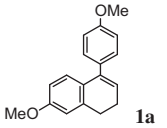
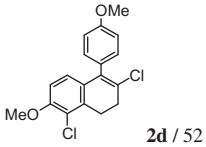
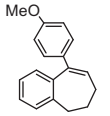
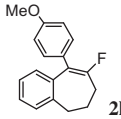
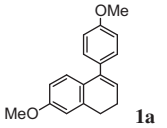
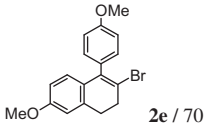
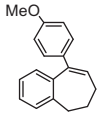
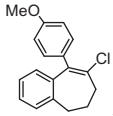
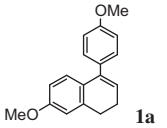
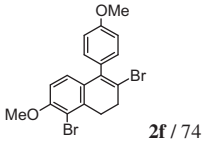
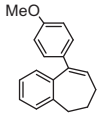
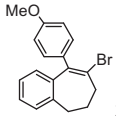
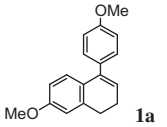
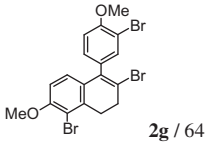
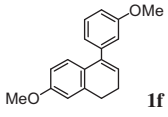
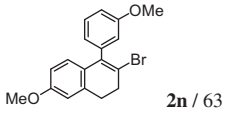
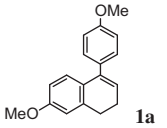
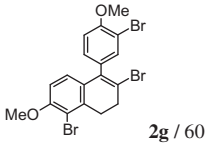
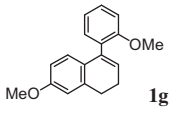
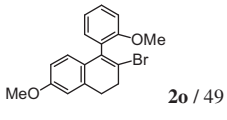
Scheme 1. Reaction of 1-aryl-1-tetralin **1** with Selectfluor.

the intermediate **A** with a benzylic cation, and followed by an intramolecular proton abstraction of intermediate **A** or intermolecular addition of water. Based on the results, it was found that the reaction of compounds **1a** and **1d**–**1g** with NCS, NBS, or Selectfluor yielded vinyl halides **2** with five-, six-, and seven-membered benzocycloalkyl rings with 42–83% yields at reflux temperature, as shown in Table 1.[10] The structures of compounds **2a**, **2c**, **2f**–**h**, and **2m** were determined using single-crystal X-ray analysis (Fig. 2).[11]

In the halogenation of the model substrate **1a** with 1.05 equiv of Selectfluor, NCS, or NBS, compound **2a**, **2c**, or **2e** with a halo group at C-2 position was produced. The total synthetic procedure could

Table 1
Synthesis of vinyl halides **2**[a]



Entry	Reactant **1**	Reagent (equiv)	Product **2**/yield (%)[a]	Entry	Reactant **1**	Reagent (equiv)	Product **2**/yield (%)[a]
1	 **1a**	Selectfluor (1.05)	 **2a** / 83	9	 **1d**	Selectfluor (1.05)	 **2h** / 77
2	 **1a**	Selectfluor (2.1)	 **2b** / 42	10	 **1d**	NCS (1.05)	 **2i** / 60
3	 **1a**	NCS (1.05)	 **2c** / 66	11	 **1d**	NBS (1.05)	 **2j** / 64
4	 **1a**	NCS (2.1)	 **2d** / 52	12	 **1e**	Selectfluor (1.05)	 **2k** / 81
5	 **1a**	NBS (1.05)	 **2e** / 70	13	 **1e**	NCS (1.05)	 **2l** / 53
6	 **1a**	NBS (2.1)	 **2f** / 74	14	 **1e**	NBS (1.05)	 **2m** / 68
7	 **1a**	NBS (3.1)	 **2g** / 64	15	 **1f**	NBS (1.05)	 **2n** / 63
8	 **1a**	NBS (6.1)	 **2g** / 60	16	 **1g**	NBS (1.05)	 **2o** / 49

[a] The isolated products are >95% pure as judged by ^{1}H NMR analysis.

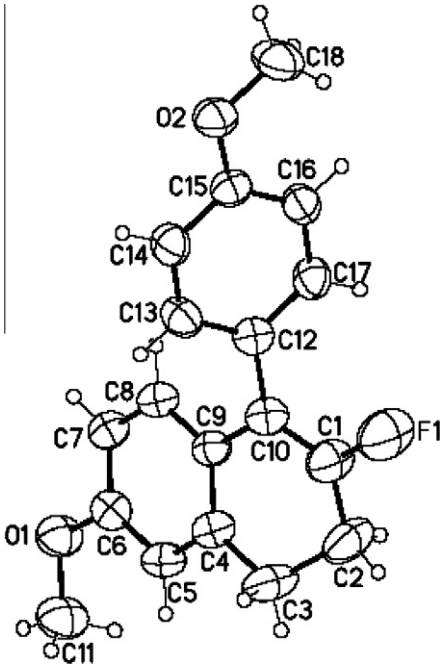
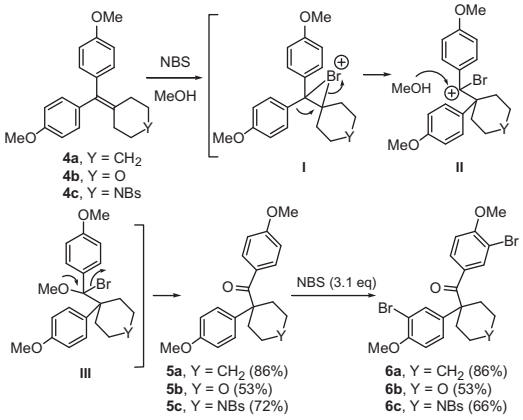


Figure 2. X-ray structure of compound **2a**.

be monitored by TLC until the reaction was completed. When the reaction of compound **1a** with 2.1 equiv of NXS was provided with compound **2b**, **2d**, or **2f**, the second halo group was introduced to the C-5 position. The third halo (X = Br) group could be regioselectively introduced to the C-2′ position by treatment of compound **1a** with 3.1 equiv of NBS. Further, compound **2g** was obtained as the major product (60%) in the resulting product mixture when excess NBS (6.1 equiv) was added to the reaction. There was an interesting regioselective bromination in the structural framework of compound **1a**, as shown in entries 5–8. This study showed that a concise and efficient synthetic approach can introduce the ordinal bromo group to be placed in an appropriate carbon position by the addition of NBS with different equivalents. For Selectfluor- or NXS-mediated halogenation reaction of compounds **1d** and **1e** with the five-membered or seven-membered ring system were shown in entries 9–11 and 12–14, respectively. For examining the reaction of compounds **1f** and **1g** with NBS, vinyl bromides **2n** and **2o** were isolated in 63% and 49% yields as shown in entries 15 and 16, respectively. In comparison with the isolated yields of 2-halobenzocycloalkenes, it was found that the 2-fluoro group was better than other 2-halo groups (Cl or Br). The possible reason might be that Selectfluor was a better monohalogenating agent than NCS or NBS in the reaction of the structural framework **1**.

The typical experimental procedure offers a general and efficient alternative to the halogenation reaction of 1-(4-methoxyphenyl)-1-benzocycloalkenes **1**. Interestingly, treatment of compound **1a** with other halogenating agents[3e] (e.g., *N*-chlorophthalimide or *N*-bromophthalimide) in methanol resulted in compounds **2c** and **2e** with 52% and 58% yields, respectively. But, attempts to perform the reaction with *N*-iodosuccinimide failed, which might be due to a more reactive iodo group. When reaction of compound **1a** with *N*-(phenylseleno)phthalimide took place under the above conditions, the *trans*-1,2-methoxyphenylselenide compound was produced as the sole product with an 88% yield.

To further explore the NBS-mediated reaction in other similar structural skeletons, treatment of bis-(4-methoxyphenyl)methylene six-membered heterocycles (*exo*-olefin) **4** is shown in Scheme 2. Reaction of *exo*-olefin **4** with different equivalents produced compounds **5** (1.05 equiv) and **6** (3.1 equiv) in methanol at reflux

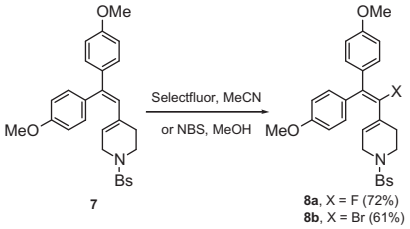


Scheme 2. Reaction of *exo*-olefin **6** with NBS.

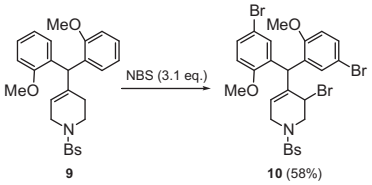
temperature. The transformation was an efficient rearrangement of a facile operation procedure; with the stability provided by tertiary carbocation, the introduction of methanol took place. The initial event might be considered as the formation of the bromonium ion **I**. The 4-methoxyphenyl group promoted the ring-opening of the brominium ion to form intermediate **II**. Methanol can trap benzylic cation and led the reaction to produce intermediate **III**, which could eliminate bromide by an oxygen lone-pair to form compounds **5a**–**5c**. Next, compounds **6a**–**6c** were provided by the addition of excess NBS (3.1 equiv). The exhibited methodology could provide a new route for the preparation of various 4-aroyl-4-aryl-heterocycles in search of useful compounds with potential biological activities.[12]

For skeleton **7** with both *endo*- and *exo*-form olefins,[13] addition of a 1.05 equiv of Selectfluor or NBS in the reaction gave compounds **8a** (72%) and **8b** (61%), respectively, as the sole isomer under the halogenation condition (Scheme 3). This result was similar to the reaction of compound **1a** with Selectfluor and NXS. But, when diene **7** reacted with excess NBS, a complex mixture was observed. In comparison with both compounds **1a** and **5a**–**5c**, a sequential bromination priority with an increasing amount of NBS has not been tested on skeleton **7**.

The excess NBS (3.1 equiv) mediated reaction of skeleton **9** without the 1,1-diarylalkene motif yielded allylic bromide **10** (Scheme 4). The structures of compounds **8a** and **9**–**10** were determined using single-crystal X-ray analysis.[14]



Scheme 3. Reaction of diene **7** with *endo*- and *exo*-olefin.



Scheme 4. NBS-mediated reaction of *endo*-olefin **9**.

3. Conclusion

In summary, a one-step novel synthetic methodology for producing a series of vinyl halides by the Selectfluor- or NXS-mediated reaction was presented in this Letter. For a skeleton with *endo*-olefin or *exo*-olefin, the bromination priority with different equivalents was well-investigated. Several structures of the target products were confirmed by X-ray crystal analysis. Further studies on the biological evaluation of the available compounds are actively underway in laboratories.

Acknowledgments

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References and notes

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10. A representative synthetic transformation of skeleton **2** from **1** is as follows: Selectfluor or NXS (1.05 mmol) was added to a solution of skeleton **1** (1.0 mmol) in acetonitrile or methanol (10 mL) at rt. The reaction mixture was stirred at rt for 2–3 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 10:1–6:1) afforded **2**. For compound **2a**: mp = 95–96 °C; HRMS (ESI, M^++1) calcd for $C_{18}H_{18}FO_2$ 285.1291, found 285.1293; ^{1}H NMR (400 MHz): δ 7.27–7.24 (m, 2H), 6.99–6.95 (m, 2H), 6.77 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 2.8, 8.8 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.04 (dt, J = 2.4, 8.4 Hz, 2H), 2.67 (dt, J = 5.6, 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 158.76, 157.79 (d, J = 49.2 Hz), 154.90, 134.66, 131.20 (2×), 128.19 (d, J = 5.3 Hz), 127.69, 126.30 (d, J = 7.6 Hz), 125.97, 116.21 (d, J = 13.7 Hz), 113.80, 113.74 (2×), 110.85, 55.21, 29.04 (d, J = 6.8 Hz), 25.25 (d, J = 25.0 Hz). Anal. Calcd for $C_{18}H_{17}FO_2$: C, 76.04; H, 6.03. Found: C, 76.43; H, 6.32.
11. CCDC 784042 (**2a**), 789504 (**2c**), 789886 (**2f**), 776260 (**2g**), 790221 (**2h**), and 789691 (**2m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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