Mild Benzylic Monobromination of Methyl Toluates in Aqueous CTAB

Kancharla Rajendar Reddy, Kamatala C. Rajanna,* Marri Venkateswarlu, P. K. Saiprakash

Department of Chemistry, Osmania University (O.U), Hyderabad-500 007, A.P., India
Fax +91(40)27090020; E-mail: kcrajannaou@yahoo.com

Received: 26.06.2014; Accepted after revision: 26.07.2014

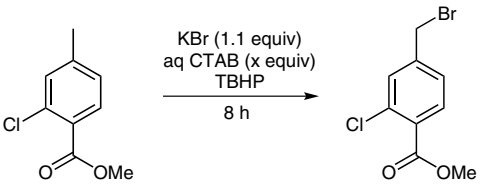
Abstract: A strategy has been developed for the regioselective monobromination of methyl toluates by using *tert*-butylhydrogen peroxide and potassium bromide (TBHP/KBr) in a cetyltrimethylammonium bromide (CTAB) micellar medium. Ultrasonic and microwave-assisted protocols recorded increased rates and product yields under mild reaction conditions, coupled with a straightforward isolation procedure.

Key words: bromination, monobromo methyl toluates, cetyltrimethylammonium bromide, microwaves, ultrasound

Bromoarenes, bromoalkylbenzenes, and bromoalkylbenzoates are widely used synthetic intemediates.[1] Apart from their use in C–C coupling reactions, they are used as precursors to organometallic species and in nucleophilic substitutions. They are also useful in the synthesis of pharmaceuticals, agrochemicals, antitumor, antifungal, antibacterial, antineoplastic, and antiviral compounds.[1,2] However, the use of molecular bromine has drawbacks arising from its toxic and corrosive nature, difficulty in handling, and its high reactivity; the latter often resulting in exothermic and nonselective reactions. Additional problems arise from the generation of hydrogen bromide as a byproduct. Reports have shown that *N*-bromoimides are useful for benzyl bromination and for electrophilic aromatic ring bromination, although electron-rich substrates are usually required for the latter reaction.[3–14] Alternatively, oxidative bromination of arenes has been developed using in situ generated bromonium species by oxidation of potassium bromide with hydrogen peroxide or sodium perborate in the presence of sodium tungstate or ammonium molybdate as catalysts.[15] In another protocol,[16] a combination of $NaClO_2$, NaBr, and $Mn(acac)_3$ supported on montmorillonite K10 or silica gel has been used for regioselective monobromination of aromatic ethers. As part of our ongoing study on micellar surfactants as catalysts,[17] we have undertaken a study of the selective bromination of methyl 2-chlorotoluate with *tert*-butylhydrogen peroxide (TBHP)/potassium bromide (KBr) in the presence of aqueous cationic micelles using cetyltrimethylammonium bromide (CTAB). In addition to the use of micelles, we also focused our attention on the use of nonconventional energy sources such as ultrasound[18] and microwaves[19] to initiate and enhance the reactions.

In order to demonstrate the effect and role of CTAB in micelle-mediated reactions, initial bromination reactions were carried out with methyl 2-chlorotoluate in the presence and absence of CTAB. In the absence of CTAB, reaction did not proceed even under forcing conditions. However, in the presence of CTAB, reaction occurred smoothly. The optimum reaction conditions of substrate (1.0 mmol), TBHP (0.4 mL), KBr (1.1 mmol), and aqueous CTAB solution (5 mL) were used for benzylic bromination of various methyl toluate derivatives and, on completion of reaction, the organic products could be obtained by simple phase separation, while in small-scale experiments extraction with an appropriate organic solvent was applied (Table 1).

Table 1 Effects of Catalyst System on the Reaction and Activity of Bromination Reactions with Methyl 2-Chlorotoluate



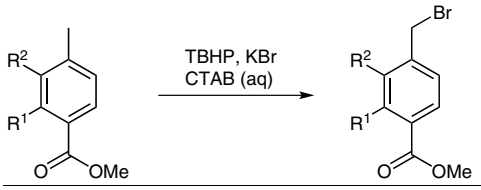
CTAB (x equiv)	Yield (%)[a]
0	0
0.0001	68
0.00025	72
0.0005	83
0.001	88
0.005	88

[a] Isolated yields.

A range of variously substituted methyl toluates were efficiently brominated at the benzylic position in this aqueous micellar medium at ambient temperature under acid-free conditions; while such reactions did not proceed under standard conditions (Table 2). Methyl 2-methyltoluate underwent bromination more effectively than methyl 3-methyltoluate, which could be due to the steric hindrance of the adjacent methyl group present in the *meta* position. This TBHP/KBr/CTAB bromination protocol appears to be superior to NBS bromination,[20] affording higher yields. The mild reaction conditions, straightforward isolation procedure, and use of inexpensive reagents make

SYNLETT 2014, 25, 2485–2487
Advanced online publication: 26.08.2014
DOI: 10.1055/s-0034-1379005; Art ID: st-2014-d0547-l

Table 2 Selective Benzylic Monobromination of Methyl Toluates with KBr in Aqueous CTAB Medium[a]



Entry	Product	R^1	R^2	Yield (%)[b] Conventional	MW	US
1	**2a**	Cl	H	88	93	90
2	**2b**	Br	H	87	94	90
3	**2c**	Me	H	85	93	89
4	**2d**	H	Me	64	72	69
5	**2e**	Et	H	83	91	89
6	**2f**	OMe	H	86	91	88
7	**2g**	*t*-Bu	H	82	93	88
8	**2h**	*i*-Pr	H	83	90	89
9	**2i**	CN	H	85	91	89
10	**2j**	CF_3	H	87	94	91
11	**2k**	H	F	81	93	87
12	**2l**	H	Cl	83	92	87
13	**2m**	H	Et	81	90	88
14	**2n**	H	OMe	84	94	90
15	**2o**	H	CN	82	93	91
16	**2p**	H	CF_3	81	94	91

[a] Reaction times: conventional, 8 h; microwave, 7–10 min; sonication, 40–50 min.
[b] Isolated yields.

such micellar-mediated brominating methodology a useful alternative to other reported brominating protocols.

A further advantage of benzylic bromination using this protocol is the simple isolation of products. This is made straightforward because the only reaction residue, CTAB, is soluble in water, meaning that any solid product workup consists of filtration; albeit if an oily product is formed in a small-scale experiment then liquid–liquid extraction is necessary. Column chromatography can then be used (SiO_2, hexane–EtOAc) to give the pure monobromo methyl toluates.

It is proposed that the surfactant forms micelles with the organic substrate concentrated in the interior of spherical aggregates, which act as hydrophobic reaction sites. Thus the hydrophobic interior of the micelles acts to shift the equilibrium towards the desired product. This explanation is schematically presented in Scheme 1.

Reaction times were further reduced from eight hours to about 40–50 minutes under sonication[21] and 7–10 minutes under microwave irradiation.[22]

In summary, we have developed a mild and simple practical method for the selective benzylic bromination of methyl toluates in the presence of aqueous cationic micelles under conventional, as well as sonication and microwave conditions. The reactions afford very good yields at room temperature.

Acknowledgment

The authors are indebted to Professor T. Navaneeth Rao (Former Vice-Chancellor, O.U), Principal, Nizam College and Head, Department of Chemistry, O.U) for constant encouragement and provision of facilities.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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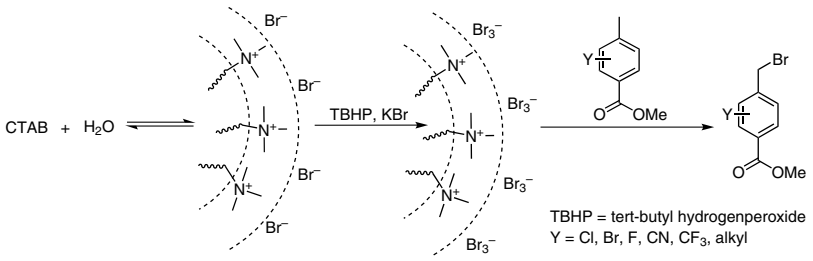

Scheme 1 Bromination of methyl-4-methylbenzoates in the presence of micellar media

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(21) The reaction mixture was sonicated in an ultrasonic bath, with a frequency of 33 kHz and 100 W electric power rating. The final products were isolated by silica gel column chromatography using an EtOAc–hexane gradient.

(22) The reaction mixture was treated in a controlled microwave synthesizer (Biotage Initiator+SP Wave model, 0–200 W at 2.45 GHz, capped at 60 W during steady state) for several minutes (the reaction attained 120 °C at 1 bar pressure). The final products were isolated by column chromatography using an EtOAc–hexane gradient.

