[(*E*)-2-bromovinyl]trimethylsilane, 41309-43-7.

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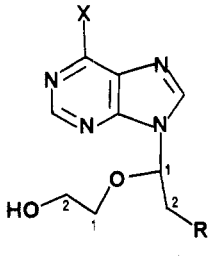
Acyclic Nucleoside Analogues: Synthesis of Open-Ring Riboside or Deoxyriboside Analogues Lacking C(3′) or the C(3′)–C(4′) Bond

Summary: 2-Alkyl-1,3-dioxolanes were treated with trimethylsilyl iodide to generate iodoalkyl (trimethylsilyloxy)ethyl ethers which were used to provide acyclic nucleoside analogues lacking C(3′) or the C(3′)–C(4′) bond.

Sir: Several reports have appeared recently describing the very potent antiviral activity of nucleoside analogues in which the cyclic sugar component has been replaced by an acyclic side chain.[1-4] 9-(2,3-Dihydroxypropyl)adenine (DHPA) inhibits replication of a number of DNA and RNA viruses,[1,2] while 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine) demonstrates selective inhibition toward *Herpes simplex* virus type I.[3,4] Interestingly, DHPA includes the C(1′)–C(2′)–C(3′) portion of a ribofuranosyl moiety, whereas acycloguanosine contains the C(1′)–O–C(4′)–C(5′) part of the natural nucleoside. In view of the biological activity which has accompanied the substitution of a sugar segment for a ribose in a nucleoside, we considered it desirable to synthesize acyclic nucleosides which incorporated both types of side chain. We describe herein efficient syntheses of (*R,S*)-9-[1-(2-hydroxyethoxy)-ethyl]adenine (**1a**), (*R,S*)-9-[1-(2-hydroxyethoxy)-2-hydroxyethyl]adenine (**1b**), and (*R,S*)-9-[1-(2-hydroxyethoxy)-3-hydroxypropyl]adenine (**1c**) as examples of a very general and simple synthetic methodology suitable for the formation of a wide range of acyclic nucleoside analogues.

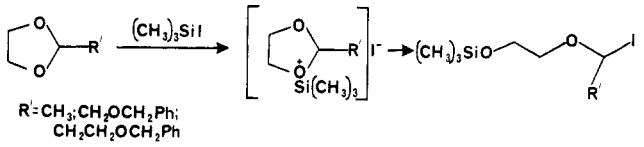


1a X = NH_2; R = H
b X = NH_2; R = OH
c X = NH_2; R = CH_2OH

2a X = Cl; R = H
b X = Cl; R = OCH_2Ph
c X = Cl; R = CH_2OCH_2Ph

3b X = NH_2; R = OCH_2Ph
c X = NH_2; R = CH_2OCH_2Ph

Scheme I



Recently we reported that 1,3-dioxolane and 1,3-oxathiolane could be treated with trimethylsilyl iodide at low temperature to generate efficiently iodomethyl (trimethylsilyloxy)ethyl ether or thioether, respectively.[5] We have now extended the scope of this reaction to include the ring opening of various 2-substituted dioxolanes with trimethylsilyl iodide to provide acyclic sugar analogues which are lacking only C(3′) or the C(3′)–C(4′) bond (Scheme I). This result is interesting when one considers the dealkylation which normally accompanies the reaction of acetals with trimethylsilyl iodide.[6] Although Jung et al. observed the formation of iodomethyl methyl ether upon treatment of methylal with trimethylsilyl iodide at room temperature, the authors suggest this is a result of the totally unhindered methylene center in the acetal.[7] Our reaction conditions avoid a dealkylation and are sufficiently mild that a benzyloxy group, normally sensitive at room temperature to trimethylsilyl iodide,[8] can function as a latent hydroxyl group on the generated acyclic sugar moiety. Furthermore, the use of substituted cyclic acetals as precursors for acyclic riboside analogues is attractive in that the requisite dioxolanes are readily available.[9] In a typical reaction, trimethylsilyl iodide (Aldrich or PCR, 0.16 mL, 1.1 mmol) in cyclohexene (0.5 mL) was added to 2-(benzyloxymethyl)-1,3-dioxolane[10] (215 mg, 1.1 mmol) in cyclohexene (0.5 mL) at −78 °C. After 15 min this alkylating reaction mixture was added to the sodium salt of 6-chloropurine (1 mmol, generated with NaH) in dry DMF at −63 °C. The mixture was warmed to 25 °C over 2 h and after the addition of aqueous 10% KF and 10% $NaHCO_3$, the solvent was evaporated and the residue extracted ($CHCl_3$). Concentration of the organic layer followed by chromatography on neutral alumina ($CHCl_3$) afforded analytically pure (*R,S*)-9-[2-benzyloxy-1-(2-hydroxyethoxy)ethyl]-6-chloropurine (**2b**): yield 65%; NMR ($CDCl_3$) δ 3.5–3.9 (m, 4, OCH_2CH_2O), 3.96 (d, J = 6 Hz, 2, OCH_2), 4.55 (s, 2, CH_2Ph), 6.03 (t, J = 6 Hz, 1, NCHO), 7.28 (s, 5, ArH), 8.32 (s, 1, purine CH), 8.71 (s, 1, purine CH).[11] Similarly obtained in 50–70% yield were

(1) De Clercq, E.; Descamps, J.; DeSommer, P.; Holý, A. *Science* **1978**, *200*, 563.
(2) De Clercq, E.; Holý, A. *J. Med. Chem.* **1979**, *22*, 510.
(3) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
(4) Fyfe, J. A.; Keller, P. M.; Furman, P. A.; Miller, R. L.; Elion, G. B. *J. Biol. Chem.* **1978**, *253*, 8721.

(5) Keyser, G. E.; Bryant, J. D.; Barrio, J. R. *Tetrahedron Lett.* **1979**, 3263. 1-[2-(Trimethylsilyloxy)ethoxy]ethyl iodide (R = CH_3, Scheme I) shows ^{1}H NMR [($CDCl_3$) δ 0.15 (s, 9, $Si(CH_3)_3$), 2.27 (d, J = 6 Hz, 3, CH_3), 3.61 (s, 4, OCH_2CH_2O), 6.12 (q, J = 6 Hz, 1, ICHO)] which is in agreement with iodoalkyl ethers previously reported (Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3698) and not in agreement with the expected ^{1}H NMR spectra of alkyloxonium ions like the intermediate shown in Scheme I. Similarly consistent ^{1}H NMR were also obtained with other trimethylsilyl iodide–2-substituted-1,3-dioxolane reaction products. See also ^{1}H NMR of **1a–c**, **2a–c**, **3b**, and **3c** for comparison. Unfortunately various attempts to isolate the iodomethyl (trimethylsilyloxy)ethyl ethers were unsuccessful, similar to the reports of Jung et al. (vide supra) for aldehyde iodohydrin trimethylsilyl ethers. However, the solutions of the iodoalkyl ethers were stable at low temperatures and could be used directly in further reactions.
(6) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *4175*.
(7) Jung, M. E.; Mazurek, M. A.; Lim, R. M. *Synthesis* **1978**, 588.
(8) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.
(9) 2-Methyl-1,3-dioxolane can be purchased from Eastman Chemical Co.; 2-(bromomethyl)-1,3-dioxolane and 2-(2-bromoethyl)-1,3-dioxolane are available from Tridom/Fluka A. G.
(10) The 2-(benzyloxyalkyl)-1,3-dioxolanes were prepared by reaction of the corresponding 2-(bromoalkyl)-1,3-dioxolanes with sodium benzylate in toluene, followed by fractional distillation.

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(*R,S*)-6-chloro-9-[1-(2-hydroxyethoxy)ethyl]purine (**2a**)[12] and (*R,S*)-9-[3-benzyloxy-1-(2-hydroxyethoxy)propyl]-6-chloropurine (**2c**).[13]

The substituted chloropurines were treated with methanolic ammonia at 110 °C in a sealed tube for 18 h to generate the corresponding acyclic adenosine analogues **1a**, **3b**, and **3c** in 80–90% yield.[14-16] The debenzylation of **3b** and **3c** was done according to the general procedure of Broom et al. and provided essentially quantitative conversion to compounds **1b** and **1c**.[17-19]

The ready availability of substituted dioxolanes and the excellent alkylating properties demonstrated by the derived iodoalkyl (trimethylsilyloxy)ethyl ethers make this an attractive synthetic methodology. In addition, our preparation now offers the possibility of synthesizing a variety of specifically substituted compounds, many of which would be quite difficult to obtain by conventional methods.

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Registry No. **1a**, 71516-41-1; **1b**, 71564-04-0; **1c**, 71516-42-2; **2a**, 71516-43-3; **2b**, 71516-44-4; **2c**, 71516-45-5; **3b**, 71516-46-6; **3c**, 71516-47-7; 2-methyl-1,3-dioxolane, 497-26-7; 2-(benzyloxymethyl)-1,3-dioxolane, 71516-48-8; 2-(2-benzyloxyethyl)-1,3-dioxolane, 71516-49-9; 6-chloropurine, 87-42-3; trimethylsilyl iodide, 16029-98-4.

Supplementary Material Available: Experimental details for the preparation of the compounds described in this paper (6 pages). Ordering information is given on any current masthead page.

(11) Only representative spectral data are provided to identify the compounds described. Microanalyses determined for C, H, N for all compounds are correct to within 0.4% of the calculated values.

(12) Compound **2a**: mp 89.5–90 °C; NMR ($CDCl_3$) δ 1.88 (d, J = 6 Hz, 3, CH_3), 2.39 (br s, 1, OH), 3.3–3.9 (m, 4, OCH_2), 6.09 (q, J = 6 Hz, 1, NCHO), 8.35 (s, 1, purine CH), 8.73 (s, 1, purine CH).

(13) Compound **2c**: mp 79.5–80.5 °C; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2, $CHCH_2$), 3.25–3.85 (m, 6, OCH_2), 4.42 (s, 2, CH_2Ph), 6.08 (t, J = 7.5 Hz, 1, NCHO), 7.28 (s, 5, ArH), 8.24 (s, 1, purine CH), 8.72 (s, 1, purine CH).

(14) Compound **1a**: mp 147.5–148.5 °C; NMR ($(CD_3)_2SO$) δ 1.71 (d, J = 6 Hz, 3, CH_3), 3.2–3.5 (m, 4, OCH_2), 4.53 (br, 1, NH or OH), 5.83 (q, J = 6 Hz, 1, NCHO), 7.15 (s, 2, NH or OH), 8.08 (s, 1, purine CH), 8.25 (s, 1, purine CH).

(15) Compound **3b**: NMR ($CDCl_3$) δ 2.75 (br, 1, NH or OH), 3.5–3.85 (m, 4, OCH_2CH_2O), 3.93 (d, J = 6 Hz, 2, OCH_2), 4.55 (s, 2, CH_2Ph), 5.90 (br, 2, NH or OH), 5.94 (t, J = 6 Hz, 1, NCHO), 7.25 (s, 5, ArH), 7.98 (s, 1, purine CH), 8.31 (s, 1, purine CH).

(16) Compound **3c**: mp 134–135 °C; NMR (CD_3OD) δ 2.33–2.61 (m, 2, $CHCH_2$), 3.33–3.73 (m, 6, OCH_2), 4.36 (s, 2, CH_2Ph), 5.97 (t, J = 6 Hz, 1, NCHO), 7.20 (s, 5, ArH), 8.19 (s, 1, purine CH), 8.23 (s, 1, purine CH).

(17) Christensen, L. F.; Broom, A. D. *J. Org. Chem.* **1972**, *37*, 3398.

(18) Compound **1b**: NMR ($(CD_3)_2SO$) δ 3.20–3.65 (m, 4, OCH_2CH_2O), 3.89 (d, J = 6 Hz, 2, OCH_2), 5.77 (t, J = 6 Hz, 1, NCHO), 7.27 (br, 1, NH or OH), 8.13 (s, 1, purine CH), 8.24 (s, 1, purine CH).

(19) Compound **1c**: NMR ($(CD_3)_2SO$) δ 2.10–2.40 (m, 2, $CHCH_2$), 3.25–3.60 (m, 6, OCH_2), 4.57 (br, 2, NH or OH), 5.85 (t, J = 6 Hz, 1, NCHO), 7.19 (br, 2, NH or OH), 8.13 (s, 1, purine CH), 8.28 (s, 1, purine CH).

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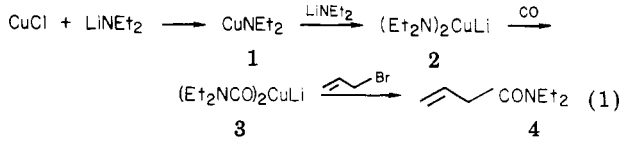
Lithium Bis(*N,N*-diethylcarbamoyl)cuprate. A Reagent for Direct Carbamoylation

Summary: Thermally stable lithium bis(*N,N*-diethylcarbamoyl)cuprate, which was readily prepared from CO and lithium bis(*N,N*-diethylamino)cuprate, was effective for direct carbamoylation.

Sir: Introduction of a carbonyl functionality into an organic compound is a useful interconversion reaction in organic synthesis. For example, several acyllithium equivalent reagents have been developed for the introduction of an acyl group because of the inaccessibility of acyllithium.[1] Here we report lithium bis(*N,N*-diethylcarbamoyl)cuprate, $(Et_2NCO)_2CuLi$ (**3**), as a useful reagent for direct carbamoylation.



The following procedures were carried out under nitrogen. An equimolar reaction of CuCl and $LiNEt_2$ in a mixed solvent of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) (4:1) at −20 °C produced a precipitate of $CuNEt_2$ (**1**), which was dissolved by an additional 1 equiv of $LiNEt_2$ to form an homogeneous solution. This solution absorbed 2 equiv of carbon monoxide under ordinary pressure at ambient temperature. Treatment of the resulting solution with allyl bromide gave *N,N*-diethyl 3-butenamide (**4**) in 45% yield based on $LiNEt_2$ with concomitant evolution of CO nearly equivalent to copper. The same reaction under CO pressure of 50 kg/cm^2 produced **4** in 76% yield. These results may be reasonably interpreted by the intermediacy of bis(*N,N*-diethylcarbamoyl)cuprate (**3**) generated from the CO insertion into bis(*N,N*-diethylamino)cuprate (**2**) (eq 1). The CO absorption by **2** contrasts in a striking way with the inertness of **1** toward CO at ambient temperature. Similarly, lithium bis(carbamoyl)cuprate derived from morpholine gave the corresponding 3-butenamide in 93% yield based on $LiNCH_2CH_2OCH_2CH_2$ under CO of 50 kg/cm^2. The formation of **3** and its trapping by allyl bromide at ambient temperature are interesting compared to the behavior of $LiNEt_2$ toward CO. $LiNEt_2$ prepared from $HNEt_2$ and *n*-BuLi absorbed an equimolar amount of CO at −78 °C in THF–HMPA (4:1). However, the treatment of the resulting solution with allyl bromide did not produce **4**, which suggests that *N,N*-diethylcarbamoyllithium cannot exist even at −78 °C probably due to its facile self-condensation.[2]

In the following experiments, **3** was prepared under CO pressure of 50 kg/cm^2. Heating the solution of **3** after the purge of the compressed CO gas at 60 °C for 2 h followed by the addition of allyl bromide did not give **4**, which indicates the decomposition of **3**. On the other hand, heating the solution of **3** at 60 °C for 2 h under CO pressure of 50 kg/cm^2 produced **4** in 64% yield by the treatment with allyl bromide. Similar reactions under CO pressure at 80 and 100 °C showed that **3** was thermally

(1) D. Seebach and K. H. Geiss in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, The Netherlands, 1976, pp 1–92.

(2) Sterically hindered *N,N*-diisopropylcarbamoyllithium generated from the reaction of lithium *N,N*-diisopropylamide and CO can exist at −78 °C; V. Rautenstrauch and M. Joyeux, *Angew. Chem., Int. Ed. Engl.*, 18, 83 (1979).

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