Bromoacetaldehyde Diethyl Acetal

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 diethylacetol 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 dihydronorane 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-1H-indol-4(5H)-one 15 (R = H). Application of substituted 1,3-dicarbonyl compounds 14 expanded the scope of this efficient approach to a variety of pyrroles.9

(D) Dicyano acetal 17 was prepared from 1 and malononitrile 16, and was further transformed into a pyrimidine derivative, a precursor to 7H-pyrido[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 phosphate 22 gave phosphonate 23, which was transformed into (E)-diethyl 2-ethoxyvinylphosphonate and further into a vinylphosphinate. 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.2

References

(1) Yu, Q.; Carlsten, P. Molecules 2008, 13, 701.