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Catalytic Ferrier Rearrangement of Unsaturated Nucleosides

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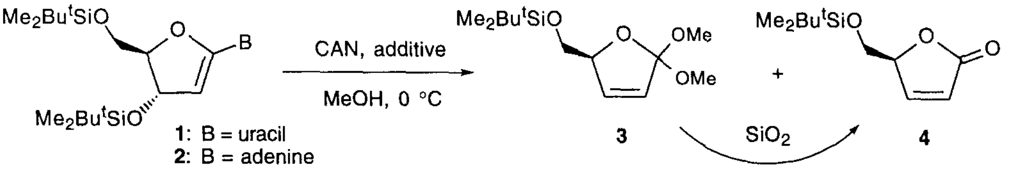
Abstract: The attempted intermolecular addition of malonyl radicals to 1′,2′-unsaturated nucleosides has led to the unexpected formation of furanones. Thus, only catalytic amounts of ceric(IV) ammonium nitrate (CAN), induce a Ferrier rearrangement. The unsaturated lactone was isolated in good yield and can serve as a precursor for the synthesis of optically active products.

Keywords: Nucleosides; Radical Reactions; Rearrangements

During the past decade ceric(IV) ammonium nitrate (CAN) has become increasingly attractive for the oxidative generation of radicals from CH-acidic precursors under mild conditions [1]. Very recently, we revealed the first application of this methodology in carbohydrate chemistry, which allowed the convenient synthesis of carbohydrate 2-*C*-analogs from easily available glycals [2]. To further extend the scope of such reactions, we became interested in the analogous addition of dialkyl malonates to 1′,2′-didehydro-2′-deoxy-nucleosides **1** [3] and **2** [4], since this strategy would provide an easy entry to 2′-*C*-branched nucleosides.



However, the attempted addition of dialkyl malonates to the compounds **1** and **2** failed, since a fast Ferrier rearrangement [5] to the ortho ester **3** competes with the C-C-bond formation (Table 1, entries 1 and 2). Under the acidic reaction conditions and after silica gel chromatography, the unstable ortho ester **3** is cleaved to the lactone **4**, which serves as an important building block in the synthesis of optically active products [6]. Furthermore, only catalytic amounts of CAN are sufficient to induce the Ferrier rearrangement of nucleoside **1** at 0 °C (entry 3) [7]. This result is remarkable, since related reactions of glycals require one equiv of Lewis acid and higher temperatures [5,8]. On the other hand, the transformation of nucleoside **2** proceeds less efficiently (entry 4). This can be rationalized by the basic amino group of adenine, which functions as a buffer. Thus, 1.4 equiv of CAN are necessary to obtain full conversion (entry 5).

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Table 1. Ferrier rearrangement of the unsaturated nucleosides **1** and **2**.

entry	nucleoside	CAN, equiv	additive (equiv)	time, min	conv., %	**3** : **4** [a]	**4** (%)[b]
1	**1**	3.00	$CH_2(CO_2Me)_2$ (10)	40	> 95	20 : 80	73
2	**2**	3.00	$CH_2(CO_2{}^iPr)_2$ (10)	20	> 95	30 : 70	c
3	**1**	0.02	-	30	> 95	70 : 30	76
4	**2**	0.20	-	60	10	50 : 50	c
5	**2**	1.40	-	40	> 95	60 : 40	70
6	**1**	1.00	$NaHCO_3$ (2)	60	< 10	-	c

[a] Product ratios determined by ^1H NMR analysis of the crude product (200 MHz). [b] Isolated product after silica gel column chromatography. [c] Product not isolated.

Indeed, in a control experiment with nucleoside **1**, the Ferrier rearrangement was inhibited completely by addition of $NaHCO_3$ (entry 6). Finally, other Lewis acids (Ce_2SO_4, $ZnCl_2$) were investigated under the same reaction conditions, but afford lower yields of lactone **4**. In conclusion, ceric(IV) ammonium nitrate (CAN), which was used for the first time to induce Ferrier rearrangements, has proven to be the reagent of choice for the synthesis of the useful lactone **4**, which serves as an important building block in the synthesis of optically active products [6].

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[7] A solution of 0.50 mmol of the 1′,2′-didehydro-2′-deoxynucleoside **1** in 10 ml of methanol was cooled under argon to 0 °C. 0.01 mmol CAN were added at this temperature and the mixture was stirred for 30 min. The reaction was quenched with 50 ml of an ice cold diluted sodium thiosulphate solution, extracted with 4 x 30 ml of dichloromethane, dried (Na_2SO_4), and the solvent was evaporated. The lactone **4** (76 %) was isolated by silica gel column chromatography (hexane / ethyl acetate 9:1) ($R_f = 0.27$) as a white solid, mp 30-31 °C $[a]^{20}_{D} = -138.4$ (c = 1.20, $CHCl_3$) [ref. [6] mp 32 °C $[a]^{20}_{D} = -136.2$ (c = 1.13, $CHCl_3$)].

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