

Dichloroiodoisocyanuric Acid: A New Reagent for Regioselective Coiodination of Alkenes and Iodination of Activated Arenes[#]

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O ácido dicloro-iodo-isocianúrico foi preparado em 93% de rendimento através do aquecimento do ácido tricloro-isocianúrico com 1,05 equiv. mol de iodo. Esse novo reagente se mostrou bastante eficiente para a iodação regioseletiva de arenos ativados. Os alquenos reagem com o ácido dicloro-iodo-isocianúrico na presença de solventes nucleofílicos oxigenados (água, álcoois, ácido acético) para gerar, respectivamente, iodidrinás, β -iodoéters e β -iodoacetatos em menos de um minuto de reação e em alto grau de regioseletividade. Enol-éteres levam à formação regioseletiva dos iodo-dialquilacetals correspondentes. Os resultados experimentais juntamente com os cálculos por DFT mostraram que, para reações com sistemas insaturados, o ácido dicloro-iodo-isocianúrico é mais reativo do que o ácido triiodo-isocianúrico.

Dichloroiodoisocyanuric acid was prepared in 93% by heating trichloroisocyanuric acid with 1.05 mol equiv. of iodine. This new reagent is very efficient for regioselective electrophilic iodination of activated arenes. Alkenes react with dichloroiodoisocyanuric acid in the presence of oxygenated nucleophiles (water, alcohols, and acetic acid), leading to the corresponding iodohydrins, β -iodoethers and β -iodoacetates with reaction times of less than one minute and with a high degree of regioselectivity. Enol ethers resulted in the regioselective formation of the corresponding iodine-dialkylacetals. Experimental results and DFT calculations showed that dichloroiodoisocyanuric acid is more reactive with unsaturated systems than triiodoisocyanuric acid.

Keywords: alkenes, arenes, electrophilic addition, electrophilic aromatic substitution, halogenation

Introduction

Iodo-organic compounds are valuable and versatile synthetic intermediates that have found diverse applications in polymer chemistry, pharmacology, medicine, etc.¹ Aside from their principal application in organic synthesis,² the discovery of the bioactivity of naturally organic iodides³ has increased the interest in such compounds. The introduction of an iodine atom into organic molecules is frequently an important step in organic synthesis as the iodine atom can easily be replaced by another group in a nucleophilic process, free radical substitution⁴ or a transition metal catalyzed reaction, for example, the Heck and related Pd catalyzed cross-couplings.⁵ However, the poor electrophilicity of molecular iodine, compared with molecular bromine and chlorine, makes direct iodination

difficult in many cases.⁶ Hence, many different synthetic methods (direct and indirect), or their improvements, have been reported for the preparation of iodo compounds.⁷

Recently, we have introduced trihaloisocyanuric acids (Figure 1) as efficient halogenating reagents for organic compounds. Thus the cohalogenation of alkenes (halogenation in the presence of a nucleophilic solvent⁸) with trichloroisocyanuric (TCCA),⁹ tribromoisocyanuric (TBICA),¹⁰ or triiodoisocyanuric (TICA)¹¹ acids led to the formation of β -halo-substituted alkanes in high regioselectivity. These reagents have also proved to be useful for the halogenation of activated^{12,13} and deactivated¹⁴ arenes, β -dicarbonyl compounds,¹⁵ and halofluorination of alkenes.¹⁶ The trihaloisocyanuric acids containing different halogen atoms are also of great interest and in a previous study we showed that bromodichloroisocyanuric acid (BDCCA) is also a very good regioselective brominating agent.¹⁷

Herein we introduce the preparation of a new compound, dichloroiodoisocyanuric acid (DCICA, Figure 1), and

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[#]Dedicated to Prof. José Barluenga for his many achievements in synthetic organic chemistry.

investigate its application towards alkene coiodination and arene iodination reactions.

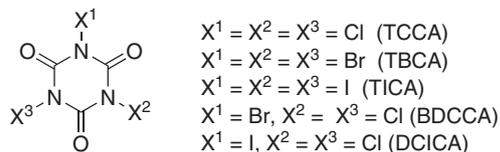
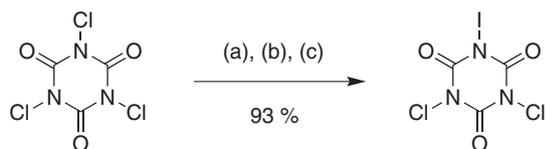


Figure 1. The trihaloisocyanuric acids.

Results and Discussion

Dichloroiodoisocyanuric acid was prepared in 93% yield from the commercially available trichloroisocyanuric acid (Scheme 1). The reaction was performed in a sealed tube by heating TCCA with 1.05 mol equiv. of I_2 at 170 °C for 18 h, followed by distillation of ICl and another heating for 24 h at 220 °C.



(a) I_2 / 170 °C / 18 h; (b) distillation of ICl ; (c) 220 °C / 24 h

Scheme 1. Preparation of dichloroiodoisocyanuric acid.

The scope of the coiodination reactions using DCICA in oxygenated nucleophilic solvents was explored with simple alkenes (cyclohexene, 1-methylcyclohexene, styrene, α -methylstyrene, and 1-octene) and with activated alkenes (enol ethers, such as butyl vinyl ether, dihydropyran and 1-methoxycyclohexene), being the results shown in Table 1. The reactions were carried out in less than 1 min using 2 mmol of alkene and 2 mmol of DCICA at room temperature and led to the vicinal iodo functionalized products.

The reaction of alkenes with an equimolar amount of DCICA in the presence of alcohols (MeOH, EtOH, and i PrOH), aqueous acetone and acetic acid/acetic anhydride resulted in the respective β -iodoethers, iodoalcohols, and β -iodoacetates. The reactions with styrene, α -methylstyrene, and 1-methylcyclohexene were highly regioselective, and products were formed in accordance with Markovnikoff additions; no regioisomers could be detected on analyzing the crude reaction products by HRGC-MS, ^1H and ^{13}C NMR spectroscopy. Enol ethers also produced the corresponding iodo-dialkylacetals in a regioselective manner. As previously observed in similar reactions,²⁸ exceptions were observed in the reactions using 1-octene where a mixture of regioisomers was produced, with the primary iodide being preferentially formed.

Furthermore, as previously observed in the reactions with bromodichloroisocyanuric acid,¹⁷ no chlorinated products that could arise from electrophilic chlorine transfer from DCICA were detected by the analytical methods employed.

High *trans*-stereoselectivity was also observed for additions to cyclohexene, 1-methylcyclohexene and dihydropyran, as can be seen by the values of the vicinal coupling constants for the methine hydrogen atoms CHOR and CHI in the iodoalcohols and β -iodoethers derived from cyclohexane (Table 2). In these cases the obtained values of J greater than 9.0 Hz indicate they are in an antiperiplanar position.²⁹ Furthermore, the additional vicinal couplings depicted in Table 2 support the *trans*-selectivity of the reaction. In the case of the reaction of DCICA with 1-methylcyclohexene, the iodoalcohol formed shows the methine CHI hydrogen with vicinal couplings $J_{\text{ax-ax}}$ 12.1 Hz and $J_{\text{ax-eq}}$ 4.3 Hz, clearly indicating that the iodine is in the equatorial position.²⁹

Iodination of some activated arenes were carried out at room temperature using equimolar amounts of the substrate and DCICA in acetonitrile (Table 3). After work-up, the corresponding iodinated products were obtained in excellent yields and with high regioselectivity, as observed the formation of 4-substituted monoiodo arenes and 1-iodo-2-methoxynaphthalene. Even weakly activated arenes, such as toluene, were iodinated after 1.5 h. Diiodination products can also be obtained by using 2 mol equiv. of DCICA in the case of durene. On the other hand, non-activated arenes, e.g. benzene reacted very slowly. Once again, no chlorinated products could be detected by HRGC-MS and ^1H and ^{13}C NMR spectroscopy.

In previous studies using triiodoisocyanuric acid (TICA, Figure 1), the iodination reactions of the same arenes¹² or the coiodination of the same alkenes¹¹ were found to require longer reaction times than those observed in this present study with DCICA, as shown in Table 4.

Comparing the reactivity of DCICA with TICA towards iodonium ion (I^+) transfer to alkenes and arenes, we observed that DCICA is far more reactive. This could be explained in terms of the greater electronegativity of chlorine in relation to iodine. This would result in the N–I bond of DCICA being more electrophilic in comparison to the N–I bonds of TICA (Figure 2).

In order to better understand the reactivity differences between TICA and DCICA, we have performed DFT calculations on these structures and on their complexes with ethylene and benzene. All calculations were performed at M06-2X/6-311++G(d,p)//M06-2X/6-311++G(d,p) level using the program Gaussian 09.³⁵ Charges were computed using the CHELPG scheme,³⁶ considering the radii of 2.20 Å for iodine.³⁷

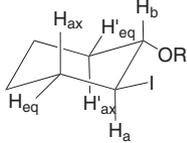
Table 1. Coodination of alkenes with DCICA and oxygenated nucleophiles

Alkene	Product	Solvent	Yield / (%) ^a	Ref. to product
		MeOH	99	18
		EtOH	98	19
		ⁱ PrOH	98	19
		MeOH	75	20
		ⁱ PrOH	76	21
Hex		MeOH	80 ^b	22
		H ₂ O/Me ₂ CO (5:1)	87	19
		H ₂ O/Me ₂ CO (5:1)	99	23
		H ₂ O/Me ₂ CO (5:1)	83	18
		H ₂ O/Me ₂ CO (5:1)	42	24
Hex		H ₂ O/Me ₂ CO (5:1)	85 ^b	23
		HOAc/Ac ₂ O (1:1)	89	25
BuO		MeOH	99	11
		MeOH	99	26
		MeOH	51	27

^aYield of pure product based on alkene. ^bFormed along with *ca.* 20% of the regioisomer (by HRGC-MS).

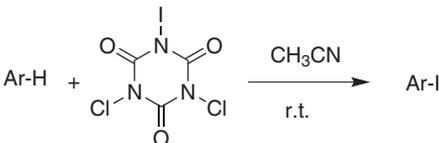
Figure 3 shows the optimized geometries, with selected geometric parameters. One can observe that the charge on the iodine atoms is slightly more positive and the N–I bond is larger for DCICA than for TICA, which suggests

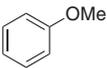
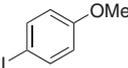
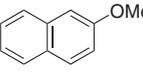
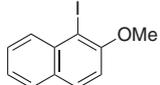
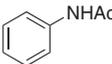
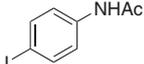
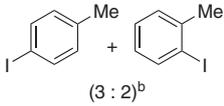
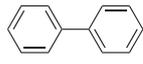
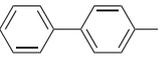
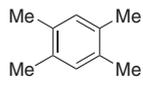
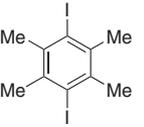
Table 2. Coupling constants for the iodo-alkoxycyclohexanes prepared



Coupling	<i>J</i> / Hz		
	R = H	R = Me	R = ⁱ Pr
H _a -H _b	9.8	9.0	8.9
H _a -H _{eq}	4.4	3.8	4.4
H _a -H _{ax}	12.3	9.0	10.9
H _b -H' _{eq}	4.4	4.1	4.4
H _b -H' _{ax}	9.8	9.0	8.9

Table 3. Iodination of activated arenes with DCICA



Substrate	Product	<i>t</i> / min	Yield ^a / %	Ref. to product
		6	97	30
		1	99	31
		20	96	30
	 (3 : 2) ^b	100	91	12
		150	99	32
		72 h 67 days	trace 31	33
		180	90 ^c	34

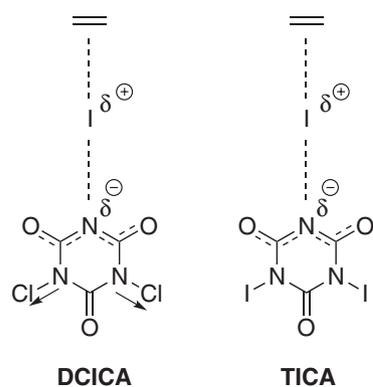
^aYield of pure product based on arene. ^bDetermined by HRGC-MS. ^cReaction using 2 mol equiv. of DCICA.

its higher electrophilicity. However, more differences are found on their π -complexes with ethylene (Figure 4) and benzene (Figure 5). The DCICA is more closely attached to the olefin in relation to TICA and the dissociation enthalpies of these complexes are 6.8 kcal mol⁻¹ and 5.6 kcal mol⁻¹ for DCICA and TICA, respectively. This shows that the interaction of ethylene with DCICA is slightly stronger than with TICA, reflecting the higher electrodeficiency of its compared to TICA. On the other hand, the enthalpy for dissociation of both complexes of DCICA and TICA with benzene is 6.7 kcal mol⁻¹.

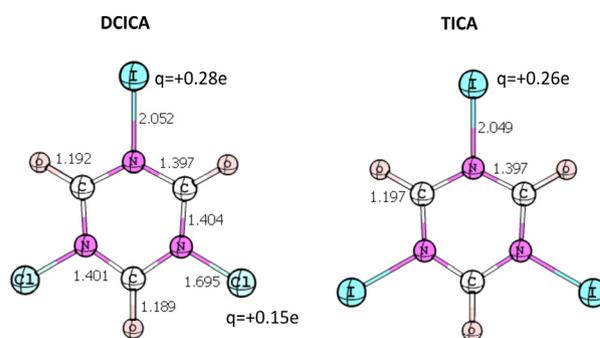
We have also carried out calculations of the transition states for I⁺ transfer of both reagents and the results are shown in Figure 6. One can see from the enthalpies of activation that the chlorine within the isocyanuric moiety leads to a decrease in the activation barrier from 20.2 kcal mol⁻¹ (TICA) to 17.7 kcal mol⁻¹ (DCICA). This can be explained by the greater ability of the chlorine atoms in DCICA to stabilize the negative charge formed

Table 4. Comparison of electrophilic iodination reactions using DCICA and TICA

Reaction	Reagent	time	Yield / %
	DCICA	1 min	99
	TICA ¹¹	15 min	90
	DCICA	1 min	89
	TICA ¹¹	40 min	73
	DCICA	1 min	99
	TICA ¹¹	20 min	98
	DCICA	1 min	76
	TICA ¹¹	20 min	74
	DCICA	1 min	99
	TICA ¹¹	2 min	83
	DCICA	6 min	97
	TICA ¹²	240 min	90
	DCICA	1 min	99
	TICA ¹²	45 min	90
	DCICA	20 min	96
	TICA ¹¹	17 h	90
	DCICA	1.5 h	91
	TICA ¹²	48 h	73
	DCICA	3 h	90
	TICA ¹²	20 h	90

**Figure 2.** Transfer of I⁺ from DCICA and TICA to an unsaturated system.

in the transition state of I⁺ transfer in relation to TICA. These findings are also in agreement with the experimental results, which indicate DCICA being the most reactive of the two compounds.

**Figure 3.** Optimized geometries with selected geometric parameters for DCICA and TICA obtained at M06-2X/6-311++G(d,p) level.

In summary, we have reported here the preparation of dichloroiodoisocyanuric acid and its higher reactivity toward some unsaturated hydrocarbons as compared to triiodoisocyanuric acid. This reagent proved to be very

useful for the iodination of alkenes and arenes in clean and fast reactions.

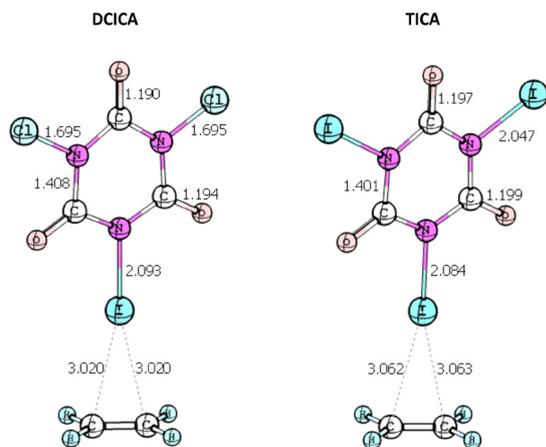


Figure 4. π -Complexes between ethylene and DCICA and TICA obtained at M06-2X/6-311++G(d,p) level.

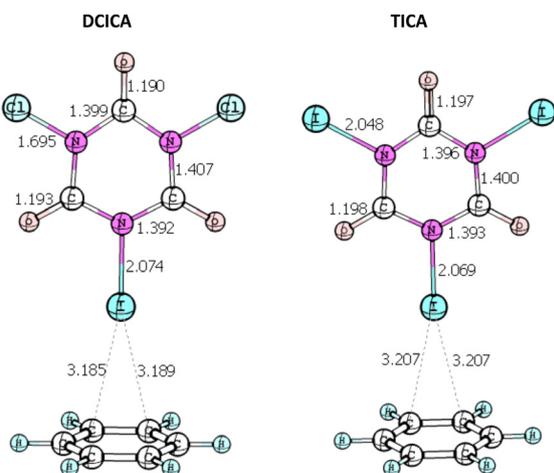


Figure 5. π -Complexes between benzene and DCICA and TICA obtained at M06-2X/6-311++G(d,p) level.

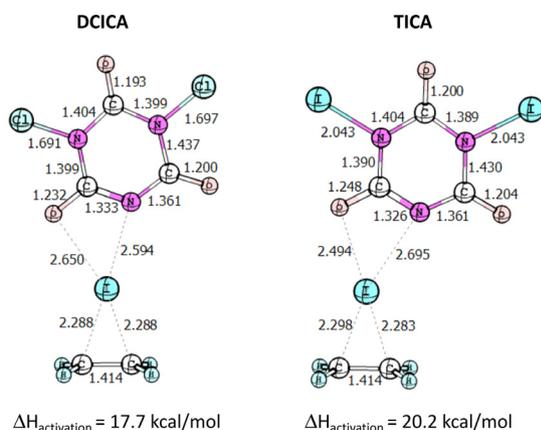


Figure 6. Transition states for I^+ transfer of DCICA and TICA obtained at M06-2X/6-311++G(d,p) level.

Experimental

General

Trichloroisocyanuric acid (commercial grade, 98%), and other chemicals and solvents were used as received. The 1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ or $DMSO-d_6$ solutions with TMS as internal standard. ^{13}C MAS-NMR spectrum was obtained on a Bruker DRX300 spectrometer (75MHz). High-resolution gas chromatography (HRGC) was performed on a HP-5890-II gas chromatograph with FID using a 30 m (length), 0.25 mm (ID), and 25 μm (phase thickness) RTX-5 capillary column and H_2 (flow rate 50 $cm\ s^{-1}$) as carrier gas (split: 1:10). HRGC-MS analyses were performed on a Shimadzu GCMS-QP2010S gas chromatograph with electron impact (70 eV) by using a 30 m DB-5 silica capillary column. IR spectra were recorded on a Nicolet 740 FT-IR spectrometers (NaCl film). Elemental analysis was determined on a Perkin-Elmer 2400 apparatus. All reactions involving DCICA must be performed in the absence of light.

Dichloroiodoisocyanuric acid (DCICA)

Crushed iodine (26.65 g, 105 mmol) and trichloroisocyanuric acid (23.25 g, 100 mmol) were added to a 100 cm^3 sealed tube and heated in a sand bath at 170 $^\circ C$. After 18 h, the ICl produced was distilled off under reduced pressure and the sealed tube was heated again at 220 $^\circ C$ during 24 h. Evaporation of ICl under reduced pressure and heating gave a solid that was crushed and washed with CH_2Cl_2 to produce dichloroiodoisocyanuric acid (DCICA) as a beige solid (30.13 g) in 93% yield. This reagent must be stored in the dark as some decomposition occurs in the presence of light; mp > 300 $^\circ C$. Anal. Calc. for $C_3N_3O_3Cl_2I$: C, 11.11, N, 12.96. Found: C, 10.74, N, 12.48. ^{13}C MAS-NMR: δ 150.1 ppm. IR ν_{max}/cm^{-1} : 1837, 1716, 1697, 1662, 1457, 1362, 762, 534.

General procedure for coiodination of alkenes with DCICA in oxygenated nucleophilic solvents

To a stirred solution of the alkene (2 mmol) in an appropriate solvent (10 cm^3 of acetone/2 cm^3 of H_2O for iodohydrins, or 10 cm^3 of alcohols for β -iodoethers, or 5 cm^3 acetic acid/5 cm^3 Ac_2O for β -iodoacetates), DCICA (2 mmol) was added at room temperature and in the absence of light. After 1 min, CH_2Cl_2 (10 cm^3) was added, cyanuric acid was filtered off and the resulting solution was treated

with 10% aq. NaHSO₃ (50 cm³). The aqueous phase was washed with CH₂Cl₂ (2 × 10 cm³), the organic extract was dried (anhydrous Na₂SO₄) and filtered. The solvent was evaporated on a rotatory evaporator to give the product.

General procedure for iodination of activated arenes with DCICA

To a stirred solution of the arene (2 mmol) in acetonitrile (10 cm³), was added DCICA (2 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 3, CH₂Cl₂ (10 cm³) was added, cyanuric acid was filtered off and the resulting solution was treated with 10% aq. NaHSO₃ (60 cm³). The aqueous phase was extracted with CH₂Cl₂ (2 × 10 cm³), the combined organic extract was washed with H₂O (60 cm³), dried (anhydrous Na₂SO₄) and filtered. The solvent was evaporated in a rotatory evaporator to give the product.

Supplementary Information

Experimental procedure, data spectra and spectra of synthesized compounds are available free of charge at <http://jbcas.sbcq.org.br>

Acknowledgments

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