Synthesis of Acyclonucleoside Derivatives of 5-Alkoxymethyluracils

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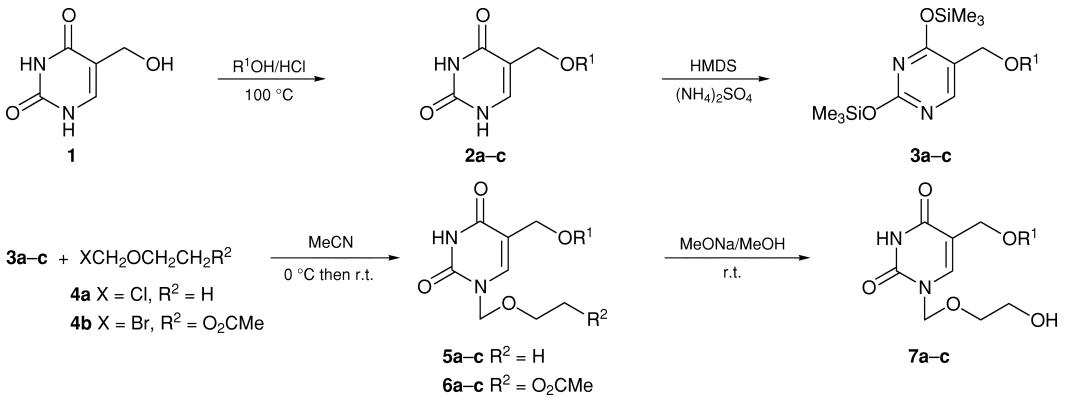
J. Chem. Research (S), 1998, 756–757
J. Chem. Research (M), 1998, 3192–3197

The silyl derivatives **3a**–**c** were treated with ethoxymethyl chloride (**4a**) or (2-acetoxyethoxy)methyl bromide (**4b**) to afford **5a**–**c** and **6a**–**c**, respectively; **7a**–**c** were prepared by treating **6a**–**c** with MeONa; treatment of **5a**–**c** or **6a**–**c** with tris(1*H*-1,2,4-triazole-1-yl)phosphine oxide and subsequent reaction of **8a**–**c** and **9a**–**c** with ammonia in dioxane to give **10a**–**c** and **11a**–**c**; ammonolysis of **11a**–**c** yielded the hydroxyalkyl derivatives **12a**–**c**.

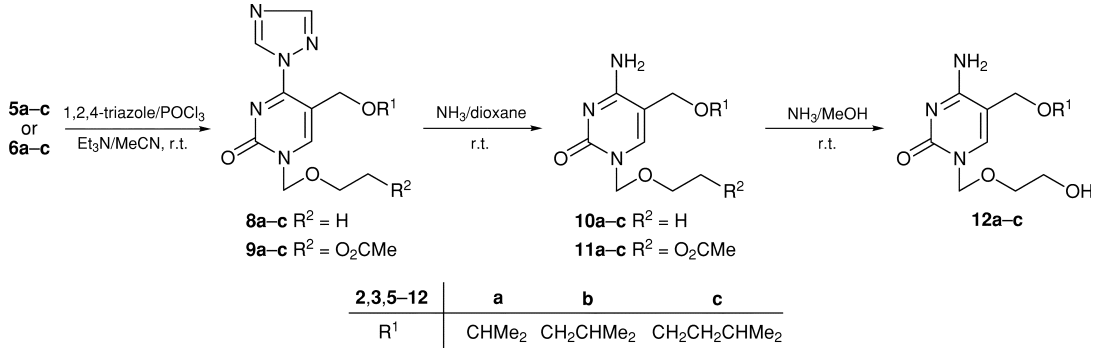
Since the discovery of human immunodeficiency virus (HIV) as the causative agent of acquired immunodeficiency syndrome (AIDS),[1,2] many nucleoside derivatives have been recognized as potent and selective inhibitors of replication of the human immunodeficiency virus (HIV). In particular, the costly 3′-azido-3′-deoxythymidine (AZT),[3] is a useful drug against HIV. Recently, acyclic nucleosides of the HEPT type, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine, have shown high selectivity towards HIV-1,[4] and it was found that replacement of the sulfur atom with a methylene group resulted a new series of potent HEPT analogues, of which MKC-442 (6-benzyl-1-ethoxymethyl-5-isopropyluracil) was found to be extremely potent.[5,6] On the other hand 9-(2′-hydroxyethoxymethyl)guanine was shown to have pronounced activity against Type I herpes virus, with low host toxicity.[7] Synthesis of a series of new pyrimidine nucleosides in which the carbohydrate moiety has been replaced by an acyclic side chain is desirable and it is important to consider low cost compounds as possible candidates with activity against AIDS.

5-Alkoxymethyluracils **2a**–**c** were prepared by acid catalyzed reaction of 5-hydroxymethyluracil[8] (**1**) with isopropyl alcohol,[9] isobutyl alcohol[10] and isopentyl alcohol. Silylation of 5-alkoxymethyluracils **2a**–**c** was performed according to Wittenburg[11] prior to their coupling as silylated derivatives **3a**–**c** with ethoxymethyl chloride **4a** or (2-acetoxyethoxy)-methyl bromide **4b** using the method of Robins and Hatfield[12] in dry acetonitrile to afford **5a**–**c** and **6a**–**c**. Treatment of **6a**–**c** with sodium methoxide in methanol gave **7a**–**c** (Scheme 1).

4-(1,2,4-Triazole-1-yl)pyrimidin-2-ones **8a**–**c** and **9a**–**c** were prepared by treating **5a**–**c** and **6a**–**c** with putative tris(1*H*-1,2,4-triazole-1-yl)phosphine oxide[13] in the presence of 1,2,4-triazole and triethylamine in MeCN. Reaction of



Scheme 1



2,3,5–12	a	b	c
R^1	$CHMe_2$	CH_2CHMe_2	$CH_2CH_2CHMe_2$

Scheme 2

*To receive any correspondence.

the 4-triazolo derivatives **8a**–**c** and **9a**–**c** with ammonia in dioxane yielded the cytosine derivatives **10a**–**c** and **11a**–**c**. Treatment of **11a**–**c** with a 1:1 mixture of methanol and conc. ammonia afforded **12a**–**c** (Scheme 2).

Techniques used: mp, ^{1}H and ^{13}C NMR, mass spectrometry, microanalysis

References: 13

Schemes: 2

Received, 15th April 1998; Accepted, 7th September 1998
Paper E/8/02837K

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