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Tribromoisocyanuric acid as a green reagent for benzylic bromination of alkylarenes

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

Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, CP 68545, 21945-970, Rio de Janeiro, Brazil

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ABSTRACT

The reaction of diverse alkylarenes with tribromoisocyanuric acid (0.34 mol equiv) in reflux EtOAc in the absence of any catalysts or light irradiation produced the corresponding benzyl bromides in 53–88% yield.

Benzylic bromides are important precursors in the synthesis of pharmaceuticals, agrochemicals, bioactive compounds, etc.[1] Diverse methodologies are described in the literature for their preparation, especially from benzylic alcohols or alkylarenes.[2] Considering green chemistry aspects,[3] however, some methodologies are not attractive as they use harmful reagents, hard conditions, or generate a large amount of waste. The preparation of benzylic bromides from the corresponding benzylic alcohols is a drawback due to the utilization of the corrosive HBr or hazardous reagents such as phosphorus compounds.[4] The free-radical benzylic bromination of alkylarenes is easily achieved using molecular bromine or *N*-bromo compounds, being the popular NBS the most used reagent in such reactions (the so-called 'Wohl-Ziegler bromination').[5] However, molecular bromine is toxic, hazardous, corrosive, and a strong oxidizing low-boiling liquid;[6] its handling, storage, transport, and manipulation are difficult and problematic, especially on a large scale. On the other hand, NBS has to be used in a 1:1 molar proportion and presents low atom economy,[7] as it can transfer only up to 45% of its mass. Furthermore, both reactions are frequently performed in polychlorinated solvents, which involve serious environmental concerns.[8] Besides, the presence of a radical initiator is always required in such reactions.[9] Therefore, the development of alternative methodologies for a green and efficient benzylic bromination is a subject of intense research.[10]

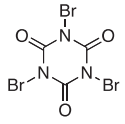

Figure 1. Tribromoisocyanuric acid (TBCA).

Unfortunately, despite its hazardous effects, molecular bromine is still very common in industry as well as in academia.[11] Diverse other safer brominating agents have been developed, however, their preparations involve the utilization of molecular bromine at some stage. Some years ago, we have introduced the system KBr/oxone™ as a green alternative to produce N-Br compounds.[12]

Within this context, tribromoisocyanuric acid (TBCA, Fig. 1) is a stable solid, easily prepared[12a] from cyanuric acid, KBr, and oxone™ that has been efficiently used for diverse brominating reactions.[13] Considering green aspects,[3,7] tribromoisocyanuric acid possesses advantages compared to other *N*-bromo analogues as it is capable of transferring three atoms of bromine to the substrate (corresponding to up to 65% of its mass). Consequently, the stoichiometry of reactions involving TBCA is frequently 3:1 (substrate/TBCA).

Continuing our interest on the chemistry of tribromoisocyanuric acid,[14] herein we communicate its utilization for benzylic bromination of alkylarenes under free-radical conditions.

Ethylbenzene was chosen as a model substrate to develop the best conditions for the benzylic bromination using tribromoisocyanuric acid (Table 1). Initial studies utilizing equi-molar quantities of the reagents and a catalytic amount of benzoyl peroxide as a

* Corresponding authors.
E-mail addresses: pesteves@iq.ufrj.br (P.M. Esteves), mmattos@iq.ufrj.br (M.C.S. de Mattos).

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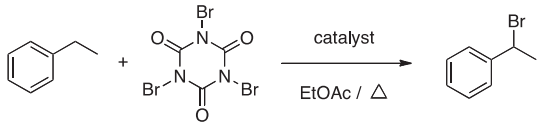
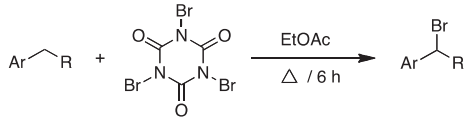
Table 1
Reaction of ethylbenzene with TBCA

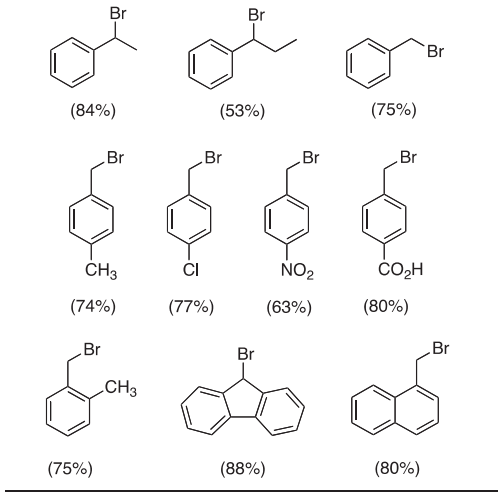


Catalyst	PhEt/TBCA[a]	Time (h)	Conversion[b] (%)
$(BzO)_2/h\nu$	1.00/0.34	2	80[c]
$(BzO)_2$	1.00/0.34	2	80[c]
—	1.00/0.34	6	100
—	1.00/0.47	2	100

[a] In mmol.
[b] Determined by GC–MS.
[c] Incomplete reaction.

Table 2
Benzylic bromination of alkylarenes with TBCA

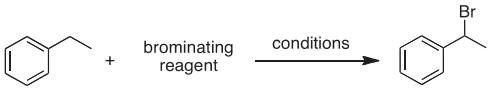


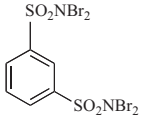
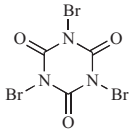
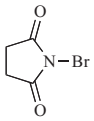


radical initiator under light irradiation led to 1-bromo-1-phenylethane in 80% yield. Interestingly, a similar conversion was observed when the reaction was performed in the absence of light. However, the best conversions were obtained using 0.34 mol equiv of TBCA for 6 h or using an excess of TBCA for 2 h, both reactions performed in the absence of catalyst and without irradiation (Table 1).

Based on the above results, the preparation of 1-bromo-1-phenyethane was performed by stirring 2.0 mmol of ethylbenzene and 0.68 mmol of TBCA at reflux in EtOAc for ca 6 h. The reaction proceeded smoothly and at the end of the reaction, cyanuric acid was removed by filtration and pure 1-bromo-1-phenylethane was isolated from the filtrate in 84% yield after work-up. Extension of these conditions to various alkylarenes led to the corresponding benzylic bromides in 53–88% yield (Table 2), being the products characterized by analytical methods and by comparison with previously reported data.[4a,11,15–19] Although the reactions could be performed in shorter reaction time (about 2 h) using an excess of TBCA, this reduction in time has not proved useful as small amounts of a dibrominated product (8–10%) were detected in some cases (toluene, xylenes, 1-methylnaphtalene, etc.). The benzylic bromination using TBCA is very selective and no products arising from electrophilic aromatic ring bromination[20] were detected in the crude products using GC and ^1H and ^{13}C NMR spectroscopy. We have also observed that ring substitution has no effect on the bromination yields.

Table 3
Benzylic bromination of ethylbenzene



Brominating reagent	Conditions	Yield (%)	Atom economy (%)	Atom efficiency (%)	Ref.
	EtOAc reflux/2 h	92	76	70	21
	EtOAc reflux/6 h	84	81	68	This work
	AIBN/CCl_4 reflux/4 h	90	65	59	22
Br_2	$La(OAc)_3$ CCl_4/60 °C	90	70	63	23

A comparison of the benzylic bromination of ethylbenzene performed by diverse reagents[21–23] using green metrics,[24] such as atom economy (mass of atoms in desired product/mass in atoms in reactants)[7] and atom efficiency (atom economy vs chemical yield)[25] is shown in Table 3. Although TBCA gave lower yields than other traditional brominating reagents, it presents the best atom economy and consequently the atom efficiency is comparable to *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide.[21]

In summary, we have developed a convenient method to carry out the radical benzylic bromination reaction of alkylarenes that does not involve special conditions or hazardous reagents. It is noteworthy that the utilization of TBCA in radical reactions has also the additional advantage that the by-product, cyanuric acid, is not corrosive and can be used to regenerate TBCA.[26] Furthermore, our methodology does not produce the corrosive HBr, since hydrogen ends up into the isocyanuric acid in the form of an NH bond, thus providing a facile and efficient process that is in full agreement with the tenets of green chemistry.[3,27,28]

Acknowledgments

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27. *General procedure for benzylic bromination of arenes with TBCA:* a solution of the arene (2.0 mmol) and TBCA (0.25 g, 0.68 mmol) in EtOAc (20 mL) was refluxed for 6 h with stirring. At the end of the reaction, the precipitated cyanuric acid was then separated by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was passed through a short chromatographic column (SiO_2, eluted with 15:1 hexane–ethyl acetate) to give the purified products.[28] Selected analytical data: *1-bromo-1-phenylethane:* colorless liquid (0.31 g, 84%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07 (d, 3H, *J* 7.0 Hz), 5.23 (q, 1H, *J* 7.0 Hz), 7.29–7.53 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.8, 49.5, 126.8, 128.3, 128.6, 143.2. MS (70 eV): *m*/*z* 186 [M^++2], 184 [M^+], 171, 169, 119, 117, 105 (100%), 103, 79, 77, 63, 51; *4-nitrobenzyl bromide:* colorless solid (0.27 g, 63%), mp. 98–99 °C (from hexane, Lit.[16] 100 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (s, 2H), 7.59 (d, 2H), 8.22 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1, 124.0, 130.0, 145.1, 147.5. MS: *m*/*z* 217 [M^++2], 215 [M^+], 136 (100%). 106, 90, 89, 78; *4-chlorobenzyl bromide:* colorless solid (0.31 g, 77%), mp. 51–53 °C (from EtOH, Lit.[29] 48–51 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.40 (s, 2H), 7.30 (d, 2H), 7.45 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.3, 129.0, 130.5, 134.1, 136.0; *9-bromofluorene:* colorless solid (0.43 g, 88%), mp 100–101 °C (from EtOH, Lit.[18] 99–102 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.00 (s, 1H), 7.31–7.44 (m, 4H), 7.66–7.69 (d, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.0, 120,2, 126.3, 128.0, 129.1, 139.7, 144.1 ppm. MS: *m*/*z* 246 [M^++2], 244 [M^+], 165 (100%), 139, 115, 83, 70; *(1-bromomethyl)naphtalene:* colorless solid (0.35 g, 80%), mp. 56–58 °C (from hexane, Lit.[19] 55 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.00 (s, 2H), 7.40–7.60 (m, 4H), 7.85–8.10 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.5, 123.7, 125.5, 126.0, 126.4, 127.5, 128.3, 130.0, 131.1, 133.0, 133.8.
28. *Caution!* Benzylic bromides are eye and skin irritants, hence due care must be taken during work-up and in handling.[6,11]
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