# Catalyst and solvent-free bromination of toluene derivatives by $HBr-H_2O_2$ with visible-light photocatalysis using a continuous-flow micro reactor

Wu-bin Yu, Dong-ping Yu, Ming-ming Zheng, Shu-ting Shan, Yu-jin Li and Jian-rong Gao\*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310032, P. R. China

The efficiency of the bromination of toluene derivatives has been improved significantly by utilising a combination of hydrogen peroxide (30%) and hydrogen bromide (40%) in a continuous-flow micro reactor. This catalyst and solvent-free reaction takes place by visible-light photocatalysis.

Keywords: oxidative bromination, continuous-flow micro reactor, visible-light photocatalysis

Brominated aromatic compounds are widely applied in functional dye, flame-retardant, pharmaceutical, agrochemical and other fine chemicals.<sup>1,2</sup> Thus, considerable effort has been devoted toward the development of an efficient methodology for their synthesis.3 The most common brominating reagent for synthesis of brominated aromatic compounds is molecular bromine. However, it suffers from disadvantages such as toxicity, corrosive nature, difficulty in handling and its high reactivity, which results in highly exothermic and nonselective reactions. Moreover, the use of chlorinated solvent and the corrosive by-product HBr generated from the reaction is also not environmentally friendly. Therefore, some protocols for the synthesis of brominated aromatic compounds using alternative brominating reagents, such as N-bromosuccinimide<sup>4-7</sup> and pyridinium and tetraalkylammonium tribromides8-10 have attracted great interest. However, these brominating reagents also suffer from disadvantages such as low atom efficiency, leaving a residue of reagent and requiring molecular bromine for their preparation.

One possible way to circumvent these drawbacks is to utilise a suitable oxidant to oxidise bromide anion to form molecule bromine *in situ.*<sup>3,11</sup> Recently, aromatic side-chain halogenations with NaBrO<sub>3</sub>–NaBr–HCl,<sup>12</sup> NaBr–H<sub>2</sub>O<sub>2</sub>–H<sub>2</sub>SO<sub>4</sub><sup>13</sup> or HBr–H<sub>2</sub>O<sub>2</sub><sup>14</sup> as brominating reagents have been reported. However, dibrominated derivatives were always obtained as byproducts. Moreover, most of these procedures suffer from disadvantages such as long reaction times, high reaction temperatures, use of metal catalysts, use of solvents or tedious work-up.<sup>15</sup>

Here, we report a safe and efficient visible-light photocatalysed bromination process using HBr–H<sub>2</sub>O<sub>2</sub> as brominating reagent in a continuous flow micro reactor. This protocol offers significant improvements in selectivity and conversion compared to conventional batch processes due to a precise control of residence time, heating and mass transport.<sup>16,17</sup>

# **Results and discussion**

A model study was initiated with toluene as substrate (Scheme 1). The conversion of bromine atoms (uptake into toluene) was used to evaluate the bromination reaction.



<sup>\*</sup> Correspondent. E-mail: yuwb@zjut.edu.cn

In continuous flow experiments, a simple process was set up by using a glass micro reactor from the Mikroglas Chemtech GmbH Company. Three single-channel micro-injection pumps (LSP01-1A) were connected to the reactor allowing a precise control of the flow rates of the three reagent solutions (Fig. 1). The T-mixer was used to mix the  $H_2O_2$  and HBr before they entered the reactor, because there were only two channels in the reactor.

From Table 1, it is seen that the side-chain bromination selectivity was excellent and that light can effectively promote the conversion of bromide. The best conversion of 83.1% was obtained with the ratio of **2a/3a** at 97.6/2.5 (Table 1, entry 3) under the incandescent lamp. Thus, we presumed that the oxidative bromination process may be a visible-light induced free-radical reaction.

Based on the preliminary results of the single-factor experimental design, an  $L_9$  (3<sup>4</sup>) orthogonal design<sup>18</sup> was used to optimise bromination by employing the HBr–H<sub>2</sub>O<sub>2</sub> as brominating reagent in the continuous-flow micro reactor. The concept of orthogonal design is to find the setting for each of a number of input parameters that optimises the output(s) of the process. It allows a decrease in the number of experiments performed with only slightly less accuracy than full factor testing. In a set of experiments, the bromination temperature was preset at room temperature and the level factors of orthogonal design are shown in Table 2.

According to Table 3, nine groups (entries 1–9) of experiments were carried out and the results of the orthogonal design are shown in Tables 3 and 4. The conversion of bromine atom obtained from the Taguchi  $L_9$  (3<sup>4</sup>) orthogonal array experiments ranged from 49.7 to 91.8% (Table 3). The results



Fig. 1 Schematic diagram of the reactor setup for the continuous flow bromination of toluene derivatives with the  $HBr-H_2O_2$ . The light was placed 5 cm away above the glass reactor.

Table 1 Conditions and results for  $HBr-H_2O_2$  bromination of toluene 1a

Entry	Conditions <sup>a</sup>	Br atom	Product °	
		conversion /% <sup>b</sup>	2a <sup>d</sup>	3a
1	T <sub>B</sub> , dark	0	0	0
2	$T_{B}$ , sunlight	65.5	97.3%	2.7%
3	T <sub>R</sub> , 100W incan- descent lamp	83.1	97.6%	2.5%
3	T <sub>R</sub> , 125W UV light	73.5	96.5%	3.5%

<sup>a</sup>The ratio of the reactants is  $1a:H_2O_2:HBr=1.0:1.0:1.5$ , T<sub>R</sub> refers to the room temperature (25 °C).

<sup>b</sup>The ratio of the products and starting material was determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

<sup>c</sup>GC product proportions.

<sup>d</sup>See Caution in the Experimental section.

Table 2 Level and factor of orthogonal design

Level	Factor				
	A:Molar ratio (1:H <sub>2</sub> O <sub>2</sub> : HBr) <sup>a</sup>	B:Residence time /min <sup>a,b</sup>	C:Power of light bulb/W <sup>a</sup>		
1	1.0:1.5:1.0	3	60		
2	1.5:1.5:1.0	4	100		
3	2.0:1.5:1.0	5	150		

<sup>a</sup>Symbols A, B, C represent factors of molar ratio, residence time and power of light bulb. 1, 2, and 3 represent concentration levels of each factor.

<sup>b</sup>Residence time refers to time to react the premixed peroxide/ HBr solution with the toluene

**Table 3** An  $L_{g}$  ( $_{3}^{4}$ ) orthogonal array and experimental results

Entry	A	В	С	Br atom conversion /%ª -	Product <sup>b</sup>	
					<b>2a</b> ° /%	3a/%
1	1	1	1	49.7	98.0	2.0
2	1	2	2	64.0	96.7	3.3
3	1	3	3	71.6	94.7	5.3
4	2	1	2	79.1	98.4	1.6
5	2	2	3	81.5	96.0	4.0
6	2	3	1	76.1	98.9	1.1
7	3	1	3	91.8	98.7	1.3
8	3	2	1	84.8	98.4	1.6
9	3	3	2	89.6	98.9	1.1
10	3	1	3	90.3	98.6	1.4
11	3	3	3	93.6	98.2	1.8

<sup>a</sup>The ratio of the products and starting material was determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>b</sup>GC product proportions

<sup>o</sup>See Caution in the Experimental section.

**Table 4** Results of intuitive analysis of toluene bromination

Mean value	А	В	С
1	61.8	73.5	70.2
2	78.9	76.8	77.6
3	88.7	79.1	81.7
Range	27.0	5.6	11.5

indicate that molar ratio plays a significant role in the bromination process from the pre-determined factor levels and light intensity was more influential than residence time. Moreover, utilisation of bromine atoms was increased by increasing molar ratio, prolonging reaction time and enhancing light intensity. Based on the analysis, the optimum process condition was A3B1C3 (entry 7) or A3B3C3, although A3B3C3 was not carried out in the experiment. Therefore, with the optimised conditions (entries 10–11) in hand, the bromination of **1a** was carried out with high conversion (up to 93.6%) under relatively short residence time (5 min), incandescent light (150 W) and molar ratio( $n_{1a}$ :  $n_{H2O2}$ :  $n_{HBr} = 2.0$ : 1.5: 1.0) to give the desired **2a** as the main product (entry 10).

These results represent the first example of the safe and efficient bromination of toluene derivatives with HBr– $H_2O_2$  in a continuous-flow micro reactor. Moreover, the process eliminates the use of metal catalysts and of solvents for bromination.

The process was then applied to different toluene derivatives (Table 5) with both electron-withdrawing and electrondonating groups on the aromatic ring. Toluene derivatives with electron-donating groups, such as 1c and 1d were brominated to the corresponding ring substituted bromo compound 3 in highly selectivity with an overall almost 100 % conversion of bromine atoms, while 1e and 1f gave benzyl bromination 2 in less than 80% conversion. From this observation, we can conclude that aromatic ring with an electron-donating group can speed up the reaction. Moreover, with the enhancements of the electronic effect at the aromatic ring, aromatic ring bromination occurred instead of benzyl C–H bromination.

# Conclusions

In summary, we have reported a safe and efficient bromination of toluene derivatives using  $HBr-H_2O_2$  as brominating reagent in a continuous-flow micro reactor under environmentally friendly conditions. The advantages of this protocol are its continuousness, high efficiency and selectivity, short reaction time, mild reaction conditions and freedom from metal catalysts and solvents.

## Experimental

### Bromination of toluene; typical procedure

Hydrogen peroxide (30%), hydrogen bromide (40%) and toluene and substituted toluenes were commercially available. The glass micro reactor is a triangle cross-type single-channel micro-glass (a special photosensitive) mixer, which was made by Mikroglas Chemtech GmbH Company. The reaction channel is 806 mm long, 0.455 mm wide and about 0.5 mm depth, with an area of 3647 mm<sup>2</sup> and a channel volume of 1326 mm<sup>3</sup>. There are a total of 30 micro-design added in the reaction channel including 29 designs each with 4337 micro-column design, while the micro unit of only the mixed region has a 1033 micro-column design. The single-channel micro-injection pumps (LSP01-1A) were made by the Baoding Lange Constant Pump Co., Ltd.

Table 5 Continuous-flow bromination of toluene derivatives by  $HBr\text{-}H_2O_2$ 

$ \begin{array}{c} CH_3\\ R\\ R\\ I \end{array} + HBr + H_2O_2 \longrightarrow $	$H_2Br$ Cl + $R$ + $R$	$H_3 \qquad CH_2Br \\ H_2Br + H_2O \\ R \\ $
1a:R=H; 1b:R=3-CH <sub>3</sub> ; 1d:R=4-OCH <sub>3</sub> ; 1e:R=3-Cl;	1c:R=3,5-CH <sub>3</sub> ; 1f:R=4-NO <sub>2</sub> ;	

Entry	Substrate	Br atom	Product <sup>b</sup>		
		conversion /% <sup>a</sup>	<b>2</b> °/%	<b>3/</b> %	<b>4</b> /%
1	1b	99.3	80.6	14.2	5.2
2	1c	100.0	1.8	98.2	_
3	1d	100.0	_	100.0	_
4	1e	78.8	100.0	_	_
5	1f	54.8	100.0	—	—

<sup>a</sup> The ratio of the products and starting material was determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>b</sup> GC product proportions.

°See Caution in the Experimental section.

A typical procedure for the oxidative bromination of toluene or a substituted toluene by HBr/H<sub>2</sub>O<sub>2</sub> in the micro reactor under incandescent light conditions at room temperature is as follows (see Fig. 1). The hydrogen peroxide solution, the hydrogen bromide solution and the (substituted) toluene were each pumped through one of three single-channel micro-injection pumps. The hydrogen peroxide and hydrogen bromide solutions were premixed before entering the two-channel reactor. The molar ratio of reactants and the reaction (residence) time were controlled by varying the flow rates of the pumps. The product mixture was filtered and the filtrate was washed with aqueous NaHSO<sub>3</sub> to remove the unreacted Br<sub>2</sub> and H<sub>2</sub>O<sub>2</sub> and dried over anhydrous Na-SO<sub>4</sub>.

For toluene the product benzyl bromide was recovered by distillation under reduced pressure. The product  $2a^{19}$  was then analysed by <sup>1</sup>H NMR spectroscopy. <sup>1</sup>H NMR  $\delta_{\rm H}$  (CDCl<sub>3</sub>,500 MHz, TMS) 4.48 (2H, m, CH<sub>3</sub>Br), 7.10–7.92 (5H, m, ArH).

**CAUTION:** Benzyl bromide and the other bromomethyl compounds are lachrymatory and strong irritants and due precautions to prevent exposure to them should be taken.

*l*-(*Bromomethyl*)-3-*methyl*-benzene (**2b**):<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, TMS):4.43 (2H, m, CH<sub>2</sub>Br), 2.4 (3H, m, CH<sub>3</sub>),7.0–8.0 (4H, m, ArH).

2,4,6-Trimethybromobenzene (**3c**):<sup>19</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, TMS):2.28–2.42 (9H, s, –CH<sub>3</sub>), 6.86 (2H, s, ArH).

- 3-Bromo-4-methoxytoluene (**3d**):<sup>19</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, TMS): 2.25(3H, s, CH<sub>3</sub>), 3.83(3H, s, OCH<sub>3</sub>), 6.78–7.35(3H, m, ArH). *1-(Bromomethyl)-3-chloro-benzene* (**2e**):<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>,
- 500 MHz, TMS):4.43 (2H, m, CH<sub>2</sub>Br), 7.0–8.0 (4H, m, ArH). *1-(Bromomethyl)-4-nitrobenzene* (2f):<sup>19</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>,
- 500 MHz, TMS):4.43 (2H, m, CH<sub>2</sub>Br), 7.0–8.0 (4H, m, ArH).

This project was supported by the National Natural Science Foundation of Zhejiang Province (Y407306) and the National Natural Science Foundation of China (20876148). Received 2 December 2011; accepted 24 February 2012 Paper 1101023 doi: 10.3184/174751912X13333614619977 Published online: 10 May 2012

### References

- 1 S. Mallick and K.M. Parida, Catal. Commun., 2007, 8, 889.
- 2 M.J. Dagani, H.J. Barda, T.J. Benya and D.C. Sanders, *Ullmann's* encyclopedia of industrial chemistry: bromine compounds, Wiley-VCH, Weinheim, 2002.
- 3 P. Ajda, Z. Marko and I. Jernej, Angew. Chem., Int. Ed., 2009, 48, 8424.
- 4 R. Rajagopal, D.V. Jarikote, R.J. Lahoti, T. Daniel and K.V. Srinivasan, *Tetrahedron Lett.*, 2003, 44, 1815.
- 5 I. Pravst, M. Zupan and S. Stavber, Green Chem., 2006, 8, 1001.
- 6 G.A. Heropoulos, G. Cravotto, C.G. Screttas and B.R. Steele, *Tetrahedron Lett.*, 2007, 48, 3247.
- 7 I. Pravst, M. Zupan and S. Stavber, Tetrahedron, 2008, 64, 5191.
- 8 C. Chiappe, E. Leandri, and D. Pieraccini, Chem. Commun., 2004, 2536.
- 9 V. Kavala, S. Naik and B.K. Patel, J. Org. Chem., 2005, 70, 6556.
- 10 J. Salazar and R. Dorta, Synlett, 2004, 1318.
- 11 P.V. Vyas, A.K. Bhatt and G. Ramachandraiah, *Tetrahedron Lett.*, 2003, 44, 4085.
- 12 D. Kikuchi, S. Sakaguchi and Y. Ishii, J. Org. Chem., 1998, 63, 6023.
- 13 R. Mestres and J. Palenzuela, Green Chem., 2002, 4, 314.
- 14 A. Podgorsek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron Lett.*, 2006, 47, 7245.
- 15 Y. Li, J. Ju and J. Jia, Chin. J. Chem., 2010, 28, 2428.
- 16 B.P. Mason, K.E. Price, J.L. Steinbacher, A.R. Bogdan and D.T. McQuade, *Chem. Rev.*, 2007, **107**, 2300.
- 17 P.F. Li, and S.L. Buchwald, Angew. Chem., Int. Ed., 2011, 50, 6396
- 18 G. Taguchi, S. Chowdhury and Y. Wu, *Taguchi's quality handbook*, Wiley, Hoboken, New Jersey, 2004.
- 19 A. Podgorsek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron*, 2009, 65, 4429.
- 20 S. Adimurthy, S. Ghosh, P.U. Patoliya, G. Ramachandraiah, M. Agrawal, M.R. Ghandi, S.C. Upadhyay, P.K. Ghosh and B.C. Ranu, *Green Chem.*, 2008, **10**, 232.

Copyright of Journal of Chemical Research is the property of Science Reviews 2000 Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.