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Formation of Five-Membered Cyclic Orthoesters from Tribromides with Participation of a Neighboring Carbonyl Group

Guddeangadi N. Gururaja,[a] Shaikh M. Mobin,[b] and Irishi N. N. Namboothiri*[a]

Dedicated to Prof. Ronald Breslow on the occasion of his 80th birthday

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The Mg-mediated conjugate addition of bromoform to enones followed by alcoholysis of the resulting keto tribromides proceeds through an unusual course, affording cyclic orthoester (dihydrofuran) intermediates under neutral workup conditions. However, acid workup of the reaction mixture or treatment of the isolated dihydrofurans with acid provides the expected but synthetically useful γ-keto esters. The intermediacy of dihydrofurans in the one-pot transformation of keto tribromides into γ-keto esters provides evidence for the active participation of the neighboring carbonyl group in the alcoholysis of the tribromide moiety.

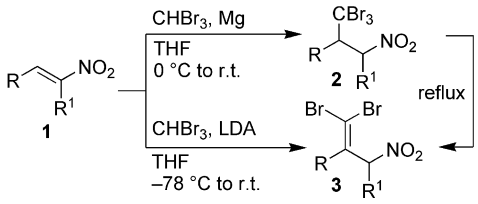
Introduction

Orthoesters are valuable substrates for the synthesis of glycosides,[1] carboxylic esters, and acetals.[2] The intermediacy of orthoesters in the Johnson–Claisen rearrangement[3] and in protecting group chemistry[4] is well documented. Due to the presence of latent hydroxy groups, orthoesters are also exquisite building blocks for the synthesis of environmentally friendly polymers.[5] Although numerous methods for the synthesis of orthoesters are available,[2] treatment of trihalo compounds with alkoxides is an effective and convenient strategy.[2,6] However, participation of a neighboring carbonyl group in the transformation of a trihalo compound to an orthoester, to the best of our knowledge, is unreported. Furthermore, the synthesis of orthoesters possessing a dihydrofuran (2,2-dialkoxydihydrofuran) motif has not received much attention.[7–9] Such dialkoxyfurans are also structurally related to synthetically useful 2-alkoxyfurans[10] and butenolides.[11] Of the two reported approaches, one is based on the copper-catalyzed decomposition of α-diazo carbonyl compounds in the presence of ketene acetals.[7] The other method involves treatment of *gem*-dichlorocyclopropyl ketones with sodium alkoxides.[8] There are also no reports, to the best of our knowledge, for the transformation of keto tribromides, especially by a one-pot procedure, into γ-keto esters,[12] which are precursors to a variety of bioactive heterocycles, pharmaceuticals, and natural products.[13]

We report here the generation of γ-keto tribromides through the Mg-mediated conjugate addition of bromoform to enones and alcoholysis of the tribromides under basic conditions. The unusual course taken by the latter step to afford 2,2-dialkoxydihydrofurans with the participation of the neighboring carbonyl group and the facile one-pot transformation of the tribromides into γ-keto esters are also reported here.

Results and Discussion

We recently disclosed the Mg- and LDA-mediated conjugate addition of bromoform to nitroalkenes **1** (Scheme 1).[14–15] Whereas the LDA-mediated reaction provided dibromomethylenated nitroalkenes **3** at low temperature (–78 °C), the Mg-mediated reaction furnished nitrotribromides **2** at 0 °C to room temperature, which underwent elimination under reflux conditions to form dibromides **3**.



Scheme 1. Conjugate addition of bromoform to nitroalkenes **1**.

[a] Department of Chemistry, Indian Institute of Technology Bombay,
Mumbai 400076, India
Fax: +91-22-2576-7152
E-mail: irishi@iitb.ac.in
Homepage: www.chem.iitb.ac.in/~irishi
[b] National Single-Crystal X-ray Diffraction Facility, Indian Institute of Technology Bombay,
Mumbai 400076, India

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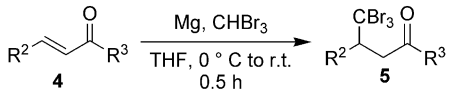
We felt that addition of bromoform to other activated alkenes such as enones **4** would provide synthetically useful γ-keto tribromides **5** (Table 1). Accordingly, chalcone **4a** was treated with bromoform in the presence of Mg at 0 °C, and the reaction mixture was warmed to room temperature over 30 min (Table 1, Entry 1). Much to our delight, complete conversion of **4a** was observed, and after aqueous workup and purification, keto tribromide **5a** was isolated in excellent yield (85%). Under the same conditions, chalcones **4b**–**e** possessing electron-donating groups on the β-aryl ring were treated with $CHBr_3$/Mg to afford tribromides **5b**–**e** in good to excellent yield (Table 1, Entries 2–5).

Table 1. Mg-mediated addition of bromoform to enones **4**.[a]



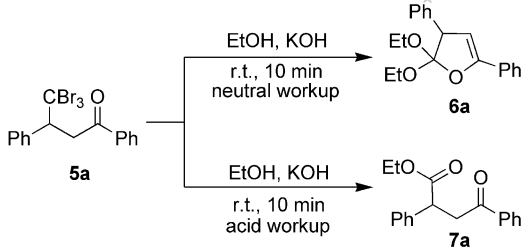
Entry	Enone **4**	R^2	R^3	**5**	Yield [%][b]
1	**4a**	Ph	Ph	**5a**	85
2	**4b**	4-$MeOC_6H_4$	Ph	**5b**	82
3	**4c**	3,4-$(MeO)_2C_6H_3$	Ph	**5c**	80
4	**4d**	3,4,5-$(MeO)_3C_6H_2$	Ph	**5d**	70
5	**4e**	4-$Me_2NC_6H_4$	Ph	**5e**	77
6	**4f**	4-$O_2NC_6H_4$	MeC_6H_4	**5f**	60
7	**4g**	2-furyl	Ph	**5g**	58
8	**4h**	2-thienyl	Ph	**5h**	90
9	**4i**	Ph	Me	**5i**	35[c]

[a] THF/$CHBr_3$ (10:1, 4 M), Mg (8 equiv.), and $CHBr_3$ (22 equiv.) were used. [b] Isolated yield after purification by silica gel column chromatography. [c] The 1,2-adduct was formed in 41% yield.

Although chalcones possessing an electron-withdrawing β-aryl moiety and a β-heteroaryl moiety such as **4f** and **4g** provided tribromides **5f** and **5g**, respectively, in moderate yield (58–60%; Table 1, Entries 6 and 7), chalcone **4h** possessing a 2-thienyl substituent underwent smooth conjugate addition of bromoform to give tribromide **5h** in excellent yield (Table 1, Entry 8). Similar reaction of bromoform with benzylideneacetone (**4i**) was less impressive, giving a mixture of 1,4-adduct **5i** and 1,2-adduct (Table 1, Entry 9).

Having obtained a variety of γ-keto tribromides **5a**–**i** in good to excellent yield in most cases by addition of bromoform to enones **4** under mild conditions (Table 1), we explored the possible transformation of the CBr_3 moiety into a carboxylate function under basic conditions. Much to our surprise, treatment of **5a** with ethanolic KOH at room temperature for 10 min followed by neutral workup, involving concentration of the reaction mixture, treatment of the residue with water, extraction of the aqueous layer with EtOAc, and concentration, afforded **6a** in 68% yield instead of expected γ-keto ester **7a** (Scheme 2). However, on acid workup, γ-keto ester **7a** was indeed isolated in 81% yield. These observations suggested that **6a** is an intermediate in the formation of **7a**.

In view of the above, we proceeded to optimize the conditions for the formation of **6a** (Table 2). Although the yield was only 68% when the reaction was carried out in EtOH as solvent (Table 2, Entry 1), it improved substantially to



Scheme 2. Alcoholysis of keto tribromide **5a**.

78% when THF was used as the solvent (Table 2, Entry 2). Further improvement in the yield was observed when the reaction was conducted in EtOAc (Table 2, Entry 3), which made the reaction mixture homogeneous. In the absence of EtOH, no **6a** was isolated (Table 2, Entry 4), confirming that EtOH, which takes part in the reaction, was not formed or formed only very slowly by hydrolysis of EtOAc under our experimental conditions. Finally, the reaction performed in EtOH/H_2O provided **6a** only in moderate yield (Table 2, Entry 5).

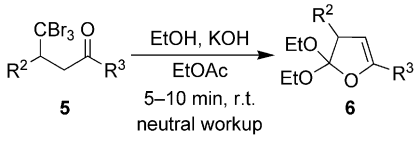
Table 2. Optimization of the reaction conditions for the conversion of keto tribromide **5a** into dihydrofuran **6a**.

Entry	Solvent	Yield [%][a]
1	EtOH	68
2	EtOH/THF (1:1)	78
3	EtOH/EtOAc (1:1)	95
4	EtOAc	–
5	EtOH/H_2O (1:1)	45

[a] Isolated yield after purification by silica gel column chromatography.

Under the above optimized conditions (Table 2, Entry 3), keto tribromides **5b**–**i** were treated with ethanolic KOH, and the reaction mixtures were subjected to neutral workup to afford dihydrofurans **6b**–**i** (Table 3).

Table 3. Transformation of keto tribromide **5** into dihydrofuran **6**.[a]

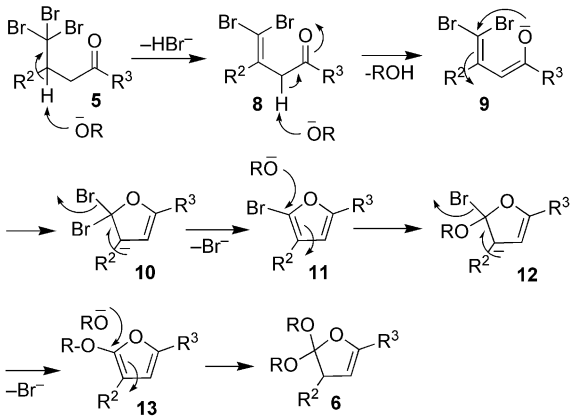


Entry	Tribromide **5**	R^2	R^3	**6**	Yield [%][b]
1	**5a**	Ph	Ph	**6a**	95
2	**5b**	4-$MeOC_6H_4$	Ph	**6b**	68
3	**5c**	3,4-$(MeO)_2C_6H_3$	Ph	**6c**	82
4	**5d**	3,4,5-$(MeO)_3C_6H_2$	Ph	**6d**	92
5	**5e**	4-$Me_2NC_6H_4$	Ph	**6e**	[c]
6	**5f**	4-$O_2NC_6H_4$	Ph	**6f**	[c]
7	**5g**	2-furyl	Ph	**6g**	58
8	**5h**	2-thienyl	Ph	**6h**	72
9	**5i**	Ph	Me	**6i**	70

[a] EtOH and EtOAc were used in 1:1 ratio in all the cases. [b] Isolated yield after purification by silica gel column chromatography. [c] Complex mixture.

Although no clear trend was observed, keto tribromides **5a**–**d** possessing phenyl and electron-donating aryl groups α to CBr_3 furnished dihydrofurans **6a**–**d** in higher yields (Table 3, Entries 1–4) as compared to **5g** and **5h**, which contain a heteroaryl group (Table 3, Entries 7 and 8). It is noteworthy that strongly electron-donating and strongly electron-withdrawing aryl groups do not favor the transformation of **5** into **6** under our experimental conditions (Table 3, Entries 5 and 6). Enone **5i** also underwent smooth transformation into its corresponding dihydrofuran **6i** (Table 3, Entry 9).

The proposed mechanism for the formation of dihydrofuran **6** involves initial dehydrohalogenation of keto tribromide **5** by the alkoxide ion to form keto dibromide **8** followed by enolization of **8** into **9** and intramolecular cyclization of **9** to form dibromodihydrofuran **10** (Scheme 3). Elimination of bromide from **10** and subsequent displacement of bromide from **11** by the alkoxide ion through an addition–elimination sequence provided *gem*-dialkoxydihydrofuran **6**, which is stable under nonacidic conditions.



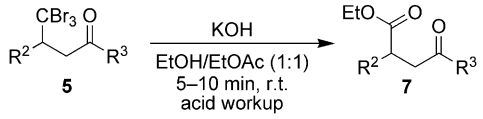
Scheme 3. Proposed mechanism for the formation of dihydrofuran **6**.

Having isolated and fully characterized key intermediates **6** in the transformation of keto tribromides **5** into γ-keto esters **7** (see dialkoxyfurans **6**, Table 3 and Scheme 3), we proceeded to perform the one-pot transformation of **5** into **7** by acid workup of the reaction mixture (Table 4). As desired, γ-keto esters **7** were isolated in good to excellent yield (Table 4, Entries 1–4, 7–9) except in the cases of **5e** and **5f** (Table 4, Entries 5 and 6). Interestingly, γ-lactone **17** (Scheme 4) was not observed in any of the cases.

The alcoholysis of keto tribromides **5** to afford dihydrofurans **6** and γ-keto esters **7** under different workup conditions was further generalized with various alcohols (Table 5). For instance, reaction of keto tribromide **5a** with KOH in methanol, 2-propanol, benzyl alcohol, and allyl alcohol afforded dihydrofurans **6j**–**m** under neutral workup conditions and keto esters **7j**–**m** under acid workup conditions in moderate to good yield (Table 5, Entries 2–5).

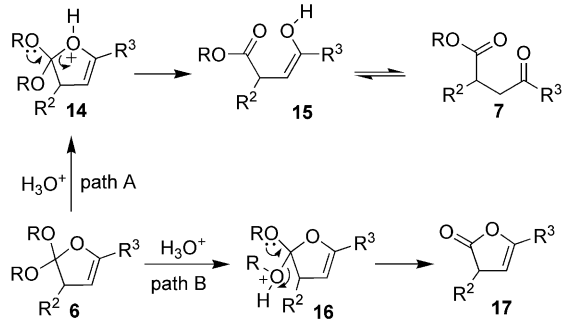
The above experiments demonstrated the simplicity and efficiency in the synthesis of γ-keto esters **7** from readily

Table 4. Transformation of keto tribromides **5** into γ-keto esters **7**.



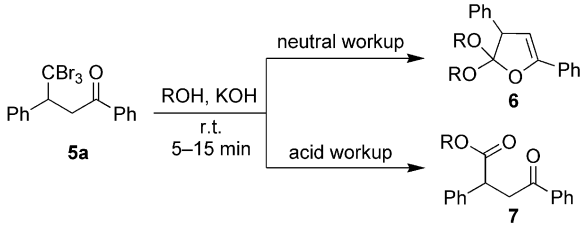
Entry	Tribromide **5**	R^2	R^3	**7**	Yield [%][a]
1	**5a**	Ph	Ph	**7a**	98 (86)
2	**5b**	4-$MeOC_6H_4$	Ph	**7b**	73 (60)
3	**5c**	3,4-$(MeO)_2C_6H_3$	Ph	**7c**	62 (69)
4	**5d**	3,4,5-$(MeO)_3C_6H_2$	Ph	**7d**	96 (84)
5	**5e**	4-$Me_2NC_6H_4$	Ph	**7e**	[b]
6	**5f**	4-$O_2NC_6H_4$	Ph	**7f**	[b]
7	**5g**	2-furyl	Ph	**7g**	58 (50)
8	**5h**	2-thienyl	Ph	**7h**	76 (64)
9	**5i**	Ph	Me	**7i**	60 (52)

[a] Isolated yield after purification by silica gel column chromatography; yield in parentheses is that obtained when isolated and purified **6** was treated with acid to get **7**. [b] Complex mixture.



Scheme 4. Proposed mechanism for the formation of γ-keto ester **7** and γ-lactone **17**.

Table 5. Scope of dihydrofuran **6** and γ-keto ester **7** formation with different alcohols.



Entry	R	**6**	Yield [%][a]	**7**	Yield [%][a]
1[b]	Et	**6a**	95	**7a**	98
2	Me	**6j**	60	**7j**	58
3[b]	*i*Pr	**6k**	41 (63)[b]	**7k**	37 (68)[b]
4	Bn	**6l**	57	**7l**	48
5	allyl	**6m**	70	**7m**	64

[a] Isolated yield after purification by silica gel column chromatography. [b] Yields in Entry 1 and those in parenthesis (Entry 3) refer to reactions in which ROH and ROAc were used in a 1:1 ratio. In all other cases, no solvent was used.

available enones **4** through keto tribromides **5** and isolable synthetic intermediates such as **6**. The structure of key dihydrofuran intermediates **6** was unambiguously established by

single-crystal X-ray diffraction analysis of representative compound **6k** (Figure 1, see also the Supporting Information).

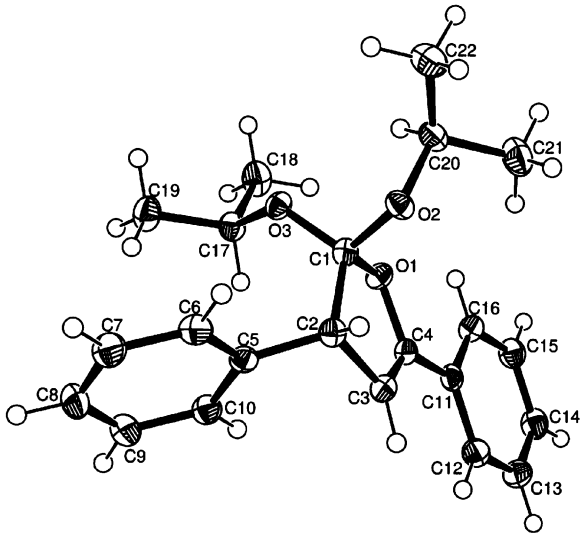


Figure 1. Single crystal X-ray structure of **6k**.

The acid hydrolysis of dihydrofuran **6** leads to γ-keto ester **7** through protonation of the ring oxygen atom as in **14** followed by ring opening of **14** into **15** and tautomerization of **15** into **7** (Scheme 4). Alternatively, protonation of the exocyclic oxygen atom as in **16** and elimination of ROH would give rise to γ-lactone **17**. However, in our hands, γ-lactone **17** was not formed in any of the cases (Table 4).

More importantly, although the alcoholysis of keto tribromide **5** into γ-keto esters **7** can take place without the participation of the carbonyl group (Supporting Information, Scheme S1), our studies provide evidence to the contrary through isolation and characterization of key dihydrofuran intermediate **6**.

Conclusions

In conclusion, 2,2-dialkoxydihydrofurans were formed, instead of γ-keto orthoesters, when γ-keto tribromides were treated with alcoholic KOH. This transformation of trihalides into orthoesters with the participation of a neighboring carbonyl group is unusual and is mechanistically and synthetically interesting. Possible applications of the hitherto poorly explored 2,2-dialkoxydihydrofurans, besides the demonstrated in situ transformation into γ-keto esters, are currently being pursued in our laboratory.

Experimental Section

General Procedure for the Mg-Mediated Addition of Bromoform to Enones 4: To a stirred solution of magnesium (96 mg, 4 g atom) and enone **4** (0.5 mmol) in THF (10 mL) under an atmosphere of N_2 was added bromoform (2.7 g, 1 mL, 11 mmol) dropwise over a period of 10 min at 0 °C. The reaction mixture was gradually brought to room temperature over a period of 0.5 h, during which time the solution turned dark brown. The reaction mixture was subsequently quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with ethyl acetate (5 × 10 mL), and the combined organic layers were washed with H_2O (3 × 10 mL), dried (anhyd. Na_2SO_4), and concentrated in vacuo to afford the crude product, which was subjected to silica gel column chromatography (ethyl acetate/hexane mixture, gradient elution) to afford pure 1,4-adduct **5**.

General Procedure for the Transformation of Keto Tribromides 5 into Dihydrofurans 6: To a stirred solution of keto tribromide **5** (0.5 mmol) in alkyl acetate (0 or 2 mL) and alcohol (2 mL) at room temperature was added KOH (0.112 g, 2 mmol). The reaction mixture was stirred at room temperature for 5–10 min, during which time the solution turned dark brown. After complete consumption of the starting material (monitored by TLC), the reaction mixture was concentrated in vacuo, and the crude residue was diluted with water (10 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL), dried (anhyd. Na_2SO_4) and concentrated in vacuo. The residue was subjected to column chromatography (Et_3N washed silica gel, ethyl acetate/hexane mixture, gradient elution) to afford pure *gem*-dialkoxydiaryl 2,3-dihydrofuran **6**.

General Procedure for the One-Pot Transformation of Keto Tribromides 5 into γ-Keto Esters 7: To a stirred solution of 1,4-adduct **5** (0.5 mmol) in alkyl acetate (0 or 2 mL) and alcohol (2 mL) was added KOH (112 mg, 2 mmol). The reaction mixture was stirred at room temperature for 10 min, during which time the solution turned dark brown. Upon complete consumption of the starting material (monitored by TLC), the reaction mixture was concentrated in vacuo, the residue was diluted with water (20 mL), and the aqueous layer was extracted with ethyl acetate (5 × 10 mL). The combined organic layer was washed with H_2O (3 × 10 mL) and 10% HCl (10 mL), dried (anhyd. Na_2SO_4), and concentrated in vacuo. The residue was subjected to silica gel column chromatography (ethyl acetate/hexane mixture, gradient elution) to afford pure γ-keto esters **7**.

CCDC-805518 (for **6k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Complete characterization data for all the new compounds, X-ray data tables for **6k**, and copies of the NMR spectra for all new compounds.

Acknowledgments

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