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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 activity[2] 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 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]

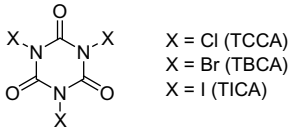

Figure 1. Trihaloisocyanuric acids.

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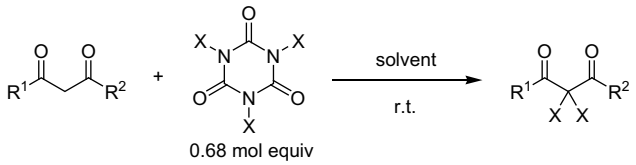
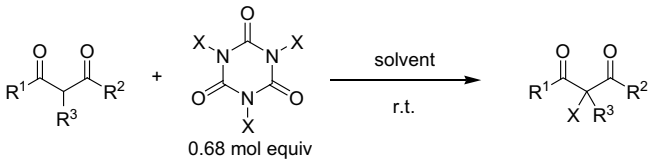
Table 1
α,α-Dihalogenation of β-dicarbonyl compounds



R^1	R^2	X	Solvent	*T* (h)	Yield[a,b] (%)
Me	OEt	Br	H_2O	20	60[18]
Me	OEt	Cl	H_2O/Me_2CO (5:2)	15	100[18]
OEt	OEt	Br	H_2O	3	81[16]
OEt	OEt	Cl	H_2O/Me_2CO (5:2)	18	73[16]
Me	Ph	Br	H_2O	20	94[16]
Me	Ph	Cl	H_2O/Me_2CO (5:2)	1	81[16]
Me	Me	Br	H_2O	15	70[4b]
$-(CH_2)_3-$		Br	H_2O	6	57[19]
$-CH_2-CMe_2-CH_2-$		Cl	H_2O/Me_2CO (5:2)	1.5	76[18]

[a] Yield of pure product based on the β-dicarbonyl compound.
[b] Reference to product.

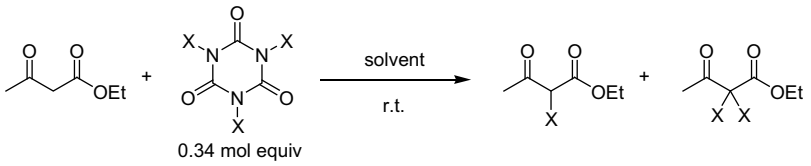
Table 3
α-Monohalogenation of β-dicarbonyl compounds



R^1	R^2	R^3	X	Solvent	*T* (h)	Yield[a] (%)
Me	OEt	H	Br	H_2O	0.8	74[4c]
Me	OEt	H	Cl	$CHCl_3$	6	76[4c]
Me	$-(CH_2)_4-$		Br	H_2O	21	81[4a]
Me	$-(CH_2)_4-$		Cl	H_2O/Me_2CO[b]	1.25	83[4a]
Me	Ph	H	Cl	$CHCl_3$	1.7	82[4c]
$-(CH_2)_3-$		H	Br	H_2O	20	54[4c]

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

Table 2
Halogenation of ethyl acetoacetate



Solvent	X	Selectivity (%)[a]
		α-halo/α,α-dihalo
H_2O	Br	100/0[b]
H_2O/Me_2CO (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-cloro- and α,α-dichloroethyl acetoacetates in different proportions. The selective α-monochlorination of ethyl acetoacetate was accomplished by using $CHCl_3$ 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 $CHCl_3$, whilst the α-bromo compound was obtained using H_2O 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 mild, and the quantity of halogen incorporated in the substrate is dependent on the ratio of trihaloisocyanuric acid/substrate.

Acknowledgments

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References and notes

1. De Kimpe, N.; Verhé, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; John Wiley: Chichester, UK, 1988; pp 1–119.
2. Ishida, J.; Ohtsu, H.; Tachibana, Y.; Nakanishi, Y.; Bastow, K. F.; Nagai, M.; Wang, H.-K.; Itokawa, H.; Lee, K.-H. *Bioorg. Med. Chem.* **2002**, *10*, 3481.
3. Yoshida, J.-i.; Yano, S.; Ozawa, T.; Kawabata, N. *J. Org. Chem.* **1985**, *50*, 3467.
4. Recent examples: (a) Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* **2008**, *64*, 5191; (b) Salgaonkar, P. D.; Shukla, V. G.; Akamanchi, K. G. *Synth. Commun.* **2007**, *37*, 275; (c) Lee, J. C.; Park, H. J. *Synth. Commun.* **2007**, *37*, 87; (d) Sreedhar, B.; Reddy, P. S.; Madhavi, M. *Synth. Commun.* **2007**, *37*, 4149.
5. (a) Das, B.; Venkateswarlu, K.; Holla H.; Krishnaiah, M. *J. Mol. Catal A: Chem.* **2006**, *253*, 107; (b) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429; (c) Arbuj, S. S.; Waghmode, S. B.; Ramaswamy, A. V. *Tetrahedron Lett.* **2007**, *48*, 1411; (d) Hoffmann, R. V.; Weiner, W. S.; Maslouh, N. *J. Org. Chem.* **2001**, *66*,

5790; (e) Khan, A. T.; Ali, M. A.; Goswami, P.; Choudhury, L. H. *J. Org. Chem.* **2006**, *71*, 8961.
6. Kolvani, E.; Ghorbani-Choghamarani, A.; Salehi, P.; Shirini, F.; Zolfigol, M. A. *J. Iran Chem. Soc.* **2007**, *4*, 126; de Souza, S. P. L.; da Silva, J. F. M.; de Mattos, M. C. S. *Quim. Nova* **2006**, *29*, 1061.
7. For our works on electrophilic halogenation with trihaloisocyanuric acids see: (a) Mendonca, G. F.; Magalhães, R. M.; de Mattos, M. C. S.; Esteves, P. M. *J. Braz. Chem. Soc.* **2005**, *16*, 695; (b) de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Synlett* **2007**, 1687; (c) de Souza, A. V. A.; Mendonça, G. F.; Bernini, R. B.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2007**, *18*, 1575; (d) Ribeiro, R. S.; Esteves, P. M.; de Mattos, M. C. S. *Tetrahedron Lett.* **2007**, *48*, 8747; (e) Ribeiro, R. S.; Esteves, P. M.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2008**, *19*, 1239.
8. Recent examples: (a) Zolfigol, M. A.; Chehardoli, G.; Ghaemi, E.; Madrakian, E.; Zare, R.; Azadbakht, T.; Niknam, K.; Mallakpour, S. *Monatsh. Chem.* **2008**, *139*, 261; (b) Pore, D. M.; Mahadik, S. M.; Desai, U. V. *Synth. Commun.* **2008**, *38*, 3121; (c) Bigdeli, M. A.; Dostmohammadi, H.; Mahdavinie, G. H.; Nemati, F. *J. Heterocycl. Chem.* **2008**, *45*, 1203; (d) Niknam, K.; Zolfigol, M. A.; Madrakian, E.; Ghaemi, E. *South Afr. J. Chem.* **2007**, *60*, 109; (e) Zolfigol, M. A.; Niknam, K.; Bagherzadeh, M.; Ghorbani-Choghamarani, A.; Koubaki, N.; Hajjami, M.; Kolvari, E. *J. Chin. Chem. Soc.* **2007**, *54*, 1115; (f) Bonk, J. D.; Amos, D. T.; Olson, S. J. *Synth. Commun.* **2007**, *37*, 2039.
9. Wengert, M.; Sanseverino, A. M.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2002**, *13*, 700.
10. de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Synlett* **2006**, 1515.
11. (a) Mendonça, G. F.; de Mattos, M. C. S. *Quim. Nova* **2008**, *31*, 798; (b) de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Synthesis* **2006**, 221.
12. Tozetti, S. D. F.; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2007**, *18*, 675.
13. Hiegel, G. A.; Peyton, K. B. *Synth. Commun.* **1985**, *15*, 385.
14. *General procedure for dihalogenation of β-dicarbonyl compounds*: To a stirred solution of the β-dicarbonyl compound (2 mmol) in the appropriate solvent (30 mL—see Table 1) was added the trihaloisocyanuric acid (0.68 mmol) at room temperature in small portions. After the end of the reaction (determined by the color disappearance of a wet iodide-starch test paper treated with an aliquot of the reaction media[15]), the product was extracted with CH_2Cl_2 (2×15 mL) and the organic layer was subsequently washed with saturated solution of $NaHSO_3$, water, and then dried (Na_2SO_4). After filtration and evaporation of the solvent at reduced pressure, the product was characterized by standard analytical techniques. *Selected analytical data*: *Diethyl 2,2-dibromomalonate*: δ_H ($CDCl_3$, 200 MHz) = 1.32 (t, 1H, *J* 7.03 Hz), 4.33 (q, 2H, *J* 7.03 Hz) ppm. δ_C ($CDCl_3$, 50 MHz) = 13.7, 50.7, 64.8, 163.2 ppm. *Ethyl 2,2-dichloroacetoacetate*: δ_H ($CDCl_3$, 200 MHz) = 1.31 (t, 1H, *J* 7.00 Hz), 2.46 (s, 3H), 4.33 (q, 2H, *J* 7.00 Hz) ppm. δ_C ($CDCl_3$, 50 MHz) = 14.0, 23.6, 64.8, 82.0, 163.5, 191.5 ppm. *2,2-Dichloro-5,5-dimethyl-1,3-cyclohexanodione:* δ_H ($CDCl_3$, 500 MHz) = 1.04 (s, 6H), 2.96 (s, 4H) ppm. δ_C ($CDCl_3$, 125 MHz) = 28.2, 30.6, 49.1, 100.2, 192.4 ppm.
15. Mendonça, G. F.; Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis* **2003**, 45.
16. Kim, J.-J.; Kweon, D.-H.; Cho, S.-D.; Kim, H.-K.; Lee, S. G.; Yoon, Y.-J. *Synlett* **2006**, 194.
17. Smith, M. B.; March, J. In *Advanced Organic Chemistry—Reactions, Mechanisms, and Structure*; John Wiley: New York, 2001; pp 73–74.
18. Meketa, M. L.; Mahajan, Y. R.; Weinreb, S. M. *Tetrahedron Lett.* **2005**, *46*, 4749.
19. Nazarov, I. N.; Zav'yalov, S. I. *Izv. Akad. Nauk. Sssr, Ser. Khim.* **1959**, 668.
20. General procedure for monohalogenation of β-dicarbonyl compounds: To a stirred solution of the β-dicarbonyl compound (2 mmol) in the appropriate solvent (30 mL—see Table 3) was added the trihaloisocyanuric acid (0.34 mmol) at room temperature in small portions. After the end of the reaction (determined by the color disappearance of a wet iodide-starch test paper treated with an aliquot of the reaction media[15]), the workup was similar to that described above. *Selected analytical data*. *Ethyl 2-bromoacetoacetate*: δ_H ($CDCl_3$, 200 MHz) = 1.30 (t, 3H, *J* 6.92 Hz), 2.42 (s, 3H), 4.25 (q, 2H, *J* 6.92 Hz), 5.75 (s, 1H) ppm. δ_C ($CDCl_3$, 75 MHz) = 14.0, 26.5, 49.2, 63.3, 165.2, 196.4 ppm. *2-Chloro-2-acetylcyclohexanone*: δ_H ($CDCl_3$, 200 MHz) = 1.70–2.33 (m, 6H), 2.50–2.69 (m, 1H), 2.85–3.05 (m, 1H), 2.35 (s, 3H) ppm. δ_C ($CDCl_3$, 50 MHz) = 21.7, 26.9, 27.1, 37.9, 39.0, 77.0, 201.3, 203.2 ppm.