New fluorinated nucleoside analogues with 2-butenolide rings prepared by nucleophilic vinylic fluorine displacement in 4,4-dialkyl-2,3-difluorobut-2-en-4-olides

Oldřich Paleta,*[a] Zdeněk Duda[a] and Antonín Holý[b]

[a] *Department of Organic Chemistry, Institute of Chemical Technology, 16628 Prague, Czech Republic. Fax: +4202 2431 1082; e-mail: paletao@vscht.cz*

[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 16610 Prague, Czech Republic*

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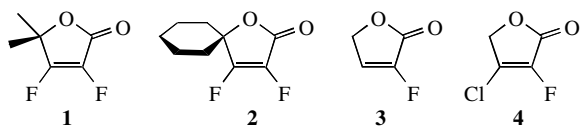
Sodium salts of adenine, 2,6-diaminopurine, cytosine, 4-methoxypyrimidin-2-one and aliphatic or alicyclic amines reacted with 4,4-dialkyl-2,3-difluorobut-2-en-4-olides by vinylic substitution of fluorine to give 3-substituted butenolides as nucleoside analogues or enamines, while sodium and lithium salts of aliphatic and aromatic amines reacted as hard nucleophiles to attack the carbonyl group thus causing butenolide ring opening.

A number of bioactive natural compounds contain butenolide rings.[1] Some of them display HIV-enzyme inhibiting,[2] anti-cancer,[3,4] anti-tumour[5] and cytostatic[6] properties. On the other hand, fluoro substituents are known as strong modifiers of bioactivity.[7–9] On this basis, it can be assumed that a combination of a fluorinated butenolide ring with a pharmacophore moiety, *e.g.*, a nucleoside base, can create biological activity. Nucleoside analogues possessing a butenolide ring instead of a sugar part in the molecule have not been reported in the literature. As a general strategy for the synthesis of these compounds with potential bioactivity, we decided on a study of the modification of 4,4-dialkyl-2,3-difluorobut-2-en-4-olides **1** and **2** by vinylic displacement of fluorine with nitrogen nucleophiles. The reasons for this methodology have been accessible butenolides **1**[10,11] and **2**[†] and our recent observations[11–14] in the chemistry of fluorinated butenolides.

It has been observed[11–14] that the reactivity of fluorinated but-2-en-4-olides possessing fluorine atoms attached to the double bond, as in compounds **1**, **2**, **3**[14] and **4**[13] (Scheme 1), is strongly dependent on their structure and character of a reagent: *e.g.*, **1** and **2** reacted with various oxy anions by vinylic fluorine displacement,[11,12] while the same reagents caused ring opening in fluorobutenolide[13] **3** or only tars formation in the reaction with chlorofluorobutenolide[14] **4**.

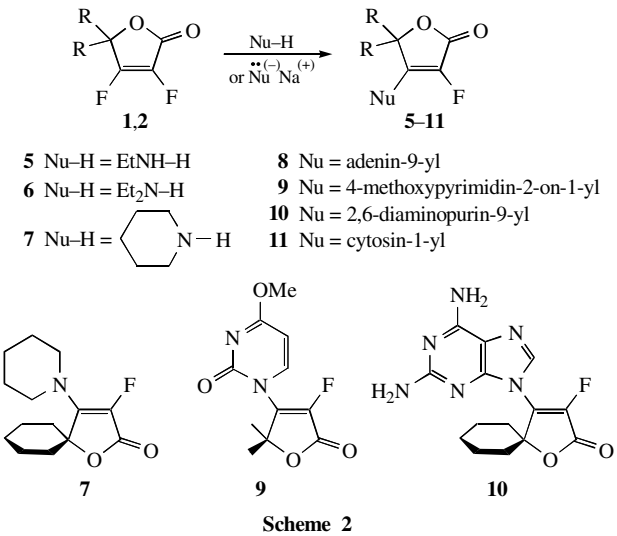


Scheme 1

Different results have also been obtained in reactions of halobutenolides (including 2,3-dichlorobutenolide[15]) with nitrogen nucleophiles[13,14] and hard or soft organometals.[11–13] The literature data suggest that the following three types of reactions of nitrogen nucleophiles with butenolides **1** and **2** can be expected: displacement of β-fluorine, nucleophilic addition to the double bond and ring opening by a carbonyl group attack.

The N-nucleophiles employed in this study included aliphatic or aromatic amines, alkali salts of the amines and sodium salts of nucleoside bases as delocalised soft N-nucleophiles. Generally, the nucleophiles reacted in two different ways, *i.e.*, with displacement of β-fluorine or with a carbonyl group attack followed by butenolide ring opening.

Aliphatic amines[‡] and sodium salts of nucleoside bases[§] reacted with butenolides **1** and **2** by the displacement of vinylic fluorine (Scheme 2) with the formation of enamine-type products possessing neighbouring vinylic fluorine (**5**–**11**). It can be presumed that in the reaction mechanism 1,4-addition intermediates are formed primarily[11,12] from which a β-fluorine atom is expelled. The reactions with sodium salts of nucleoside bases were carried out at lower temperatures than those reported for non-fluorinated species[16] and were completely regioselective to



Scheme 2

Table 1 Reactions of butenolides **1** and **2** with N-nucleophiles.

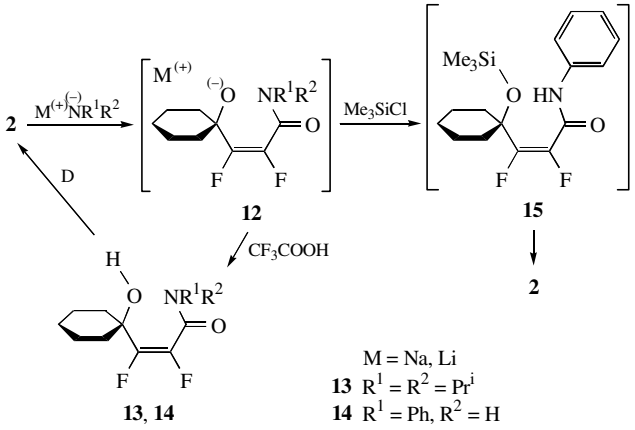
Starting compound	Nucleophile	Product	Yield[a] (%)	^{19}F NMR[b]
2	$EtNH_2$	**5**	80	–182.1
1	Et_2NH	**6**	69	–186.8
2	Piperidine	**7**	70	–177.7
1	$Nu^{(-)}Na^{(+)}$ Nu = adenin-9-yl	**8**	32	–145.7
1	$Nu^{(-)}Na^{(+)}$ Nu = 4-methoxypyrimidin-2-on-1-yl	**9**	60	–142.6
2	$Nu^{(-)}Na^{(+)}$ Nu = 2,6-diaminopurin-9-yl	**10**	51	–145.3
2	$Nu^{(-)}Na^{(+)}$ Nu = cytosin-1-yl	**11**	81	–144.85
2	$(Pr^i)_2NLi$	**13**	59	–135.1 (s) –144.9 (s)
2	PhEtNNa	**14**	(100)[c]	–127.8 (s) –143.6 (s)
2	PhNHLi, Me_3SiCl	**15**	43[d]	–114.1 (s) –152.2 (s)

[a]Isolated yields. [b]Shifts δ in ppm downfield from $CFCl_3$. [c]Complete conversion, then reverse reaction to form **2**. [d]Calculated from NMR spectra.

[†] New spirocyclic butenolide **2** [2,3-difluoro-4,4-(pentane-1,5-diyl)but-2-en-4-olide] was prepared analogously[10] to compound **1**. Cyclohexanol was added to methyl 2,3,3-trifluoroacrylate under photochemical or radical (dibenzoyl peroxide) initiation; the intermediate adduct [$R_2C(OH)CF_2CHFCOOMe$] cyclised spontaneously to butanolide during distillation (50–65% yield). The conversion of the intermediate butanolide to target butenolide **2** was performed by a novel procedure using triethylamine as a dehydrofluorinating agent (acetonitrile, room temperature, 10 h), 65–75% yield, bp 102–103 °C (8 mmHg). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.9 (s, CH_2), 24.6 (s, CH_2), 33.4 (s, CH_2), 80.5 (s, C), 127.1 (d, CF, $^1J_{CF}$ 288 Hz), 160.0 (d, CF, $^1J_{CF}$ 299 Hz), 162.9 (s, C=O). ^{19}F NMR (75.4 MHz, $CDCl_3$) δ: –166.4 (s, 1F), –127.4 (s, 1F). Found (%): C, 57.11; H, 5.55. Calc. for $C_9H_{10}F_2O_2$ (%): C, 57.45; H, 5.36.

nucleoside bases. Examples of new enamino compounds and nucleoside analogues (**7**, **9**, **10**) are shown in Scheme 2. The ^{19}F NMR spectra of new compounds **5–11** show singlet signals with a characteristic shift for each compound class (enamine or nucleoside analogue, Table 1). Aniline and *N*-ethylaniline, as well as free nucleoside bases, were completely unreactive even on heating to 80 °C. We observed no difference in the reactivity of butenolides **1** and **2** from the kinetic point of view during preparative reactions. This observation is in a sharp contrast to the reactions of butenolides with thiophenol or soft carbanions where butenolide **2** appeared to be completely unreactive.[17]

Sodium and lithium salts of aliphatic or aromatic amines reacted with butenolides **1** and **2**, contrary to reactions of alkoxides,[11,12] at the hard electrophilic centre of the carbonyl group with ring opening (Scheme 3).¶ This observation is also in contrast with the reactions[15] of dichloro- or dibromobutenolides where vinylic displacement was observed. Hydroxyamides **13** and **14**, obtained by quenching the mixture with trifluoroacetic acid, were unstable, and they were rapidly converted to starting butenolide **2** on distillation or slowly converted on storage (the process could be monitored by ^{19}F NMR spectra); hydroxyamide **13** was more stable. To confirm the formation of intermediate **12**, we trapped it as trimethylsilyl derivative **15** by silylation at –70 °C.



Scheme 3

‡ *Typical procedure for preparation of enamines* **5–7**. In an inert atmosphere, an amine (2.5 mmol) solution in dry and purified tetrahydrofuran (THF, 4 ml) was cooled at –20 to –30 °C and a solution of butenolide (1.2 mmol) in THF (5 ml) was added dropwise during 10–15 min. The mixture was stirred at –10 °C for 6 h and then allowed to warm to room temperature; next, volatile components were evaporated. The residue was purified by column chromatography (silica gel, dichloromethane); the product was recrystallised (chloroform–light petroleum).

§ *Typical procedure for preparation of nucleoside analogues* **8–11**. In an inert atmosphere, a mixture of sodium hydride (60% suspension in mineral oil, 1.9 mmol), dry dimethyl formamide (DMF, 10 ml) and a nucleoside base (1.6 mmol) was intensely stirred at room temperature (or elevated temperatures) for 1 h and then cooled at –20 to –40 °C. A butenolide (1.1 mmol) solution in DMF (5 ml) was added dropwise to the nucleoside base solution for 10–15 min, the solution was stirred at –20 to –40 °C for 1–2 h and then allowed to warm to room temperature. Volatile components of the reaction mixture were evaporated in a vacuum, and the solid residue was purified by column chromatography (silica gel), the product was once or twice recrystallised (methanol–light petroleum).

¶ *Typical reactions of butenolides with the alkali salts of amides*. In an inert atmosphere, an amine (1.25 mmol) solution in dry and purified THF (2 ml) was cooled to *ca*. –70 °C and a butyllithium (1.3 mmol, 2.47 M solution) was added dropwise with intense stirring for 30 min. A solution of butenolide (1.1 mmol) in THF (2 ml) was added dropwise (10–15 min) to the cooled solution at *ca*. –60 °C, the mixture was stirred for 1 h and then warmed to room temperature for 2 h. The ^{19}F NMR spectrum was measured (100% conversion of butenolide). Then, trifluoroacetic acid was added (equivalent to butyllithium), the mixture was neutralised with Na_2CO_3, volatile components were evaporated, and the residue was chromatographed (silica gel, dichloromethane) to obtain a mixture of the product and the starting butenolide.

The ^{19}F NMR spectra of **15** and hydroxyamides **13** and **14** show two singlets (Table 1); the absence of mutual fluorine coupling as in starting butenolide **2** confirms (*Z*)-configuration for the propenamide structure.

The structures of all the compounds synthesised were elucidated on the basis of ^{1}H, ^{13}C and ^{19}F NMR spectra, the formulae of isolated products **5–11** were confirmed by microanalysis for carbon and hydrogen.

The reported reactions of N-nucleophiles have extended the use of 2-fluoro-3-halogenobut-2-en-4-olides as new fluorinated synthons with a special interest in the preparation of a new type of nucleoside analogues.

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