



Original Research Article

The effect of substitutes on chemoselective C-H functionalization of arens by H₂O₂-HBr in waterHossein Paghandeh^a, Maryam Khalili Foumeshi^{b,*}, Mohammad Ghaffarzadeh^a^a Chemistry and Chemical Engineering Research Center of Iran, PO Box 14335-186, Tehran, Iran^b Faculty of Chemistry, Kharazmi University, P. O. Box 15719-14911, 49 Mofateh St., Tehran, Iran

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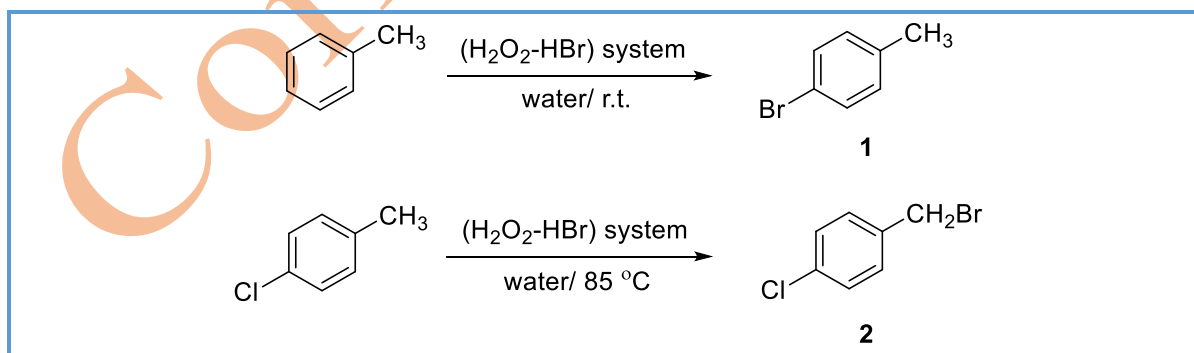
H₂O₂-HBr system
 Toluene
 Chemoselective
 C-H Functionalization

ABSTRACT

A novel, practical and environmentally friendly method has been developed for bromination of toluene derivatives by using H₂O₂-HBr system in water as a green solvent with a mild condition. This direct and straightforward method approaches to a chemoselective and regioselective substitution. Different toluene derivatives were used in which, type of functional group has affected on chemoselectivity and the situation of them has affected on regioselectivity of the reaction. Bromination was done on aromatic rings and alkane chain by different reaction conditions. Brominated toluene derivatives are isolated in moderate to high yields, different spectroscopic techniques were used to characterize the compounds, including GC-MS, ¹H NMR, and ¹³C NMR.

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Graphical Abstract



Introduction

Aromatic and heteroaromatic bromides are very important compounds in organic synthesis due to their potential application in synthesis of natural products which have biological activity as intermediate [1, 2], in pharmaceutical science, dye and pesticide [2]. On the other hands, functionalization of aromatic or alkane non-active C-H bond has been one of the most important topics in organic chemistry. Substitution of C, S instate of H in organic synthesis is very valuable, because scientist can use this method to prepare many of natural products intermediate (which usually contain aromatic groups) [3]. In the recent years numerous bromination methods for direct bromination of aromatic and heteroaromatic compounds have been reported, in which different kinds of brominating agent were used, such as FeBr₃ as catalyst [4], Trip-SMe (Trip= triptyceny) as Lewis base catalyst and *N*-halosuccinimides [5], Erythrosine B as catalyst and NBS [6], H₂O₂, HBr in different solvent [7, 1, 8], Br₂/SbF₃/HF [9], NBS/H₂SO₄/CF₃COOH [10], NBS/NaOH [11], NH₄Br/H₂O₂/CH₃COOH [12], Br₂/SO₂Cl₂ over microporous catalyst [13]. Using transition metals as catalyst for C-H activation has been well studied. These methods are expensive and time consuming. There are some reports in which cheap catalyst was used; however, the reactions take a long time [14] and a few reports with catalyst free condition and a short reaction time for C-H functionalization [15].

Traditionally, bromo compounds are prepared by reaction with elemental halogen in presence of a metal catalyst and often involving harsh reaction conditions. The use of molecular bromine has several drawbacks arising out of its hazardous nature, difficult handling, low atom efficiency, low selectivity, and the formation of HBr as a by-product [16].

However, bromination reactions have associated environmental hazards with respect to transport, handling, storage, and waste control of bromine [17].

In order to solve the problem of HBr preparation waste control in the reaction with elemental bromine in presence of a metal catalyst in this protocol, oxidation method of bromide with H₂O₂, which is a powerful and environmentally friendly oxidant was chosen. To fulfil the increased demands for green chemistry replacement of the organic solvent by water was done in this new method.

Experimental

Materials and methods

All the chemicals used in this protocol were purchased from Merck (Darmstadt, Germany), Fluka (Neu-Ulm, Germany), and Sigma-Aldrich (St. Louis, MO, USA) companies. All synthesized compounds had appropriate spectroscopic data. ¹H NMR (80 MHz) spectra were recorded on a Bruker 80 MHz spectrometer in CDCl₃ using TMS as internal standard. A GC-MS method for the analysis of mixtures and pure products was applied; A Fisons instruments gas chromatograph 8000 connected to a mass detector (Trio1000) with 70 eV was used. A 30 m × 0.25 mm column packed with WCOT fused silica CP-sil 5CBMS was employed. Column temperature was programmed from 80 to 270 °C at 10 °C/min. Injection was performed at 280°C. The carrier gas was helium and the inlet pressure was 10 psi.

General procedure for synthesis of **1a-i**

To a mixture of H₂O₂ (1.1 mmol), and HBr (1.1 mmol) in water (3 mL), Toluene (1 mmol) was added. The mixture was stirred at room temperature for 90 min and the reaction was followed by TLC and GC. After completion of the

reaction, the mixture was purified directly by column chromatography (SiO₂; EtOAc/ *n*-hexane, 1/5).

1-bromo-4-methylnaphthalene (1a)

Colorless liquid, ¹H NMR (80 MHz, CDCl₃): δ 8.67 (d, *J* = 1.68 Hz, 3H), 8.03 (t, *J* = 3.72 Hz, 1H), 7.98-7.34 (m, 3H), 7.20 (d, *J* = 1.5 Hz, 1H), 2.77 (s, 3H). MS (EI) (70 eV): *m/z* (%) 222 (100) [M+2], 220 (81) [M+], 141 (70), 115 (25).

4-bromo-1-methoxy-2-methylbenzene (1b)

Off white solid, mp 66-68 °C, ¹H NMR (80 MHz, CDCl₃): δ 7.25 (q, *J* = 1.92 Hz, 2H), 6.67 (d, *J* = 1.84 Hz, 1H), 3.79 (s, 3H), 2.17 (s, 3H). MS (EI) (70 eV): *m/z* (%) 202 (100) [M+2], 200 (89) [M+], 187 (42), 121 (26), 106 (11), 91 (25), 78 (50), 77 (36), 51 (19).

4-bromo-2-methylaniline (1c)

Pale brown solid, mp 56-59 °C, ¹H NMR (80 MHz, CDCl₃): δ 7.16 (m, 2H), 6.77 (m, 1H), 3.63 (d, *J* = 9.96 Hz, 2H), 2.15 (s, 3H). MS (EI) (70 eV): *m/z* (%) 187 (94) [M+2], 185 (100) [M+], 106 (92), 104 (11), 79 (17).

4-bromo-3-methylaniline (1d)

Yellow solid, mp, 81-84 °C, ¹H NMR (80 MHz, CDCl₃): δ 7.25 (m, 1H), 6.52 (m, 2H), 3.62 (s, 2H), 2.23 (s, 3H). MS (EI) (70 eV): *m/z* (%) 187 (100) [M+2], 185 (71) [M+], 106 (31).

2-bromo-4-methylphenol (1e)

Colorless liquid, ¹H NMR (80 MHz, CDCl₃): δ 7.14 (m, 2H), 6.92 (t, *J* = 4.35 Hz, 1H), 5.91 (m, 2H), 2.16 (m, 3H). MS (EI) (70 eV): *m/z* (%) 188 (100) [M+2], 186 (97) [M+], 107 (94), 77 (62), 79 (25), 51 (22).

4-bromo-2-methylphenol (1f)

Off white solid, mp, 63-67 °C, ¹H NMR (80 MHz, CDCl₃): δ 7.22 (m, 2H), 6.75 (d, *J* = 1.69 Hz, 1H), 6.24 (s, 1H), 2.31 (s, 3H). MS (EI) (70 eV): *m/z* (%) 188 (100) [M+2], 186 (97) [M+], 107 (94), 77 (55), 79 (33), 51 (17).

2-bromo-1,4-dimethylbenzene (1g)

Colorless liquid, ¹H NMR (80 MHz, CDCl₃): δ 7.40 (d, *J* = 1.10 Hz, 1H), 7.06 (m, 2H), 2.26 (m, 6H). MS (EI) (70 eV): *m/z* (%) 186 (100) [M+2], 184 (91) [M+], 105 (100), 103 (25).

1-bromo-4-ethylbenzene (1h)

Colorless liquid, ¹H NMR (80 MHz, CDCl₃): δ 7.50 (d, *J* = 0.27 Hz, 2H), 7.14 (d, *J* = 1.63 Hz, 2H), 2.69 (q, *J* = 4.54 Hz, 2H), 2.32 (t, *J* = 3.05 Hz, 3H). MS (EI) (70 eV): *m/z* (%) 185 (100) [M+2], 183 (96) [M+], 104 (77.5), 103 (29), 78 (16), 51 (12.5).

1-bromo-4-methylbenzene (1i)

Pale yellow liquid, ¹H NMR (80 MHz, CDCl₃): δ 7.32 (m, 4H), 2.08 (s, 3H). MS (EI) (70 eV): *m/z* (%) 171 (100) [M+1], 170 (15) [M+], 169 (100) [M-1], 90 (45), 63 (24), 50 (12.5).

General procedure for synthesis of 2a-h

To a mixture of H₂O₂ (1.5 mmol), and HBr (3 mmol) in water (3 mL), Toluene derivatives (1 mmol) was added. The mixture was stirred at 85 °C for 150 min and the reaction was followed by TLC and GC. After completion of the reaction, the mixture was purified directly by column chromatography (SiO₂; EtOAc/ *n*-hexane, 1/4).

1-bromo-4-(bromomethyl)benzene (2a)

Pale brown solid, mp 62-65 °C, ¹H NMR (80 MHz, CDCl₃): δ 7.50 (m, 2H), 7.31 (m, 2H), 4.50 (d, *J* = 14.12 Hz, 2H). MS (EI) (70 eV): *m/z* (%) 252 (85) [M+2], 250 (100) [M+], 171 (37.5), 169 (60), 107 (9), 90 (45), 63 (22.5), 50 (12.5).

1-bromo-4-(bromomethyl)naphthalene (2b)

Oily viscose liquid, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 8.36 (dd, $J = 1.40$ Hz, 1H), 8.20 (dd, $J = 1.40$ Hz, 1H), 7.77 (d, $J = 1.6$ Hz, 1H), 7.70 (m, 2H), 4.96 (s, 2H). MS (EI) (70 eV): m/z (%) 300(15) [M^+], 221 (100), 219 (75), 140 (22.5).

1-(bromomethyl)-4-chlorobenzene (2c)

Yellow solid, mp, 48-50 °C, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 7.22 (d, $J = 3.96$ Hz, 4H), 4.38 (s, 2H). MS (EI) (70 eV): m/z (%) 206(12.5) [$\text{M}+2$], 204 (10.5) [M^+], 127 (30), 125 (100), 89 (35), 63 (17.5).

1-(bromomethyl)-3-chlorobenzene (2d)

Yellow liquid, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 7.21 (m, 4H), 4.36 (s, 2H). MS (EI) (70 eV): m/z (%) 206(10) [$\text{M}+2$], 204 (8) [M^+], 127 (35), 125 (100), 89 (22.5), 63 (12.5).

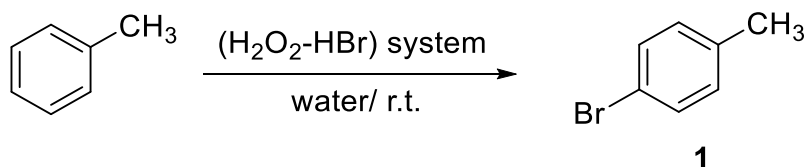
1-(bromomethyl)-2-chlorobenzene (2e)

Yellow solid, mp, 81-84 °C, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 7.27 (m, 4H), 4.53 (s, 2H). MS (EI) (70 eV): m/z (%) 206(5) [$\text{M}+2$], 127 (30), 125 (100), 89 (30), 63 (20).

1-(bromomethyl)-3-nitrobenzene (2f)

White solid, mp, 58-60 °C, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 7.90 (m, 1H), 7.38 (m, 3H), 4.43 (s, 2H). MS (EI) (70 eV): m/z (%) 216(5), 199 (7.5), 136 (100), 90 (12.5), 89 (15).

1-(bromomethyl)-4-Idobenzene (2g)



Scheme 1. The model reaction for preparing 4-Br-C₆H₄-CH₃

Pale brown solid, mp, 78-80 °C, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 7.75 (dd, $J = 23.2$ Hz, 2H), 7.15 (dd, $J = 11.14$ Hz, 2H), 4.35 (s, 2H). MS (EI) (70 eV): m/z (%) 296(7.5) [M^+], 217 (100), 90 (17.5), 63 (10).

1-(bromomethyl)-4- nitrobenzene (2h)

Pale yellow solid, mp, 98-100 °C, $^1\text{H NMR}$ (80 MHz, CDCl_3): δ 8.08 (m, 2H), 7.42 (m, 2H), 4.44 (s, 2H). MS (EI) (70 eV): m/z (%) 217(2.5) [$\text{M}+2$], 201 (5), 138 (100), 106 (17.5), 89 (25), 78 (35).

Results and Discussion

The reaction between the HBr and H₂O₂ lead to both ionic and radical bromine, then both radical and ionic reactions of bromine are probable. In this protocol we have studied and compared these two reactions with different toluene derivatives. We start our investigation with a reaction of toluene, aquas H₂O₂ and HBr in water as solvent at room temperature (Scheme 1). By using 1 equivalent of toluene and 0.5 equivalent of H₂O₂ & HBr desired product (1) was achieved with good yield in 60 minutes (Table 1, entry 1). Increasing the equivalent of H₂O₂ & HBr in the same reaction condition yield were increased (Table 1, entries 2,3). Increasing the reaction time to 90 min yield of desire product (1) was increased (Table 1, entry 4). But increasing the reaction time to 120 min desired product (1) yield improvement didn't happen (Table 1, entry 5).

Table 1. Optimization of the model reaction for preparing 4-Br-C₆H₄-CH₃

Entry	C ₆ H ₅ -CH ₃	H ₂ O ₂ (mol)	HBr	Time (min)	Yield (%) ^a
1	1	0.5	0.5	60	40
2	1	1.1	1.1	60	55
3	1	2	2	60	55
4	1	1.1	1.1	90	65
5	1	1.1	1.1	120	65

^a GC Yield

After optimization of the reaction conditions, the scope of this methodology was investigated by using various aromatic ring derivatives (Scheme 2). Structurally diverse brominate compound with different substituents on the aromatic rings afforded the corresponding products in good to excellent yields.

In the reaction of aromatic rings which are activated with two electron donating group side

product was produced which seems that was dibromo compound. To have the best yield of planned product, the reaction condition was changed for some starting material (Table 2). After mentioned time in Table 2 a precipitate was appeared, which contained planned product. Changing the mole ratio of H₂O₂ and HBr as Table 2 lead to best yield of desire product.

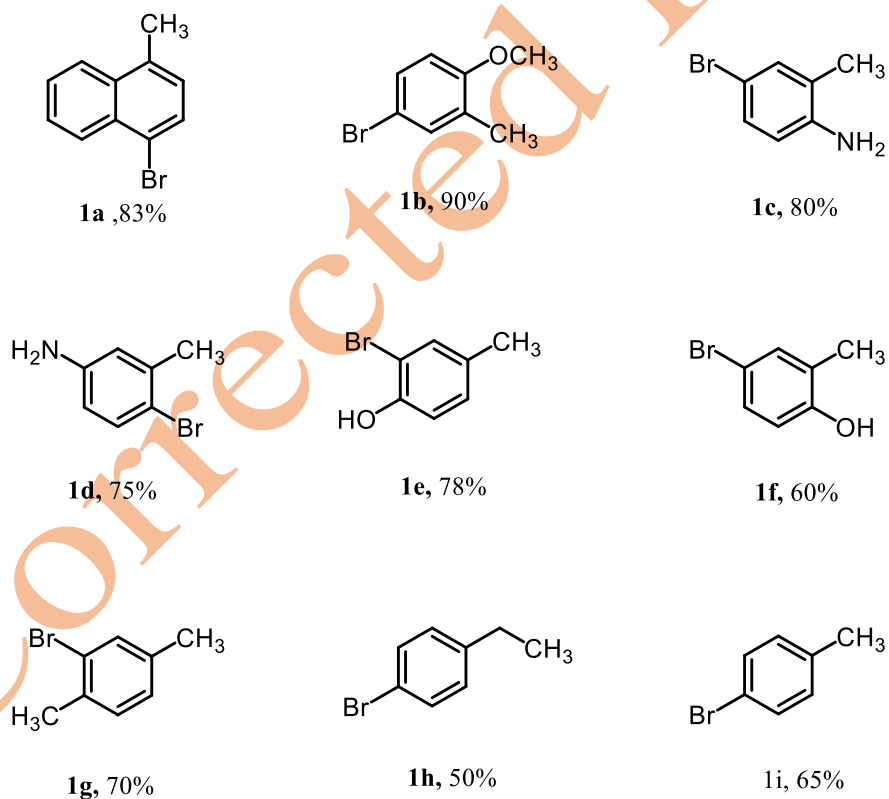
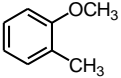
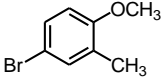
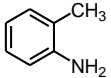
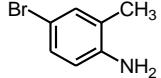
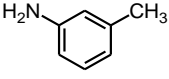
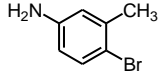
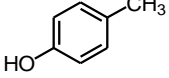
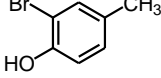
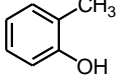
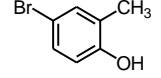
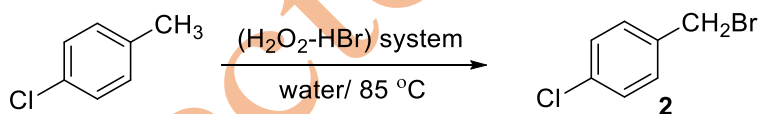
**Scheme 2.** Scope of brominated aromatic rings which are activated with electron donating group

Table 2. Reaction condition for aromatic rings which are activated with two electron donating group

Entry	Substrate	Product	1: HBr: H ₂ O ₂ (mol ratio)	Time
1			1: 1: 1	10 min
2			1:2: 1	20 min
3			1:2: 1	20 min
4			1:1: 1	10 min
5			1:1: 1	10 min

To improve our investigation, bromination of the alkane chain of aromatic rings was studied. To find an optimum method for bromination of alkane chain reaction between 4-chloro toluene, aquas H₂O₂ and HBr in water as solvent and in 65 °C was choose as model reaction (Scheme 3). By using 1 equivalent of 4-chloro toluene and 0.5 equivalent of H₂O₂ & 1 equivalent HBr desired product (1) was

achieved with good yield in 90 minutes (Table 3, entry 1). By increasing the equivalents of H₂O₂ & HBr percentage of yield was increase in the same condition. Best mole ratio (Table 3, entry 3) was choosing for time and temperature optimization. Mole ratio of 4-chlorotoluene, H₂O₂ & HBr (1: 1.5: 3), temperature 85 °C and 150 minutes was the optimum reaction condition (Table 3, entry 10).

**Scheme 3.** The model reaction for preparing 1-(bromomethyl)-4-chlorobenzene**Table 3.** Optimization of the model reaction for preparing 1-(bromomethyl)-4-chlorobenzene

Entry	4-Cl-C ₆ H ₄ -CH ₃ : H ₂ O ₂ : HBr (mol ratio)	Time (min)	Temperature (°C)	4-Cl-C ₆ H ₄ -CH ₂ Br Yield(%) ^a
1	1: 0.5: 1	90	65	50
2	1: 1: 2	90	65	60
3	1: 1.5: 3	90	65	65
4	1: 2: 4	90	65	60
5	1: 1.5: 3	150	65	70
6	1: 1.5: 3	210	65	68
7	1: 1.5: 3	150	25	25
8	1: 1.5: 3	150	45	37
9	1: 1.5: 3	150	65	70
10	1: 1.5: 3	150	85	73
11	1: 1.5: 3	150	100	73

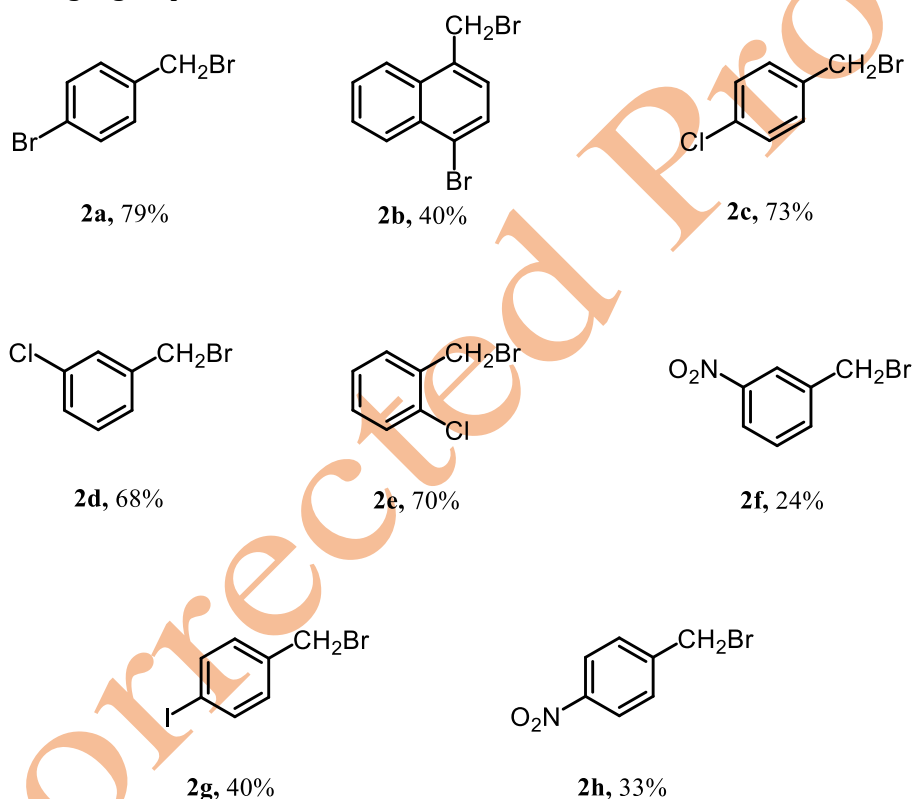
^a GC Yield

After optimization of the reaction conditions, the scope of this methodology was investigated by using various aromatic ring derivatives (Scheme 4). Structurally diverse brominate compound with different substituents on the aromatic rings afforded the corresponding products in good to excellent yields.

The reaction time for nitro compound was change to 24 hours to had the best yield of planned product 2.

Substitution of bromine on aromatic rings affected by the functional groups on the rings, electron donating group was done the

substitution on aromatic ring and electron withdrawing group was done the radical substitution on alkane chain at α situation. The situation of functional group on aromatic rings has affected on bromination too. Type of functional group has affected on Chemoselectivity and the situation of the has affected on Regioselectivity of the reaction. Another important item for the aromatic ring with electron donating groups, in these reactions is, decreasing the solubility in water the yield of desired product was increase.



Scheme 4. Scop of brominated aromatic rings which have electron withdrawing group

Conclusions

Different toluene derivatives were brominated with H_2O_2 -HBr system in hot water. By using different reaction conditions, aromatic rings and alkane chains were brominated. Functional groups on aromatic rings are

affected on chemoselectivity and regioselectivity of this method. Chemoselectivity is linked to the types of functional groups while regioselectivity is linked to their positions. Using water as green solvent, green bromination agent, catalyst free condition, chemoselectivity, regioselectivity,

short reaction time, moderate (24 to 79 percent for substitution on alkane chain) to high (60 to 90 percent for substitution on aromatic rings) yields and the scope of reaction are the advantages of this new method.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at DOI: 10.22034/ajgc.2021.xxxx

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