Bromoacetaldehyde Diethyl Acetal

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Introduction

Bromoacetaldehyde diethyl acetal (**1**) is widely used in chemistry for the synthesis of a variety of antibiotics (including erythromycin and cephalosporins) and other drugs. It is an important and highly reactive bifunctional compound with a good leaving group and a masked aldehyde function. It can be used as a starting material in a variety of reactions to provide N-alkylated compounds,¹ lactams,² aldehydes,³ oximes,⁴ azides,⁵ and acyclic di-/polyselenides.³

Preparation

Bromoacetaldehyde diethyl acetal (**1**) is commercially available and can be prepared by several procedures: from diethylacetal **2** and bromosuccinimide,⁶ from vinyl acetate **3** with bromine in ethanol,⁷ and from 2,4,6-trimethyl-1,3,5-trioxane **4** with bromine in ethanol.⁸

Table 1 Use of Bromoacetaldehyde Diethyl Acetal

(A) The reaction of bromoacetaldehyde diethyl acetal **1** with *iso*-butyronitrile **5** afforded dihydrofuranone **6** in high yield. Reductive amination of **6** with *N*-benzyl-*N*-(2-phenylethyl)amine led to an ester after EDCI/HOBt-assisted coupling with benzyl alcohol. The oxidative *N*-debenzylation with CAN allowed to cleanly convert the ester into lactam **7**.²

(B) Diaryl-1,2,4-triazoles **11** bearing an *N*-hydroxyurea moiety can be obtained in a reaction sequence beginning with the preparation of oxime **9** from bromoacetal **1**, followed by the bromide displacement in **9** after reaction with the thiol **10**, and a two-step installation of a carbamoyl fragment.⁴

(C) 2-Azido-1,1-diethoxyethane **13** was prepared from **1** and sodium azide **12**. The Staudinger–aza-Wittig reaction of **13** with cyclohexane-1,3-dione **14** (R = H) afforded an enamine, which upon treatment with TFA gave 6,7-dihydro-1*H*-indol-4(5*H*)-one **15** (R = H). Application of substituted 1,3-dicarbonyl compounds **14** expanded the scope of this efficient approach to a variety of pyrroles.⁵

(D) Dicyano acetal **17** was prepared from **1** and malononitrile **16**, and was further transformed into a pyrimidine derivative, a precursor to 7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **18**.⁹

(E) Regioselective alkylation of resacetophenone **19** with **1** afforded compound **20**. Under acidic conditions, an intermediate aldehyde was formed from which substituted benzofuran derivative was obtained. Baker–Venkataraman rearrangement followed by acid-catalyzed cyclization led to the formation of furanoflavonoids **21**.¹⁰

(F) The Michaelis–Arbusov reaction of bromoacetal **1** with triethyl phosphite **22** gave phosphonate **23**, which was transformed into (*E*)-diethyl 2-ethoxyvinylphosphonate and further into a vinylphosphonate. The latter compound served as an efficient acceptor in the synthesis of acyclic nucleoside phosphonates **24**.¹¹

(G) Bromoacetal **1** was applied as a starting material in the synthesis of the Se-protected selenide **26**, which after acidic hydrolysis was used in the Ugi four-component reaction using carboxylic acid, isonitrile, and ammonium chloride (as a source of ammonia) to form bisamide **27** as selenocysteine dipeptides.³

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