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Hexabromoacetone as tribromoacetylating agent of alcohols and amines and as mediator in the conversion of carboxylic acids into amides in the presence of triphenylphosphine

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ABSTRACT

Hexabromoacetone has been used as an alternative tribromoacetylating agent of primary alcohols and amines and as mediator in the conversion of carboxylic acids into amides in the presence of triphenylphosphine. The reactions have been performed under mild conditions with moderate to good yields. All the products have been adequately characterized by their physical and spectroscopic properties.

The α-trihalogenated carbonyl compounds have been reported as very useful versatile reagents in organic synthesis. Two trichlorinated methyl groups attached to a carbonyl carbon form hexachloroacetone (HCA), a reagent which has been intensively studied with interesting results. Noteworthy examples are the trichloroacetylation of alcohols[1] and amines,[2] the mediator role of HCA in the conversion of alcohols into alkyl halides[3] and of carboxylic acids into amides.[3a,4] HCA reactions with aliphatic and aromatic diamines lead to the obtainment of the respective diamides and cyclic ureas, together with heterocyclic compounds without the carbonyl group, such as bisimidazolidine, tetrahydrobisbenzimidazolediene, and bisbenzimidazole derivatives, particularly in reactions conducted under ultrasonic energy.[5] When HCA was reacted with vicinal glycols, in the presence of different catalysts, alkylene carbonates and chloroform were obtained.[6] Also, HCA was found to be a precursor for formation of α,α,α′,α′-tetrachloro-substituted[3.2.1]bicyclic compounds.[7]

This Letter reports on our initial studies involving the use of an HCA analog, hexabromoacetone, HBA, as an alternative tribromoacylating agent for both primary alcohols and amines, and as a mediator in the conversion of carboxylic acids into amides in the presence of triphenylphosphine. HBA is not commercially available, but it is easily prepared via the Gilbert's method.[8] Although known since 1969, it is very seldom cited as a reagent in organic synthesis, except for its ability to act as a mediator in the conversion of alcohols to alkyl halides.[9]

The alkyl tribromoacetates prepared can be converted into different Z-α-bromoacrylates (known for their stereoselectivity),[10] and act in the conversion of carboxylic acid into amides with high yield under mild conditions.[11] The tribromoacetamides have practically not been explored in organic synthesis, in contrast to the trichloroacetamides, which can, for example, be converted into carbamates,[12] and mediate conversion of alcohols into alkyl chloride[3b] and obtention of *Z*-α-chloroacrylamides.[10c] Another application of α-trihalogenated carbonyl compounds is the use of alkyl trichloroacetate to get polysubstituted chlorocyclopropanes,[13] 2-substituted-1,3-dithiane,[14] and trihalo-containing acetylenes and azoles.[15]

After the preparation of the HBA by the Gilbert's method[8] it was characterized through the melting point, elemental CHN analysis, IR, ^{13}C NMR, and X-ray crystallographic analysis (Fig. 1).[16,17]

The reactions of HBA with 1.1 equiv of alcohol (methanol, ethanol, *n*-propanol, *n*-butanol, *n*-pentanol, and *i*-amyl alcohol) in the presence of 1.0 equiv of dimethylformamide (acting as a proton sponge), at 60 °C, provided, after 10 h of reaction, the respective alkyl tribromoacetates (**1**–**6**) with yields between 55% and 65%, depending on the alcohol structure.[18] The purification of alkyl tribromoacetates was carried out by column chromatography on

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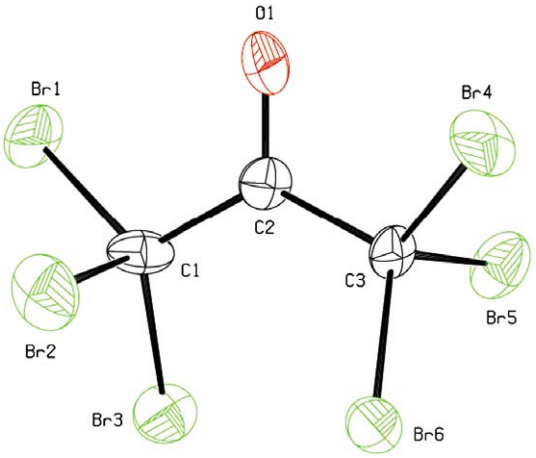


Figure 1. Molecular structure of HBA.

silica gel, using hexane–chloroform mixtures as the eluent. Table 1 summarizes the results obtained for the HBA alcoholysis. The tribromoacetates were obtained as colorless oils, and characterized through IR, ^{1}H, ^{13}C and DEPT NMR, and MS. From reactions of HBA with benzyl alcohol and with the secondary alcohols *i*-propanol and cyclohexanol, under the same experimental conditions, the respective tribromoacetates were not isolated, despite verifying the consumption of HBA through TLC analysis.

The formation of alkyl tribromoacetates and *N*-alkyl tribromoacetamides proceeds by a typical addition-elimination mechanism which begins with a nucleophilic addition of alcohols and amines, respectively, to the carbonyl group of HBA and finishes with the departure of Br_3C^-, as the leaving group, thus forming bromoform. In the reaction involving tribromoacetates formation DMF functions as a proton sponge species.

When HBA is reacted with 2 equiv of amine, in chloroform, the 2,2,2-tribromo-*N*-alkylacetamides (**7**, **8**, **10**, **12**) are obtained in yields varying from 65% to 74% for the slightly sterically hindered amines (ethylamine, *n*-propylamine, *n*-butylamine, and *n*-hexylamine), after 1 h of reaction, at room temperature.[19] Under the same experimental conditions, the reactions with the primary amines *i*-propylamine and *s*-butylamine, which are more sterically hindered, the 2,2,2-tribromo-*N*-alkylacetamides (**9a**, **11a**) were obtained with yields between 48% and 50%. However, there were also isolated 2,2-dibromo-*N*-alkylacetamides (**9b**, **11b**), with 15% and 20% yields, respectively. The sterically hindered amines would rather prefer, to some extent, a bromonium abstraction than a carbonyl group addition. Such a reaction should form the pentabromoacetone, through the respective enol, which goes then to **9b** and **11b** acetamides by the respective amine reactions.

The purifications of the products were carried out by column chromatography on silica gel, using hexane–chloroform mixtures as the eluent. Table 2 summarizes the results of the reaction of HBA with the amines. Under the same experimental conditions, the reactions of HBA with the bulky primary (*t*-butylamine) and secondary (piperidine) amines did not provide the respective amides, and the consumption of a great part of the HBA was not verified by TLC. The products of the reactions of HBA with the amines were obtained in the form of white solids, after recrystallization from 5:1 (v/v) hexane:chloroform, and were characterized through the melting point, elemental CHN analysis, and IR and ^{1}H, ^{13}C and DEPT NMR spectroscopies.

The spectral data of the alkyl tribromoacetates and the tri-, and di-bromo-*N*-alkylacetamides are very similar, following the same line, thus facilitating the characterization, particularly by IR and NMR. All products have had their purity verified by TLC and GC analysis.

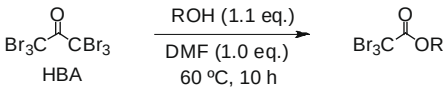
The role of HBA as a mediator in the conversion of carboxylic acids into the respective amides was tested via formation, in situ, of bromide acid, as previously reported for other carbonyl α-tribrominated compounds.[11] Reactions between benzoic and aliphatic carboxylic acids with the different aromatic and aliphatic amines were carried out in the presence of HBA/triphenylphosphine (0.3/1.5 equiv in proportion to the carboxylic acids and amines) as a brominating agent.[20] This method is a mixture of those already known, involving the use of ethyl tribromoacetate in the formation of amides,[11] and of HBA in the formation of alkyl halides from alcohols.[9] The amides (**13**–**27**) were obtained in yields of 53% to 91%. It is observed that, Table 3, aromatic acids are giving better yields than aliphatic acids. However, controlled experiments carried out on acetic acid (0.5 g, 8.3 equiv, and 1.0 g, 16.6 equiv) that yields the amide fall within the range observed for aromatic acids, 75% and 85%, respectively. So it is reasonable to conclude that the initial amount of aliphatic acid is affecting the product yield, since losses of aliphatic amides, during the purification process, are greater than those of aromatic ones.

The products, most of them already known, were characterized through melting point, IR, and ^{1}H NMR, and the data are in agreement with those reported in the literature.

The aims of this study were to find better experimental conditions for the tribromoacetylation of alcohols and amines, to explore other acids, amines, and nucleophiles (such as thioalcohols) to be converted into amides and thiocarbamates, and to extend the studies previously carried out with HCA and diamines,[5] to HBA.

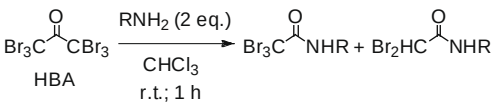
In summary, HBA was shown to be a good tribromoacetylating agent for primary alcohols and amines, both slightly sterically hindered, under mild conditions. In the reactions with *i*-propylamine and *s*-butylamine, the 2,2-dibromo-*N*-alkylacetamide subproducts were obtained along with 2,2,2-tribromo-*N*-alkylacetamides. Furthermore, HBA acting as a brominating agent, in the presence of

Table 1
Tribromoacetylation of alcohols with HBA



Entry	Alcohol	Yield (%)
1	Methanol	65
2	Ethanol	65
3	*n*-Propanol	60
4	*n*-Butanol	62
5	*n*-Pentanol	58
6	*i*-Amyl alcohol	55

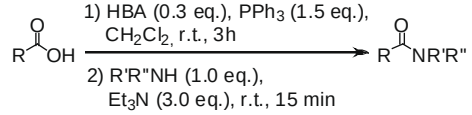
Table 2
Di- and tri-bromoacetylation of primary amines with HBA



Entry	Amine	Yield (%)	
		TBACA[a]	DBACA[b]
7	Ethylamine	74	—
8	*n*-Propylamine	70	—
9(**a**,**b**)	*i*-Propylamine	50	15
10	*n*-Butylamine	69	—
11(**a**,**b**)	*s*-Butylamine	48	20
12	Hexylamine	65	—

[a] Isolated 2,2,2-tribromo-*N*-alkylacetamides.
[b] Isolated 2,2-dibromo-*N*-alkylacetamides.

Table 3
Conversion of aliphatic and benzoic acids into the respective amides mediated by hexabromoacetone/triphenylphosphine



Entry	R	R′	R″	Yield (%)
13	Ph	*n*-But	H	86
14	Ph	*s*-But	H	72
15	Ph	*t*-But	H	70
16	Ph	*c*-Hex	H	75
17	Ph	Ph	H	85
18	Ph	4-*n*-But-Ph	H	89
19	Ph	4-NO_2-Ph	H	81
20	Ph	3,5-diNO_2-Ph	H	82
21	Ph	Et	Et	70
22	4-MeO-Ph	c-Hex	H	83
23	4-MeO-Ph	Ph	H	90
24	4-MeO-Ph	4-*n*-But-Ph	H	91
25	Me	Ph	H	60
26	Et	Ph	H	57
27	*n*-Prop	Ph	H	53

triphenylphosphine, gave good results in the conversion of benzoic acids into the respective amines.

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16. *Hexabromoacetone,* HBA: mp 108 °C (Lit.[8] 109 °C). *IR* (KBr) ν 1725, 1070, 763, 563. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6 (C=O), 24.8 (CBr_3). Anal. Calcd for C_3OBr_3: C, 6.78. Found: C, 6.82. Yield: 70%.
17. *X-ray crystallographic data*: An irregular block was cut off from a soft crystal and selected for crystallographic measurements. X-ray analysis was carried out on an Enraf-Nonius CAD-4 diffractometer with monochromatic Mo-Kα radiation (0.71069 Å), at room temperature. Cell parameters were determined from 25 centered reflections in the θ range 3.93–12.20°. One thousand nine hundred and eight poorly diffracted intensities were collected using the ω–2θ scan method, of which 1790 (R_{int} = 0.1170) are unique and 1020 with [$I > 2\sigma(I)$], with θ angle ranging from 1.98° to 25.00°. Due to high absorption coefficient of HBA, a numerical absorption correction should be indicated. However, once the selected crystal had an irregular shape, the empirical absorption correction (ψ-scan) was applied with better results with respect to numerical absorption correction. All atoms were refined with anisotropic thermal parameters. Crystal data: formula: C_3Br_6O, FW = 531.49, monoclinic, $P2_1/n$, a = 6.292(7) Å, b = 20.619(1) Å, c = 8.242(1) Å, β = 107.88(1)°, V = 107.88(1) Å^3, Z = 4, ρ_{calc} = 3.469 Mg/m^3, μ = 23.611 mm^{-1}, F(0 0 0) = 944, ψ-scan transmission factors: 0.015 and 0.101, parameters = 92, GOOF (F^2) = 0.958, R_1 [$I > 2\sigma(I)$] = 0.0986, wR_2 (all data) = 0.2574. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 713085. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
18. *General procedure for obtainment of alkyl 2,2,2-tribromoacetates:* The following reagents were placed in a round-bottomed flask: 6.70 mmol of the respective alcohols (methanol, ethanol, *n*-propanol, *n*-butanol, *n*-pentanol, and *i*-amyl alcohol), previously dried by traditional methods,[21] and 0.43 mL of DMF (5.60 mmol). After that 3.00 g (5.64 mmol of HBA was added and the solution was stirred at 60 °C, for 10 h. The products were purified by column chromatography on silica gel using hexane–chloroform mixtures as the eluent. The products were obtained as transparent oils, with yields of 55% to 65%. *Methyl tribromoacetate,* **1**: *IR* (KBr) ν 2955, 1751, 1235, 758, 609. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.0, 56.3, 28.6 (Lit.[22] 161.8, 55.8, 28.4). *MS*: *m/z* 310 (M^+), 250.8, 230.9, 171.9, 92.9, 78.9, 59.0. Yield: 65%.
19. *General procedure for the reactions of HBA with amines: obtainment of 2,2,2-tribromo-N-alkylacetamides or mixtures of 2,2,2-tribromo-N-alkylacetamides and 2,2-dibromo-N-alkylacetamides:* Firstly, 1 g (1.88 mmol) of HBA was added portionwise to a round-bottomed flask containing 3.76 mmol of amine (ethylamine, *n*-propylamine, *i*-propylamine, *n*-butylamine, *s*-butylamine, and hexylamine), previously distilled,[23] in 5 mL of chloroform. The solution was then maintained under magnetic stirring at room temperature for 1 h, monitored by TLC. After the total consumption of HBA, the chloroform was eliminated in a rotavapor, and the residue was dried and purified by column chromatography on silica gel using mixtures of hexane–chloroform as the eluent, providing the respective pure brominated acetamides after evaporation of the solvent and recrystallization in 5:1 (v/v) hexane–chloroform. *2,2,2-tribromo-N-isopropylacetamide*, **9a**: mp 80–81 °C (Lit.[24] 80 °C). *IR* (KBr) ν_{max} (cm^{-1}) 3302, 2970, 1662, 1518, 1238, 1141, 750, 682, 596. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.65 (br, 1H, NH), 4.15–4.04 (m, 1H, CH), 1.29 (d, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.6 (C=O), 44.6 (CH), 37.5 (CBr_3), 22.2 (CH_3). *DEPT* (100 MHz, $CDCl_3$) δ (ppm) 44.6 (CH), 22.2 (CH_3). Anal. Calcd for $C_5H_8NOBr_3$: C, 17.78; H. 2.39; N. 4.15. Found: C, 17.65; H, 2.50; N, 4.25. Yield: 50%. *2,2-dibromo-N-isopropylacetamide,* **9b**: mp 149–150 °C. *IR* (KBr) ν_{max} (cm^{-1}) 3282, 2971, 1654, 1551, 1458, 1194, 788, 676, 596. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.32 (br, 1H, NH), 5.79 (s, 1H, $CHBr_2$), 4.12–3.96 (m, 1H, CH), 1.22 (d, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.8 (C=O), 43.2 (CH), 37.1 ($CHBr_2$), 22.3 (CH_3). *DEPT* (100 MHz, $CDCl_3$) δ (ppm) 43.2 (CH), 37.1 ($CHBr_2$), 22.3 (CH_3). Anal. Calcd for $C_5H_9NOBr_2$: C, 23.19; H, 3.50; N, 5.41. Found: C, 23.27; H, 3.59; N, 5.47. Yield: 15%.
20. *General procedure for obtainment of amides from carboxylic acids mediated by HBA:* Firstly, 1.00 mmol of carboxylic acid was added to a solution containing 0.16 g (0.30 mmol) of HBA and 0.394 g (1.50 mmol) of triphenylphosphine, in 2 mL of dry dichloromethane. The solution was stirred at room temperature for 1 h, and then 0.31 g (3.00 mmol) of triethylamine and 1.00 mmol of the different amines were added. The solution was kept under stirring for 15 min at room temperature. The solution was then diluted in 20 mL dichloromethane and washed with water. The organic phase was dried with anhydride magnesium sulfate, the solvent evaporated in a rotavapor, and the residue purified by column chromatography on silica gel, using 4:1 (*v*/*v*) mixture of hexane:ethyl acetate in order to obtain the pure amides.
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