AN IMPROVED SYNTHESIS OF 5-ALKYL-2,3-DIHYDRO-FURAN-2,3-DIONES[1]

C. Oliver Kappe,[*a] Gert Kollenz,[a] and Curt Wentrup[b]

[a]Institute of Organic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria, and [b]Department of Chemistry, The University of Queensland, Brisbane, Qld 4072, Australia

Abstract- The synthesis of 5-*tert*-butyl-2,3-dihydrofuran-2,3-dione (**2a**) from ethenyloxysilane (**3**) and oxalyl chloride is reinvestigated. Apart from **2a**, two other reaction products, namely furan-3-yl oxalate (**6**) and difuran-3-yl oxalate (**7**) are isolated, explaining the low yield of **2a** in this process. An improved method for the preparation of **2a**, and its 5-methyl analog (**2b**) by cyclization of acylpyruvic acids (**8a,b**) is described.

2,3-Dihydrofuran-2,3-diones (**1**) are useful precursors for the generation of α-oxoketenes (acyl-ketenes). Under flash vacuum pyrolysis or matrix photolysis conditions these diones readily extrude carbon monoxide in an efficient cheletropic fragmentation to form reactive α-oxoketenes,[2] which are of considerable current interest.[3] In connection with these studies it was necessary to have access to 5-alkyl-2,3-dihydrofuran-2,3-diones as a reliable source of simple acylketenes.

A number of different methods to synthesize furan-2,3-diones is known in the literature: 4-acyl-substituted furandiones are versatile intermediates and can be readily prepared by direct cyclocondensation of 1,3-dicarbonyl compounds with oxalyl chloride.[4-7] However, this approach is not applicable for simple ketones (e.g. acetophenones), which in most cases do not react with oxalyl chloride at all, or give only very low yields of furandiones.[8] Alternatively, in a more general approach, substituted furandiones can be prepared by cyclocondensation of alkenyloxysilanes with oxalyl chloride (method A),[9] or by de-
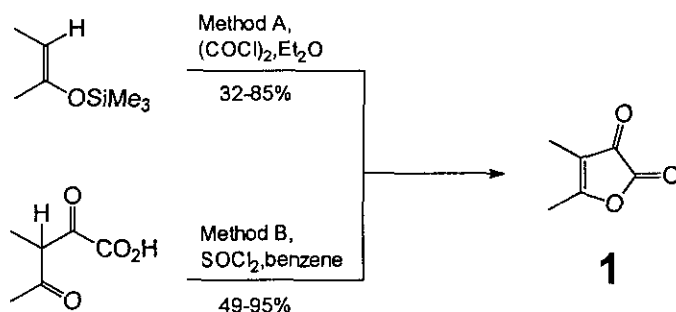
Scheme 1

hydratization of 2,4-dioxoalkanoic acids with thionyl chloride (method B).[10] Both of these methods give

satisfactory yields for 5-arylfurandiones, but are not particularly useful for the preparation of the desired 5-

alkyl derivatives. The only 5-alkyl substituted furan-2,3-dione described in the literature, 5-*tert*-butyl-2,3-

dihydrofuran-2,3-dione (**2a**), was prepared in unsatisfactory yield (see below) from ethenyloxysilane (**3**)

and oxalyl chloride *via* method A.[9] In this paper we describe an improved and experimentally simple

procedure for the cyclodehydratization of 2,4-dioxoalkanoic acids, that allows the clean preparation of

5–alkylfuran-2,3-diones.

First we reinvestigated the synthesis of furandione (**2a**) as described by Sonoda *et al.*[9] from silyl ether (**3**)

and oxalyl chloride. Following their procedure using 0.5 equivalents of oxalyl chloride and allowing the

mixture to react for 5 hours in dry ether we were able to isolate **2a** in 24% yield. This result is

comparable with the published yield of 32%,[9] although it should be noted that this amounts to only 12%

yield (or 16%) of **2a** based on silyl ether (**3**). The rather low yield strongly suggested that a number of by-

products are formed in this reaction. Importantly, with longer reaction times, the initially yellow color of

the reaction mixture, which is a strong indicator of the presence of furandiones in general,[4-11] disappeared.

By treatment of silyl ether (**3**) with one equivalent of oxalyl chloride for 20 hours we were able to isolate

two other reaction products, namely the oxalic acid ester (**6**) and the bis-ester (**7**) in a combined yield of

46%. The initial generation of dione (**2a**) and subsequent formation of furanones (**6**) and (**7**) is rationalized

in Scheme 2. Initial acylation of silyl ether (**3**) with oxalyl chloride at C-2[12] furnishes a γ-keto acid

chloride, which preferably should exist in its isomeric enolic cyclized form (**4**).[13] Subsequent elimination

of HCl from **4** leads to the desired furandione (**2a**). However, additional *O*-acylation of the intermediate

enol (**4**) with excess oxalyl chloride can lead to acid chloride (**5**) (isolated as the corresponding acid (**6**)
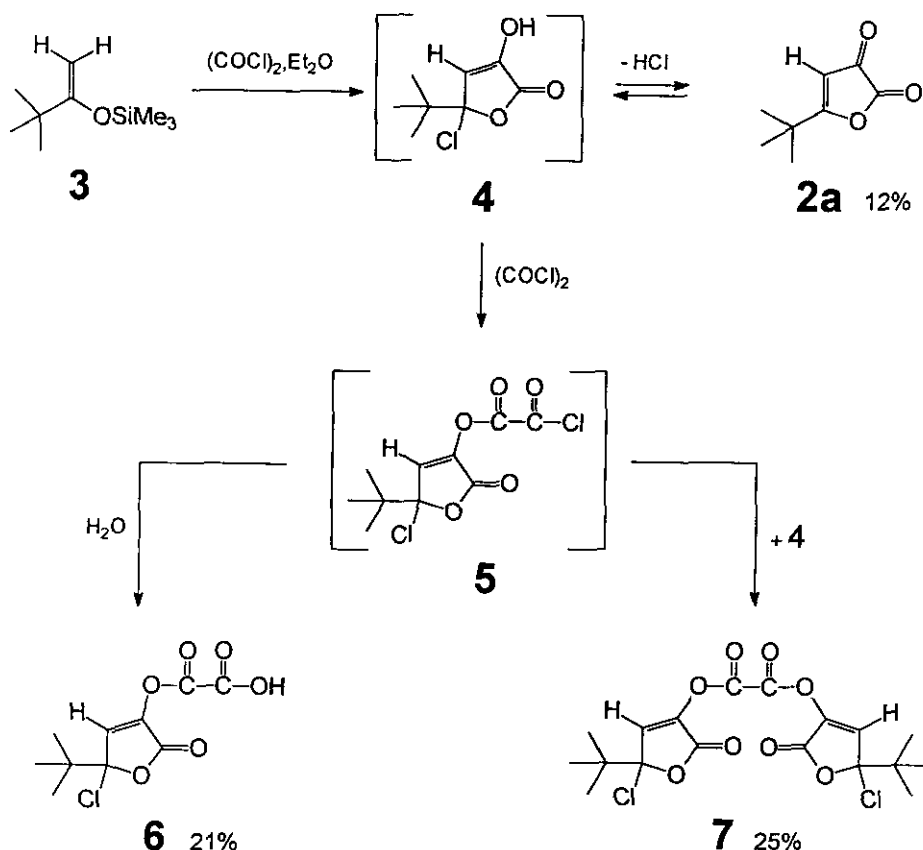
Scheme 2

upon work up), which on subsequent reaction with enol (4) may form the bis-furanyloxalic ester (7). The initial formation and subsequent consumption of the yellow furandione (2a) from silyl ether (3) and oxalyl chloride suggests that the elimination of HCl from 4 is reversible. The close structural analogy of 6 and 7 was easily deduced from spectroscopic data, in particular their ^{13}C nmr spectra, and by comparison with the data for closely related compounds.[5] It should be pointed out that the reaction pathway discussed above is similar to the reaction of dipivaloylmethane with oxalyl chloride which we have recently investigated.[5]

In view of the complex reaction sequence described above, we concluded that this approach to 5-alkyl-furandiones, following method A, is too cumbersome to warrant further studies, and therefore focused our

attention on alternative procedures related to method B (cf. Scheme 1). Although any attempts to cyclize pivaloylpyruvic acid (8a) with thionyl chloride, following the general method reported by Andreichikov et al.[10] proved to be unsuccessful, we were able to synthesize the desired 5-tert-butylfurandione (2a) by using phosphorus pentoxide instead of thionyl chloride as cyclization agent. Careful addition of phosphorus pentoxide to a solution of 8a in benzene at 50-60 °C provided furandione (2a) in 62% yield. This compound was in all respects identical with the sample prepared by method A.

The synthesis of the hitherto unknown 5-methyl-2,3-dihydrofuran-2,3-dione (2b) was of particular interest to us. However, cyclization of acetylpyruvic acid (8b) with phosphorus pentoxide gave only 20-30% yield of dione. Of the many cyclization reagents tested in this reaction (i.e. dicyclohexylcarbodiimide, acetic anhydride) we found that trifluoroacetic anhydride in the presence of catalytic amounts of KOH gave the best yields and furthermore was very easy to handle. Thus, by employing 1 equivalent of trifluoroacetic anhydride as a mild lactonization reagent, and by reducing the reaction temperature to −15 °C, the desired dione (2b) was obtained as yellow crystals in 67% yield. Furandione (2b) exhibited strong ir absorptions at 1835-1810 and 1735 cm^{-1}, in the region characteristic of furandiones,[4-11] and showed the expected resonances for the carbonyl carbons at 155.0 (C-2) and 180.4 ppm (C-3) in the ^{13}C nmr spectrum.[3,5-7,11] Furan-2,3-diones are usually rather prone to hydrolysis and hydrolyze on prolonged exposure to moisture.[4-11] The 5-alkylfurandiones (2) described in this work are particulary sensitive and when kept in the open air hydrolyze within hours to regenerate acylpyruvic acids (8).

	For 8a. P$_4$O$_{10}$,benzene	
	For 8b: (CF$_3$CO)$_2$O,Et$_2$O	
	−H$_2$O	

8a R = t-Bu   2a 62%
8b R = Me   2b 67%
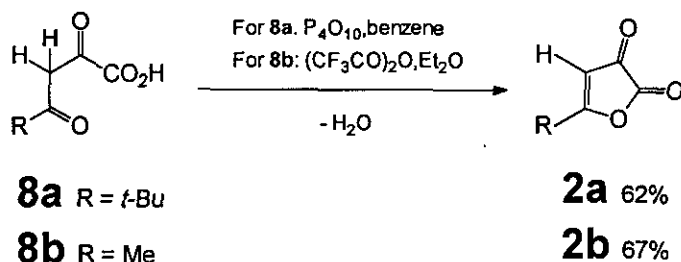
Scheme 3

In conclusion, we have demonstrated that simple 5-alkyl-2,3-dihydrofuran-2,3-diones can be conveniently prepared by lactonization of readily available acylpyruvic acids, using suitable cyclization reagents such as phosphorus pentoxide or trifluoroacetic anhydride. This clean and efficient method is far superior to the previously reported cyclocondensation reaction of silyl enol ethers with oxalyl chloride.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. [1]H Nmr spectra were recorded at 200 MHz and ^{13}C nmr spectra at 50 MHz on a Varian XL-200 instrument. Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106. Ether was dried over sodium wire and used without prior distillation. Oxalyl chloride and trifluoroacetic anhydride were purchased from Aldrich Chemical Co. and distilled before use.

5-*tert*-Butyl-2,3-dihydrofuran-2,3-dione (2a). From 3 and oxalyl chloride: The dione was prepared in 24% yield according to the previously published procedure.[9]

By cyclization of acylpyruvic acid (8a): A solution of 5,5-dimethyl-2,4-dioxohexanoic acid[14] (8a, 172 mg, 1 mmol) in dry benzene (10 ml) was stirred at 50-60 °C and phosphorus pentoxide (600 mg, 2.1 mmol) was added portionwise (3 x 200 mg, every 20 min). After the sealed reaction mixture was stirred for a total of 1 h at 50-60 °C, the yellow solution was filtered from the inorganic material. The inorganic material was further extracted with dry benzene (2 x 5 ml), and the combined benzene solutions were evaporated. The resulting yellow oil was purified by sublimation at 45 °C/0.1 mbar to afford dione (2a) as yellow crystals, yield 95 mg (62%), mp 52-53 °C (lit.,[9] 50.5-52 °C).

Mono-(5-*tert*-butyl-5-chloro-2-oxo-2,5-dihydrofuran-3-yl) oxalate (6) and di-(5-*tert*-butyl-5-chloro-2-oxo-2,5-dihydrofuran-3-yl) oxalate (7). To a solution of 3,3-dimethyl-2-trimethylsiloxy-1-butene[15] (3, 1.72 g, 10 mmol) in dry ether (20 ml), a solution of oxalyl chloride (1.27 g, 10 mmol) in dry ether (5 ml) was added dropwise over a period of 30 min. After stirring for 20 h (CaCl$_2$ tube) a colorless solid precipitated from the initially yellow solution. This product was filtered and recrystallized from benzene to give diester (7) as colorless crystals; yield 370 mg (25% based on oxalyl chloride), mp 165 °C (decompt.). The etheral mother liquor was evaporated, the resulting solid digested with hexane, and then recrystallized from cyclohexane to give mono-ester (6) as colorless solid; yield 280 mg (21% based on 3), mp 114-115 °C (decompt.). 6: Ir (KBr) 3500, 3160, 3140, 3000-2920, 1805, 1770, 1760, 1650; ^{1}H nmr (CDCl$_3$) 1.16 (s, 9H, *t*-Bu), 7.57 (s, 1H, H-4), 9.78 (br, 1H, OH); ^{13}C nmr (CDCl$_3$) 26.7 (C(CH$_3$)$_3$), 42.7 (*C*(CH$_3$)$_3$, 109.0 (C-5), 138.0 (C-4), 138.7 (C-3), 155.4 (ester CO), 158.6 (COOH), 166.8 (C-2). Anal. Calcd for C$_{10}$H$_{11}$O$_6$Cl: C, 45.72; H, 4.22; Cl, 13.49. Found: C, 45.59; H, 4.47; Cl, 13.34.

7: Ir (KBr) 3140, 3000-2920, 1820, 1790, 1650; ^{1}H nmr (CDCl$_3$) 1.18 (s, 18H, 2 *t*-Bu), 7.53 (s, 2H, H-4); ^{13}C nmr (CDCl$_3$) 25.1 (C(CH$_3$)$_3$, 41.0 (*C*(CH$_3$)$_3$), 106.7 (C-5), 136.3 (C-4), 137.3 (C-3), 151.5 (ester CO), 162.9 (C-2). Anal. Calcd for C$_{18}$H$_{20}$O$_8$Cl$_2$: C, 49.67; H, 4.63; Cl, 16.29. Found: C, 49.75; H, 4.72; Cl, 15.94.

5-Methyl-2,3-dihydrofuran-2,3-dione (2b). A solution of freshly sublimed 2,4-dioxopentanoic acid[16] (8b, 260 mg, 2 mmol) in dry ether (40 ml) containing a catalytic amount of crushed anhydrous KOH (*ca* 5 mg) was cooled to -15°C in a sealed flask. After trifluoroacetic anhydride (440 mg, 2.1 mmol) was added through a septum, the solution was kept at -15 °C for 4 h. After the ether was quickly removed on a rotary evaporater, the last traces of solvents were removed in high vacuum (10^{-2} mbar) at 0 °C. The solid residue was digested with cold ether/hexane and the resulting crude reaction product was purified by sublimation at 35°C/0.1 mbar to give 2b as yellow crystals; yield 150 mg (67%), mp 62 °C. This dione can be kept in a desiccator over P_4O_{10} at 0 °C for several weeks without any change in spectroscopic properties. Ir (KBr) 3120, 1835-1810, 1735, 1620; ^{1}H nmr (CDCl$_3$) 2.39 (s, 3H, Me), 5.85 (s, 1H, H-4); ^{13}C nmr (CDCl$_3$) 17.4 (Me), 102.5 (C-4), 155.0 (C-2), 180.4 (C-3), 195.3 (C-5). Anal. Calcd for $C_5H_6O_3$: C, 53.58; H, 3.60. Found: C, 53.23; H, 3.94.

REFERENCES AND NOTES

1. Reactions of Cyclic Oxalyl Compounds, 36. Part 35: W. Heilmayer, C. O. Kappe, H. Sterk, G. Kollenz, K. Peters, E.-M. Peters, H. G. von Schnering, and L. Walz, *Chem. Ber.*, 1993, **126**, 2061.

2. C. Wentrup, H.-W. Winter, G. Gross, K.-P. Netsch, G. Kollenz, W. Ott, and A. G. Biedermann, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 800; C. O. Kappe, R. A. Evans, C. H. L. Kennard, and C. Wentrup, *J. Am. Chem. Soc.* 1991, **113**, 4234; Yu. S. Andreichikov, G. Kollenz, C. O. Kappe, R. Leung-Toung, and C. Wentrup, *Acta Chem. Scand.*, 1992, **46**, 683.

3. For a recent literature overview see: C. O. Kappe, G. Färber, C. Wentrup, and G. Kollenz, *J. Org. Chem.*, 1992, **57**, 7078.

4. E. Ziegler, G. Kollenz, and H. Igel, *Monatsh. Chem.*, 1971, **102**, 1769.

5. G. Kollenz, C. O. Kappe, and H. Abd el Nabey, *Heterocycles*, 1991, **32**, 669.

6. R. W. Saalfrank and T. Lutz, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1041.

7. R. W. Saalfrank, T. Lutz, J. Gundel, K. Peters, and H. G. von Schnering, *Chem. Ber.*, 1991, **124**, 2289.

8. D. I. Sychev, *Zh. Org. Khim.*, 1990, **26**, 2636.

9. S. Murai, K. Hasegawa, and N. Sonoda, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 636.

10. Yu. Andreichikov, Yu. A. Nalminova, G. D. Plakine, and R. F. Saraeva, *Khim. Geterotsikl. Soedin.*, 1975, 1468.

11. M. Hnach, J. P. Aycard, and H. Zineddine, *Bull. Soc. Chim. Fr.*, 1991, **128**, 393.

12. cf. R. E. Tirpak and M. W. Rathke, *J. Org. Chem.*, 1982, **47**, 5099.

13. W. J. Elliot and J. Fried, *J. Org. Chem.*, 1978, **43**, 2708.

14. A. Meister and J. P. Greenstein, *J. Biol. Chem.*, 1948, **175**, 573.

15. P. Cazeau, F. Duboudin, F. Moulines, O. Babod, and J. Dunogues, *Tetrahedron*, 1987, **43**, 2075.

16. A. Lehninger and E. J. Witzeman, *J. Am. Chem. Soc.*, 1942, **64**, 874.