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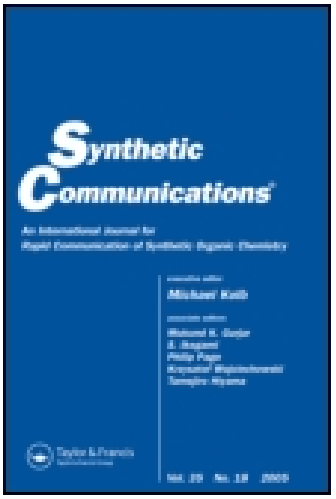

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Reaction of Methylenecyclobutanes with NXS-H_2O System

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REACTION OF METHYLENECYCLOBUTANES WITH NXS-H_2O SYSTEM

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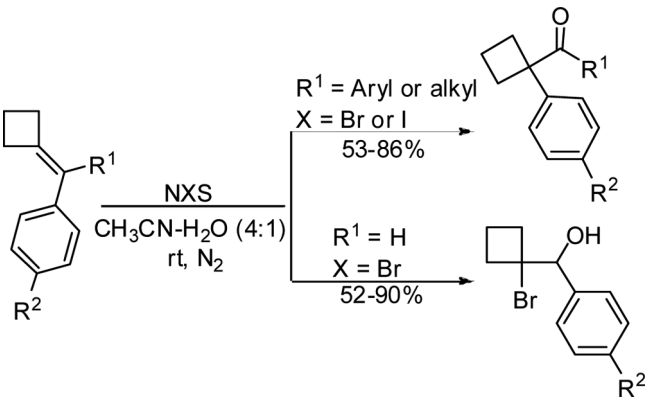
GRAPHICAL ABSTRACT



Abstract *Reactions of methylenecyclobutanes (MCBs) with NXS-H_2O system were investigated. The results were quite different from that of methylenecyclopropanes (MCPs), and an interesting aryl-transfer reaction happened to give substituted cyclobutyl ketones as products when disubstituted MCBs were employed. When monosubstituted MCBs were employed, the direct halohydroxylation gave the cyclobutyl ring untouched adducts. All of these analogs have potential application value in organic synthesis.*

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Keywords Aryl transfer; cyclobutyl ketones; electrophilic addition; halohydroxylation; methylenecyclobutanes

INTRODUCTION

During the past decade, highly activated small organic molecules have attracted the interest of chemists, and their novel reactions have been widely investigated. The highly activated small organic molecules include methycyclopropanes

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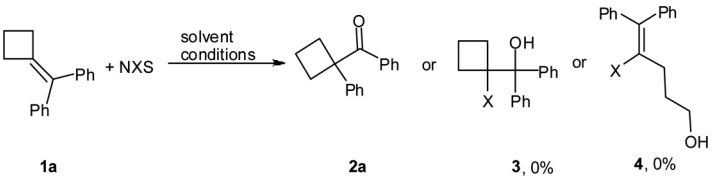
(MCPs),[1] vinylidenecyclopropanes (VCPs),[2] allenes,[3] cyclopropyl allenes,[4] and so on. Because of their high intramolecular ring strain or cumulated C=C bonds, these compounds have high reactivity and can undergo a series of interesting reactions under mild conditions, providing convenient methods for the construction of many useful organic structures. Therefore, they are all useful building blocks in organic synthesis. Containing a four-membered carbon ring and an exocyclic double bond, methylenecyclobutanes (MCBs) are very similar to MCPs. Hence, MCBs may undergo a series of reactions like MCPs and have potential applications in organic synthesis. Recently, the novel reactions of MCBs have been reported in several studies.[5]

Being able to introduce two functional groups simultaneously, halohydroxylations of the C=C double bonds are potent tools in organic synthesis.[6] In the investigation of highly activated small moleculars, Ma has reported the halohydroxylation of allenes, providing a facile access to halogen substituted allyl alcohols.[7] Huang and coworkers reported the halohydroxylation of cyclopropyl allenes using a N-halogen succinimide (NXS)–H_2O system, giving 5-halohexa-3,5-dien-1-ol derivatives as products stereoselectively.[4c] The halohydroxylation of MCPs was also reported by them recently.[8] Encouraged by these works, we became interested in the halohydroxylation of activated olefins. Herein, we report the reaction of MCBs with the NXS–H_2O system. Compared with the reported MCP reactions,[8] the experimental results are quite different.

We initially examined the reaction of MCB **1a** with N-bromo succinimide (NBS) in CH_2CN–H_2O (3:1). The reaction occurred smoothly, and the substrate **1a** disappeared in less than 30 min. However, instead of the desired cyclobutyl

Table 1. Reaction of MCB **1a** with NXS under different conditions[a]



1a **2a** **3**, 0% **4**, 0%

Entry	Solvent	Conditions	X	Time[b] (h)	Yield of **2a** (%)[c]
1	CH_3CN-H_2O (3:1)	rt/N_2	Br	<0.5	70
2	CH_3CN-H_2O (4:1)	rt/N_2	Br	<0.5	86
3	CH_3CN-H_2O (5:1)	rt/N_2	Br	<0.5	77
4	CH_3CN-H_2O (4:1)	50 °C/N_2	Br	<0.5	78
5	CH_3CN-H_2O (4:1)	80 °C/N_2	Br	<0.5	74
6	C_2H_5OH (95%)	rt/N_2	Br	4	18
7	Acetone-H_2O (4:1)	rt/N_2	Br	24	20
8	CH_3CN-H_2O (4:1)	rt/air	Br	<0.5	71
9	CH_3CN-H_2O (4:1)	rt/N_2	Cl	<0.5	0
10	CH_3CN-H_2O (4:1)	rt/N_2	I	<0.5	83

[a]0.3 mmol of **1a**, 0.6 mmol of NXS, and 1 mL of solvent were employed.
[b]The reaction was monitored by TLC (eluent: petroleum ether).
[c]Isolated yields based on **1a**.

ring-intact adduct **3** or cyclobutyl ring-opened adduct **4**, an interesting product, **2a,** was obtained (Table 1, entry 1). Four-membered carbon ring structures are widely present in natural products.[9] Containing a cyclobutyl ketone structure unit, **2a** may have value in introducing a four-membered carbon ring and acting as useful building blocks in organic synthesis.[5b,5e,10] Therefore, we tried to optimize this novel reaction, and the experimental results are listed in Table 1. It is obviously that the CH_3CN-H_2O (4:1) system was a better solvent, and heat was not needed in this reaction (Table 1, entry 2). The reaction could even be carried out without nitrogen protection, and the yield of **2a** was less (Table 1, entry 8). We then examined the reactions by employing other halogen cations and found that the yield of **2a** would not be decreased much when N-iodo succinimide was employed (Table 1, entry 10).

With the optimized conditions in hand, a series of disubstituted MCBs **1** were employed, and the corresponding cyclobutyl ketones **2** were synthesized. It is obvious that the NIS-promoted reaction has wider application scope than the NBS-promoted one (Table 2, entries 7–12).

Although the literature has reported the preparation of cyclobutyl ketones through the reactions of MCBs with an I_2–AgOAc system,[5c] the employment of 300% equivalent of expensive silver salt makes that method uneconomical and limits its further applications. Herein, we have developed a more economic method for the preparation of cyclobutyl ketones, avoiding the use of silver salt.

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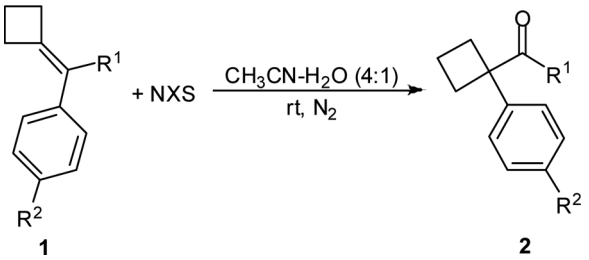
Table 2. Synthesis of substituted cyclobutyl ketones **2**

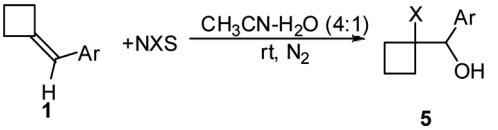


1 **2**

Entry	R^1, R^2	X	Yield of **2** (%)[a]
1	C_6H_5, H (**1a**)	Br	86 (**2a**)
2	C_6H_5, H (**1a**)	I	83 (**2a**)
3	CH_3, H (**1b**)	Br	62 (**2b**)
4	CH_3, H (**1b**)	I	70 (**2b**)
5	C_2H_5, H (**1c**)	Br	68 (**2c**)
6	C_2H_5, H (**1c**)	I	76 (**2c**)
7	*p*-FC_6H_4, F (**1d**)	Br	0
8	*p*-FC_6H_4, F (**1d**)	I	53 (**2d**)
9	CH_3, CH_3 (**1e**)	Br	0
10	CH_3, CH_3 (**1e**)	I	80 (**2e**)
11	CH_3, Cl (**1f**)	Br	0
12	CH_3, Cl (**1f**)	I	58 (**2f**)
13	C_2H_5, Br (**1g**)	Br	0
14	C_2H_5, Br (**1g**)	I	67 (**2g**)

[a]Isolated yields based on **1**.

Table 3. Synethsis of substituted halohydroxylation adducts



1 **5**

Entry	Ar	X	Yield of **5** (%)[a]
1	C_6H_5 (**1h**)	Br	88 (**5a**)
2	*p*-ClC_6H_4 (**1i**)	Br	52 (**5b**)
3	*o*-BrC_6H_4 (**1j**)	Br	90 (**5c**)
4	*p*-BrC_6H_4 (**1k**)	Br	70 (**5d**)
5	C_6H_5 (**1 h**)	I	0
6	*p*-BrC_6H_4 (**1k**)	I	0

[a]Isolated yields based on **1**.

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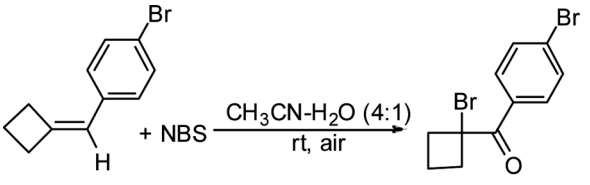
We then examined the reaction of mono-aryl-substituted MCBs with NBS, and the products were quite different. Instead of the rearranged products cyclobutyl ketones **2**, direct halohydroxylation adducts **5** were obtained (Table 3, entries 1–4). When NIS was employed, only a series of unidentified complexes were observed (Table 3, entries 5 and 6). Interestingly, when the reaction was taken without nitrogen atmosphere protection, α-bromo-substituted cyclobutyl ketone **6** was obtained (Scheme 1).

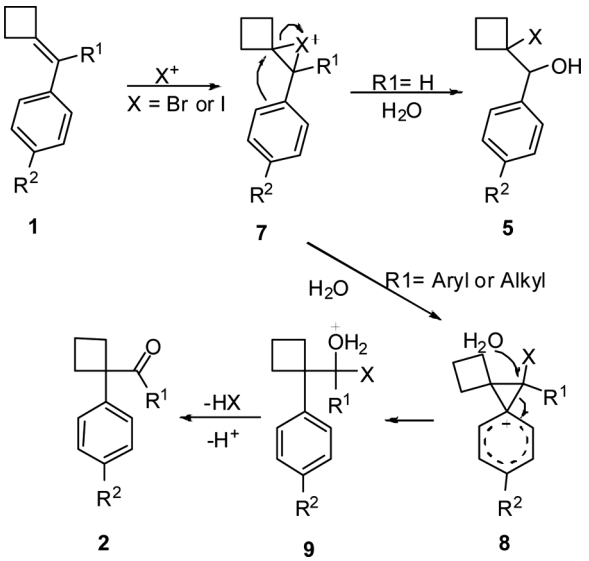
On the basis of the literature and previous experimental results, a possible mechanism of this reaction is suggested in Scheme 2. The electrophilic addition of halogen (Br or I) cation to MCBs **1** first generated the intermediate cation **7**. When monosubstituted MCBs were employed, the reaction of **7** with water offered the halo-hydroxylation adduct **5**. Correspondingly, when disubstituted MCBs were employed, water did not attack the intermediate cation **7** immediately (probably because of the steric hindrance factor), and rearrangement happened to give the intermediate **8**.[5c] The nucleophilic attack of water to **8** gave **9**, which could be transformed to the final product **2** by dehydrohalogenation.

In conclusion, we have investigated the reactions of MCBs with NXS-H_2O system and found that the results were quite different from similar reactions with MCP. When disubstituted MCBs were employed, an interesting aryl-transfer reaction happened to give the substituted cyclobutyl ketones in moderate to good yields. Correspondingly, when monosubstituted MCBs were employed, halo-hydroxylation



1k **6**, 70%

Scheme 1. Reaction of **1k** with NBS in air.



Scheme 2. Proposed mechanism for the reaction.

adducts were obtained in moderate to good yields. All of these analogs have potent application value in organic synthesis.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker Avance (600-MHz) spectrometer in $CDCl_3$ with tetramethylsilance (TMS) as the internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance (150-MHz) spectrometer in $CDCl_3$. Infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrometer. Election impact mass spectra (EIMS) were run on a HP 5989B mass spectrometer.

General Procedure for the Preparation of 2

Under N_2 atmosphere protection, a solution of **1** (0.3 mmol in 1 mL of CH_3CN-H_2O) was added to NBS or NIS (0.6 mmol). The mixture was stirred at room temperature, and the reaction was monitored by thin-layer chromatography (TLC) (eluent: petroleum ether). When the reaction terminated, the solvent was evaporated by vacuum, and the residue was separated by preparative TLC (eluent: petroleum ether/EtOAc 6:1) to give the corresponding product **2.**

General Procedure for the Preparation of 5

Under N_2 atmosphere protection, a solution of **1** (0.3 mmol in 1 mL of CH_3CN-H_2O) was added to NBS (0.6 mmol). The mixture was stirred at room temperature, and the reaction was monitored by TLC (eluent: petroleum ether). When the reaction terminated, the solvent was evaporated by vacuum, and the residue

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was separated by preparative TLC (eluent: petroleum ether/EtOAc 5:1) to give the corresponding product **5**.

Data

Compound 2a. Oil, IR (film): 3060, 2985, 2946, 2867, 1756, 1675, 1597, 1494, 1446, 1247, 912, 754, 702 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.20–7.73$ (m, 10 H), 2.91–2.96 (m, 2H), 2.54–2.58 (m, 2H), 2.07–2.09 (m, 1H), 1.90–1.92 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 16.0$, 32.3, 57.2, 125.6, 126.5, 128.1, 129.0, 129.7, 132.3, 134.2, 143.2, 201.1. MS (EI, 70 eV): m/z (%) = 236 (2) [M^+], 235 (13) [$M^+ - 1$], 55 (100). The spectral data were consistent with Ref. 5c.

Compound 2b. Oil, IR (film): 2982, 2948, 1704, 1492, 1437, 1353, 1235, 1188, 1106, 798, 757, 701 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.24–7.36$ (m, 5H), 2.73–2.77 (m, 2H), 2.40–2.45 (m, 2H), 1.93 (s, 3H), 1.85–1.91 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 15.9$, 24.4, 30.5, 59.3, 126.2, 126.7, 128.7, 143.2, 208.7. MS (EI, 70 eV): m/z (%) = 174 (8) [M^+], 131 (100), 102 (78). Anal. calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.97; H, 7.81.

Compound 2c. Oil, IR (film): 2979, 2940, 1706, 1493, 1447, 1343, 1094, 1072, 959, 913, 756, 701 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.23–7.35$ (m, 5H), 2.73–2.77 (m, 2H), 2.40–2.45 (m, 2H), 2.22–2.26 (m, 2H), 1.85–1.91 (m, 2H), 0.90 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 8.4$, 16.0, 29.7, 30.7, 58.8, 126.3, 126.6, 128.6, 143.5, 211.5. MS (EI, 70 eV): m/z (%) = 188 (11) [M^+], 131 (100), 103 (94). Anal. calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.65; H, 8.30.

Compound 2d. Oil, IR (film): 2948, 2870, 1675, 1598, 1508, 1236, 1136, 833, 613, 539, 506 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.95–7.74$ (m, 8H), 2.92–2.93 (m, 2H), 2.50–2.53 (m, 2H), 2.05–2.08 (m, 1H), 1.91–1.94 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) : $\delta = 15.9$, 32.4, 56.5, 115.4 (d, $J_{C\text{-}F} = 21.7$ Hz), 115.9 (d, $J_{C\text{-}F} = 21.2$ Hz), 127.2 (d, $J_{C\text{-}F} = 7.8$ Hz), 130.4 (d, $J_{C\text{-}F} = 2.9$ Hz), 132.3 (d, $J_{C\text{-}F} = 9.2$ Hz), 138.8 (d, $J_{C\text{-}F} = 3.3$ Hz), 161.6 (d, $J_{C\text{-}F} = 244.5$ Hz), 165.1 (d, $J_{C\text{-}F} = 253.1$ Hz), 199.3. MS (EI, 70 eV): m/z (%) = 272 (2) [M^+], 149 (100). The spectral data were consistent with Ref. 5c.

Compound 2e. Oil, IR (film): 2946, 2866, 1706, 1512, 1430, 1352, 1244, 1189, 1107, 827, 610, 562, 533 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.12 - 7.17$ (m, 4H), 2.70–2.74 (m, 2H), 2.39–2.42 (m, 2H), 2.34 (s, 3H), 1.92 (s, 3H), 1.85–1.87 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 15.9$, 21.0, 24.3, 30.5, 58.9, 126.2, 129.4, 136.4, 140.2, 208.9. MS (EI, 70 eV): m/z (%) = 188 (16) [M^+], 145 (90), 117 (100). The spectral data were consistent with Ref. 5c.

Compound 2f. Oil, IR (film): 2946, 1738, 1706, 1491, 1353, 1190, 1094, 1013, 833, 720 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.17–7.33$ (m, 4H), 2.72–2.76 (m, 2H), 2.35–2.40 (m, 2H), 1.92 (s, 3H), 1.86–1.89 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 15.8$, 24.4, 30.6, 58.8, 127.7, 128.9, 132.7, 141.7, 208.1. MS (EI, 70 eV): m/z (%) = 208 (9) [M^+], 167 (35), 165 (100). Anal. calcd. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 68.84; H, 5.99.

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Compound 2g. Oil, IR (film): 2979, 2939, 2874, 1707, 1487, 1460, 1344, 1170, 1077, 1009, 960, 831, 793, 727 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.11–7.47$ (m, 4H), 2.72–2.77 (m, 2H), 2.35–2.40 (m, 2H), 2.22–2.26 (m, 2H), 1.84–1.91 (m, 2H), 0.91 (t, $J = 7.5$ Hz). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 8.4$, 16.0, 29.8, 30.7, 58.4, 120.6, 128.1, 131.7, 142.5, 210.8. MS (EI, 70 eV): m/z (%) = 267 (3) [$M^+ + 1$], 211 (96), 130 (100). Anal. calcd. for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66. Found: C, 58.17; H, 5.80.

Compound 5a. Oil, IR (film): 3434, 2988, 2951, 2872, 1492, 1448, 1422, 1299, 1243, 1193, 1079, 1025, 915, 747, 700 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.32–7.45$ (m, 5H), 4.77 (d, J = 4.8 Hz, 1H), 2.62–2.74 (m, 4H), 2.48–2.50 (m, 1H), 2.14–2.19 (m, 1H), 1.53–1.57 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 16.7$, 35.6, 37.5, 73.3, 79.1, 127.5, 128.0, 128.2, 139.2. MS (EI, 70 eV): m/z (%) = 240 (2) [M^+], 115 (10), 107 (100). Anal. calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.56; H, 5.71.

Compound 5b. Oil, IR (film): 3441, 2993, 2953, 2874, 1491, 1406, 1383, 1091, 1014, 825, 798, 732, 672, 541 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.33$-7.39 (m, 4H), 4.75 (s, 1H), 2.64–2.69 (m, 3H), 2.58 (s, 1H), 2.46–2.52 (m, 1H), 2.18–2.22 (m, 1H), 1.59–1.61 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 16.7$, 35.5, 37.4, 72.7, 78.5, 128.2, 128.8, 134.0, 137.7. MS (EI, 70 eV): m/z (%) = 275 (1) [$M^+ + 1$], 143 (38), 141 (100). Anal. calcd. for $C_{11}H_{12}BrClO$: C, 47.94; H, 4.39. Found: C, 47.71; H, 4.10.

Compound 5c. Oil, IR (film): 3443, 2991, 2952, 1736, 1469, 1436, 1384, 1240, 1079, 1020, 912, 752, 688 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.20–7.74$ (m, 4H), 5.40 (d, $J = 4.8$ Hz, 1H), 2.63–2.75 (m, 4H), 2.45–2.47 (m, 1H), 2.19–2.23 (m, 1H), 1.67–1.69 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 17.3$, 35.0, 37.9, 73.9, 77.3, 124.2, 127.4, 129.4, 129.7, 132.7, 138.4. MS (EI, 70 eV): m/z (%) = 319 (1) [$M^+ + 1$], 187 (90), 185 (100). Anal. calcd. for $C_{11}H_{12}Br_2O$: C, 41.28; H, 3.78. Found: C, 41.03; H, 3.66.

Compound 5d. Oil, IR (film): 3442, 2992, 2952, 2872, 1638, 1592, 1486, 1424, 1403, 1241, 1073, 1027, 1010, 913, 822, 795, 729, 690 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.30–7.49$ (m, 4H), 4.71 (s, 1H), 2.64–2.65 (m, 4H), 2.47–2.50 (m, 1H), 2.19–2.22 (m, 1H), 1.58–1.62 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 16.7$, 35.5, 37.4, 72.6, 78.5, 122.2, 129.2, 131.1, 138.3. MS (EI, 70 eV): m/z (%) = 319 (1) [$M^+ + 1$], 187 (95), 185 (100). *Anal. Calcd* for $C_{11}H_{12}Br_2O$: C, 41.28; H, 3.78. Found: C, 41.08; H, 3.52.

Compound 6. Oil, IR (film): 2990, 2954, 2869, 1679, 1581, 1394, 1281, 1249, 1072, 961, 849 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.59–7.92$ (m, 4H), 3.08–3.13 (m, 2H), 2.73–2.78 (m, 2H), 2.41–2.43 (m, 1H), 1.87–1.88 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 16.5$, 36.9, 59.3, 128.5, 131.0, 131.7(d), 193.5. MS (EI, 70 eV): m/z (%) = 316 (2) [M^+], 185 (100), 157 (26). Anal. calcd. for $C_{11}H_{10}Br_2O$: C, 41.55; H, 3.17. Found: C, 41.72; H, 3.40.

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