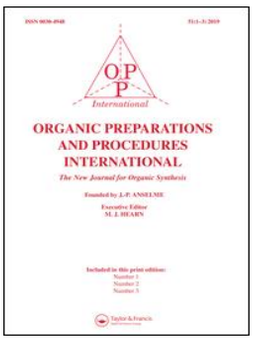

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OPPI BRIEF

Regioselective, Efficient and Sustainable Bromination Process for the Synthesis of the Antimicrobial Agent Bromiphen Bromide

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In the drug discovery process, the role of halogen atom substitution has greatly influenced outcomes in the hit-to-lead-to-candidate optimization.[1–3] Useful reasons for halogen insertion have included increasing steric hindrance or improving lipophilicity, among many others; and a recent review[4] reports that fully one-quarter of the total number of papers and patents in medicinal chemistry involves halogen atom substitution.

As an example, during our recent studies[5,6] on the degradation of domiphen bromide, we found that the *p*-bromo analogue (Scheme 1, **1**, bromiphen bromide), which had initially been seen as an undesirable impurity deriving from harsh conditions, showed improved antimicrobial activity.

As a result, compound **1** was patented[7] as a new antimicrobial agent with good activity against both Gram negative and Gram positive bacteria and against fungi. The patented synthesis (Scheme 2) applied traditional organic procedures and gave an overall yield of about 57%.

A key intermediate for the synthesis of bromiphen bromide is *p*-bromophenol, which is prepared *via* the bromination of phenol. Conventional preparations of bromophenol typically use strong oxidizing agents, a variety of metal catalysts and halogenated solvents.[8] These reagents are corrosive and toxic therefore their use is less desirable. Moreover, the lack of regioselectivity is a drawback since the phenol contains an *ortho*/*para* director which affords a mixture of isomers and requires a subsequent separation. Considering only regioselective procedures, to the best of our knowledge none is atom-economical or sustainable.

With a view to preparing larger quantities of bromiphen bromide for further biological and toxicological investigations, and based on our own past experience,[9] we sought a more regioselective, eco-friendly and sustainable synthetic method. We considered protocols focused on ecologically more acceptable bromination[10–13] and we now report the resulting regioselective procedure for bromiphen bromide, capitalizing on our observation that it could be formed from domiphen bromide. A source of bromide and an oxidizing agent were necessary to enhance the formation of Br_2 *in situ*. The

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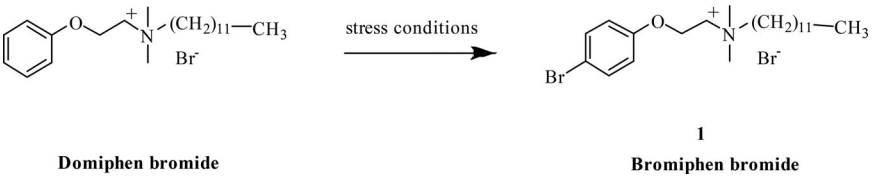
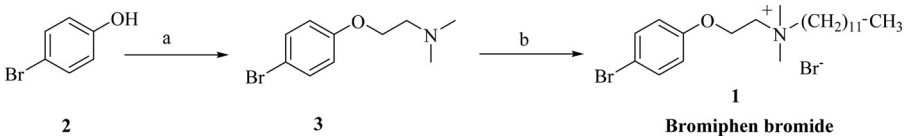


Scheme 1. Formation of bromiphen bromide (**1**) under harsh conditions.



Scheme 2. Patented synthesis of bromiphen bromide. a) Methylethylketone, Cs_2CO_3, KI, 2-chloro-N,N-dimethylethylamine hydrochloride. b) bromododecane, acetone.

$$H_2O_2 + KBr \rightarrow KOBr + H_2O$$

Scheme 3. Net reaction of peroxide with bromide in water.

oxidant needed to be atom-economical and not increase difficulties in purification, ruling out the use of Oxone, *tert*-butylhydroperoxide and dimethylsulfoxide. We chose KBr as the bromide source because of its enhanced solubility over NaBr, and we chose hydrogen peroxide as the best oxidant because its by-product is water (Scheme 3). Surmising that both domiphen bromide and bromiphen bromide should behave as surfactants, due to their charged head groups and long alkyl chains, we felt that water should be the choice of solvent. Aside from its ability to act as a heat reservoir, water reacts with Br_2 to produce HOBr, and the reaction of peroxide with KBr generates an intermediate of the form KOBr.[14]

An acidic environment is necessary for the oxidative reaction, so we examined HCl and HBr. Table 1 reports our optimization of reaction conditions, represented in Scheme 4.

The removal of inorganic salts from the crude bromiphen bromide is achieved by flash chromatography, so we evaluated different columns in order to find the best load capacity. We were able to use 12 g of C-18 silica to directly purify the crude bromiphen bromide coming from 500 mg of domiphen bromide, with 70 mL of mobile phase comprised of water and acetonitrile, with pH 3.75.

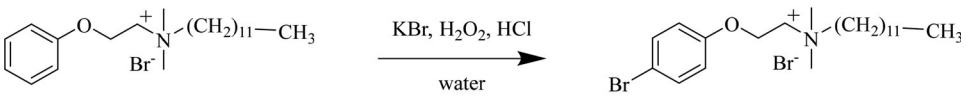
We would like to compare the environmental impact of our bromination method to one recently reported in the literature[15] which is highly regioselective. We focus our attention on the reaction to obtain *p*-bromophenol since it represents the main difference between the conventional synthesis of bromiphen bromide and the new method, described here, which starts from domiphen bromide. We have calculated the environmental factor (*E*-factor) commonly used to evaluate the greenness of a reaction (Figure 1).[16]

Comparison of the environmental impact of the two methods by means of the *E*-factors indicates that the method which includes bromination of domiphen bromide "on

Table 1. Optimization studies.

Domiphen bromide (mg)	KBr (eq.)	H_2O_2 30%	10% HBr (eq.)	10% HCl (eq.)	Time (min)	Temperature °C	Water (mL)	Full conversion
200	2	2	2			RT	0.5	No product
200	2	2	2		30	RT	1.0	Y
200	2	2		2	30	RT	1.0	Y
200	1	1	2		30	RT	1.0	N
200	1.5	1.5	2		30	RT	1.0	Y
200	1.5	1.5		1	30	RT	1.0	Y
200	1.5	1.5		0.1	40	RT	1.0	Y
200	1.0	1.0		0.1		RT	1.0	N
200	1.2	1.2		0.1	40	RT	1.0	N
500	1.2	1.2		0.1	40	RT	2.5	Y

Synthesis of bromiphen bromide by bromination on water. Complete conversion of domiphen bromide was evaluated by HPLC analysis (see Supplementary Materials). Y: complete conversion. N: reaction does not give complete conversion even though bromiphen bromide is detectable.



Domiphen bromide **1** **Bromiphen bromide**

Scheme 4. Improved preparation of bromiphen bromide.

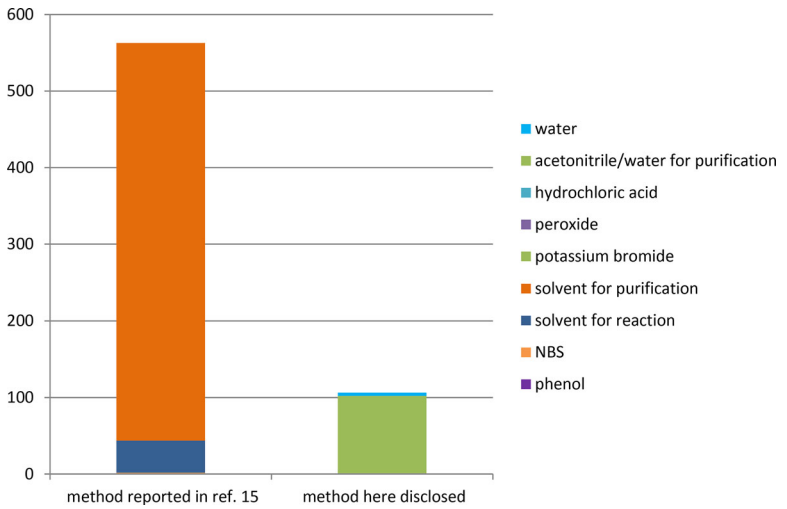


Figure 1. *E*-factor values calculated on regioselective method reported in reference 15 and on our method. (The colors that do not show up indicate extremely small values.)

water" is more sustainable with respect to the regioselective halogenation of the starting phenol.

In conclusion, we have developed a suitable and sustainable bromination "on water" to synthetize a new promising antimicrobial agent, bromiphen bromide. The new method is highly efficient and regioselective.

Experimental section

HPLC, LC/MS grade acetonitrile, LC/MS grade ammonium formate, formic acid, 30% hydrogen peroxide solution, 37% HCl, methyl ethyl ketone, acetone, dichloromethane and methanol were purchased from Merck KGaA, Darmstadt, Germany. ^{1}H-NMR spectra were recorded at 300 MHz and ^{13}C-NMR at 75.43 MHz, using a Varian Oxford 300 instrument. Chemical shifts are reported in ppm relative to residual solvent ($CHCl_3$ or DMSO) as internal standard. Purifications were performed by flash chromatography using C-18 silica gel (particle size 30 μm) on Isolera^{TM} (Biotage, Uppsala, Sweden) apparatus. A Milli-Q water purification system (Millipore, Bedford, Massachusetts, USA) was used to further purify demineralized water. HPLC analyses were performed on an Elite LaChrom HPLC (VWR/HITACHI, Milan, Italy/Tokyo, Japan) apparatus equipped with a L-2130 high pressure quaternary gradient delivery system, a L-2455 diode array detector (DAD), a L-2300 column oven and an L-2200 autosampler. The separation was achieved on an XBridge^{TM} column (4.6mm X 150 mm, 5 μm) (Waters). LC-MS experiments were performed on a Surveyor LC system, connected to a TSQ Quantum Ultra mass spectrometer through a Finnigan IonMax electrospray ionization (ESI) source assembled with a stainless steel emitter (Thermo Fisher Scientific, Rodano, MI, Italy). Complete details of the HPLC monitoring of the sustainable synthesis were submitted for review and are available in the Supplementary Material in the online version or from the corresponding author upon request.

Sustainable synthesis of dodecyldimethyl-2-(p-bromophenoxyethyl)ammonium bromide (bromiphen bromide, 1)

To a stirring solution of dodecyldimethyl-2-(phenoxyethyl)ammonium bromide (domiphen bromide) (500 mg, 1.2 mmol) in water (2.5 mL) were added 30% H_2O_2 (1.2 eq), KBr (1.2 eq), and 10% HCl (0.1 eq). The reaction was monitored by HPLC (see gradient elution conditions and data reported in the Supplementary Material). Once full conversion was obtained, the reaction mixture was directly loaded onto C-18 silica gel (12 g; mobile phase acetonitrile/ammonium formate, pH = 3.75) to obtain the title compound as a white solid (98% yield), mp 136.0 °C, lit[5] mp 136.6 °C. The residue of potassium (441 ppm) was determined via an inductively coupled plasma method. The title compound has been previously characterized,[5] but for the sake of completeness we provide the NMR data below, with original copies in the Supplementary Material, also available upon request from the corresponding author. ^{1}H NMR (CD_3OD, 300 MHz) 0.82-0.98 (m, 3H), 1.22-1.42 (m, 18H), 1.80-1.91 (m, 2H), 3.21 (s, 6H), 3.41-3.50 (m, 2H), 3.80-3.87 (m, 2H), 4.41-4.48 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H). ^{13}C NMR (CD_3OD, 75.43 MHz) δ 13.06, 22.29, 22.32, 25.97, 28.84, 29.06, 29.13, 29.22, 29.35, 31.67, 50.87, 61.80, 62.50, 65.39, 113.57, 116.30, 132.18, 156.70.

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