J. Braz. Chem. Soc., Vol. 19, No. 7, 1239-1243, 2008.
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0103 - 5053 $6.00+0.00

Communication

Triiodoisocyanuric Acid: a New and Convenient Reagent for Regioselective Iodination of Activated Arenes[#]

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O ácido triiodo-isocianúrico (TICA) foi preparado em 90% de rendimento a partir do aquecimento do ácido tricloro-isocianúrico com iodo em um tubo selado. A reação do TICA com arenos ativados em acetonitrila gera regiosseletivamente os respectivos iodo-arenos em 73-93% de rendimento isolado. Anilina e fenol também são monoiodados seletivamente usando MeOH (53%) e CH_2Cl_2 (88%) como solventes, respectivamente.

Triiodoisocyanuric acid (TICA) was prepared in 90% yield by heating trichloroisocyanuric acid with iodine in a sealed tube. The reaction of TICA with activated arenes in acetonitrile led to an efficient and highly regioselective formation of the corresponding iodoarenes, in 73-93% isolated yield. Aniline and phenol are monoiodinated regioselectively using MeOH (53%) and CH_2Cl_2 (88%) as solvents, respectively.

Keywords: triiodoisocianuric acid, iodination, activated aromatic compound, iodoarene, electrophilic halogenation

Introduction

Iodoarenes are valuable, versatile synthetic intermediates and have found wide applications in pharmacology, medicine and biochemistry.[1] Introduction of an iodine atom into organic molecules is frequently an important step in organic synthesis since the iodine atom can easily be replaced by another group in a nucleophilic, free radical substitution or transition metal catalyzed condensation, as for example, Heck, Stille, Negishi and Buchwald cross-coupling reactions to produce new C–C, C–S, C–O and C–N bonds.[2] However, the low electrophilic nature of the molecular iodine, compared to the molecular bromine and chlorine, difficults direct iodination.[3] The direct iodination is also hampered by the formation of HI, which can cause protolytic cleavage of sensitive compounds.[4] Hence many different synthetic methods (direct and indirect), or their improvements, have been reported for effective preparation of iodoarenes.[1]

Iodination of activated aromatic compounds was carried out by using molecular iodine or iodide ions together with an oxidizing agent, such as nitrogen dioxide,[5] tetrabutylammonium peroxydisulfate,[5] air/bismuth salts,[7] SiO_2–$Fe(NO_3)_3$•$9H_2O$,[8] hydrogen peroxide[9] and diiodine pentoxide/H_2SO_4/HOAc[10] in order to generate a better electrophile within the reaction. However, the oxidizing reagents can degrade sensitive groups present in the substrate. Other direct iodination methods have been recently developed using iodenium ("I^+") donating systems, such as CF_3COOAg/I_2,[11] NIBTS/CF_3CO_2H,[12] *N*-Iodosaccharin,[13] $KICl_2$,[14] $ICl/In(OTf)_3$,[4] IPy_2BF_4/CF_3SO_3H,[15] NIS/CF_3CO_2H,[16] NaOCl/NaI,[17] iodine/CAN,[18] NH_4I/oxone[19] and $NaIO_4$/KI/NaCl.[20] However, most of these methods require hazardous or toxic reagents or high reaction temperature for long reaction time.

N-Halocompounds are useful halogenating reagents in organic chemistry.[21] Recent papers have demonstrated that trihaloisocyanuric acids (Figure 1), such as trichloroisocyanuric[22] (TCCA), tribromoisocyanuric[23] (TBCA) and bromodichloroisocyanuric acids[24] are efficient halogenating agents of activated aromatic compounds, due to their capability of halenium ('X^+') atoms transfer. These trihaloisocyanuric acids are also very interesting from the green chemistry point of view,[25] since they halogenate organic compounds without using toxic and corrosive X_2 and also present good atom economy.

Triiodoisocyanuric acid (TICA, Figure 1), an analogue of TCCA and TBCA synthesized by Gottardi more than 35 years ago,[26] was recently reported by us as an

[#]Dedicated to Prof. W. Bruce Kover on the occasion of his 70th anniversary and retirement.

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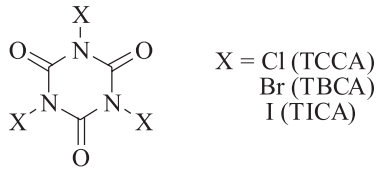


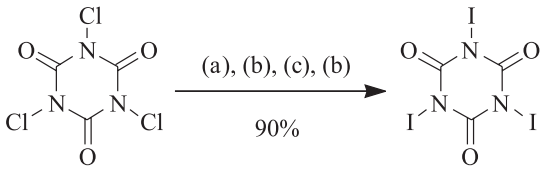
Figure 1. Trihaloisocyanuric acids.

efficient coiodination reagent of alkenes with oxygenated nucleophiles.[27] This motivated us to use it in our studies of iodination of activated aromatic compounds. TICA has also the advantage of transferring three equivalents of iodine atom to the substrate, representing an atom economy of up to 75%.

In this work we describe a new methodology for the regiosselective iodination of activated aromatic rings using TICA as the source of I^+.[28]

Results and Discussion

TICA was prepared in 90% yield by heating for 24 h the readily available trichloroisocyanuric acid[29] with 3.3 mol equiv. of I_2 at 180 °C followed by 48 h at 230 °C in a sealed tube (Scheme 1).



Reagents and conditions: (a) I_2 (3.3 mol equiv.) / 180 °C / 24 h; (b) distillation of ICl; (c) 230 °C / 48 h

Scheme 1. Preparation of TICA.

The reaction of arenes with TICA (0.34 mol equiv.) in acetonitrile at room temperature gave after work-up the corresponding monoiodo arenes in good to excellent yields (Table 1). These reactions are very simple and of easy work up, giving pure products that need no further purification. The regioselectivity of the reactions was very high and no regioisomers were detected by the analytical procedures employed (HRGC and ^{1}H and ^{13}C NMR spectroscopy). However an exception was observed in the reaction of toluene that produced both regioisomers *o*- and *p*-iodotoluene (Table 1, entry 10).

Highly activated arenes, such as aniline and phenol, were successfully monoiodinated by TICA in MeOH and CH_2Cl_2, respectively (Table 1, entries 8 and 9). On the other hand, non-activated arenes failed to undergo iodination under these conditions, e.g., benzene that gave no product after 72 hours of reaction (Table 1, entry 11). In weakly activated arene, as toluene, the reaction is slow but it is possible to observing the consumption of all substrate after 48 h with the use of a small excess TICA (Table 1, entry 10). Diiodination products can also be obtained by using 0.7 mol equiv. of TICA (Table 1, entry 7).

Experimental

Procedure for preparation of TICA

Iodine (184.6 mmol, 46.85 g) and trichloroisocyanuric acid (55.93 mmol, 13.00 g) were added to a 100 cm^3 sealed tube and heated in a sand bath at 180 °C. After 24 h, the ICl produced was distilled off under reduced pressure and the sealed tube was heated again at 230 °C during 48 h. Evaporation of ICl under reduced pressure and heating gave triiodoisocyanuric acid as a brown solid in 90% yield.[30] mp > 300 °C. IR (KBr) ν_{max}/cm^{-1}: 3211, 3053, 2884, 2830, 2780, 1700, 1665, 1459, 1372, 1145, 1061, 1051, 732, 663, 533.

General procedure for iodination of activated arenes with TICA

To a stirred solution of the arene (2 mmol) in acetonitrile (MeOH in the case of aniline or CH_2Cl_2 in the case of phenol) (5 cm^3), was added TICA (0.67 mmol) at room temperature and in the absence of light. The reaction was monitored by HRGC-MS and after the specified time showed in Table 1, CH_2Cl_2 (10 cm^3) was added, cyanuric acid was filtered off and the resulting solution was treated with 10% aq. $NaHSO_3$ (60 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 cm^3), the combined organic extract was washed with H_2O (60 cm^3), dried (anhydrous Na_2SO_4) and filtered. The solvent was evaporated on a rotatory evaporator to give the pure product. Selected analytical data:

4-Iodo-anisol

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.69 (d, *J* 8.8 Hz, 2H), 7.57 (d, *J* 8.8 Hz, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.4, 82.8, 116.5, 138.3, 159.6 ppm.

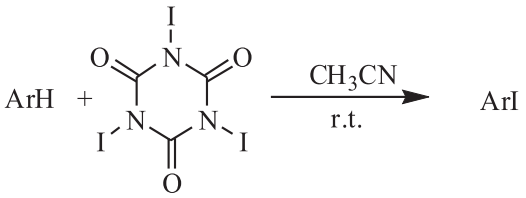
2-Iodo-1,4-dimethoxybenzene

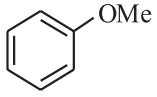
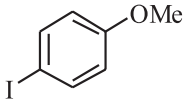
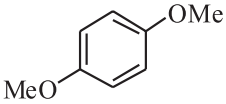
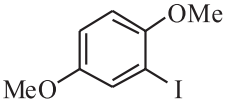
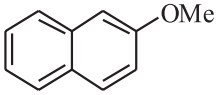
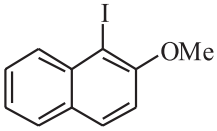
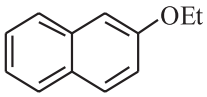
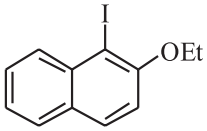
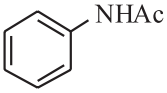
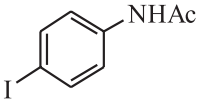
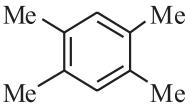
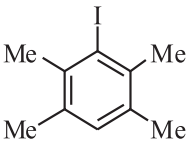
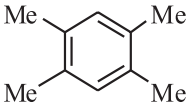
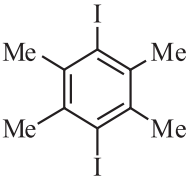
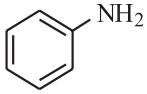
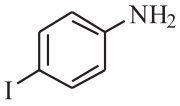
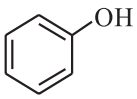
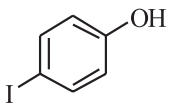
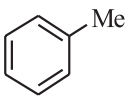
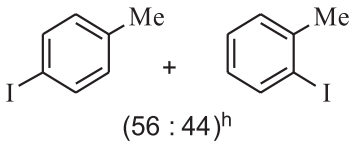
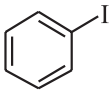
^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0, 57.1, 86.1, 111.7, 114.8, 124.9, 152.8, 154.4 ppm. MS: *m/z* 264 (M^+, 100%), 249, 233, 221, 127, 122, 107, 92, 79, 77, 63.

1-Iodo-2-methoxynaphthalene

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.03 (s, 3H), 7.21 (d, *J* 9.0 Hz, 1H), 7.40 (t, *J* 7.5 Hz, 1H), 7.56 (t, *J* 7.6 Hz, 1H),

Table 1. Iodination of activated arenes with TICA



Entry	Substrate	Product[a]	t / h	Yield / %[b]
1			4	90
2			0.7	93[c]
3			0.7	90
4			1.5	86
5			17	90
6			4	83
7[d]			20	90
8[e]			1.5	53
9[f]			1	88[g]
10		 (56 : 44)[h]	48	73
11			72	trace

[a]Reaction using 0.34 mol equiv. of TICA. [b]Isolated yield based on the arene. [c]With 8% of diiodinated product. [d]Reaction using 0.7 mmol equiv. of TICA. [e]Solvent: MeOH. [f]Solvent: CH_2Cl_2. [g]After SiO_2 chromatography with 0-10% EtOAc/hexanes. [h]Determined by HRGC-MS.

7.76 (d, *J* 8.0 Hz, 1H), 7.83 (d, *J* 9.0 Hz, 1H), 8.17 (d, *J* 8.5 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.3, 87.8, 113.0, 124.4, 128.2, 128.3, 130.0, 130.4, 131.3, 135.7, 156.7 ppm.

2-Ethoxy-1-iodonaphthalene

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (t, *J* 7.0 Hz, 3H), 4.26 (q, *J* 7.0, 2H), 7.18 (d, *J* 9.0 Hz, 1H), 7.39 (t, *J* 7.4 Hz, 1H), 7.56 (t, *J* 7.5 Hz, 1H), 7.75 (d, *J* 9.9 Hz, 1H), 7.80 (d, *J* 9.0 Hz, 1H), 8.17 (d, *J* 8.5 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.2, 66.2, 89.0, 114.6, 124.4, 128.1, 128.2, 130.0, 130.3, 131.4, 135.8, 156.3 ppm.

4-Iodoacetanilide

mp 184 °C (lit: 184 °C)[31] MS: *m/z* 261 (M^+), 245, 219 (100%), 203, 127, 105, 92, 91, 76, 65, 43.

3-Iodo-1,2,4,5-tetramethylbenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 6H), 2.47 (s, 6H), 6.92 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 26.7, 111.6, 131.5, 134.2, 137.7 ppm.

1,4-Diiodo-2,3,5,6-tetramethylbenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.65 (s, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.9, 112.3, 138.0 ppm.

4-Iodoaniline

mp 63 °C (lit: 64-65 °C)[32] IR (KBr) ν_{max}/cm^{-1}: 3406, 3299, 3200, 3058, 3028, 1629, 1582, 1482, 1275, 815. MS: *m/z* 220 (M^+ +1), 219 (M^+, 100%), 191, 127, 109, 92, 65, 63, 52.

4-Iodophenol

mp 90-92 °C (lit: 91-93°C)[33] MS: *m/z* 220 (M^+, 100%), 191, 127, 110, 93, 75, 65.

2-Iodotoluene

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.2, 101.3, 127.5, 128.2, 129.8, 139.0, 141.4 ppm. MS: *m/z* 218 (M^+), 127, 91 (100%), 65, 51.

4-Iodotoluene

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 90.3, 131.3, 137.3, 137.5 ppm. MS: *m/z* 218 (M^+), 127, 91 (100%), 65, 51.

Conclusions

In conclusion, we have developed a very simple, efficient and ecofriendly methodology for the regioselective iodination of activated aromatic rings in good to excellent yields under mild conditions. Furthermore, the reagent is very safe, easily handled and more useful in terms of atom economy than the traditional reagents used in iodination reactions.

Acknowledgments

The authors thank CNPq, CAPES, and FAPERJ for the financial support.

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Received: February 26, 2008
Web Release Date: August 5, 2008