Pergamon

Tetrahedron Letters 40 (1999) 2837–2840

TETRAHEDRON LETTERS

Anionically Induced Formation of Anomeric Spironucleosides from 1'-*C*-Cyano-2'-deoxyuridine

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Received 4 January 1999; accepted 4 February 1999

Abstract: The reaction of the 1'-*C*-cyano-2'-deoxyuridine derivative **1** with organolithium reagents can be favorably tuned to give a new class of anomeric spironucleosides.

Keywords: Nucleosides, Spiro compounds, Nitriles, Lithium and compounds

In recent years the 1'-*C*-cyano-pyrimidine nucleosides have attracted considerable interest for their biological activity [1,2]. We have recently reported the synthetic utility of 2',5'-di-*O*-(*tert*-butyldimethylsilyl)-1'-*C*-cyano-2'-deoxyuridine (**1**) as a precursor of ketone **6b** [3], which has been used in model studies of radical induced DNA damage [3-5].

Fry and coworkers have shown that the nucleophilic addition of Grignard reagents to γ,δ-unsaturated nitriles gives cyclic products [6]. Based on this strategy, we envisaged that the nucleoside derivative **1** could also be the precursor to a new class of anomeric spironucleosides by reaction with organometallic reagents. Scheme 1 shows the two alternative pathways for the intermediate imino anion **2**, which can either be quenched and converted to the ketone **3** [7] or react intramolecularly with the suitably located double bond of the pyrimidine ring to afford the spiro compound **4**. Anomeric spironucleosides are useful modifications of natural nucleosides in that they contain the base unit in a fixed conformation around the *N*-glycosidic bond and only a few synthetic approaches have proven to be successful [8]. Recently, our group has reported radical-based methodologies for the synthesis of other types of anomeric spironucleosides [9-11].

Herein we report the reaction of compound **1** with two organolithium reagents that produces either the novel anomeric spironucleoside **4** or the keto derivative **3**, depending on the experimental conditions. In fact, both the addition rate of the organometallic reagent and the molarity of the starting nucleoside in THF were shown to have a strong influence on the reaction outcome.

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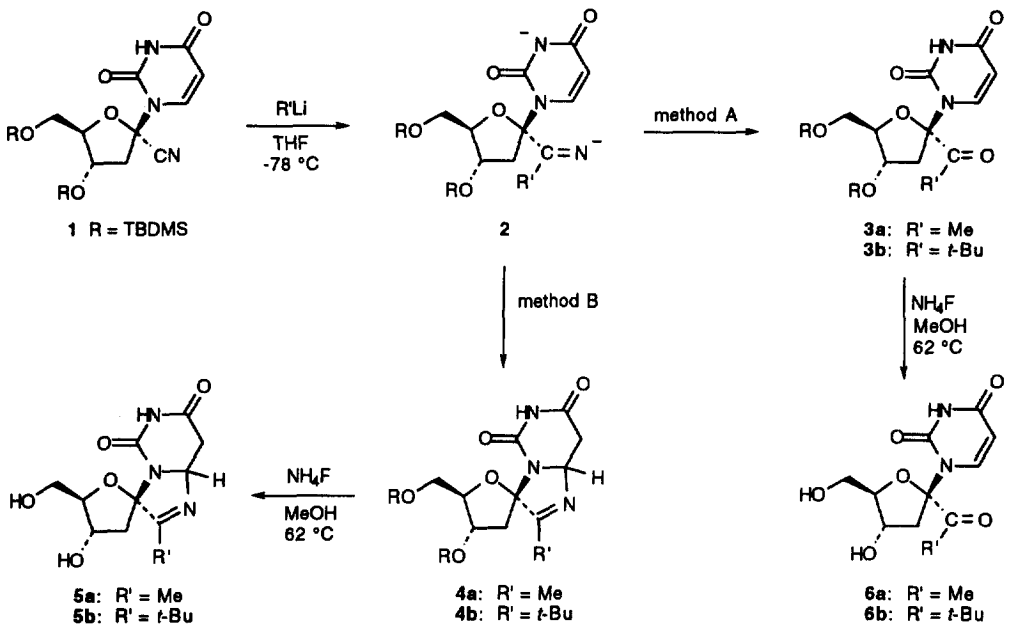
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00273-7

Scheme 1



Method A: To a stirred 0.3M THF solution of **1** kept at -78°C under an argon atmosphere, 3 equiv. of MeLi (1.6M in ether) or *t*-BuLi (1.6M in pentane) were added within a few minutes. The resulting orange-yellow solution was then immediately quenched with a sat. aqueous $NaHCO_3$ solution, followed by extraction with ethyl acetate. Flash chromatography[3] on silica gel of the reaction mixtures gave **3a** (R_f = 0.62, UV visible) in 55% yield and **3b** (R_f = 0.59, UV visible) in 45% yield, respectively, based on the recovered starting material.

Method B: To a stirred 0.1M THF solution of **1** kept at -78°C under an argon atmosphere, 3 equiv. of MeLi (1.6M in ether) or *t*-BuLi (1.6M in pentane) were added within 20 minutes. After a few more minutes at a low temperature, a sat. aqueous $NaHCO_3$ solution was added, followed by extraction with ethyl acetate. Chromatography[3] of the first crude reaction gave **4a** (R_f = 0.65, not UV visible) as a single diastereoisomer in 52% yield and **3a** (R_f = 0.62, UV visible) in 5% yield. Chromatography[3] of the second crude reaction gave **4b** (R_f = 0.62, not UV visible) as a single diastereoisomer in 60% yield and **3b** (R_f = 0.59, UV visible) in 3% yield.

Table 1 summarizes the reaction products. It is evident that method A afforded only the keto derivatives which derive from a fast quenching of the imino anion **2**. On the other hand, by method B, the fate of the intermediate **2** can be directed towards the intramolecular addition thus resulting in the formation of spironucleosides (Scheme 1).

[3] Chromatography using *n*-hexane containing increasing amounts of ethyl acetate. TLC in ethyl acetate:*n*-hexane 3:7.

Table 1
Addition of organolithium reagents to the 1'-C-cyano-2'-deoxyuridine derivative 1

RLi	Method[a]	Product (Yield, %)	
MeLi	A	**3a** (55%)	[b]
	B	**3a** (5%)	**4a** (52%)
t-BuLi	A	**3b** (45%)	[c]
	B	**3b** (3%)	**4b** (60%)

[a] See text. [b] Traces of **4a**. [c] Traces of **4b**.

Deprotection of compounds **3** and **4** by overnight treatment with ammonium fluoride in hot MeOH gave the corresponding desilylated nucleosides **6** [12] and **5** in yields higher than 80%.

It is also worth underlining that the spironucleosides **4a** and **4b** were formed as single diastereoisomers. Although the absolute configuration at C-6 has not yet been assigned, the diastereoselectivity of the reaction can be rationalized as follows: since the initially formed N(3)-lithiated species is known to adopt the *syn* conformation which is fixed by the intramolecular chelation [13,14], we suggest that this conformation directs the imino anion attack, assisting the approach preferably to one side of the double bond (Figure 1).

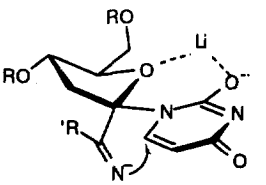


Figure 1. Proposed transition state for the formation of spironucleosides

In conclusion, 1'-*C*-cyano-pyrimidine nucleosides are shown to be flexible synthetic precursors and offer a unique opportunity for the preparation of either keto derivatives **3** or anomeric spironucleosides **4**. An extended study of these reactions is under current investigation.

Selected data for the new compounds:

Compound **3a**: ^{1}H NMR (200 MHz; C_6D_6) δ 0.06, 0.07, 0.08, 0.09 (3H each, s, SiMe), 0.87, 0.91 (9H each, s, SiBu^t), 2.20 (3H, s, Me), 2.40 (1H, dd, *J* 7.1, 14.2, 2'-H), 3.11 (1H, dd, *J* 7.6, 14.2, 2'-H), 3.81 (3H, m, 4'-H, 2x 5'-H), 4.40 (1H, q, *J* 7.3, 3'-H), 5.70 (1H, d, *J* 8.3, 5-H), 8.09 (1H, d, *J* 8.3, 6-H), 8.3 (1H, bs, NH); ^{13}C NMR (50 MHz; C_6D_6) δ -5.6, -5.0, (each 2xCH_3), 17.8, 18.3 (each C), 22.8 (CH_3), 25.6, 25.7 (each 3xCH_3), 41.1, 60.5 (each CH_2), 69.3, 88.2 (each CH), 96.5 (C), 101.4, 139.8 (each CH), 150.6, 164.1, 196.9 (each C).

Compound **3b**: Spectral characteristics identical to those reported in the literature [3].

Compound **4a**: ^{1}H NMR (200 MHz; $CDCl_3$) δ, 0.05 (6 H, s, 2x SiMe), 0.09, 0.10 (3 H each, s, SiMe), 0.89, 0.90 (9 H each, s, SiBu^t), 2.15 (1 H, dd, J 5, 14, 2'H), 2.21 (3 H, d, *J* 2, Me), 2.25 (1H, dd, J 12.7, 16.3, 5-H) 3.02 (1 H, dd, *J* 7.5, 14 2'-H), 3.16 (1 H, dd, *J* 3.7, 16.3, 5-H), 3.82 (2 H, m, 2x 5'-H), 3.96 (1 H, m, 4'-H), 4.71 (1 H, m, 3'-H), 5.45 (1 H, m, 6-H), 7.42 (1 H, bs, NH); ^{13}C NMR (50 MHz; $CDCl_3$) δ, -5.3, -4.8 (each 2 x CH_3), 15.0 (CH_3), 17.8, 18.4 (each C), 25.7, 25.9 (each 3 x CH_3), 29.6 (C) 38.0, 39.9, 63.6 (each CH_2), 73.4, 79.1, 89.8 (each CH), 100.9 (C), 148.3, 168.5, 173.4 (each C); MS (EI, 70 eV) m/z (relative intensity), 497 (M^+, 1), 492 (M^+-CH_3, 2), 440 (M^+-Bu^t, 36), 261 (100).

Compound **4b**: ^{1}H NMR (200 MHz; $CDCl_3$) δ, 0.01 (6 H, s, 2x SiMe), 0.05, 0.06 (3 H each, s, SiMe), 0.85, 0.86 (9 H each, s, SiBu^t), 1.35 (9 H, s, Bu^t), 2.18 (1 H, dd, *J* 13, 16.5, 5-H), 2.73 (2 H, d, *J* 8, 2x 2'-H), 3.14 (1 H, dd, *J* 4, 16.5, 5-H), 3.80 (2 H, d, *J* 5.6, 2x 5'-H), 4.06 (1 H, m, 4'-H), 4.80 (1 H, q, *J* 6.3, 3'-H), 5.41 (1 H, dd, *J* 4, 13 6-H), 8.70 (1 H, bs, NH); ^{13}C NMR (50 MHz; $CDCl_3$) δ, -5.20, -5.16, -4.92, -4.74 (each CH_3), 17.7, 18.4 (each C), 25.6, 25.7, 29.5 (each 3 x CH_3), 36.1 (C), 38.0, 43.4, 65.0 (each CH_2), 73.6, 77.7, 89.5 (each CH), 101.2 (C), 148.1, 168.9, 180.6 (each C); MS (EI, 70 eV) m/z (relative intensity), 539 (M^+, 1), 492 (M^+-CH_3, 3), 482 (M^+-Bu^t, 45), 261 (100).

Acknowledgment. We are grateful to the European Commission for a 'Marie Curie' post-doctoral fellowship to T. G.

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