Communication

Trichloroisocyanuric Acid in H$_2$SO$_4$: An Efficient Superelectrophilic Reagent for Chlorination of Isatin and Benzene Derivatives

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O ácido tricloro-isocianúrico (TICA) em H$_2$SO$_4$ é um reagente eficiente para a cloração regioseletiva da isatina na posição 5 e compostos aromáticos desativados, como o nitro-benzeno. Cálculos de DFT sugerem a formação de uma espécie supereletrofílica poliprotonada que pode transferir Cl$^+$ ao anel aromático mais eficientemente do que o TICA devido ao alívio da repulsão carga-carga.

Trichloroisocyanuric acid (TICA) in H$_2$SO$_4$ is an efficient reagent for regioselective chlorination of isatin at the 5-position and deactivated aromatic compounds, such as nitrobenzene. DFT calculations suggest formation of a superelectrophilic polyprotonated species that can transfer Cl$^+$ to the aromatic ring more efficiently than TICA due to charge-charge repulsion relief.

Keywords: trichloroisocyanuric acid, chlorination, superelectrophile, aromatic compounds, DFT calculations

Introduction

Isatin (1H-indole-2,3-dione) is a versatile molecule with important applications in synthetic organic chemistry.[1] Some of its derivatives, specifically 5-haloisatins, show a wide range of biological and pharmacological activity, such as antibacterial, antifungal, and anti-HIV, to name a few.[2] They can be prepared by the laborious Sandmeyer and similar methodologies from *p*-haloanilines or by direct halogenation of isatin.[1,3] Several reagents that perform the chlorination of isatin mainly in the 5-position are described in the literature. Among them, we can find *N*-chloroamides and *N*-chloroimides[3] and recently we reported the regiospecific preparation of 5-chloroisatin in 48% yield using *N*-chlorosaccharin in a heterogeneous media (SiO$_2$ / CH$_2$Cl$_2$).[4]

The chlorination of aromatic compounds is well-documented in the literature. However, direct chlorination of deactivated aromatic compounds is frequently disappointing. An efficient electrophilic chlorination of deactivated aromatic compounds with NCS / BF$_3$ / H$_2$O was recently published.[5]

Trichloroisocyanuric acid (TICA) has proven to be a mild oxidant[6] and an efficient reagent for performing the

cohalogenation of alkenes under mild conditions, thus serving as a new source of electrophilic chlorine to prepare chlorohydrins, β-chloroethers and β-chloroacetates.[7] This reagent is a stable and inexpensive solid frequently found in a large number of commercial products for swimming-pool disinfection and easily available in pool supply and some hardware stores.[8]

Continuing[7,9] our desire to use TICA as a source of electrophilic chlorine, we now communicate our results on the chlorination of isatin and other aromatic compounds.
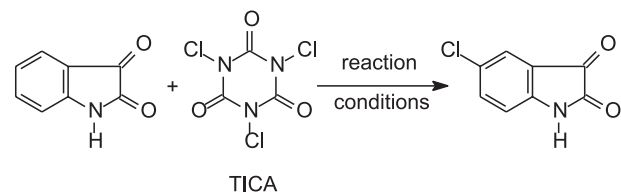
Results and Discussion

The results of the reaction of isatin with trichloroisocyanuric acid to produce 5-chloroisatin are summarized in Table 1. Using CH$_2$Cl$_2$ as solvent, the reaction was incomplete after 72 h at rt and the product was obtained in less than 2 % yield. Even with the utilization of an excess of TICA and SiO$_2$ as catalyst, 5-chloroisatin was isolated in only 29 % yield after 98 hours. However, the chlorination of isatin was efficiently achieved using just 0.34 mol equivalent of TICA in the presence of H$_2$SO$_4$ to give the desired product in 72 % of isolated yield in less than 5 minutes. No *N*-chlorination of

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isatin[10] nor significant amount of the frequently formed isomeric 7-chloroisatin[3] was detected in the crude reaction product by coinjection in HRGC (high-resolution gas chromatography) with authentic 7-chloroisatin.

Table 1. Results of chlorination of isatin with TICA

Reaction conditions	Yield (%)[a]
CH_2Cl_2 / rt / 72 h	< 2
CH_2Cl_2 / SiO_2 / rt / 98 h	29
H_2SO_4 / rt / 5 min	72

[a]Isolated yield based on isatin.

We believe that the strongly acid media promotes the formation of a superelectrophilic species[11] (*e.g.* Figure 1), where TICA being either polyprotonated or protosolvated,[12] causing the "Cl+" transfer to isatin more efficiently due to the charge-charge repulsion relief.
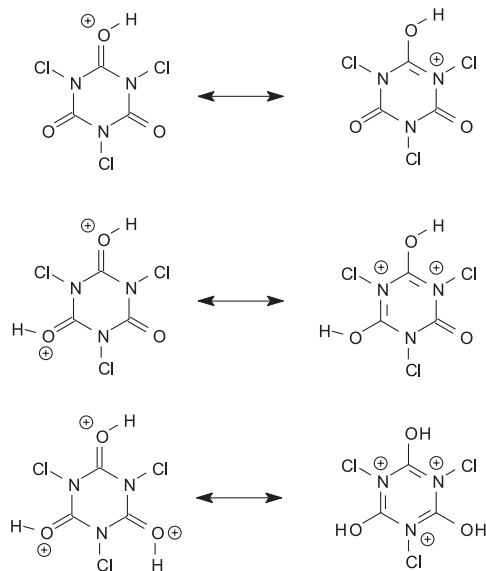

Figure 1. Superelectrophilic species obtained by protonation of TICA.

Density functional theory (DFT) calculations on TICA and its mono-, di- and triprotonated species[13] (Figure 2) could estimate their ability to release Cl+, which would be correlated with its reactivity as an electrophile. Table 2 shows the heats of reaction for loss of Cl+ from TICA and its protonated forms. As one can see, the increase of the degree of protonation of TICA leads to a more reactive intermediate that can release Cl+ to a nucleophile (*e.g.* the π system of an aromatic ring) more easily. This can be understood if one considers that the release of the Cl+ in a highly protonated form of TICA leads to a decrease in

charge-charge (coulombic) repulsion into the molecule, thus decreasing its energy. Hence the highly protonated species works as a very powerful electrophile, whose reactivity can be regulated by the acid strength of the medium. As expected, bond lengths between N-Cl in the protonated species (Figure 2) increase when going from the unprotonated species (1.705 Å) to the triprotonated species (1.734 Å), which reflect these intramolecular coulombic repulsions. Actually, monoprotonation of TICA in H_2SO_4 is exothermic by 12.0 kcal mol⁻¹. On the other hand, di- and triprotonation are endothermic respectively by 77.6 kcal mol⁻¹ and 235.9 kcal mol⁻¹ (see Supplementary Information). Thus, probably there is a higher concentration of monoprotonated species in this media. However, the *de facto* reacting species could either be any of the polyprotonated species, with the species with higher protonation degree having a stronger electrophilic character, thus being able to chlorinate weaker π nucleophiles.

Based on the relative energies for the σ-complexes involved on the chlorination of isatin at B3LYP/6-31++G** level, chlorination should take place preferentially at the 5-position, followed by the product at the 7-position, which is 4.4 kcal mol⁻¹ less stable than the former. Attacks in other positions afford intermediates that are about 20 kcal mol⁻¹ higher in energy (see Supplementary Information), thus not being favorable from the energetic point of view.
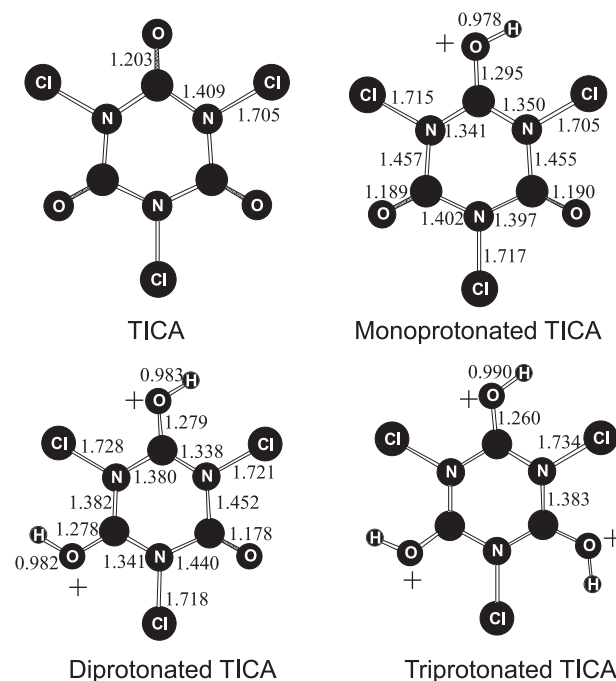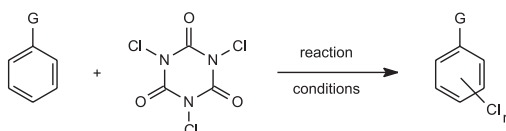
In order to test this hypothesis we used both TICA

Figure 2. Geometries for TICA and its protonated forms, obtained after optimization at B3LYP/6-31++G** level.

Table 2. Enthalpy differences (298 K, 1 atm) for single Cl$^+$ loss for TICA and its protonated forms

Species	ΔH^{298} (kcal mol^{-1})[a]
TICA	278.6
Monoprotonated TICA	51.5
Diprotonated TICA	-76.1
Triprotonated TICA	-194.2

[a]Performed at the B3LYP/6-311++G**// B3LYP/6-31++G** level, taking into account zero-point energy and thermal expansion correction. All calculations were performed with the Gaussian 98 package.

and TICA / H$_2$SO$_4$ in the chlorination of aromatic rings of different reactivity (Table 3). Anisole gave *o*- and *p*-chloroanisole (91%) in 1.5 h by the reaction with 0.34 mol equiv. TICA. However, the same reaction performed in the presence of H$_2$SO$_4$ produced mainly 2,4,6-trichloroanisole (28%) in only 5 min. Reaction of TICA with toluene produced *o*- and *p*-chlorotoluene (50% yield, incomplete reaction after 5 days) and a mixture of several chlorinated products in 20 min in the case of reaction with TICA / H$_2$SO$_4$. Chlorobenzene gave no reaction at all with TICA while its reaction with TICA / H$_2$SO$_4$ produced a mixture of dichloro- and

Table 3. Results of chlorination of aromatics with TICA

G	Reaction conditions	Products	Yield (%)[a]
OMe	MeCN / rt / 1.5 h	(1 : 5)[b]	91
OMe	H$_2$SO$_4$ / rt / 5 min		28
Me	MeCN / rt / 116 h	(1 : 1)[b]	50
Me	H$_2$SO$_4$ / rt / 20 min	(54 : 13 : 27 : 6)[b]	nd[c]
Cl	H$_2$SO$_4$ / rt / 24 h	(24 : 45 : 25 : 6)[b]	61
NO$_2$	H$_2$SO$_4$ / 80 °C / 5 h		80

[a]Yield based on aromatic compound; [b]Determined by coinjection in HRGC with authentic samples; [c]Not determined.

trichlorobenzenes. Nitrobenzene was only chlorinated with TICA / H_2SO_4 at 80 °C after 5 h to produce *m*-chloronitrobenzene in 80 % yield. Our method is easier to execute than the reaction of nitrobenzene with NCS / BF_3 / H_2O in a closed pressure tube heated to 105-110 °C over 18 h to give the same product in 69 % yield.[5]

The DFT calculations corroborate the above experimental results which show that increasing the acidity of the media led to higher yields in shorter reaction times, even for non reactive substrates, such as chlorobenzene and nitrobenzene.

Conclusions

In summary, we have developed a very attractive and simple methodology for the regiospecific preparation of 5-chloroisatin in 72 % yield, in 5 min and using just 0.34 mol equiv. of trichloroisocyanuric acid.[14] The reaction conditions employed and the isolated yield obtained seem to be considerably better than those reported in the literature.[3] Furthermore, our methodology permits the chlorination of deactivated substrates, such as nitrobenzene in high yield.

Acknowledgements

Supplementary Information

Tables containing the relative enthalpies (298K, 1 atm) of the protonation of TICA by H_2SO_4 (Table S1) and the σ-complexes involved in the chlorination of isatin (Table S2) are available free of charge as PDF file at http://jbcs.sbq.org.br.
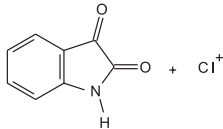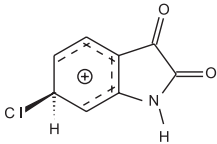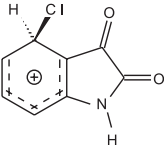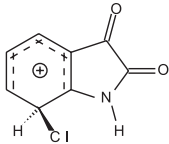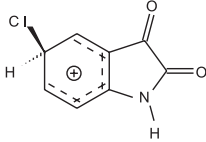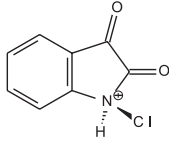
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12. It was observed the splitting of the ^{13}C NMR signals relative to the carbon atoms of TICA (a singlet in 142.9 ppm in acetonitrile) into 147.4 and 147.2 ppm of TICA in H_2SO_4.

13. We investigated all possible sites of protonation for each form (*O* and *N* protonation, in all possible combinations), and the carbonyl group was the preferred site of protonation for all cases.

14. Typical procedure for the halogenation of aromatics with TICA / H_2SO_4: Preparation of 5-chloroisatin: A suspension of isatin (10 mmol) and trichloroisocyanuric acid (3.4 mmol) in H_2SO_4 (4 cm³) was stirred at room temperature for 5 min. After the addition of cold water, the resulting solution was extracted with EtOAc (4 x 15 cm³), treated with 10% NaHCO₃ (20 cm³), filtered, washed with sat. NaCl sol. and then dried (anhyd. Na₂SO₄). The organic solvent was rotaevaporated at reduced pressure and 5-chloroisatin was isolated in 72 % yield, mp 247-250 °C (lit. 246-247 °C: Gassman, P.G.; Halweg, K.M.; *J. Org. Chem.* **1979**, *44*, 628). ^1H NMR (200 MHz, CDCl₃/DMSO-d₆) δ 6.91 (d, *J* 9.0 Hz, 1H), 7.50 (m, 2H), 10.99 (br s, 1H, NH). ^{13}C NMR (50 MHz, CDCl₃/DMSO-d₆) δ 109.2 (CH), 113.8 (C), 120.0 (CH), 123.6 (C-Cl), 133.0 (CH), 144.6 (C), 154.4 [C(O)N], 182.9 [C(O)]. IR $ν_{max}$/cm⁻¹ (KBr): 3183, 3103, 3080, 2999, 1752, 1710, 1618, 1472, 1451, 847, 749, 701, 657.

Supplementary Information

Table S1. Enthalpy differences (298 K, 1 atm) for single Cl^+ of isatin at several positions

Species	ΔH^{298} (kcal mol^{-1})[a]	Species	ΔH^{298} (kcal mol^{-1})[a]
	190.4		21.8
	23.5		4.4
	0.0		23.1

[a] Performed at the B3LYP/6-31++G** level, taking into account zero-point energy and thermal expansion correction. All calculations were performed with the Gaussian 98 package.

Table S2. Enthalpy differences (298 K, 1 atm) for protonation of TICA

Reaction	ΔH^{298} (kcal mol^{-1})[a]
$H_3SO_4^+ + TICA \rightarrow H_2SO_4 + H\text{-}TICA^+$	-12.0
$2\ H_3SO_4^+ + TICA \rightarrow 2\ H_2SO_4 + H_2\text{-}TICA^{+2}$	77.6
$3\ H_3SO_4^+ + TICA \rightarrow H_2SO_4 + H_3\text{-}TICA^{+3}$	235.9

[a] Performed at the B3LYP/6-31++G** level, taking into account zero-point energy and thermal expansion correction. All calculations were performed with the Gaussian 98 package.