Triformylmethane: An Efficient Preparation, Some Derivatives, and Spectra

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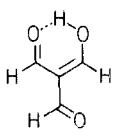
In this paper we present a simple and efficient two-step procedure for the preparation of triformylmethane from bromoacetic acid and dimethylformamide, synthesis of some triformylmethane derivatives of preparative importance, evidence for an intramolecular hydrogen bond in triformylmethane, based on its ^{1}H-NMR spectra measured in deuterochloroform in the presence of trichloroacetyl isocyanate, and comments on some recent erroneous statements[1] concerning the IR spectra of triformylmethane.

In view of the increased interest[1,2] in synthetic applications of triformylmethane (**1**), we present here some recent findings in this field, including a convenient two-step preparation of this trialdehyde, which is superior in yield and simplicity to the procedures used so far. The first synthesis of triformylmethane was achieved[3] in our laboratory by formylation of 3-dimethylamino-2-propenal (**2a**), a malonaldehyde derivative. This starting compound can advantageously be replaced by the commercially available 3-diethylamino-2-propenal (**2b**) as suggested later.[4] We also reported another approach to triformylmethane (**1**), based on the reaction of bromoacetic acid with dimethylformamide and phosphoryl chloride.[5,6] This reaction results in the formation of a precursor of **1** which was isolated as the bis-perchlorate **3a**. However, we published full experimental details of this approach to **1** only recently.[7] Following our method, the bis-tetrafluoroborate **3b** has also been prepared[8] and it has been recommended[1] as the most suitable intermediate for the synsthesis of **1** starting from bromoacetic acid.



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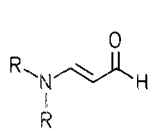
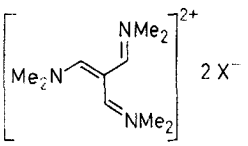


2a R = CH_3
b R = C_2H_5

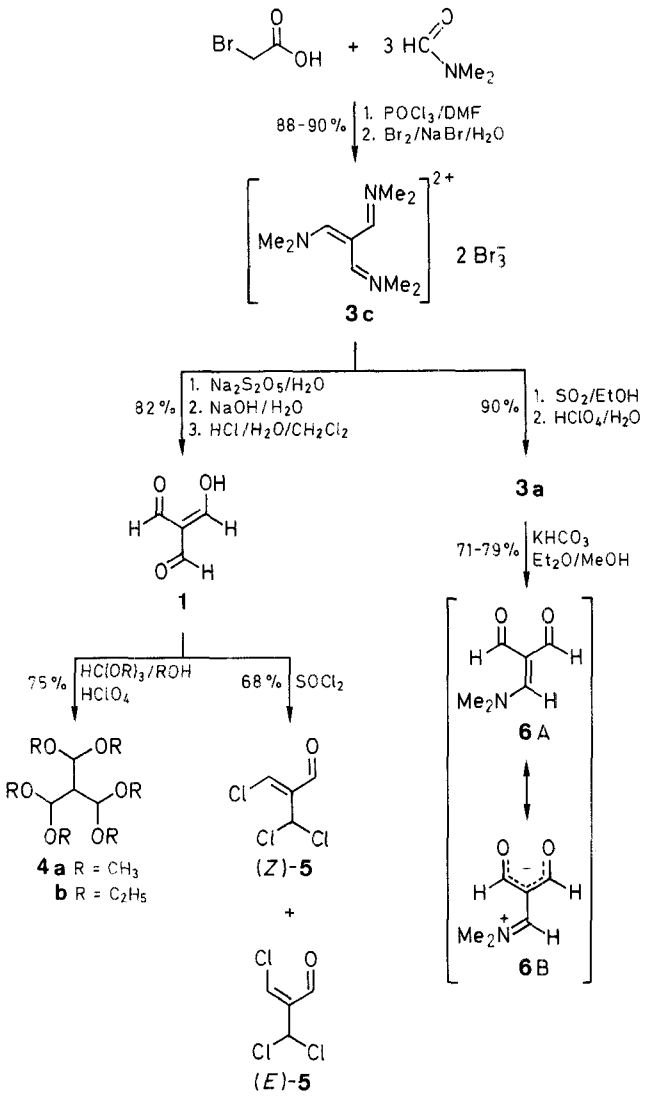


3a X^- = ClO_4^-
b X^- = BF_4^-
c X^- = Br_3^-
d $2X^-$ = $(Br_2, Br_3)^{2-}$

The procedure for the synthesis of triformylmethane (**1**) described here uses the almost water-insoluble bis-perbromide **3c**[6] as the intermediate of choice; it is obtained in yields of 88–90% by reaction of bromoacetic acid with dimethylformamide and phosphoryl chloride, decomposition of the reaction mixture with ice, and precipitation of the salt **3c** by an aqueous solution of bromine/sodium bromide. The salt **3c** can be easily converted into **1** (> 80% yield) or into most of its known derivatives. A further advantage of our new two-step preparation of **1** is that it can be scaled up as desired.

The isolated crude bis-perbromide **3c** can be stored for months and need not be purified for further applications. It may contain a small amount of the bromide-perbromide **3d**, which exhibits the same reactivity as **3c**.

Triformylmethane (**1**) is a colorless solid (mp 104–106 °C) which is relatively stable if kept in a refrigerator. In aqueous solution it readily undergoes self-condensation to 1,3,5-triformylbenzene.[9] Compound **1** is a strong acid (pKa = 2.0).[10] On the basis of its



IR spectrum, we suggested[3] the structure **1** with an intramolecular hydrogen bond. The correctness of our IR spectrum as well as its interpretation have recently been questioned.[1] However, it can be shown[11] that the questioning comments were entirely erroneous.[12] Repeating the IR spectral measurements, we confirmed that our published spectrum is correct and in accord with structure **1**. An interesting feature[13] of the IR spectrum in chloroform is the presence of a distinct sharp band close to the C–H band of chloroform but slightly shifted towards higher wave numbers ($CHCl_3$: $\nu = 3021\ cm^{-1}$, new band at $\nu = 3028\ cm^{-1}$). Measuring the IR spectrum in $CDCl_3$, we identified an analogous sharp band in the region of the C–D bands ($CDCl_3$: $\nu = 2255\ cm^{-1}$, new band at $\nu = 2259\ cm^{-1}$). The observed phenomenon is under further investigation in our laboratory.

Convincing evidence for the presence of the 6-membered chelate ring in **1**, dissolved in chloroform, can be drawn from the ^{1}H-NMR spectra. According to Lit.[1], the ^{1}H-NMR spectrum of **1** in $CDCl_3$ is rather unstable, with some signals which cannot be easily interpreted and which change within 24 hours.[14] By contrast, in our hands the ^{1}H-NMR spectrum of **1** recorded under the same conditions was stable for days, was in accordance which the spectra described earlier,[15,16] and corresponded to the assigned structure: $\delta = 9.03$ (s, 2 H, one CH=O and one =CH–OH group involved in the intramolecular hydrogen bond); 9.51 (s, 1 H, free CH=O); ca. 14.00 (br s, 1 H, concentration-dependent, acidic proton). An interesting information can be obtained from the ^{1}H-NMR spectrum of **1** recorded in the presence of trichloroacetyl isocyanate (TAI), a reagent currently used in NMR spectrometry.[17,18] Rather unexpectedly, this reagent leaves the molecule of **1** almost intact but has a very pronounced effect on its ^{1}H-NMR spectrum: while the chemical shifts do not change, the two-proton signal now appears as a doublet and the signal of the acidic proton as a triplet, with $^3J = 5.6$ Hz. We consider this interaction as a convincing evidence for the presence of a 6-membered chelate ring. We ascribe the effect of TAI to its ability to remove traces of water and/or hydrogen chloride[18] from the solution, thus minimizing the intermolecular attack of the hydrogen bond. This interesting finding is under further investigation; the results will be published separately.

Triformylmethane can be easily transformed to its acetals **4a, b** by reaction with trimethyl or triethyl orthoformate in the presence of traces of perchloric acid.[19] Acetals **4a, b** are stable liquids of considerable synthetic potential.

We have shown[7] that under dehydrating conditions, e.g., in the presence of thionyl chloride, compound **1** may be converted into 4,8-diformyl-2,6,9-trioxabicyclo[3.3.1]nona-3.7-diene and we have found that **1** on treatment with thionyl chloride without solvent is converted into a mixture of the *Z*- and *E*-isomers of 3-chloro-2-(dichloromethyl) propenal [(*Z*)-**5** + (*E*)-**5**] in the ratio 3:1. The configuration of the two aldehydes was determined using the vicinal coupling constants $^3J_{C,H}$ between the olefinic proton and the carbon atom of the aldehyde group ($^3J_{C,H} = 5.2$ and 8.1 Hz for the *Z*- and *E*-isomer, respectively) and/or between the olefinic proton and the carbon atom of the dichloromethyl group ($^3J_{C,H} = 9.4$ and 5.0 Hz for the *Z*- and *E*-isomer, respectively). These aldehydes are hydrolyzed back to **1** even by moist air. In view of this high reactivity, various synthetic applications can be anticipated for compound **5**.

Another triformylmethane derivative, 2-dimethylaminomethylenemalonaldehyde (**6**), has recently been applied as starting compound for the synthesis of methylenemalonaldehydes.[20] Compound **6**, at first prepared[3] from **1** and dimethylcarbamoyl chloride, has now been obtained by mild hydrolysis of the bis-perchlorate **3a** with potassium hydrogen carbonate in diethyl ether/methanol. The bis-perchlorate **3a** can be obtained as described[7] or according to the present communication. It is worthy of note that the bis-perchlorate **3a** is quite safe to handle (unlike many other perchlorates) and has many times been prepared in our laboratory in quantities up to 100 g. The ^{1}H-NMR spectrum of compound **6** reflects its high polarization in direction of the dipolar structure **6B**.

Solvents and common reagents were obtained commercially. Melting points were determined on a Kofler block and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 580 apparatus. NMR spectra were measured on FT NMR spectrometers: Varian XL-200 (^{1}H and ^{13}C at 200 MHz and 50.3 MHz, respectively) and Tesla BS-497.0 (^{1}H at 100 MHz).

2-Dimethylaminomethylene-1,3-bis(dimethyliminio)propane Bis-perbromide (3c):

To a stirred solution of bromoacetic acid (13.9 g, 0.1 mol) in DMF (30.9 mL, 0.4 mol), $POCl_3$ (28 mL, 0.3 mol) is added over 30 min at 15 °C. After standing for 30 min, the mixture is heated with at oil bath temperatures of 90 °C for 2 h and 110 °C for 7 h. After cooling to r.t., the mixture is poured onto crushed ice (300 g) with stirring, a solution of Br_2 (32 g, 0.2 mol Br_2) and NaBr (30.6 g, 0.3 mol) in H_2O (70 mL) is added, and stirring is continued for 1 h at ca. 10 °C. The orange precipitate is separated by suction, washed well with H_2O, and dried in a vacuum desiccator over NaOH; yield: 58.4 g (88 %); mp 105–113 °C (Lit.[6] mp 113–114 °C). The crude salt can be purified by dissolving it

(5 g) in MeCN (10 mL), filtering, and adding 1,2-dichloroethane (20 mL). However, for all transformations described here it can be used without purification.

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.40 (s, 9H, $3CH_3$); 3.55 (s, 9H, $3CH_3$); 8.45 (s, 3H, 3, =CH).

Notice: When scaling up the procedure, it is recommended to check the temperature in the reaction flask in order to prevent possible overheating during the exothermic reaction.

Isolation of the Bromide-Perbromide 3d:

Salt **3c** (10 g) is stirred with MeCN (10 mL) and the residue is separated by suction and dried *in vacuo*, yield: 100–400 mg (1–4%); mp 154°C.

$C_{10}H_{21}Br_4N_3$	calc.	N 8.35	Br 63.55
(502.9)	found	8.15	63.05

The ^{1}H-NMR spectrum (DMSO-d_6/TMS) is identical with that of salt **3c**.

Triformylmethane (1):

To the stirred ice-cooled suspension of the crude salt **3c** (6.63 g, 0.01 mol) in H_2O (15 mL) is added solid $Na_2S_2O_5$ (2.85 g, 0.015 mol). After 15 min, the pale yellow solution is made strongly alkaline by gradually adding excess solid NaOH (4 g) at 20°C. After 45 min, the mixture is cooled with an ice bath and CH_2Cl_2 (50 mL) and conc. aq. HCl (10 mL) are added. The small portion of solid salts is removed by suction and the product is extracted with CH_2Cl_2 (3 × 50 mL, 3 × 25 mL). The combined extracts are dried ($MgSO_4$), filtered (charcoal) and evaporated to dryness. The residue (ca. 0.91 g) is sublimed: yield: 0.82 g (82%); mp 104–106°C (Lit.[7] mp 101–103°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 9.03 (s, 2H, 2CH=O); 9.51 (s, 1H, CH=O); 12.35 (s, 1H, OH). After addition of TAI: δ = 9.03 (d, 2H, ^3J = 5.6 Hz, 2CH=O); 9.51 (s, 1H, CH=O); 14.70 (t, 1H, ^3J = 5.6 Hz, OH).

^{13}C-NMR ($CDCl_3$/TMS): δ = 118.18 (central C); 186.67 (CH=O); 187.16 (2 CH=O). After addition of TAI: δ = 118.18 (central C); 186.89 (CH=O); 187.24 (2CH=O).

Triformylmethane Acetals 4a, b; General Procedure:

Triformylmethane (**1**; 0.5 g, 5 mmol) is stirred in a mixture of trimethyl orthoformate (3.3 mL, 30 mmol) or triethyl orthoformate (5 mL) and MeOH or EtOH (1 mL) for 5 min. Then, 70% $HClO_4$ (ca. 10 mg) is added and the mixture is allowed to stand overnight. The acid is neutralized with a 1 M solution of NaOH in MeOH. The product **4** is isolated by distillation.

Triformylmethane Tris(dimethyl acetal) (**4a**); yield: 0.9 g (75%); bp 100°C (bath temperature)/1 kPa.

$C_{10}H_{22}O_6$	calc.	C 50.41	H 9.31
(238.3)	found	50.70	9.60

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.27 (q, 1H, ^3J = 4.5 Hz, central CH); 3.42 (s, 18H, $6OCH_3$); 4.52 (d, 3H, ^3J = 4.5 Hz, 3O–CH–O).

Triformylmethane Tris(diethylacetal) (**4b**); yield: 1.2 g (74%); bp 100°C (bath temperature)/50 Pa.

$C_{16}H_{34}O_6$	calc.	C 59.60	H 10.63
(322.4)	found	60.00	10.37

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.19 (t, 18H, ^3J = 7.5 Hz, $6CH_3$); 2.23 (q, 1H, ^3J = 4.5 Hz, central CH); 3.36–3.86 (m, 12H, $6CH_2$); 4.73 (d, 3H, ^3J = 4.5 Hz, 3O–CH–O).

3-Chloro-2-(dichloromethyl)propenal Isomers (*Z*)-5 + (*E*)-5:

Triformylmethane (**1**; 1 g, 0.01 mol) is added, with stirring and cooling with an ice bath, to excess $SOCl_2$ (7 mL). The mixture is stirred overnight at room temperature and then heated to 60°C for 1 h. Excess $SOCl_2$ is removed under reduced pressure and the product **5** (mixture of isomers) is isolated by distillation; yield: 1.18 g (68%); bp 40°C (bath temperature)/50 Pa; ratio *Z*/*E* = 3:1.

$C_4H_3Cl_3O$	calc.	C 27.70	H 1.74	Cl 61.32
(174.4)	found	27.38	1.45	60.94

^{1}H-NMR ($CDCl_3$/TMS): (*Z*)-**5**: δ = 6.84 (d, 1H, ^4J = 0.55 Hz, $CHCl_2$); 7.32 (s, 1H, =CHCl); 9.60 (d, 1H, ^4J = 0.55 Hz, CH=O). (*E*)-**5**: δ = 6.62 (d, 1H, ^4J = 0.9 Hz, $CHCl_2$); 7.90 (dd, 1H, ^4J = 0.9, 0.35 Hz, =CHCl); 10.12 (d, 1H, ^4J = 0.35 Hz, CH=O).

^{13}C-NMR ($CDCl_3$/TMS): (*Z*)-**5**: δ = 61.37 ($CHCl_2$); 140.27 (C-2); 140.99 (=CHCl); 185.59 (CH=O). (*E*)-**5**: δ = 64.16 ($CHCl_2$); 139.30 (C-2); 142.22 (=CHCl); 185.17 (CH=O).

2-Dimethylaminomethylene-1,3-bis(dimethyliminio)propane Bisperchlorate (3a):

Into a stirred suspension of the bis-perbromide **3c** (6.63 g, 0.01 mol) in EtOH (50 mL), SO_2 (5–7 g) is introduced at 20°C. The resultant pale yellow solution is filtered if necessary and a solution of 70% $HClO_4$ (1.8 mL, 0.02 mol) in EtOH (5 mL) is added at 20°C over 5 min. The product is separated by suction, washed with cold EtOH (3 × 3 mL) and with Et_2O, and dried in a desiccator; yield: 3.44 g (90%); mp 219–221°C (Lit.[7] mp 224°C).

2-Dimethylaminomethylenemalonaldehyde (6):

The bis-perchlorate **3a** (19.1 g, 0.05 mol) and $KHCO_3$ (15 g, 0.15 mol) are vigorously stirred in Et_2O (250 mL) + MeOH (25 mL) for 48 h. The solids are removed by suction and the filtrate is evaporated to dryness. The residue is dissolved in a mixture of benzene/Et_2O (1:1, ca. 30 mL), the solution is filtered, and the solvents are removed under reduced pressure. The remaining crude compound **6** is crystallized from MeOH (25 mL) at −70°C (overnight); yield: 4.5–5.0 g (71–79%); mp 45–47°C; identical with compound **6** described earlier[3] (mp 41–42°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.43 (d, 3H, ^4J = 0.6 Hz, NCH_3); 3.44 (d, 3H, ^4J = 0.6 Hz, NCH_3); 7.64 (br s, 1H, =CH–); 9.52 (d, 2H, ^4J = 0.8 Hz, 2CH=O).

^{13}C-NMR ($CDCl_3$/TMS): δ = 43.78 (NCH_3); 48.37 (NCH_3); 110.84 (central C); 159.19 (=CH–); 187.91 (2CH=O).

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(11) In our paper,[3] written in German, we spoke about the *presence* (Anwesenheit) of three bands in the double-bond region and the *absence* (Abwesenheit) of a free OH band. The mentioned authors of Ref. 1 evidently misunderstood the German text and consequently ascribed wrong conclusions to us.
(12) For reasons which are not clear, the authors of Ref. 1 when reproducing our IR spectrum[3] in their communication inadmissibly changed our transmittance scale to an absorbance scale.
(13) We find it rather strange that this remarkable effect has not been observed by the authors of Ref. 1 during their detailed examination of the IR spectrum of **1**.
(14) We assume that this strange behavior may be due to traces of some impurity: it cannot be excluded that such an impurity arises from the tetrafluoroborate anion under the strongly acidic conditions used during the conversion of the salt **3b** to **1**.
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