A New Regioselective Bromination of Activated Aromatic Rings

Leonardo S. de Almeida, Pierre M. Esteves,* Marcio C. S. de Mattos*

Instituto de Química, Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, Cx. Postal 68545, 21945-970 Rio de Janeiro, Brazil
Fax +55(21)25627133; E-mail: mmattos@iq.ufrj.br; E-mail: pesteves@iq.ufrj.br

Received 27 June 2005; revised 28 July 2005

Abstract: An efficient and highly regioselective bromination of activated aromatic rings promoted by tribromoisocyanuric acid by in situ generation of Br^+ has been developed. A range of aromatic compounds were reacted with tribromoisocyanuric acid and trichloroisocyanuric acid and sodium bromide.

Key words: aromatic rings, bromination, trichloroisocyanuric acid, tribromoisocyanuric acid

The direct halogenation[1] of aromatic rings employs halogens in the X_2 form and generates HX, which are very toxic, corrosive, and polluting agents. In order to decrease toxic waste, some papers report alternative electrophilic halogenating reagents, such as *N*-halosuccinimides[2] and *N*-halosaccharines,[3] which are stable, easy to manipulate, and produce less toxic imides as by product. Some interesting methodologies for bromination of aromatic rings also involve in situ generation of Br^+ by oxidation of a bromide ion by nitric acid,[4a] hydrogen peroxide,[4b] and Oxone®.[4c]

Trichloroisocyanuric acid[5] (TCCA) (Figure 1), an inexpensive solid used as a bleaching agent, in disinfectants, and as a bactericide, is an interesting compound due to its function as a chlorinating agent and oxidant. TCCA was first reported for the electrophilic halogenation of aromatic systems in the presence of catalysts by Juenge et al.[6] Bromination of some aromatic compounds by mono- or dibromoisocyanuric derivatives are described in the literature.[7] To the best of our knowledge, tribromoisocyanuric acid (TBCA) (Figure 1), an analogue of TCCA synthesized by Gottardi,[8] has not yet been reported as a brominating agent. These haloisocyanuric acids are very interesting from the green chemistry point of view,[9] as it is possible to halogenate organic compounds[10] without using X_2. They also have advantages from the view point of atom economy, as they can transfer the majority of their mass to the substrate, for example, TBCA can transfer up to 65% of its mass.

In this paper, we describe a new methodology for the regioselective bromination of activated aromatic rings using TCCA in bromide and TBCA as the source of Br^+.

The reaction of arene and TBCA or TCCA and sodium bromide, in methanol or water (just for *N*-methylacetanilide) at room temperature gave after work-up the corresponding monobromo arenes in good to excellent yields (Table 1). The regioselectivity in both reactions was very high and no regioisomers were detected by the analytical procedures employed (HRGC and ^1H and ^{13}C NMR spectroscopy). However, in the case of TCCA/Br^-, traces of chlorinated products were detected (checked by coinjection with authentic samples by HRGC).

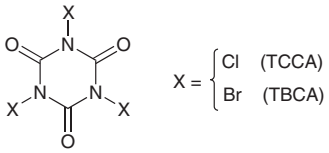


Figure 1 Trihaloisocyanuric acids.

Both reactions are very simple and the products from the reaction using TCCA/Br^- are easily purified by recrystalization from hexane. On the other hand, when using TBCA, the products are pure, needing no further purification.

In general, reactions with TCCA/Br^- are faster than with TBCA, due to the in situ generated Br^+, which is more electrophilic than the bromine atom in TBCA. The solubility of the substrates and sodium bromide, as well as the polar protic solvents employed seemed to influence the reaction time; when the reaction was attempted with other solvents, very low conversions were observed.

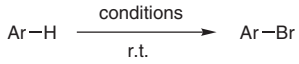
Non-activated or weakly activated arenes failed to undergo bromination or were brominated slowly. The reaction of toluene with TBCA, for example, gave traces of brominated products in 72 hours while the reaction with benzene gave no product after 168 hours (Table 1).

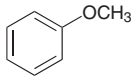
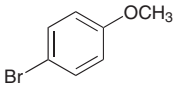
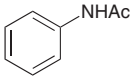
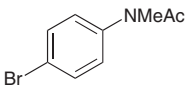
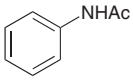
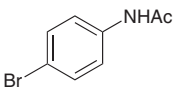
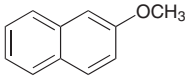
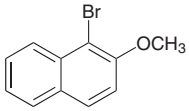
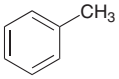
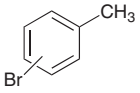
In conclusion, the present method proved to be an efficient and ecofriendly alternative for the regioselective bromination of activated aromatic rings in good to excellent yields. The reaction conditions are mild and the method is simpler then the traditional routes employed to synthesize these compounds from arenes. Furthermore, the reagents are inexpensive, readily prepared, very safe, and more useful in terms of atom economy than the traditional reagents used in bromination reaction.

TBCA was prepared analogously to *N*-bromosaccharine.[3a] Trichloroisocyanuric acid (commercial grade, 98%), and other chemicals and solvents were used as received. The ^1H and ^{13}C spectra were recorded on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. GC was performed on a HP-5890-II gas chromatograph with

SYNTHESIS 2006, No. 2, pp 0221–0223
Advanced online publication: 21.12.2005
DOI: 10.1055/s-2005-918511; Art ID: M04205SS

Table 1 Bromination of Activated Aromatic Rings



	Substrate	Product	Conditions	Yield (%)[a]
1			TBCA, MeOH, 2 h TCCA, NaBr, MeOH, 1 h	98 89
2			TBCA, H_2O, 24 h TCCA, NaBr, H_2O, 1 h	80 85
3			TBCA, MeOH, 72 h TCCA, NaBr, MeOH, 18 h	81 83
4			TBCA, MeOH, 0.5 h TCCA, NaBr, MeOH, 0.5 h	90 90
5			TBCA, MeOH, 72 h TBCA, MeCN, 72 h TCCA, NaBr, MeOH, 72 h	Trace Trace Trace
6		–	TBCA, MeOH, 168 h TCCA, MeCN, 168 h TCCA, NaBr, MeOH, 168 h	No reaction[b] No reaction[b] No reaction[b]

[a] Isolated yield based on arene.
[b] Substrate was recovered.

FID using a 30 m (length), 0.25 mm (ID), by 25 μm (phase thickness) RTX-5 capillary column and H_2 (flow rate 50 cm/s) as carrier gas (split: 1:10).

Reaction of Arenes with TBCA or TCCA/Br^-; General Procedure

To a stirred solution of arene (5 mmol) in MeOH (25 mL) or H_2O (50 mL, for *N*-methylacetanilide), was added TBCA (1.67 mmol) or TCCA (1.85 mmol) and NaBr (6 mmol) at r.t. in small portions. The reaction was monitored by GC. After the time shown in Table 1, CH_2Cl_2 (30 mL) and H_2O (50 mL) were added, cyanuric acid was filtered off, and the resulting solution was treated with 10% aq Na_2SO_3 (20 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 30 mL) and the combined organic layer was dried over anhyd Na_2SO_4. After evaporation of the solvent on a rotary evaporator, the product was collected.

4-Bromoanisole

^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H), 6.78 (d, *J* = 8.90 Hz, 2 H), 7.37 (d, *J* = 8.90 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 55.4 (CH_3), 112.8 (C), 115.7 (CH), 139.2 (CH), 158.7 (C).

4-Bromo-*N*-methylacetanilide

Mp 91 °C (lit.[11] 95 °C).

^{1}H NMR ($CDCl_3$): δ = 1.83 (s, 3 H), 3.20 (s, 3 H), 7.04, (d, *J* = 8.30 Hz, 2 H), 7.50 (d, *J* = 8.30 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.4 (CH_3), 37.0 (CH_3), 121.4 (C), 128.7 (CH), 132.9 (CH), 143.5 (C), 205.6 (C=O).

4-Bromoacetanilide

Mp 166 °C (lit.[12] 167 °C).

^{1}H NMR (DMSO-d_6): δ = 2.03 (s, 3 H), 7.43, (d, *J* = 8.92 Hz, 2 H), 7.54 (d, *J* = 8.92 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 24.0 (CH_3), 114.5 (C), 120.8 (CH), 131.5 (CH), 138.7 (C), 168.5 (C=O).

1-Bromo-2-methoxynaphthalene

Mp 82 °C (lit.[13] 85 °C).

^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3 H), 7.26 (d, *J* = 9.67 Hz, 1 H), 7.41 (t, *J* = 7.90 Hz, 1 H), 7.59 (t, *J* = 7.90 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 7.81 (d, *J* = 9.67 Hz, 1 H), 8.26 (d, *J* = 7.90 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 56.9 (CH_3), 108.6 (C), 113.6 (CH), 124.2 (CH), 126.0 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.8 (C), 133.0 (C), 153.7 (C).

Acknowledgment

Authors thank CAPES, CNPq, and FAPERJ for financial support.

References

(1) (a) De La Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, **1976**, Chap. 5.
(b) De La Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, **1976**, Chap. 7.
(2) Duan, S.; Turk, J.; Speigle, J.; Corbin, J.; Baker, R. J. *J. Org. Chem.* **2000**, *65*, 3005.

(3) (a) De Souza, S. P. L.; Da Silva, J. F. M.; De Mattos, M. C. S. *Synth. Commun.* **2003**, *33*, 935. (b) De Souza, S. P. L.; Da Silva, J. F. M.; De Mattos, M. C. S. *J. Braz. Chem. Soc.* **2003**, *14*, 832.
(4) (a) Joshi, A. V.; Baidossi, M.; Mukhopadhyay, S.; Sasson, Y. *Org. Process Res. Dev.* **2004**, *8*, 568. (b) Goodman, M. A.; Detty, M. R. *Organometallics* **2004**, *23*, 3016. (c) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.
(5) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.
(6) Juenge, E. C.; Beal, D. A.; Duncan, W. P. *J. Org. Chem.* **1970**, *35*, 719.
(7) (a) Malm, J.; Hörnfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, *31*, 521. (b) Gottardi, W. *Monatsh. Chem.* **1968**, *99*, 815. (c) Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098. (d) Sumida, T.; Kikuchi, S.; Imafuku, K. *Synth. Commun.* **2004**, *34*, 4273.
(8) Gottardi, W. *Monatsh. Chem.* **1967**, *98*, 1613.
(9) Sanseverino, A. M. *Quím. Nova* **2000**, *23*, 102.
(10) (a) Mendonça, G. F.; Sanseverino, A. M.; De Mattos, M. C. S. *Synthesis* **2003**, 45. (b) Mendonça, G. F.; Ramos, R. M.; Esteves, P. M.; De Mattos, M. C. S. *J. Braz. Chem. Soc.* **2005**, *16*, 695.
(11) Olah, G.; Ohannesian, L.; Arvanaghi, M. *Synthesis* **1986**, 868.
(12) Yamasaki, R.; Tanatani, A.; Azumaya, I.; Saito, S.; Yamagushi, K.; Kagechika, H. *Org. Lett.* **2003**, *5*, 1265.
(13) Miyano, S.; Okada, S.; Suzuki, T.; Handa, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2044.