Pergamon

Tetrahedron Letters 42 (2001) 9167–9170

TETRAHEDRON LETTERS

Synthesis of acyclic nucleosides and other C-1 substituted alditols from carbohydrates using a tandem alkoxyl radical β-fragmentation–nucleophilic addition

Alicia Boto, Rosendo Hernández* and Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de la Esperanza, 3., 38206 La Laguna, Tenerife, Spain

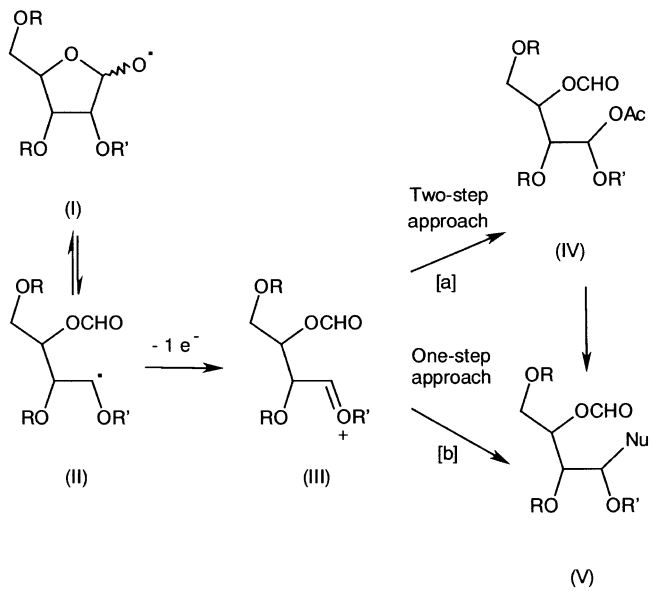
Received 11 October 2001; accepted 25 October 2001

Abstract—The oxidative β-fragmentation of alkoxyl radicals generated from easily available carbohydrates is an efficient methodology to obtain acyclic nucleosides and other C-1 substituted alditols. In the reaction conditions an oxycarbenium ion is generated, which can be trapped by a variety of oxygen, carbon and nitrogen nucleophiles, in good yields and stereoselectivities.

The remarkable antiviral activity of some acyclic nucleotide and nucleoside analogues[1] has stimulated the efforts to synthesize this class of compounds and to develop structure–activity (SAR) studies. A nucleotide analogue, PMEA,[1b,c] displays an impressive in vitro activity against retroviruses, the HIV in particular. Several nucleoside analogues, such as acyclovir,[1a] ganciclovir[1a] and famciclovir[1f] have potent antiherpes activity. These compounds have shown that the biological activity can be retained even with important modifications of the sugar moiety. The change of the base unit has been studied to obtain acyclic nucleoside or nucleotide analogues with improved bioavailability,[2a] and also to achieve other activities of interest, as in the case of triadimenol and other triazolyl fungicides that are useful for crop protection.[2b]

As a promising way to introduce modified sugar chains and/or base units in the nucleoside analogues we decided to study the β-fragmentation reaction of anomeric alkoxyl radicals[3] (I) (Scheme 1), derived from carbohydrates on treatment with (diacetoxy)-iodobenzene (DIB) and iodine. The fragmentation produced a carbon radical (II) which was oxidized in the reaction mixture to an oxycarbenium ion (III). This, in turn, was trapped by an acetate moiety (Scheme 1, path a) to give the acetoxy derivatives (IV). We reasoned that these products (IV) could be treated with different nucleophiles (such as purine or pirimidinic bases), in the presence of a Lewis acid, to give C-1 substituted derivatives (V).

Moreover, this methodology could be modified to introduce, in one step, carbon and heteroatom nucleophiles onto the linear chains (Scheme 1, path b). This would result in increased atom economy,[4] as no work-up or purification of the acetoxy intermediates (IV) would be needed. In this article we show the feasibility of this approach.



Scheme 1. Synthesis of C-1 substituted alditols.

Keywords: alcoxyl radical; fragmentation; diastereoselective synthesis; alditols; nucleosides.

* Corresponding authors. Fax: 34-922-260135; e-mail: rhernandez@ipnacs.csic.es

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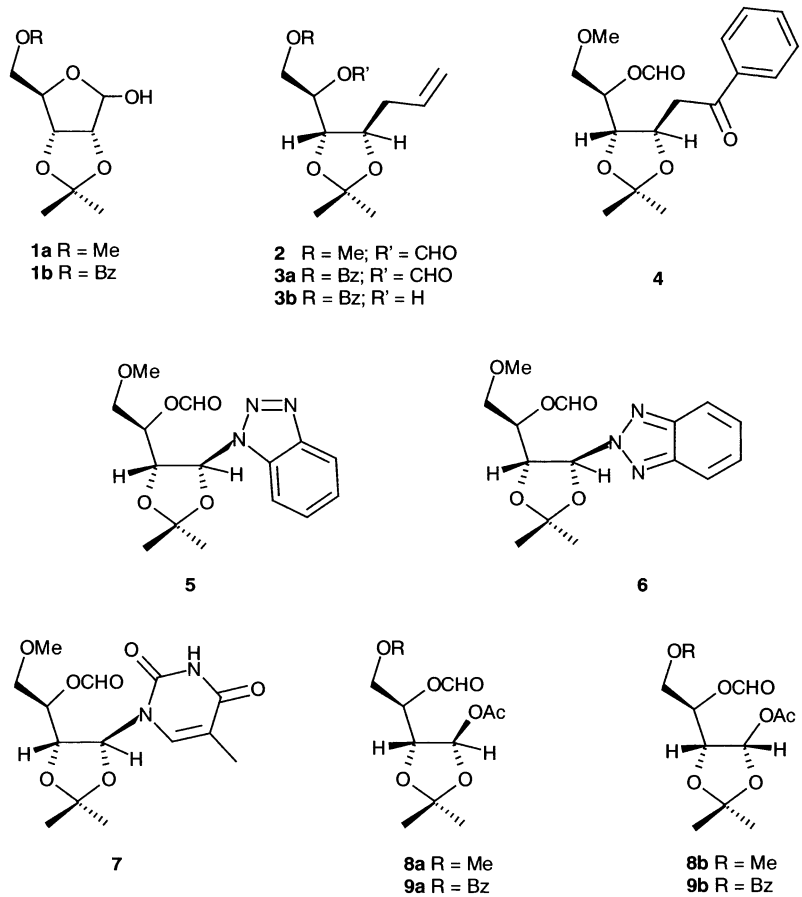
PII: S0040-4039(01)02016-0

The fragmentation of carbohydrates **1a** and **1b** (Scheme 2) and their tandem conversion to C-1 substituted alditols was carried out by treatment with DIB and iodine in dry dichloromethane or acetonitrile at room temperature, under irradiation with visible light. After 1 h, the nucleophile (Table 1) was added and then the reaction mixture was cooled before adding the Lewis acid. Different conditions were tried for each nucleophile, and the optimized ones are shown in Table 1. This tandem reaction afforded alditol derivatives **2**, **3a**, and **4**–**7** (Scheme 2). The allylated derivative **2** (entry 1) proved to be volatile, and low yields were obtained (entry 1). However, the yields improved considerably for the less volatile analogue **3a** (entries 2 and 3). Both **2** and **3a** were mainly obtained as the *trans* diastereomers (*trans*:*cis*, 98:2).[5]

It is remarkable that the formate group withstands the mild reaction conditions; however, it can be selectively removed in the presence of the benzoate by treatment



Scheme 2. Synthesis of acyclic nucleoside analogues and other C-1 substituted alditols.

Table 1. One-pot oxidative β-fragmentation–nucleophilic addition

Entry	Substrate[a]	Solvent	Nucleophile[b] (equiv.)	Lewis acid (equiv.)	Products (%)[e]	d.r. *trans*:*cis*[f]
1	**1a**	CH_2Cl_2	A (4.0)	$BF_3{\cdot}Et_2O$ (3.0)[c]	**2** (21)	98:2
2	**1b**	MeCN	A (4.0)	TMSOTf (2.0)[c]	**3a** (53)	98:2
3	**1b**	CH_2Cl_2	A (4.0)	TMSOTf (2.0)[c]	**3a** (43)	98:2
4	**1a**	MeCN	B (4.0)	TMSOTf (2.5)[c]	**4** (16)	>99:1
5	**1a**	CH_2Cl_2	C (1.5)	$BF_3{\cdot}Et_2O$ (2.5)[d]	**5**:**6** (69, 6:1)	>99:1
6	**1a**	CH_2Cl_2	D (1.5)	TMSOTf (2.7)[d]	**7** (61)	>99:1

[a] In all cases, the fragmentation step was performed under nitrogen at rt, using irradiation with two 80 W tungsten filament lamps for 1 h. Dry solvents (10 mL) containing (diacetoxyiodo)benzene (DIB) (1.2 mmol) and iodine (0.6 mmol per mmol of substrate) were used.

[b] A: allyltrimethylsilane; B: 1-phenyl(trimethylsilyloxy)ethylene; C: 1-(trimethylsilyl)-1*H*-benzotriazole; D: bis(trimethylsilyl)thymine.

[c] After the addition of the nucleophile, the reaction mixture was cooled to –40°C and the Lewis acid was added dropwise for 0.5 h. Then the temperature was allowed to rise to 0°C and the reaction mixture was stirred for 2 h.

[d] After the addition of the nucleophile, the reaction mixture was cooled to 0°C and the Lewis acid was added dropwise for 0.5 h. Then the temperature was allowed to rise to rt and the reaction mixture was stirred for 2 h.

[e] Yields are given for products purified by chromatography on silica gel.

[f] The diastereomeric ratio was determined by ^1H NMR experiments.

with 1% $NaHCO_3$, (methanol, rt, 1 h) affording the alcohol **3b** in 91% yield. The phenone derivative **4** was isolated exclusively as the *trans* isomer,[5] albeit in low yield (entry 4). Particularly interesting were products **5**–**7**, which are analogues of acyclic nucleosides. The benzotriazolyl derivatives were obtained as separable mixtures of the 1-*N*- and 2-*N*-isomers[6] **5** and **6**, respectively (entry 5), but in both cases only the *trans* diastereomers were formed. Since several cyclic benzotriazolyl nucleosides have shown promising antitumoral activity,[7] the study of their acyclic analogues is of interest. Analogously, many cyclic thymidine derivatives have shown potent antiviral activity[8] (such as AZT against HIV), and the synthesis of derivatives with modified sugar chains has been undertaken by several groups. The thymine nucleophile was formed following the Vorbrüggen protocol,[9] yielding also exclusively the *trans* diastereomer **7** (entry 6).

To compare the one-step with the two-step procedure, we studied the fragmentation of the carbohydrates **1a** and **1b** to give the acetoxy derivatives **8a**,**b** and **9a**,**b** (Scheme 2), and the subsequent transformation of these acetates in the C-1 substituted alditols. When **1a** was treated with DIB and iodine in dichloromethane at room temperature and under irradiation with visible light, the diastereomeric 1-acetoxy derivatives **8a** and **8b** were obtained in good yields (83%, **8a**:**8b**, 21:1). Similarly, the photolysis of **1b** afforded derivatives **9a** and **9b** in 81%, albeit with smaller stereoselectivity (**9a**:**9b**, 4:1). The photolysis of **1a** and **1b** in acetonitrile yielded smaller yields (60% for **8a**,**b** and 61% for **9a**,**b**, respectively).

The purified diastereomeric mixtures of the acetates **8a**,**b** or **9a**,**b** were then treated with the nucleophile and the Lewis acid under similar conditions to those reported for the one-step procedure, affording products **2**, **3a**, and **4**–**7** with excellent stereoselectivities. The overall yields for the two-step sequence (22% for **2** from **1a**, 51% for **3a** from **1b**, 79% for **4** from **1a**, 63% for **5**+**6** from **1a** and 76% for **7** from **1a**) are comparable to those obtained with the one-pot method. An exception is the phenone **4**, whose yield improved using the two-step procedure. However, in most cases the good yields and the operational simplicity of the one-step methodology make it preferable to the two-step sequence.

In summary, we have developed both a two-step and a one-step methodology to obtain, in satisfactory yields and with excellent stereoselectivities, a variety of acyclic nucleosides and other C-1 substituted alditols from easily available carbohydrates. Currently, all the nucleoside analogues described are undergoing biological evaluation as potential antibiotic, antiviral or anticancer agents. The results of these studies will be published in due course.

Acknowledgements

This work was supported by the Investigation Programmes Nos. PB96-1461 and PPQ2000-0728 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerio de Ciencia y Tecnología

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5. All compounds were fully characterized by ^1H and ^{13}C NMR, IR, MS, HRMS or elemental analysis. The stereochemistry was assigned by ^1H and 2D COSY–NOESY NMR. Selected spectroscopic data (^1H NMR, MS and HRMS or elemental analysis) for compounds **2**–**9** are given.
   Compound **2**: Inseparable diastereomeric mixture (>98:2); ^1H NMR (500 MHz, $CDCl_3$) δ major diastereomer 1.39 (3H, s), 1.42 (3H, s), 2.35 (1H, ddd, $J=14.4$, 7.1, 7.1 Hz), 2.44 (1H, ddd, $J=14.6$, 6.3, 6.3 Hz), 3.38 (3H, s), 3.62 (1H, dd, $J=11.0$, 5.8 Hz), 3.67 (1H, dd, $J=11.0$, 3.6 Hz), 3.91 (1H, dd, $J=7.0$, 6.3 Hz), 4.03 (1H, ddd, $J=7.4$, 7.3, 4.3 Hz), 5.13 (1H, dd, $J=18.5$, 1.4 Hz), 5.15 (1H, d, $J=10.3$ Hz), 5.19 (1H, ddd, $J=5.9$, 5.9, 3.6 Hz), 5.88 (1H, dddd, $J=17.2$, 10.3, 6.9, 6.8 Hz), 8.31 (1H, s); δ minor diastereomer 1.37 (3H, s), 1.50 (3H, s), 3.39 (3H, s), 4.43 (1H, dd, $J=12.3$, 6.4 Hz), 4.81 (1H, dd, $J=12.3$, 1.1 Hz), 5.38 (1H, dd, $J=7.2$, 1.1 Hz), 8.07 (1H, s). Some signals are not described due to overlapping with the major diastereomer signals; MS m/z (%) 229 (M^+-CH_3, 100); HRMS calcd for $C_{11}H_{17}O_5$ 229.1076, found 229.1042.

Compound **3a**: Inseparable diastereomeric mixture (> 98:2); ^{1}H NMR (500 MHz, $CDCl_3$) major diastereomer δ 1.43 (3H, s), 1.44 (3H, s), 2.39 (1H, ddd, J=14.7, 7.1, 7.1 Hz), 2.47 (1H, ddd, J=14.6, 6.1, 4.9 Hz), 3.97 (1H, dd, J=7.2, 7.1 Hz), 4.09 (1H, ddd, J=7.2, 7.2, 4.5 Hz), 4.46 (1H, dd, J=12.2, 7.0 Hz), 4.72 (1H, dd, J=12.2, 2.9 Hz), 5.15 (1H, dd, J=9.8, 1.4 Hz), 5.16 (1H, dd, J=18.8, 1.2 Hz), 5.44 (1H, ddd, J=6.6, 6.6, 2.8 Hz), 5.87 (1H, dddd, J=17.1, 10.3, 6.9, 6.9 Hz), 7.45 (2H, dd, J=7.9, 7.7 Hz), 7.58 (1H, dd, J=7.5, 7.4 Hz), 8.02 (2H, d, J=7.4 Hz), 8.13 (1H, s). The signals of the minor diastereomer are overlapped with other signals, and could not be properly described; MS m/z (%) 319 (M^+–CH_3, 43), 105 (100). Anal. calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.66; H, 6.79.

Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (6H, s, 2×CH_3), 3.26 (1H, dd, J=16.8, 4.0 Hz), 3.37 (3H, s), 3.39 (1H, dd, J=16.7, 7.5 Hz), 3.67 (1H, dd, J=11.0, 5.4 Hz), 3.71 (1H, dd, J=11.0, 3.4 Hz), 4.42 (1H, dd, J=7.4, 6.3 Hz), 4.64 (1H, ddd, J=7.6, 7.6, 4.0 Hz), 5.20 (1H, ddd, J=5.8, 5.8, 5.4 Hz), 7.47 (2H, dd, J=7.8, 7.7 Hz), 7.57 (1H, dd, J=7.4, 7.4 Hz), 7.93 (2H, d, J=7.3 Hz), 8.07 (1H, s); MS m/z (%) 307 (M^+–CH_3, 4), 105 (100). Anal. calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.35; H, 6.77.

Compound **5**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.53 (3H, s), 1.55 (3H, s), 2.91 (3H, s), 3.49 (1H, dd, J=11.0, 3.6 Hz), 3.64 (1H, dd, J=11.0, 2.9 Hz), 5.52 (1H, ddd, J=3.8, 3.8, 3.4 Hz), 5.70 (1H, dd, J=4.8, 4.8 Hz), 6.58 (1H, d, J=5.2 Hz), 7.42 (1H, dd, J=7.6, 7.6 Hz), 7.55 (1H, dd, J=7.2, 7.2 Hz), 7.70 (1H, d, J=8.6 Hz), 8.09 (1H, d, J=8.6 Hz), 8.15 (1H, s); MS m/z (%) 321 (M^+, <1), 103 (100). Anal. calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.12; H, 6.21; N, 12.85.

Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.65 (3H, s), 2.59 (3H, s), 3.15 (1H, dd, J=11.0, 4.5 Hz), 3.18 (1H, dd, J=11.0, 3.6 Hz), 5.45 (1H, ddd, J=4.3, 4.3, 3.9 Hz), 5.63 (1H, dd, J=4.8, 4.2 Hz), 6.90 (1H, d, J=5.3 Hz), 6.90–7.00 (2H, m), 7.48 (1H, s), 7.70–7.80 (2H, m); MS m/z (%) 321 (M^+, 6), 99 (100). Anal. calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.09; H, 6.18; N, 12.90.

Compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (3H, s), 1.57 (3H, s), 1.94 (3H, s), 3.33 (3H, s), 3.61 (1H, dd, J=10.6, 3.5 Hz), 3.63 (1H, dd, J=11.2, 4.6 Hz), 4.24 (1H, dd, J=6.6, 6.1 Hz), 5.32 (1H, ddd, J=7.4, 4.0, 4.0 Hz), 6.24 (1H, d, J=6.2 Hz), 7.13 (1H, s), 8.09 (1H, s), 9.44 (1H, br s); MS m/z (%) 313 (M^+–CH_3, 20), 99 (100). Anal. calcd for $C_{14}H_{20}N_2O_7$: C, 51.22; H, 6.14; N, 8.53. Found: C, 51.09; H, 5.98; N, 8.30.

Compound **8a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (3H, s), 1.47 (3H, s), 2.07 (3H, s), 3.34 (3H, s), 3.59 (2H, dd, J=4.2 Hz), 4.38 (1H, dd, J=5.8, 2.3 Hz), 5.15 (1H, ddd, J=4.4, 4.4, 4.4 Hz), 6.25 (1H, d, J=2.3 Hz), 8.09 (1H, s); MS m/z (%) 247 (M^+–CH_3, 100). Anal. calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.28; H, 7.02.

Compound **8b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (3H, s), 1.52 (3H, s), 2.05 (3H, s), 3.40 (1H, dd, J=9.3, 3.5 Hz), 3.41 (3H, s), 3.66 (1H, dd, J=11.3, 4.9 Hz), 3.72 (1H, dd, J=11.2, 2.1 Hz), 5.39 (1H, ddd, J=9.3, 4.9, 2.1 Hz), 6.31 (1H, d, J=3.5 Hz), 8.01 (1H, s); MS m/z (%) 247 (M^+–CH_3, 73), 145 (100). Anal. calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.30; H, 7.01.

Compound **9a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.508 (3H, s), 1.514 (3H, s), 2.04 (3H, s), 4.44 (1H, dd, J=6.4, 2.2 Hz), 4.49 (1H, dd, J=12.3, 5.8 Hz), 4.67 (1H, dd, J=12.3, 3.1 Hz), 5.43 (1H, ddd, J=6.0, 6.0, 3.1 Hz), 6.32 (1H, d, J=2.2 Hz), 7.46 (2H, dd, J=7.8, 7.7 Hz), 7.58 (1H, dd, J=7.5, 7.4 Hz), 8.02 (2H, d, J=7.3 Hz), 8.13 (1H, s); MS m/z (%) 337 (M^+–CH_3, 41), 105 (100). Anal. calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 57.79; H, 5.95.

Compound **9b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (3H, s), 1.54 (3H, s), 2.09 (3H, s), 4.42 (1H, dd, J=9.0, 3.5 Hz), 4.46 (1H, dd, J=12.3, 6.3 Hz), 4.82 (1H, dd, J=12.3, 2.4 Hz), 5.65 (1H, ddd, J=8.7, 6.3, 2.2 Hz), 6.38 (1H, d, J=3.5 Hz), 7.46 (2H, dd, J=7.9, 7.7 Hz), 7.58 (1H, dd, J=7.5, 7.4 Hz), 8.02 (1H, s), 8.03 (2H, d, J=7.2 Hz); MS m/z (%) 337 (M^+–CH_3, 30), 105 (100). Anal. calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 58.06; H, 6.00.

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