A General Method for the Highly Regioselective Introduction of Substituents into the 3-Position of 5-Unsubstituted 4-*O*-Alkyl Tetronates

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Dedicated to Prof. Dr. Klaus Görlitzer on the occasion of his 65th birthday.

Abstract: A new, general method for the highly regioselective introduction of substituents into the 3-position of 5-unsubstituted 4-*O*-alkyl tetronates has been developed. 3-Lithiated 4-alkoxy-2-triisopropylsilyloxyfurans generated from the corresponding 3-iodoprecursors via halogen-metal exchange serve as key intermediates.

Key words: tetronates, iodination, lithiation, regioselectivity, furans

5-Unsubstituted 4-O-alkyl tetronates (4-alkoxy-5H-furan-2-ones) 1 bearing an alkyl or acyl group at C-3 serve as versatile building blocks in natural product synthesis as well as for the construction of complex heterocyclic scaffolds in general.¹ Probably, the most direct approach to compounds 1 is the regioselective alkylation or acylation of an appropriate 5-unsubstituted 4-O-alkyl tetronate building block (Scheme 1).² To date, however, little work has been directed toward this goal. Ley et al. reported the direct palladium-catalyzed acylation of 3-tributylstannyl 4-O-methyl tetronate (3) with a variety of acid chlorides to afford the corresponding 3-acyl tetronates in reasonable to good yields.³ Preliminary attempts, conducted in the same laboratory, to regioselectively acylate the 3-lithiated dianion 2 failed and were not pursued further.^{4–6} More recently, we have introduced the chelation-controlled C-3 selective hydroxyalkylation of boron 4-methoxy-2-furanolates 4 with aldehydes leading to 3-acyl tetronates after oxidation of the intermediate alcohols.⁷ This method, however, although highly regioselective and good yielding, is essentially restricted to aliphatic aldehydes and thus limited in scope.

We now report a new, general and highly efficient method for the regioselective introduction of a wide variety of substituents into the C-3 position of 5-unsubstituted 4-*O*alkyl tetronates involving 3-lithiated 2-triisopropylsilyloxyfurans **5** as key intermediates. These intermediates were envisioned to arise from 4-alkoxy-3-iodo-2-triisopropylsilyloxyfurans **8** via a halogen-metal exchange. Indeed, treatment of compound **8a** with either 1.1 equivalents of *n*-BuLi or 2.0 equivalents of *t*-BuLi in THF at -78 °C for 15 minutes and subsequent quenching with

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Scheme 1

deuterated methanol followed by phosphate buffer pH 5.5 led to C-3 mono-deuterated tetronate (²H)-**6a** in high yields containing >95% deuterium (Scheme 2).⁸ Neither deuterium incorporation at C-5 of (²H)-**6a** nor formation of C-5 deuterated 3-iodo tetronate **7a**, indicating a competing deprotonation of **8a** at C-5,⁹ was observed.

As depicted in Scheme 2, the 3-iodo-substituted precursors **8a** and **8b** could be obtained in two steps from the readily available 4-*O*-alkyl tetronates **6a**¹⁰ and **6b**,¹¹ respectively. First, C-3-selective iodination of the tetronates **6** has to be achieved. To the best of our knowledge, to date there is only one report in the literature concerning the iodination of 4-*O*-alkyl tetronates: Campos et al. described



Scheme 2 *Reagents and conditions*: (a) I_2 (4.0 equiv), pyridine (1.0 equiv), DMF, r.t. (**7a**: 86%; **7b**: 80%); (b) TIPSOTf, Et₃N, CH₂Cl₂, 0 °C (**8a**: 95%; **8b**: 91%); (c) *n*-BuLi (1.1 equiv) or *t*-BuLi (2.0 equiv), THF, -78 °C; (d) i) CD₃OD, -78 °C; ii) phosphate buffer pH 5.5 (quant.; >95% ²H).

the reaction of compound **6a** with bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) in the presence of two equivalents of triflic acid to give iodide **7a** in a 54% yield.¹² We found that simple treatment of 4-*O*-alkyl tetronates with excess iodine (4.0 equiv) and 1.0 equivalents of pyridine in DMF at room temperature is a much cheaper and even more efficient alternative. In this way 3iodo tetronates **7a** and **7b** were obtained in 86% and 80% yield, respectively, from the corresponding 3-unsubstituted tetronates **6**.¹³ Somewhat lower yields were observed in the absence of pyridine. The 3-iodo-substituted 2-triisopropylsilyloxyfurans **8a** and **8b** were then generated in high yields (95% and 91%, respectively) by treatment of the corresponding tetronates **7** with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) in the presence of triethylamine (CH₂Cl₂, 0 °C).¹⁴

Starting from the 3-iodofurans **8a** and **8b**, a number of 3-substituted tetronates **1** were prepared. The lithiated intermediates **5** were generated as described above and then reacted with a variety of carbon-, sulfur- and silicon-centered electrophiles $(1.1-2.0 \text{ equiv}, -78 \degree \text{C} \text{ to r.t.}).^{15}$ The results are summarized in Table 1. In the case of

	5 t-BuLi (2.0 THF, –78	equiv), s °C RO	1. E⁺, −78 °C to r.t. 2. buffer pH 5.5			
8a: R = Me 8b: R = Bn		5a: R = Me 5b: R = Bn		1a–I		
Entry	Iodide	Electrophile	Product	R	Е	Yield (%) ^a
1	8a	MeI (2.0 equiv)	1a ¹⁷	Me	Me	92
2	8b	MeI (2.0 equiv)	1b	Bn	Me	91
3	8b	$n-C_{12}H_{25}I$ (2.0 equiv)	1c	Bn	<i>n</i> -C ₁₂ H ₂₅	82
4	8a	CH ₂ =CHCH ₂ Br (2.0 equiv)	1d	Me	CH ₂ =CHCH ₂	85
5	8a	BnBr (2.0 equiv)	1e ¹⁷	Me	Bn	88
6	8b	$\overset{\circ}{\frown}$	1f	Bn	ОН	57
7	8a	$H_{21}C_{10}$ (2.0 equiv) $H_{12}C_{10}$	1g ⁷	Me	$H_{21}C_{10}$	84
8 ^b	8b	(1.1 equiv) $H_{23}C_{11}$ H	1h	Bn	ОН Н ₂₃ С ₁₁ <u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u></u>	70
9°	8a	(1.1 equiv)	11 ^{3,7}	Me	Ph	62
10 ^c	8a	BnO CN (1.25 equiv)	1j	Me	BnO	44
11	8a		1k	Me	PhS	70
12 ^b	8a	TMSCl (1.25 equiv)	11	Me	TMS	91

Table 1 Reaction of 3-Lithiated 4-Alkoxy-2-Triisopropylsilyloxyfuranes 5 with Various Electrophiles

^a Yield of isolated, purified product base on 8.

^b *n*-BuLi (1.1. equiv) was used for halogen-metal exchange.

^c Reactions were run at –78 °C.

primary alkyl iodides, allyl bromide and benzyl bromide high yields of the corresponding 3-alkylation products were obtained (entries 1-5). Even with an epoxide the result was satisfactory (entry 6). Reactions with both aliphatic and aromatic aldehydes proceeded smoothly to afford the corresponding 3-hydroxyalkylation products in good yields (entries 7, 8). This is particularly remarkable, since product 1g had hardly been accessible with our previously reported boron furanolate-based 3-hydroxyalkylation method.⁷ 3-(1-Hydroxyalkyl) tetronates, e.g. 1g, are known to be readily oxidized with various reagents such as IBX⁷ or MnO₂¹⁶ to give the corresponding 3-acyl tetronates. However, 3-acyl tetronates are also directly accessible from intermediates 5 by reaction with acid chlorides at -78 °C (entry 9). Analogously, the benzyloxycarbonyl derivative 1j was obtained by reaction with benzyl cyanoformate albeit in only a moderate yield (entry 10). Finally, intermediate 5a was trapped with heteroatom-centered electrophiles. In this way the 3-phenylthio derivative 1k was prepared by reaction with Nphenylthiophthalimide (entry 11), while the 3-silylated tetronate 11 could be readily obtained by treatment with trimethylsilyl chloride (entry 12).

In conclusion, we have developed a new, general and efficient method for the regioselective introduction of a wide variety of substituents into the 3-position of 5-un-substituted 4-*O*-alkyl tetronates.

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- (13) Typical Procedure.
- A solution of iodine (10.15 g, 40 mmol) in DMF (20 mL) was added to an ice-cold solution of **6a** (1.14 g, 10 mmol) and pyridine (807 μ L, 10 mmol) in DMF (20 mL). The mixture was allowed to warm to r.t. and stirred under the exclusion of light for 22 h, at which time it was poured into sat. aq NaHCO₃ (100 mL). The mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with aq Na₂S₂O₃ and H₂O, dried (MgSO₄) and evaporated under reduced pressure. The resulting residue was recrystallized from EtOAc to give **7a** (2.06 g, 86%) as pale yellow crystals; mp 158–160 °C. IR (KBr): 3001, 2950, 1732, 1643, 1621 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 4.14 (s, 3 H), 4.81 (s, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 50.5, 58.4, 68.4, 170.7, 178.5. Anal. Calcd for C₃H₃IO₃: C, 25.02; H, 2.10; I, 52.88. Found: C, 25.01; H, 2.05; I, 52.84.
- (14) Typical Procedure.

TIPSOTf (867 µL, 3.15 mmol) was slowly added to an icecold solution of **7a** (720 mg, 3.0 mmol) and Et₃N (481 µL, 3.45 mmol) in CH₂Cl₂ (3 mL). After stirring for 1 h at 0 °C the mixture was poured into ice-cold half-sat. aq NaHCO₃ and extracted with Et₂O. The combined organic extracts were washed with ice-cold half-sat. aq NaHCO₃ and brine, dried (MgSO₄) and evaporated under reduced pressure to afford a mixture of **7a** and **8a**. To separate the product from starting material the residue was dissolved in *n*-hexane, filtered and evaporated under reduced pressure to leave **8a** (1.13 g, 95%, \geq 97% pure as determined by ¹H NMR spectroscopy) as a pale yellow oil. ¹H NMR (500 MHz, CD₂Cl₂): δ = 1.09 (d, *J* = 7.3 Hz, 18 H), 1.27 (sept, *J* = 7.3 Hz, 3 H), 3.68 (s, 3 H), 6.56 (s, 1 H).

(15) Typical Procedure.

A solution of *t*-BuLi (1.5 M in hexane, 666 μ L, 1.0 mmol) was added dropwise to a solution of **8a** (198 mg, 0.5 mmol) in THF (5 mL) at -78 °C. After stirring for 15 min at -78 °C, benzyl bromide (121 μ L, 1.0 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h and then was allowed to warm to r.t. during 2 h. Phosphate buffer (pH 5.5, 5 mL) was added and the resulting mixture was stirred for another

30 min at r.t. before it was extracted with Et₂O. The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (*n*-hexane–CH₂Cl₂–Et₂O, 20:20:60) to give **1e**¹⁷ (90 mg, 88%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 3.60 (s, 2 H), 3.93 (s, 3 H), 4.69 (s, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 27.8, 57.7, 65.4, 102.7, 126.4, 128.3, 128.5, 139.1, 173.0, 174.6.

HRMS: m/z calcd for $C_{12}H_{12}O_3$ [M⁺]: 204.0787. Found: 204.0774.

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