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The regiospecific ω-bromination of 2-trichloroacetylcycloalkanones

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Abstract—Six novel ω-brominated-2-trichloroacetylcycloalkanones were regiospecifically obtained in reactions from four 2-trichloroacetylcycloalkanones and bromine. ^{1}H and ^{13}C NMR data reveal that ω-brominated β-diketones are predominantly in keto–keto form.

1. Introduction

We have systematically studied enol ether acylation as an efficient route for the production of 1,1,1-trichloromethyl-4-alkoxy-3-alken-2-ones.[1–3] To the best of our knowledge their hydrolysis is the only selective and convenient method for the synthesis of trichloromethyl β-diketones.[4,5] Trichloromethyl substituted 1,3-dielectrophiles have demonstrated versatility and efficiency in the synthesis of a wide range of heterocycles.[6–8]

Our results from structural studies have shown that 1,1,1-trichloropent-2,4-dione and 4,4,4-trichloro-1-phenylbut-1,3-dione have chemical and structural behaviors similar to their trifluorinated analogues.[5–8] However, 2-trichloroacetylcycloalkanones have demonstrated unusual structural behavior, different from that of 2-trifluoroacetylcycloalkanones and others ordinary 2-acylcycloalkanones. 2-Trichloroacetylcycloalkanones are predominantly found in the keto–keto form and at ^{1}H NMR scale was observed none enol concentration.[4] As a result of our interest in halogenated 1,3-dielectrophiles as building blocks for heterocyclic synthesis we conjectured that the bromination of 2-trichloroacetylcycloalkanones may be an attractive approach.

2. Results and discussion

β-Diketones bromination reactions are classic synthetic procedures and have been widely used.[9–11] From the mechanistic point of view it is accepted that reactive enol species attack molecular bromine.[12] Thus when 2-trichloroacetylcycloalkanones **1a–d** were reacted with 1 mol equiv of molecular bromine, a characteristic red color loss and a intense acid vapour release were observed immediately. The reactions were carried out in aprotic $CHCl_3$ or CH_2Cl_2 solvent and after the addition of bromine, the solution was stirred for 10 min and pyridine was added to trap HBr. Based on analytical data for the crude reaction products, we produced only 6-bromo-2-trichloroacetylcyclohexanone (**2a**) from **1a**, 6-bromo-2-trichloroacetyl-4-*tert*-butylcyclohexanone (**2b**) from **1b**, 7-bromo-2-trichloroacetylcycloheptanone (**2c**) from **1c** and finally 8-bromo-2-trichloroacetylcyclooctanone (**2d**) from **1d** (Scheme 1). These results demonstrate the unusual chemical behavior of 2-trichloroacetylcycloalkanones compared with that of 2-acetylcycloalkanones, 2-benzoylcycloalkanones and 2-ethoxycarbonylcycloalkanones in halogenation reactions with Br_2. In the latter β-dicarbonyl compounds, the reactive site is the α-carbon for both carbonyl groups (carbon-2), the preferable enolizable site in ordinary β-dicarbonyl compounds (Scheme 2).[13] Importantly we found that 2-trichloroacetylcycloalkanones **1a–d** are regiospecifically ω-brominated with molecular bromine supply a convenient general method. Products **2a–d** were colorless crystalline solids purified by recrystallization from hexane.

Similar reactions with 2 mol equiv of the molecular bromine lead exclusively to 6,6-dibromo-2-trichloroacetylcyclohexanones **3a** and **3b** from **1a** and **1b**, respectively (Scheme 1). However, from reactions of **2c** and **2d** with 2 mol equiv of molecular bromine lead to complex

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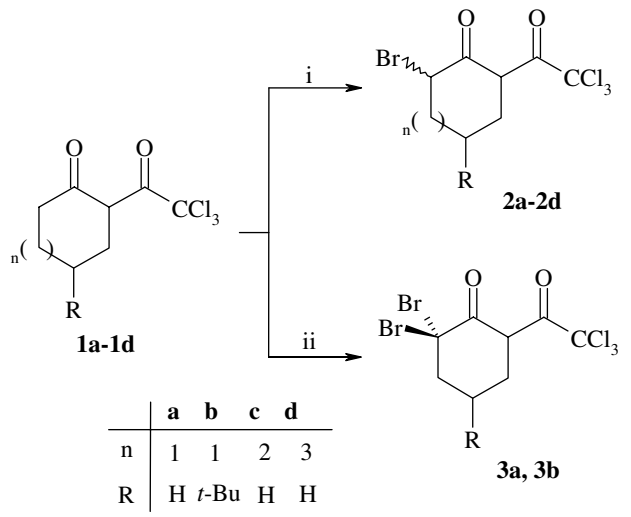
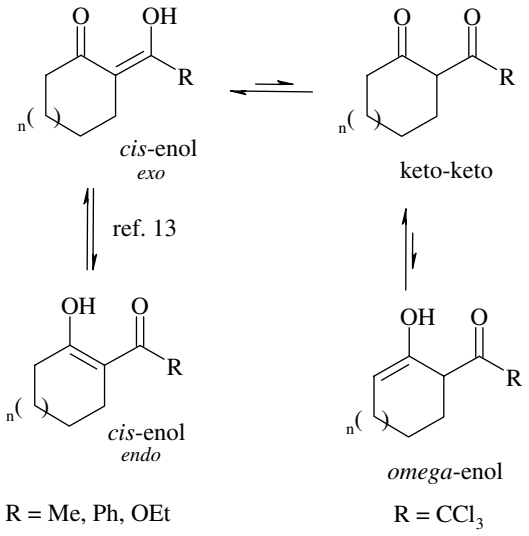


Scheme 1. Reagents and conditions: (i) (1) Br_2, $CHCl_3$, 2–3 h, 25 °C; (2) pyridine, 15 min; (ii) (1) $2Br_2$, $CHCl_3$, 2–3 h, 25 °C; (2) 2 mol equiv pyridine, 15 min.



Scheme 2.

mixtures of unidentified bromination and condensations products. Products **3a** and **3b** were colorless crystalline solids purified by recrystallization from hexane solutions. All the isolated brominated products were identified by ^1H and ^{13}C NMR and IR spectroscopy. Bromination regiochemistry allow us to deduce a small degree of enolization, not observed in NMR spectra,[4] for the highly reactive ω-enol shown in Scheme 2. The pK_a of H2 in 2-trichloroacetylcycloalkanones still remains unknown, but investigations are currently in progress. Nonetheless, haloform substitution was observed when 2-trichloroacetylcycloalkanones were dissolved in MeOH with catalytic amounts of K_2CO_3.

^1H NMR data and IR C=O stretching frequencies for compounds **2a**–**d**, **3a** and **3b** are summarized in Table 2. The ^1H NMR spectra of compounds **2a**–**d** exhibited complex multiplets at lower frequencies (1.5–3.0 ppm) for the ring methylene hydrogens and characteristic signals for methyne hydrogens H-2 and H-ω at brominated ω-carbon.

The two sets of signals in ^1H and ^{13}C NMR spectra showed that bromination of racemic **1a** led to two diastereomers for 6-bromo-2-trichloroacetylcyclohexanone **2a**. The double doublet signals from H-2 demonstrate that the **2a** diastereomers in $CDCl_3$ solutions are predominantly keto–keto β-diketones (Table 2). The signals at 4.73 ppm with $^3J_{2,3ax}$ 12.4 Hz and $^3J_{2,3eq}$ 6.0 Hz and at 5.23 ppm with $^3J_{2,3ax}$ 11.8 Hz and $^3J_{2,3eq}$ 5.8 Hz indicate that the H-2 occupy a pseudo-axial position and that the trichloroacetyl group is equatorial. One of the H-6 signal appeared as double doublet at 4.45 ppm with $^3J_{6,5ax}$ 12.4 Hz and $^3J_{6,5eq}$ 6.0 Hz indicating that the H-6 also occupy a pseudo-axial position for one enantiomer pair. Thus, the bromine is pseudo-equatorial. However, the H-6 signal from the other enantiomer pair appeared as a triplet with $^3J_{6,5}$ 3.4 Hz, indicating a pseudo-equatorial position for the H-6 and indicating that bromine is pseudo-axial.

^1H and ^{13}C NMR spectra of product **2b** showed only one set of signals. ^1H NMR spectrum showed a signal for H-2 as a double doublet at 5.22 ppm with $^3J_{2,3ax}$ 13.2 Hz and $^3J_{2,3eq}$ 5.2 Hz indicating the H-2 is a pseudo-axial, and that the trichloroacetyl group is equatorial. The signal from H-6 as a triplet at 4.48 ppm with $^3J_{6,5}$ 3.6 Hz indicates a pseudo-equatorial position, and consequently that the bromine is axial (Fig. 1). Certainly this result is a consequence of the conformational rigidity of 2-trichloroacetyl-4-*tert*-butylcyclohexanone (**1b**).

As 6-bromo-2-trichloroacetylcyclohexanone (**2a**), ^1H and ^{13}C NMR spectra of brominated product **2c** showed two sets of signals indicating two diastereomers (Table 2). The ^1H NMR spectrum of 7-bromo-2-trichloroacetylcycloheptanone (**2c**) showed two signals with same intensity for H-2, a double doublet at 4.91 ppm with $^3J_{2,3ax}$ 10.50 Hz and $^3J_{2,3eq}$ 5.20 Hz and a triplet at

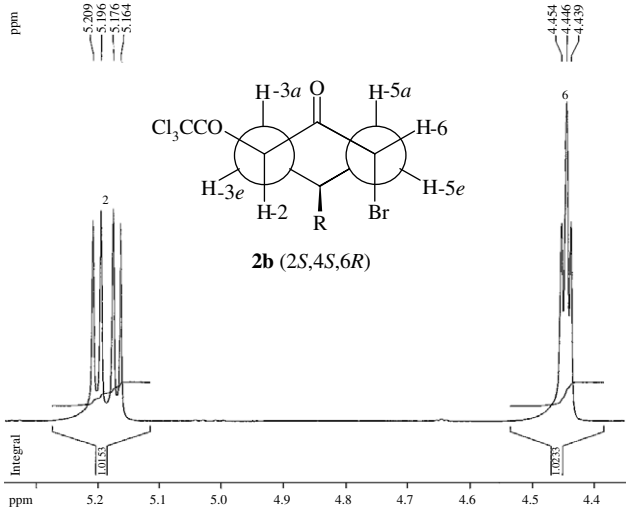


Figure 1. ^1H NMR H2 and H6 signals for 6-bromo-4-*tert*-butyl-2-trichloroacetylcyclohexanone (**2b**).

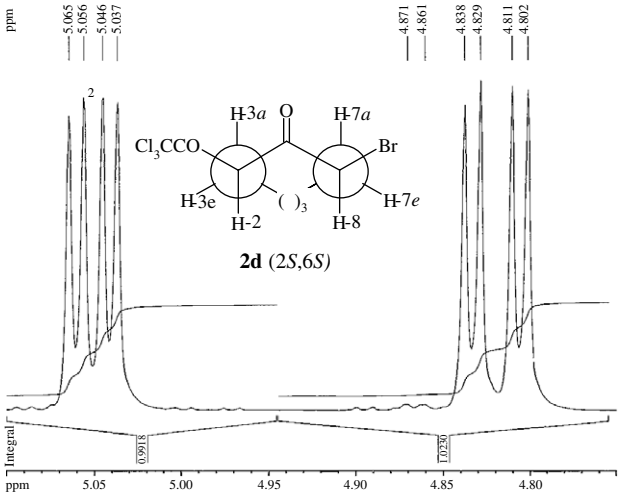


Figure 2. ^{1}H NMR H2 and H8 signals for 8-bromo-2-trichloroacetylcyclooctanone (**2d**).

4.97 ppm with $^{3}J_{2,3}$ 6.40 Hz. For H-6 two double doublets were observed, one at 4.51 ppm with $^{3}J_{7,6ax}$ 10.0 Hz and $^{3}J_{7,6eq}$ 3.6 Hz and another at 4.69 ppm with $^{3}J_{7,6ax}$ 9.60 Hz and $^{3}J_{7,6eq}$ 4.40 Hz. For 8-bromo-2-trichloroacetylcyclooctanone (**2d**) the ^{1}H NMR spectrum showed only one set of signals with two double doublets at 5.95 ppm with $^{3}J_{2,3ax}$ 7.60 Hz and $^{3}J_{2,3eq}$ 3.60 Hz attributed to H-2 and at 4.82 ppm with $^{3}J_{2,3ax}$ 10.8 Hz and $^{3}J_{2,3eq}$ 3.60 Hz attributed to H-8 (Fig. 2).

The ^{1}H NMR spectra of **3a** and **3b** showed signals for the methylene hydrogens and the characteristic H-2 signal as double of doublet at 5.35 ($^{3}J_{2,3ax}$ 12.2 Hz and $^{3}J_{2,3eq}$ 6.0 Hz) and 5.31 ppm ($^{3}J_{2,3ax}$ 13.2 Hz and $^{3}J_{2,3eq}$ 5.2 Hz), respectively.

The ^{13}C chemical shifts for compounds **2a–d**, **3a** and **3b** are summarized in Table 3. The characteristic methyne carbon (DEPT135 and HMQC) at 49.14–56.82 ppm confirmed the keto–keto form to these β-diketones.

NMR spectra indicated that compounds **2** and **3** were predominantly in the keto–keto tautomeric form. H-2 signals at 4.73–5.35 ppm and the characteristic coupling constants $^{3}J_{H2H3}$ values demonstrated that the keto–enol equilibrium for brominated trichloromethyl-β-diketones is unlikely in the NMR scale. Moreover, these results allowed us to conclude that the cyclohexanone ring has a chair conformation with the trichloroacetyl group in a pseudo-equatorial position. In addition, the signals for C2 at 49.1–55.8 ppm and coupling constant of value J_{C2H2} 132.0 Hz confirmed these β-diketones prefer the keto–keto form.

3. Conclusions

Although NMR and IR analytical data have demonstrated that 2-trichloroacetylcycloalkanones that are only enolizable to small degree, their chemical behavior in reactions with molecular bromine has demonstrated an important and decisive degree of enolization to ω-carbon direction. ^{1}H and ^{13}C NMR data demonstrated that brominated 2-trichloroacetyl cycloalkanones are also β-diketones predominantly in keto–keto form in $CDCl_3$.

The 2-trichloroacetylcycloalkanones prefer the keto–keto form with small degree of enolization to ω-carbon direction probably because of thermodynamic factors. Endocyclic or exocyclic *cis*-enol forms increase molecular strain by planar placement of the bulky trichloroacetyl group.

4. Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were taken on a melting point microscope Reichert-Thermovar and are uncorrected. The ^{1}H and ^{13}C NMR spectra (1D and 2D experiments) were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz, ^{13}C at 100.62 MHz) with 5 mm sample tubes, at 300 K, in 0.02 mol/L $CDCl_3$/TMS solutions. The 2-trichloroacetylcycloalkanones **1a–d** were synthesized according to the *acetal acylation* method reported previously.[4]

4.1. General procedure for 2-trichloroacetylcycloalkanones brominations

To a stirred solution of 2-trichloroacetylcycloalkanones **1a–d** (21 mmol) in chloroform (50 mL) kept at 25 °C, a solution of molecular bromine (1.1 mL; 3.36 g;

Table 1. Yield, melting point and elemental analysis of brominated trichloromethyl β-diketones **2** and **3**

Product	Molecular formula	Yield[a] (%)	Melting point (°C)[b]	Elemental analysis (calcd/found)[c]			
				C	H	C	H
2a	$C_8H_8BrCl_3O_2$	90	101–102	24.30	2.00	24.15	2.12
2b	$C_{12}H_{16}BrCl_3O_2$	88	88–90	38.10	4.30	38.31	4.32
2c	$C_9H_{10}BrCl_3O_2$	85	105–110	32.13	3.00	32.50	3.15
2d	$C_{10}H_{12}BrCl_3O_2$	98	72–74	34.27	3.45	34.09	3.41
3a	$C_8H_7Br_2Cl_3O_2$	85	77–80	23.90	1.80	24.12	1.90
3b	$C_{12}H_{15}Br_2Cl_3O_2$	70	80–82	31.50	3.30	31.20	3.50

[a] Yield of the reaction before hexane recrystallization.
[b] Melting points are uncorrected. Obtained from pure predominant diastereoisomer.
[c] Elemental analyses were performed on a CHNS-Vario El Elementar Analysensysteme.

Table 2. ^{1}H NMR data and IR stretching frequencies for brominated 2-trichloroacetylcycloalkanones **2** and **3**

Product	^{1}H NMR δ ppm[a]			IR C=O stretching ($\nu_{C=O}$ cm^{-1})[b]	
	H-2 (mult. ^{3}J Hz)	CHBr (mult. ^{3}J Hz)	–$(CH_2)_n$–	C=O	Cl_3CC=O
2a	4.73 (dd, 12.4, 6.0)	4.45 (dd, 12.4, 6.0)	2.75 (1H), 2.28 (2H), 2.24 (1H), 2.10 (1H), 1.96 (1H)	1700	1747
2a	5.23 (dd, 11.8, 5.8)	4.50 (t, 3.4)	2.28 (6H)	1700	1750
2b	5.22 (dd, 13.2, 5.2)	4.48 (t, 3.6)	2.38 (1H), 2.26 (1H), 2.16 (1H), 2.11 (1H), 2.08 (1H), 2.02 (1H), 0.96 (9H)	1709	1755
2c	4.91 (dd, 10.5, 5.2)	4.51 (dd, 10.0, 3.6)	1.25–2.60 (8H)	1698	1752
2c	4.97 (t, 4.8)	4.68 (dd, 9.6, 4.4)	1.25–2.60 (8H)	—	—
2d	5.05 (dd, 10.0, 3.6)	4.82 (dd, 10.8, 5.2)	2.68 (1H), 2.31 (1H), 2.01 (2H), 1.96 (2H), 1.75 (1H), 1.51 (2H), 1.11 (1H)	1704	1758
3a	5.35 (dd, 12.2, 6.0)	—	3.06 (1H), 2.77 (1H), 2.25 (3H), 1.91 (1H)	1715	1745
3b	5.31 (dd, 13.2, 5.2)	—	3.06 (1H), 2.54 (1H), 2.26 (1H), 2.08 (2H)	1712	1750

[a] ^{1}H NMR spectra measured at 400 MHz in 0.01 mol/L $CDCl_3$/TMS solutions, in a Bruker DPX 400 spectrometer.
[b] KBr pellets.

Table 3. ^{13}C NMR data[a] for brominated 2-trichloroacetylcycloalkanones **2** and **3**

Product	^{13}C NMR δ ppm					
	C1	C2	CRBr	Cl_3CC=O	Cl_3C	Others
2a	195.3	55.8	54.5	184.8	95.8	25.3, 32.5, 39.6
2a	198.2	51.1	51.0	186.0	96.0	19.2, 32.0, 35.0
2b	198.7	50.8	50.6	186.3	96.0	27.5, 32.1, 33.3, 36.1, 40.4
2c	189.6	55.1	52.8	185.3	96.1	26.4, 27.6, 31.8, 34.9
2c	197.6	54.9	51.4	185.1	95.8	26.6, 27.5, 32.0, 35.3
2d	201.0	53.8	49.9	184.6	96.0	23.8, 25.4, 25.7, 33.7, 36.0
3a	190.3	49.9	66.6	185.1	95.7	22.9, 31.5, 49.7
3b	190.6	49.1	66.9	185.3	95.7	27.5, 32.3, 32.9, 44.3, 51.2

[a] 0.01 mol/L $CDCl_3$/TMS solutions in a Bruker DPX 400 spectrometer with SF 100.62 MHz for ^{13}C.

21 mmol) in chloroform (50 mL) was added dropwise (CAUTION). The mixture was stirred at 25 °C until obtaining the characteristic red bromine color loss (2-3 h). The mixture was quenched with Pyridine (1.7 mL, 21 mmol) and stirred for 15 min. The organic solution was washed with water (3×50 mL) and dried with anhydrous Na_2SO_4, the solvent was evaporated, and the monobrominated products were obtained in good yields (Table 1) and high purity (by ^{1}H NMR). All crystalline compounds **2a**–**d** were purified for analytical data acquisition by recrystallization from hexane. The ω-bromo-2-trichloroacetylcycloalkanones were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Tables 2 and 3). 6,6-Dibromo-2-trichloroacetylcyclohexanones **3a** and **3b** were obtained starting from 21 mmol of 2-trichloroacetylcyclohexanones **1a** and **1b** and 43 mmol of bromine (2.2 mL; 6.9 g) using the procedure described. The analytical data for 6,6-dibromo-2-trichloroacetylcyclohexanones are showed in Tables 1–3.

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