



Trihaloisocyanuric acids as convenient reagents for regioselective halogenation of β -dicarbonyl compounds

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ABSTRACT

The reaction of β -dicarbonyl compounds (β -ketoesters and β -diketones) with 0.34 mol equiv of trichloro- and tribromoisocyanuric acids produced regioselectively the corresponding α -monohalo β -dicarbonyl compound. On the other hand, utilization of 0.68 mol equiv of the trihaloisocyanuric acid produced the α,α -dihalo β -dicarbonyl compound.

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α -Halo carbonyl compounds are versatile compounds in organic synthesis that can be transformed into a variety of useful structures.¹ Recently, α -halo and α,α -dihalo β -dicarbonyl compounds have received considerable attention due to their biological activity² and possible organic transformations.³ Several methodologies are described in the literature for the halogenation of β -ketoesters and β -diketones.⁴ However, direct α -monohalogenation of β -dicarbonyl compounds remains a challenge as α,α -dihalogenated products are often obtained as by-products.⁵

N-halo reagents (amides, saccharins, sulfonamides, etc.) are widely used to perform halogenation of organic substrates.⁶ Among the *N*-halo reagents, the trihaloisocyanuric acids (Fig. 1) are very efficient halogenating agents, due to their capability of transferring halogen atoms to unsaturated substrates in electrophilic reactions.⁷ Besides, trihaloisocyanuric acids proved to be very useful oxidizing reagents too.⁸

Trichloroisocyanuric acid (TCCA) is a stable and inexpensive solid frequently used for swimming pool disinfection and is easily available in pool supply and in some hardware stores.⁹ Tribromoisocyanuric acid (TBCA) is easily and safely prepared from cyanuric acid, KBr, and oxone.¹⁰ These trihaloisocyanuric acids are very interesting from a Green Chemistry point of view, as they are easily

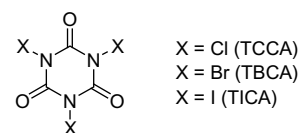


Figure 1. Trihaloisocyanuric acids.

handled stable solids and also present a very good atom economy, once they can transfer most part of their mass to the substrate (TCCA can transfer up to 45.5% and TBCA up to 65%).¹¹ Furthermore, in these reactions, cyanuric acid precipitates as a by-product, which can be recovered by filtration and reused to prepare more trihaloisocyanuric acid.¹²

Some years ago, Hiegel and Peyton showed that ketones react with TCCA to produce α -mono-, α,α -di- or α,α,α -trichlorinated products by just an adjustment of the mol equiv of the halogenating reagent employed.¹³ Herein, we show our results on the utilization of TCCA and TBCA as efficient reagents for regioselective mono- and dihalogenation of 1,3-dicarbonyl compounds (β -ketoesters and β -diketones).

The reaction of diverse β -dicarbonyl compounds (ethyl acetoacetate, diethyl malonate, acetylacetone, benzoylacetone, 1,3-cyclohexanodione, and dimedone) with 0.68 mol equiv of the trihaloisocyanuric acids produced regioselectively the corresponding α,α -dihalo β -dicarbonyl compounds (Table 1).¹⁴ The reactions proceeded very smoothly at room temperature. Water was the

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Table 1
 α,α -Dihalogenation of β -dicarbonyl compounds

R ¹	R ²	X	Solvent	T (h)	Yield ^{a,b} (%)
Me	OEt	Br	H ₂ O	20	60 ¹⁸
Me	OEt	Cl	H ₂ O/Me ₂ CO (5:2)	15	100 ¹⁸
OEt	OEt	Br	H ₂ O	3	81 ¹⁶
OEt	OEt	Cl	H ₂ O/Me ₂ CO (5:2)	18	73 ¹⁶
Me	Ph	Br	H ₂ O	20	94 ¹⁶
Me	Ph	Cl	H ₂ O/Me ₂ CO (5:2)	1	81 ¹⁶
Me	Me	Br	H ₂ O	15	70 ^{4b}
Me	Me	Cl	H ₂ O	6	57 ¹⁹
Me	Me	Cl	H ₂ O/Me ₂ CO (5:2)	1.5	76 ¹⁸
Me	-(CH ₂) ₃ -	Br	H ₂ O	6	57 ¹⁹
Me	-(CH ₂) ₃ -	Cl	H ₂ O/Me ₂ CO (5:2)	1.5	76 ¹⁸

^a Yield of pure product based on the β -dicarbonyl compound.^b Reference to product.**Table 2**
Halogenation of ethyl acetoacetate

Solvent	X	Selectivity (%) ^a
		α -halo/ α,α -dihalo
H ₂ O	Br	100/0 ^b
H ₂ O/Me ₂ CO (5:2)	Cl	0 ^b /100
MeCN	Cl	0 ^b /100
HOAc	Cl	79/21
Hexane	Cl	76/24
CHCl ₃	Cl	100/0 ^b

^a Determined by HRGC.^b Not detected.

solvent for α,α -dibromination using TBCA, while aqueous acetone was employed for α,α -dichlorination by TCCA. Conversely to previous works,^{5b,16} there was no need of acid-catalysis, even for substrates with low enol content, such as diethyl malonate.¹⁷

Ethyl acetoacetate was chosen as a model substrate to the reaction conditions for performing the α -monohalogenation of β -dicarbonyl compounds using 0.34 mol equiv of trichloro- and tribromoisocyanuric acids (Table 2). The reaction with TBCA in water produced the α -monobromo compound. On the other hand, at the same conditions, TCCA produced only the α,α -dichloro compound along with unreacted substrate. Changing the solvent in this reaction produced a mixture of α -chloro- and α,α -dichloro-ethyl acetoacetates in different proportions. The selective α -monochlorination of ethyl acetoacetate was accomplished by using CHCl₃ as solvent.

Based on the above results, the preparation of α -monohalo β -dicarbonyl compounds was accomplished using 0.34 mol equiv of TCCA at room temperature in CHCl₃, whilst the α -bromo compound was obtained using H₂O as solvent (Table 3).²⁰

In conclusion, the present work describes the utilization of trihaloisocyanuric acid as an efficient halogenating reagent for β -dicarbonyl compounds. The reaction conditions are safe and

Table 3
 α -Monohalogenation of β -dicarbonyl compounds

R ¹	R ²	R ³	X	Solvent	T (h)	Yield ^a (%)
Me	OEt	H	Br	H ₂ O	0.8	74 ^{4c}
Me	OEt	H	Cl	CHCl ₃	6	76 ^{4c}
Me	-(CH ₂) ₄ -	Br	H	H ₂ O	21	81 ^{4a}
Me	-(CH ₂) ₄ -	Cl	H	H ₂ O/Me ₂ CO ^b	1.25	83 ^{4a}
Me	Ph	H	Cl	CHCl ₃	1.7	82 ^{4c}
Me	-(CH ₂) ₃ -	H	Br	H ₂ O	20	54 ^{4c}

^a Yield of pure product based on the β -dicarbonyl compound.^b 1:5.

mild, and the quantity of halogen incorporated in the substrate is dependent on the ratio of trihaloisocyanuric acid/substrate.

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