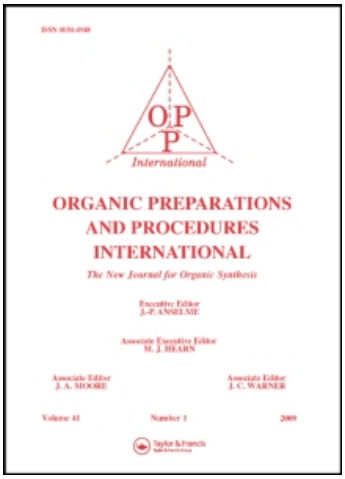

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BROMOACETALDEHYDE AND IODOACETALDEHYDE BY OZONOLYSIS OF ALLYL BROMIDE AND ALLYL IODIDE

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BROMOACETALDEHYDE AND IODOACETALDEHYDE BY OZONOLYSIS OF ALLYL BROMIDE AND ALLYL IODIDE†

Submitted by (12/14/93)

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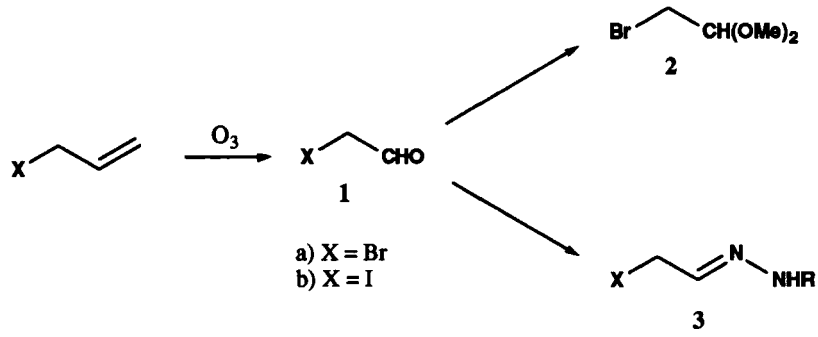
Bromoacetaldehyde (**1a**) and its dimethyl acetal (**2**) are very useful intermediates for the synthesis of various heterocyclic compounds of special biological interest. For example, **1a** is used for the preparation of ethenoguanosine derivatives[2,3] and imidazo[1,2-c]quinazolines,[4] which represent reactions of α-aminopyrimidines with **1a** forming annulated 5-membered rings; **2** is utilized for the synthesis of Tamoxifen derivatives, useful as anticancer agents,[5] as well as for the synthesis of chromone derivatives as allergy inhibitors.[6] Bromoacetaldehyde (**1a**) can be prepared by heating parabromoacetaldehyde[7] or by bromination of acetaldehyde in dioxane followed by purification by preparative gas chromatography.[8] Because of the instability of **1a**, it is often better to use the dimethyl acetal **2**, for which a number of preparations have been reported. The most convenient route has been the addition of bromine to vinyl acetate or alkyl vinyl ethers.[9-15] For the preparation of iodoacetaldehyde (**1b**), only two old references are known, starting from chloroacetaldehyde and potassium

iodide[16] or from acetaldehyde, iodine and iodic acid.[17] This paper describes a new and easy route for the preparation of bromoacetaldehyde (**1a**) and iodoacetaldehyde (**1b**) by ozonization of the corresponding allyl halides, similar to our published preparation of cyanoacetaldehyde from allyl cyanide.[1]



a) X = Br, R = 2,4-$(NO_2)_2C_6H_3$
b) X = Br, R = CO_2Me
c) X = Br, R = CO_2Et
d) X = Br, R = $CONHC_6H_5$
e) X = I, R = 2,4-$(NO_2)_2C_6H_3$

The allyl derivatives were ozonized at -40° in methanol and dichloromethane and then reduced with dimethyl sulfide to give solutions of **1a** and **1b**, which may be used directly for further reactions; **1a** was transformed to its stable dimethyl acetal (**2**) by reaction with trimethyl orthoformate in an overall yield of 65% starting from allyl bromide. Compound **2** is easily purified by distillation and, if required, hydrolyzed again in 70% yield by suspension of the strong acid ion exchange resin Amberlyst-15.[18] The similar acetalization of **1b** under the same conditions has so far not been successful. Reaction of **1** with hydrazine derivatives gave the corresponding hydrazones **3a-e.**

EXPERIMENTAL SECTION

Melting points were determined on a Tottoli apparatus and are uncorrected. Elemental analysis was done with a Carlo Erba Analyzer. Allyl bromide and allyl iodide were purchased from Aldrich Chemical Co. and Amberlyst-15 from Fluka A. G. ^1H NMR spectra (200 MHz) were recorded on a Varian XL-200 spectrometer; TMS was used as the internal standard. IR spectra were obtained on a Perkin-Elmer 421 spectrometer. Ozone was generated by using a Fischer instrument model 503.

Preparation of Bromoacetaldehyde (1a) and Iodoacetaldehyde (1b). General Procedure.- A solution of allyl halide (41 mmol) in a mixture of dichloromethane (100 mL) and methanol (25 mL) was ozonized with a 4-5 vol% O_3/O_2 mixture at -40°, until formation of iodine was observed in a KI solution, which was connected to the reaction vessel. N_2 was passed through the mixture for 5 min, dimethyl sulfide (5 mL) was added, and the solution was brought slowly to r.t. Formaldehyde was removed by concentrating the solution under reduced pressure to 20 mL. The formation of **1a** and **1b** was detected by their further reaction with phenylhydrazine.

Bromoacetaldehyde Dimethylacetal (2-bromo-1,1-dimethoxyethane 2).- To a freshly prepared solution of **1a** (4.2 g) by the foregoing procedure, trimethyl orthoformate (16.5 g, 155 mmol) and TsOH (1.5 g, 7.9 mmol) were added, and the mixture was stirred at 50° for 2 hrs. Then, the solvents were removed under reduced pressure. The oily residue obtained was treated with 25 mL of water and 50 mL of chloroform, the organic layer was washed with 25 mL of water, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting oil was purified by distillation to give 4.0 g (71%) colorless liquid, bp. 51°/18 mm, lit.[9] 48-51°/18 mm; IR: 2930, 2830 cm^{-1}; ^1H NMR. ($CDCl_3$): δ 3.37 (d, J = 6 Hz, 2H, CH_2); 3.39 (s, 6H, 2 x CH_3); 4.52 (t, J = 6 Hz, 1H, CH).

Anal. Calcd for $C_4H_9BrO_2$: C, 28.30; H, 5.36. Found: C, 27.93; H, 5.36

Hydrolysis of 2.- To a solution of **2** (1.64 g, 10 mmol) in acetone (40 mL) and water (0.6 mL), Amberlyst-15 (0.4 g) was added, and the mixture was stirred at r.t. for 24 hrs. The completeness of the reaction was observed by TLC. After separation of the ion exchange resin by filtration the resulting solution can be used directly for condensation with hydrazine.

Preparation of Hydrazones 3a-c, 3e and Semicarbazone 3d. General Procedure. To a freshly prepared solution of **1** (38 mmol) the corresponding hydrazine (38 mmol) or 4-phenylsemicarbazide (38 mmol) was added, and the mixture was stirred at r.t. or heated under reflux for the time shown below. The solvents were removed under reduced pressure to furnish **3a-e**, which were recrystallized from ethanol.

Bromoacetaldehyde 2,4-Dinitrophenlhydrazone (3a). The general procedure using heating under reflux for 3.5 hrs was used to give 3.2 g (80%) of brownish crystals, mp. 164°; IR: 3300, 3090, 1615 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.35 (d, J = 6 Hz, 2H, CH_2), 7.88 (d, J = 10 Hz, 1H, atom. H), 8.18 (t, J = 6 Hz, 1H, CH=), 8.38 and 8.48 (dd, J = 3 and 6 Hz, 1H, arom. H), 8.84 (d, J = 3 Hz, 1H, arom. H), 11.58 (s, 1H, NH).

Anal. Calcd for $C_8H_{15}BrN_4O_4$: C, 32.04; H, 2.34; N, 18.70; Found: C, 32.53; H, 2.60; N, 18.89

Bromoacetaldehyde (N-Methoxycarbonyl)hydrazone (3b).- The general procedure using stirring at r.t. for 1.5 hr was used to give 3.3 g (85%) of brownish crystals, mp. 105°; IR: 3210, 3050, 2950, 1725 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.67 (s, 3H, OCH_3) 4.18 (d, J = 6 Hz, 2H, CH_2), 7.42 (t, J = 6 Hz, 1H, CH=), 11.08 (s, 1H, NH).

Anal. Calcd for $C_4H_7BrN_2O_2$: C, 24.61; H, 3.61; N,14.35. Found: C, 26.34; H, 4.11; N, 14.58

Bromoacetaldehyde (N-Ethoxycarbonyl)hydrazone (3c).- The general procedure using stirring at r.t. for 1.0 hr was used to give 3.5 g (85%) of brownish crystals, mp. 115°; IR: 3250, 3055, 2965, 1720 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.22 (t, 3H, CH_3), 4.10 (q, 2H, CH_2); 4.16 (d, J = 6 Hz, 2H, CH_2) 7.40 (t, 1H, CH=), 11.08 (s, 1H, NH).

Anal. Calcd for $C_5H_9BrN_2O_2$: C, 28.69; H, 4.33; N, 13.38; Found: C, 28.59; H, 4.43; N, 13.43

Bromoacetaldehyde 4-Phenylsemicarbazone (3d).- The general procedure using heating under reflux for 6.0 hrs was used to give 4.7 g (89%) of brownish crystals, mp. 143-144°; IR: 3385, 3190, 3070, 2945 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.25 (d, J = 6 Hz, 2H, CH_2), 7.00 (t, J = 6 Hz, 1H, CH=), 7.22-7.70 (m, 6H, atom. 5H and NH),8.75 (s, 1H, NH).

Anal. Calcd for $C_9H_{10}BrN_3O$: C, 42.17; H, 3.93; N,16.39. Found: C, 42.21; H, 4.13; N, 16.43

Iodoacetaldehyde 2,4-Dinitrophenylhydrazone (3e).- The general procedure using heating under reflux for 4.0 hrs was used to give 3.1 g (86%) of brownish crystals, IR: 3300, 3100, 1620 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.20 (d, *J* = 6 Hz, 2H, CH_2), 7.88 (d, *J* = 10 Hz, 1H, arom. H), 8.15 (t, *J* = 6 Hz, 1H, CH=), 8.38 and 8.42 (dd, *J* = 3 and 6 Hz, 1H, arom. H), 8.85 (d, *J* = 3 Hz, 1H, arom. H), 11.52 (s, 1H, NH).

Anal. Calcd for $C_8H_7IN_4O_4$: C, 27.44; H, 2.15; N, 16.00. Found: C, 27.26; H, 2.12; N, 15.79.

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SYNTHESIS OF SPIN-LABELED TRIAZENES

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5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide (dacarbazine, DTIC) is the single most effective agent in the treatment of human disseminated malignant melanoma.[1,2] A serious disadvantage of DTIC as a cancer chemotherapeutic agent derives from its photosensitivity that leads to a rapid decomposition and development of a red color.[3] The replacement of the imidazole ring with an aryl- or other heteroaryl ring stabilizes the triazenes and, in most of cases, does not adversely affect their activity.[4,5] On the other hand, the presence of stable nitroxyl radicals in biologically active compounds reduces their toxicity,[6] and they possess antitumour[7] and radiosensitizing properties[8] and accumulate mainly in pigment melanomas.[9] Hence, we assumed that a combination of triazene and the nitroxyl moieties could lead to a more viable drug. The present work reports the synthesis and structure elucidation of triazenyl substituted 2,2,6,6-tetramethylpiperidine-1-oxyls which are structurally related to biologically active 1-aryl- or 1-heteroaryl-3,3-dimethyltriazenes (Schemes 1 and 2).

A general method of triazene synthesis involves the N-coupling of arenediazonium salts with aliphatic or aromatic amines.[10] Due to the acid-labile nature of a nitroxide radical center, diazonium salts have not been used in the chemistry of nitroxide radicals and attempts to synthesize spin-labeled triazenes have so far not been described. We investigated the conditions of coupling of the arenediazonium salts with the nitroxylamine and established that high yields of spin-labeled triazenes could be obtained in basic solution (pH = 10-12) and temperature -5° to 0°. Compound **3** was prepared by the reductive amination of 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl with methylamine in the presence of sodium cyanoborohydride.[11] The compounds **4a-i** were synthesized by diazotization of the corre-