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ORIGINAL PAPER

New insights into bromination process: effective preparation of Ambroxol

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Ambroxol used as an expectorant in treating respiratory diseases was effectively prepared with a total yield of 62 %, with *o*-toluidine as the feedstock via successive procedures of electrophilic bromination, acetylation, radical benzylic bromination, *N*-alkylation and hydrolysis processes. The addition of aqueous hydrogen peroxide could enhance the utilisation of liquid bromine in the electrophilic bromination of *o*-toluidine, avoiding the hazardous HBr generated as a by-product. In addition, liquid bromine promoted by MnO_2 was used efficiently for the radical benzylic bromination of *N*-acetyl-*N*-(2,4-dibromo-6-methylphenyl)acetamide under mild conditions.
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Keywords: Ambroxol, electrophilic bromination, radical benzylic bromination, total synthesis

Introduction

Ambroxol, chemically described as *trans*-4-[(2-amino-3,5-dibromobenzyl)-amino]-cyclohexanol, is a potent mucolytic agent used in the treatment of respiratory disorders associated with abnormal mucus secretion and impaired mucus transport (Malerba & Ragnoli, 2008; Weiser, 2008). It is an active ingredient with a long history of use that affects the parameters considered as the basis for the physiological production and transport of bronchial mucus (Olivieri et al., 1987). Furthermore, Ambroxol exhibits anti-inflammatory and antioxidant properties that are beneficial in balancing inflammatory reactions to alleviate the symptoms of coughs and colds (Beeh, 2008). It also exerts a local anaesthetic effect, which serves to relieve pain in acute sore throats. Given Ambroxol's multi-factorial properties, it is highly significant to investigate the synthesis and technology of Ambroxol preparation.

The research published to date on Ambroxol preparation has varied according to the starting materials. In general, methyl *o*-aminobenzoate was used as the starting material, which subsequently underwent bromination, hydrazinolysis, methyl sulphonylation, condensation with *trans*-4-aminocyclohexanol and reduction to afford the title compound (Yu et al., 1996). In addition, *o*-aminobenzaldehyde underwent bromination on the aromatic ring, condensation with *trans*-4-aminocyclohexanol and finally reduction to the target compound (Ratz et al., 1991; Latli et al., 2010; Romeo et al., 1986; Liebenow & Grafe, 1985). However, both of the above entailed condensation and reduction processes, which produced large amounts of by-products and bore high costs. In the present study, a modified and efficient way for the synthesis of Ambroxol with a total yield of 62 % was conducted towards an industrial application, using *o*-toluidine as the feedstock with various organic units involving electrophilic bromination, acetylation, radical benzylic bromination, *N*-alkylation and hydrolysation (Fig. 1).

Experimental

General

All chemical reagents and solvents (analytical grade) were used as supplied (Aladdin, China) unless otherwise stated. All experiments were monitored by

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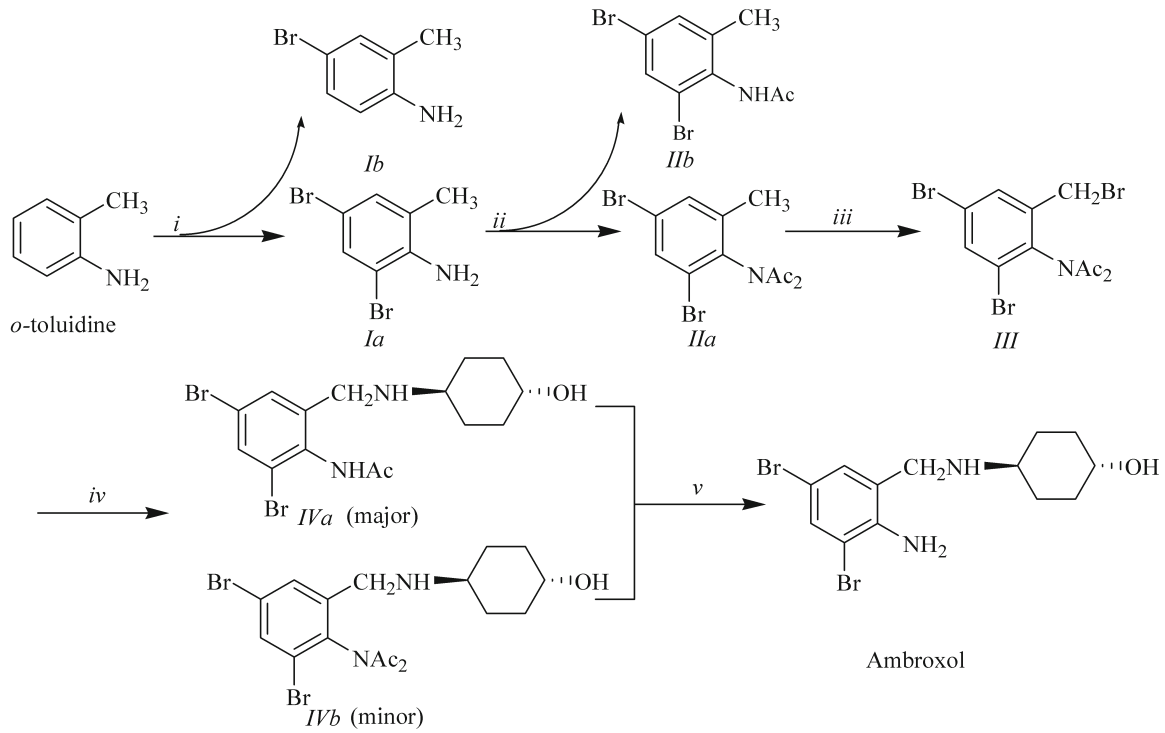

Fig. 1. Synthetic route to Ambroxol: *i*) H_2O_2 (2.0 eq.)/Br_2 (1.0 eq.), r.t., CH_2Cl_2/H_2O, 8 h, 90 %; *ii*) acetic anhydride, reflux, H_2SO_4 (96 %; cat.), 6 h, 96 %; *iii*) MnO_2 (2.0 eq.)/Br_2 (1.0 eq.), r.t., CH_2Cl_2, 1.5 h, 86 %; *iv*) trans-4-aminocyclohexanol (3.0 eq.), KOH (cat.), reflux, ethanol, 5 h, 94 %; *v*)H_2SO_4 (0.5 M), refluxing, ethanol, 20 h, 89 %.

thin-layer chromatography (TLC). The spots on the TLC plates were made visible by exposure to ultraviolet light (254 nm). Column chromatography was carried out using silica gel (45–75 μm). HPLC analysis was performed using an Agilent 1200 (USA) equipped with a 250 mm × 4.6 mm capillary column (ZORBAX Eclipse XDB-C_{18}, 5 μm; solvent system MeOH/H_2O (φ_r = 9 : 1); flow-rate 1 mL min^{-1}; λ = 254 nm). ^{1}H NMR spectra were recorded on a Bruker Avance III 500 MHz Digital NMR Spectrometer (Germany) at 500 MHz using $CDCl_3$ or DMSO-d_6 as solvents. The coupling constants are reported in hertz (Hz) and the chemical shifts in δ relative to internal standard (TMS). Melting points were determined using a Buchi 535 (Switzerland) melting point apparatus and are uncorrected. All MALDI-TOF mass spectra analyses were obtained using a Bruker Microflex LRF instrument and Agilent 1100 series liquid chromatography-mass spectrometer (LC-MS) by the ESI method of ionisation.

Typical example procedure for o-toluidine bromination with H_2O_2-Br_2 system

o-Toluidine (5.0 mmol) was dissolved in dichloromethane (15 mL) and water (15 mL). Liquid bromine (800 mg, 5.0 mmol) in dichloromethane (5 mL) was added dropwise over a period of 2 h under vigorous agitation. At the same time, a 30 mass % aqueous solution of H_2O_2 (mass fraction, 10.0 mmol) was added dropwise. The reaction mixture was then stirred at ambient temperature and the progress of the reaction was monitored by TLC. At the end of the reaction (6–8 h), the mixture was transferred into a separating funnel and a solution of 5 mM $NaHSO_3$ (10 mL) was added. The crude product was then extracted using dichloromethane (10 mL) and the organic phases washed with water (2 × 10 mL). The mixture was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture isolated by column chromatography (hexane/EtOAc, φ_r = 5 : 1) and the pure product was identified by comparison with data in the literature (Bagmanov, 2009).

2,4-Dibromo-6-methylbenzenamine (Ia)

White needle crystals; yield 90 % (1.18 g), m.p. 47.4–48.0 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.20 (s, 3H, -CH_3), 4.03 (bs 2H, -NH_2), 7.13 (d, J = 1.9 Hz, 1H, -ArH), 7.43 (d, J = 1.9 Hz, 1H, -ArH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 18.2, 109.1, 109.4, 124.9, 131.9, 132.0, 141.4. MS (m/z, ESI): 264.501 $[M + H]^+$ (calc. for $C_7H_8Br_2N$, 264.503).

Typical example procedure procedure for protection of amino group in Ia

Ia (5.0 mmol) was dissolved in acetic anhydride (15 mL), catalytic amounts of concentrated sulphuric

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acid (two drops) was added with stirring. The mixture was heated to reflux. The reaction progress was monitored by TLC and on completion (5–6 h) the mixture was quenched by the addition of 100 g cracked ice. The white solid precipitate (1.73 g, yield of 98 %) formed was filtered and washed with water (100 mL) and purified by recrystallisation from petroleum ether (15 mL).

N-acetyl-N-(2,4-dibromo-6-methylphenyl) acetamide (IIa)

White needle crystals; yield 1.67 g (96 %), m.p. 88.4–89.0 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.20 (s, 3H, -CH_3), 2.29 (s, 6H, 2 × -$COCH_3$), 7.45 (d, J = 1.8 Hz, 1H, -ArH), 7.71 (d, J = 1.8 Hz, 1H, -ArH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 18.4, 26.1, 123.4, 124.6, 123.3, 133.6, 136.8, 140.1, 171.5. MS (m/z, ESI): 349.788 $[M + H]^+$ (calc. for $C_{11}H_{12}Br_2NO_2$, 349.781). Elemental analysis calculation for $C_{11}H_{11}Br_2NO_2$: C, 37.69; H, 3.09; N, 4.12; found: C, 37.85; H, 3.18; N, 4.01.

Typical example procedure for radical reaction on bromination of N-acetyl-N-(2,4-dibromo-6-methylphenyl)acetamide with MnO_2/Br_2

IIa (1.0 mmol) was dissolved in dichloromethane (10 mL). Commercially available non-activated MnO_2 (2.0 mmol) was added first and then liquid bromine (1.0 mmol) in 5 mL dichloromethane was added dropwise over a period of 2 h under vigorous agitation at ambient temperature using an ambient temperature water bath. The entire progress of the reaction was monitored by TLC. After 1 h the reaction was quenched by the addition of water (20 mL) and the precipitated MnO_2 was filtered and washed with dichloromethane (10 mL). The combined organic phase was washed to neutral reaction and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and a brown solid was formed. The crude product (3.50 g, yield of 92 %) was purified by recrystallisation from hexane (30 mL) and white needles were obtained.

N-acetyl-N-(2,4-dibromo-6-(bromomethyl)-phenyl)-acetamide (III)

White needle crystals; yield 3.67 g (86 %), m.p. 118.2–119.4 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.38 (s, 6H, 2 × -$COCH_3$), 4.26 (s, 2H, -CH_2Br), 7.67 (d, J = 2.1 Hz, 1H, -ArH), 7.84 (d, J = 2.1 Hz, 1H, -ArH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 26.4, 27.5, 123.6, 125.5, 133.8, 136.3, 136.6, 139.1, 171.9. MS (m/z, ESI): 427.490 $[M + H]^+$ (calc. for $C_{11}H_{11}Br_3NO_2$, 427.493). Elemental analysis calculation for $C_{11}H_{10}Br_3NO_2$, C, 30.87; H, 2.36; N, 3.27; found: C, 31.00; H, 2.45; N, 3.15.

Typical example procedure for N-alkylation with trans-4-aminocyclohexanol

Trans-4-aminocyclohexanol (3.0 mmol) and aqueous 10 mass % potassium hydroxide (5.0 mmol) in 10 mL of ethanol was vigorously agitated. Next, *III* (1.0 mmol) in ethanol (15 mL) was added over a period of 1 h. The mixture was refluxed gently until completion monitored by TLC (4–5 h), then the mixture was poured into water and kept in a refrigerator overnight. The crude product thus formed was quantitatively analysed by HPLC (Table 1S). The pure product was isolated using column chromatography (hexane/EtOAc, φ_r = 8 : 1).

Trans-4-(2-acetylamino-3,5-dibromobenzyl) aminocyclohexanol (IVa)

Light yellow needle crystals; yield 3.37 g (80 %), m.p. 128.3–129.1 ℃, ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 1.39–1.48 (m, 2H, -CH_2), 1.64 (bs, 3H,-CHOH, -NH), 1.70–1.76 (m, 4H,-CH_2), 2.10–2.14 (m, 2H, -CH_2), 2.26 (s, 3H, -$COCH_3$), 3.60–3.68 (m, 2H, -CH,-NH), 4.33 (s, 2H,-CH_2NH), 6.94 (d, J = 2.1 Hz, 1H, -ArH), 7.55 (d, J = 2.1 Hz, 1H, -ArH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 26.4, 27.5, 30.9, 33.7, 34.3, 60.9, 123.6, 125.43, 133.8, 136.3, 136.5, 139.1, 171.9. MS (m/z, ESI): 420.981 $[M + H]^+$ (calc. for $C_{15}H_{21}Br_2N_2O_2$, 420.987). Elemental analysis calculation for $C_{15}H_{20}Br_2N_2O_2$, C, 42.93; H, 4.90; N, 6.58; found: C, 42.88; H, 4.80; N, 6.67.

Typical example procedure procedure for preparation of title compound by hydrolysis

IVa (1.0 mmol) in aqueous H_2SO_4 (0.5 mol L^{-1}; 10 mL) and ethanol (10 mL) were mixed together. The mixture was refluxed until completion monitored by TLC (20 h). Once cooled, a saturated aqueous solution of Na_2CO_3 (≈ 30 mL) was added slowly to adjust the pH of the solution to 12. Next, the organic phase was extracted using dichloromethane (20 mL) and washed with water (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated, purified by recrystallisation using ethanol (15 mL) and identified by comparison with the data in the literature (Larsson et al., 1997).

Ambroxol

White needle crystals; yield 3.37 g (89 %) m.p. 92.0–93.1 ℃ (lit. 92.4 ℃); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 1.11–1.19 (m, 2H, -CH_2), 1.27–1.61 (bs and m, 5H, -OH, -NH, -CH_2), 1.85–1.74 (m, 1H, -CH_2), 1.99–2.00 (m, 4H, -CH_2), 2.44–2.50 (m, 1H, -CHN), 3.60–3.66 (m, 1H, -CH), 3.80 (s, 2H, -ArCH_2N), 5.31 (bs, 2H, -ArNH_2), 7.10 (d, 1H, J = 2.1 Hz, -ArH), 7.48 (d, 1H, J = 2.1 Hz, -ArH).

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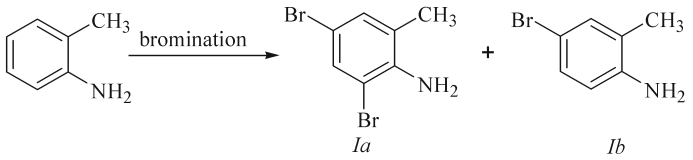
Table 1. Effect of reaction conditions on synthesis of 2,4-dibromo-6-methylbenzenamine



Ia *Ib*

Entry	Reaction conditions[a]	Conversion[b]/%	Yield[c]/%	
			Ia	*Ib*
1	2NBS-H_2O[d](1NBS-H_2O)	99.0 (79.0)	87.0 (30.5)	– (8.5)
2	2NBS-CCl_4[d](1NBS-CCl_4)	94.5 (77.5)	83.4 (11.8)	– (46.0)
3	2NBS-EtOAc[d](1NBS-EtOAc)	86.3 (77.9)	76.0 (12.9)	– (48.4)
4	2NBS-CH_2Cl_2[d](1NBS-CH_2Cl_2)	93.1 (71.7)	80.8 (3.8)	– (61.5)
5	2NBS-EtOH[d](1NBS-EtOH)	85.2 (70.1)	74.7 (8.1)	– (50.1)
6	2Br_2-H_2O(1Br_2-H_2O)	85.1 (52.1)	59.7 (15.7)	8.1 (17.1)
7	2Br_2-$ClCH_2CH_2Cl$	86.3	48.9	35.0
8	2Br_2-EtOH	75.4	45.3	29.1
9	2Br_2-EtOAc	77.6	46.0	27.3
10	2Br_2-CH_2Cl_2(1Br_2-CH_2Cl_2)	87.2 (54.1)	50.3 (16.3)	34.1 (18.1)
11	2Br_2-CH_2Cl_2-H_2O	96.5	89.4	–
12	2Br_2-$ClCH_2CH_2Cl$-H_2O	93.4	84.1	–
13	2Br_2-EtOH-H_2O	78.7	66.3	4.1
14	2Br_2-EtOAc-H_2O	90.2	81.2	3.0
15[e]	2H_2O_2-1Br_2– CH_2Cl_2-H_2O	92.5	89.8	–
16[f]	4H_2O_2-2HBr– CH_2Cl_2-H_2O	90.0	88.2	–

a) The number preceding the chemical reagent denotes the mole equivalent to the substrate, a suspension of 2-toluidine (5.0 mmol) in 30 mL of solvent and the volume ratio was controlled to 1 : 1 for the mixed solvent, r.t.; the values in parenthesis means another bromination conditions and corresponding results; *b*) determined by gas chromatographic analysis; *c*) isolated yields after column chromatography; *d*) 3.0 % of 2-amino-3,5-dibromobenzaldehyde was also formed; *e*) molecular bromine (800 mg, 5.0 mmol) in 5 mL dichloromethane followed by 30 % aqueous hydrogen peroxide (10.0 mmol) were added dropwise to *o*-toluidine (5.0 mmol) in 15 mL of dichloromethane and 15 mL of water under vigorous agitation at ambient temperature; *f*) 10 mass % aqueous hydrogen bromide 10.0 mmol) followed by 30 % aqueous hydrogen peroxide (20.0 mmol) were added dropwise to *o*-toluidine (5.0 mmol) in 15 mL of dichloromethane and 15 mL of water under vigorous agitation.

MS (m/z, ESI): 378.713 $[M + H]^+$ (calculated for $C_{13}H_{19}Br_2N_2O$ 378.717).

Results and discussion

o-Toluidine was a typical electron-rich feedstock which occurred readily by electrophilic aromatic substitution in the benzene ring including bromination. First, *N*-bromosuccinimide (NBS) was employed in the preparation of *Ia* for ease of handling and high selectivity. Water was used as the reaction medium for its environmentally benign properties (Sheldon, 2005). Other organic solvents, such as ethyl acetate, halohydrocarbons and ethanol, failed to achieve the selectivity of *Ia* (Table 1, Entries 1–5,). *Ia* was formed with good yields accompanied by small amounts of an oxidation by-product of 2-amino-3,5-dibromobenzaldehyde in water (Table 1, Entry 1). Similar results were reported for the oxidative ability of NBS (Krishnaveni et al., 2004; Mayhoub et al., 2010). Meanwhile, over 50 % 4-bromo-2-methylbenzenamine (*Ib*) was isolated in various media using the mole ratio of *o*-toluidine/NBS of 1 : 1. It was found that water improved the selectivity of *Ia* as compared with other organic solvents.

Although the liquid bromine activity in the reaction was lower than the activity of NBS, the use of liquid bromine is very common in industry and academic research. Similarly, solvents affected the formation of *Ia* with 50.3 % yields in dichloromethane while achieving 59.7 % yields in water (Table 1, Entries 6–10) and a mole ratio of bromine to substrate of 1 : 1 exhibited poor selectivity for *Ia* and *Ib*. However, an excellent selectivity for *Ia* with over 80 % yields in the organic-water double phase system was achieved with prospects of efficient industrial preparation by using twice the amount of liquid bromine (Table 1, Entries 11–14,). As the HBr, evolved by mono-bromination, combined with the amino group on the aromatic ring to its protonated NH_3^+ form, which led to a weak π-electron density on the aromatic ring, discouraged further bromination resulting in the formation of *Ia*, the moisture readily promoted a functional hydrolysis in which the free amino group was released to further afford a dibrominated product. In addition, water with a high dipole moment and dielectric constant could favour the heterolysis of liquid bromine. Bromination using molecular bromine exhibits 50 % atom utilisation in terms of stoichiometry. Accordingly, hydrogen peroxide was successfully employed to reduce

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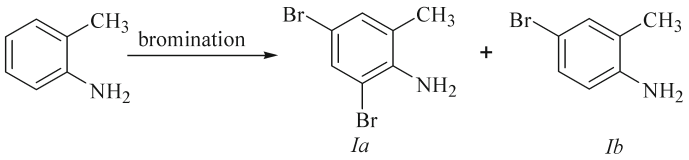
Table 2. Effect of reaction conditions on amino group-protection of 2,4-dibromo-6-methylbenzenamine[a]

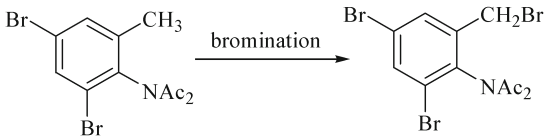


Ia *Ib*

Entry	Protective agent	Catalyst[b]	Temperature/ °C	Product distribution[c]/%	
				IIa	*IIb*
1	acetic acid	H_2SO_4 (96 %)	r.t.	0	96
2	acetic acid	–	reflux	5	91
3	acetic acid	H_2SO_4 (96 %)	reflux	10	86
4	acetic anhydride	H_2SO_4 (96 %)	r.t.	52	38
5	acetic anhydride	–	reflux	56	36
6	acetic anhydride	H_2SO_4 (96 %)	reflux	96	2

a) 5.0 mmol *Ia* in 15 mL of protective agent; *b*) two drops of catalyst; *c*) isolated yields after recrystallisation.

Table 3. Effect of radical reaction on bromination of *III* with various bromination systems[a]



IIa *III*

Entry	Reaction conditions	Reaction time/h	Conversion[b]/%	Yield[c]/%
1	NBS-CCl_4, 5 mass % AIBN[d]	5	86	80
2	Br_2, 5 mass % AIBN[d]	5	70	61
3	Br_2, *hv* (40 W)[e]	12	83	72
4	NaBr/$NaBrO_3$[f]	6	74	69
5	$NaBrO_3$/$NaHSO_3$[g]	4	80	73
6	H_2O_2-HBr, *hv* (40 W)[e]	12	83	76
7	H_2O_2-Br_2, *hv* (40 W)[e]	12	83	78
8	MnO_2/Br_2	1.5	92	86
9	MnO_2/Br_2[h]	1.5	90	84
10	MnO_2/Br_2[h,i]	1.5	90	84

a) 1.0 mmol of *IIb* dissolved in dichloromethane (10 mL), bromination agents (NBS, Br_2, HBr 1.0 mmol), H_2O_2 and MnO_2 2.0 mmol, ambient temperature unless stated otherwise; *b*) determined by gas chromatographic analysis; *c*) isolated yields after recrystallisation; *d*) refluxing temperature; *e*) incandescent light bulb; *f*) sodium bromide/sodium bromate (mole ratio 5 : 1, 1.0 mmol available atomic Br) in water solution (8 mL) and 6 mol L^{-1} HCl (1.5 mmol) was added to the mixture dropwise over a period of 1 h; *g*) sodium bromate (3.0 mmol) and sodium hydrogen sulphite (3.0 mmol) each in 5 mL aqueous solution, reaction progress was monitored by TLC or GC; *h*) larger scale experiment (10.0 mmol of *IIb*, 10.0 mmol Br_2, 20.0 mmol MnO_2, 50 mL dichloromethane); *i*) reused MnO_2.

the amount of bromine by oxidation of the hydrogen bromide formed in the reaction (Sels et al., 2001; Yonehara et al., 2011; Zhang et al., 2013; Wang et al., 2013; Firouzabadi et al., 2009; Eissen & Lenoir, 2008; Podgoršek et al., 2007; Rothenberg & Clark, 2000). When performing the reaction in the H_2O_2-Br_2 system, 90 % yields of *Ia* were afforded (Table 1, Entry 15). Moreover, the bromination of *o*-toluidine with the H_2O_2-HBr couple supported the results (Table 1, Entry 16).

The initial attempt to achieve directly free radical bromination of *Ia* to afford 2,4-dibromo-6-(bromomethyl)-aniline failed with NBS using 2,2′-azobis(2-methyl-propionitrile) (AIBN) as an initiator, since the activated amino group was easily susceptible to oxidation of the various amino group-protecting reagents, (Greene & Wuts, 1999) the readily available and cheap acetic acid and acetic anhydride were used for amine protection in the form of the acetylamino group.

N-(2,4-dibromo-6-methylphenyl)-acetamide (*IIb*) was afforded in acetic acid media using catalytic amounts of H_2SO_4 at ambient temperature (Table 2, Entry 1). Small amounts of the dual protective product *N*-acetyl-*N*-(2,4-dibromo-6-methyl-phenyl)-acetamide (*IIa*) were observed at reflux temperature (Ta-

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ble 2, Entries 2–3). However, *IIa* was mainly formed in the acetic anhydride system at ambient temperature (Table 2, Entry 4). Also, the formation of *IIa* was much enhanced with the increase in temperature (Table 2, Entry 6), which was selected for further reaction.

Various processes involving NBS (Djerassi, 1948), Br_2 (Shaw et al., 1997), $NaBr/NaBrO_3$ (Adimurthy et al., 2008, 2006; Joshi & Adimurthy, 2011), H_2O_2/HBr (Podgoršek, 2006, 2009), H_2O_2/KBr (Galloni et al., 2013), $NaBrO_3/NaHSO_3$ (Kikuchi et al., 1998) have been developed in the side-chain bromination of arenes such as toluene, *o*-xylene, *p*-xylene and *m*-xylene, etc. Traditional Wohl–Ziegler bromination at benzylic positions is performed with NBS in boiling carbon tetrachloride. Here, an acceptable yield of *N*-acetyl-*N*-(2,4-dibromo-6-(bromomethyl)-phenyl)-acetamide (*III*) was achieved by using traditional brominating agents in the presence of AIBN (Table 3, Entries 1–2). Moreover, the bromination of *IIa* with liquid bromine under light irradiation instead of AIBN appeared to be more effective, with the yield of *III* up to 72 % (Table 3, Entry 3).

The combined $NaBr/NaBrO_3$ was successful for the bromination of alkenes and alkynes, which was attempted for the α-bromination of *IIa* and resulted in an isolated 69 % yield of *III* (Table 3, Entry 4). Similarly, $NaBrO_3/NaHSO_3$ served as an effective α-bromination of alkylbenzenes, affording *III* in 73 % yields (Table 3, Entry 5). Moreover, H_2O_2/HBr and H_2O_2/Br_2 under an incandescent light bulb afforded 76 % and 78 % yields of *III*, respectively (Table 3, Entries 6–7). Liquid bromine promoted by unactivated MnO_2 was successfully used for the chemo-selective mono-bromination of alkanes (Jiang et al., 2005). This was more effective for the bromination of *IIa* (Table 3, Entry 8). In addition, the bromination of *IIa* on a larger scale (10.0 mmol) could lead to *III* with a 84 % yield after crystallisation (Table 3, Entry 9).

The *N*-alkylation of *trans*-4-aminocyclohexanol with *III* under basic conditions produced mainly *trans*-4-(2-acetylamino-3,5-dibromobenzyl)amino-cyclohexanol (*IVa*) with a small amount of *trans*-4-(2-diacetylamino-3,5-dibromobenzyl)aminocyclohexanol (*IVb*). Various conditions were investigated to improve the reaction (Table 1S). A conversion of 98 % for *III* and selectivity of 94 % for *IVa* were obtained under optimal conditions (Table 1S, Entry 9). The *N*-alkylation products formed were directly hydrolysed in an acid system to form Ambroxol with an isolated yield of 89 % under optimal conditions (Table 2S).

Conclusions

In conclusion, Ambroxol starting from *o*-toluidine was effectively synthesised with a total yield of 62 % under mild conditions via a series of processes. The methodology appears to hold promise for future industrial applications.

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