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1-TRIMETHYLSILYL-3-TRIMETHYLSILYLOXYISOBENZOFURAN - A POTENTIALLY USEFUL SYNTHON FOR LINEAR POLYCYCLICS

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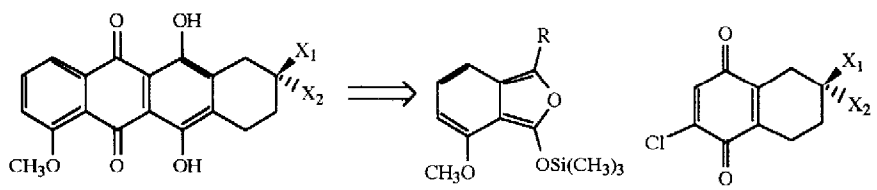
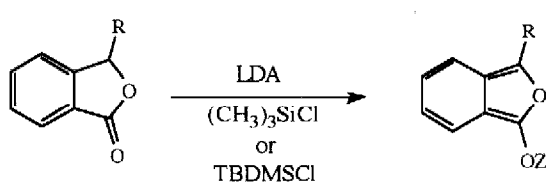
Abstract: *1-Trimethylsilyl-3-trimethylsilyloxyisobenzofuran* **7** *may be prepared in a simple one-pot procedure from phthalide as a model for the corresponding 4-methoxy derivative* **2b**, *a potentially useful anthracycline synthon.*

Isobenzofurans (IBF) have been receiving an increased amount of attention as useful synthons, and they have been the subject of a recent review by Rickborn[1], who developed the most general method for their preparation as described below. Recent synthetic studies of ours have involved the chloroquinone synthon **3**, which is potentially capable of both regiospecific and stereospecific reactions to provide a standard type of anthracycline synthon **1**, provided that a satisfactory co-synthon could be found. In this vein, we were attracted to the isobenzofuran **2a**.



1 **2a** R= H **3**
2b R= $Si(CH_3)_3$

As a model for our studies, we were interested in methods for the preparation of the parent system lacking the methoxy. We noted that the 3-phenylphthalide **4a** had been converted to the corresponding IBF **5a** by Iwao,[2] so we decided to investigate whether or not this approach could be extended to the parent system, i.e. the

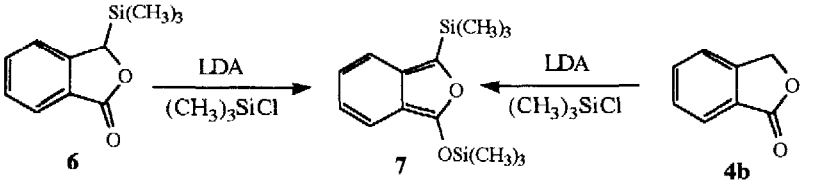


4a R=C_6H_5
4b R=H

5a R=C_6H_5 Z=TBDMS
5b R=H Z=$(CH_3)_3Si$

conversion of **4b** to **5b**. When we quenched the anion of phthalide derived *via* LDA in THF with TMSCl, we obtained not the O-silyl **5b** but rather the C-silyl derivative **6**.[3] Obtention of **6** naturally raised the question as to

whether, if we recycled this C-silyl derivative, additional C-silylation would be obtained or, alternatively, if we could convert **6** to a desired carbon/oxygen bis-silylated synthon **7**. We found that, indeed, recycling **6** could

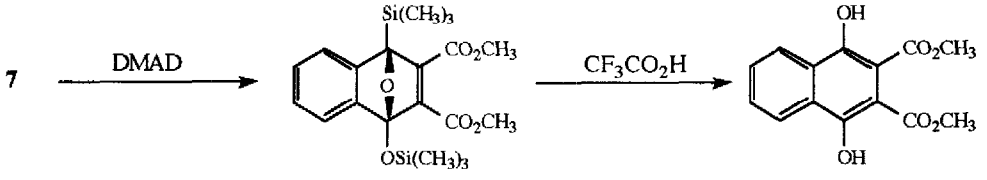


6 **7** **4b**

produce **7**[4] ; moreover, **7** could be produced directly from **4b** by a one pot procedure[5], provided that the necessary and sufficient excess reagents were employed.

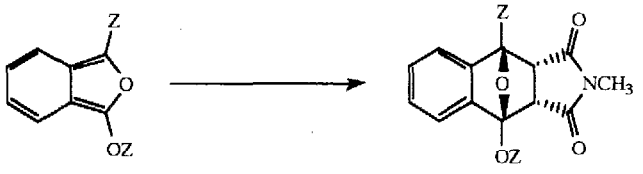
Although we were initially prompted to publish our observations upon noting that the C-silylated derivative **6** had been prepared and used recently in an alkaloid synthesis by others [6], it has since come to our attention that the original preparation of this synthon was by Rickborn's group and that this synthon, moreover, was noted in his recent review on isobenzofurans. [1]

Because of its lability it was not possible to fully characterize the bis-silylated derivative **7**; however, we could obtain the adduct **8** with dimethyl acetylenedicarboxylate (DMAD).[7] Treatment of **8** with trifluoroacetic acid gave the known ester **9** which was previously prepared by condensing dimethyl succinate and dimethyl phthalate. [8]



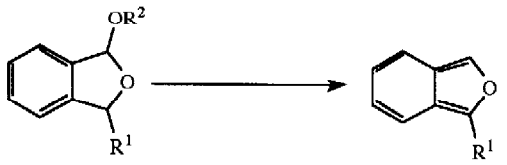
8 **9**

During the review process, we were made aware that some studies similar to ours had been made by the Rickborn group.[9] An attempt to form the bis-TMS derivative **7** *via* the LTMP/TMSCl system and isolation of the N-methylmaleimide (NMM) adduct **10** was not successful; however, LTMP/TESCl (triethyl chlorosilane) did result in the isolation and characterization of the bis-silylated derivative **11b.**[10] We believe that our method for preparation of the bis-silylated derivative **7** using the inexpensive LDA and TMSCl, in a one pot process, is particularly easy and convenient and represents an important prototype for the regiospecific synthesis as noted below.



7 Z=TMS **10** Z=TMS
11a Z=TES **11b** Z=TES

The phthalide based synthons provide a useful alternative to the standard method of producing isobenzofurans developed by Rickborn in which compounds of type **12** are converted to isobenzofurans *via* alkyllithiums using a catalytic amount of LDA to produce compounds of the type **13.**[11]



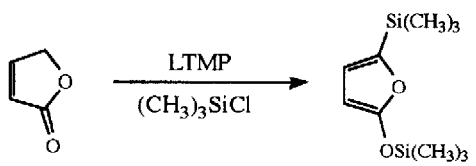
12 R^1= alkyl, phenyl ... R^2= alkyl

13 R^1= alkyl, phenyl ...

We are currently investigating the extension of the synthetic method of the known 7-methoxyphthalide to IBF **2b**, which should be preparable *via* the same methodology as for phthalide.[12] The obvious application of this synthesis is to regiospecific Diels-Alder reactions with chloroquinones. In particular, chloroquinones of general type **3** with **2b** should produce satisfactory regiocontrolled anthracycline synthons complete with the correct oxygenation and specifically placed methoxy group, and such studies are currently in progress.

REFERENCES AND NOTES

1. Rickborn, B. in *Advances In Theoretically Interesting Molecules*; Thummel, R.P., Ed.; JAI Press, London, **1989**, Vol. 1, p.1-135.
2. Iwao, M.; Inoue, H.; Kuraishi, T. *Chem. Lett.*, **1984**, 1263-1266.
3. Compound **6** ^{1}H NMR ($CDCl_3$) : δ 0.13 (s, 9H), 5.32 (s, 1H), 7.38 (d, 1H, J=7.5 Hz), 7.47 (t, 1H, J=7.5 Hz), 7.65 (t, 1H, J=7.5 Hz), 7.93 (d, 1H, J=7.5 Hz) : ^{13}C NMR ($CDCl_3$) : δ −4.27, 78.00, 120.76, 124.55, 125.79, 127.44, 133.61, 150.36, 171.86 : MS m/z (%) : 206(86), 207(13), 177(96), 163(100), 104(69). Compound **6** is stable to water for a brief period of time, but will decompose to phthalide **4b** on standing.
4. In the review noted above (reference 1, p.93) it was observed that evidence (not specified) had been obtained for the conversion of 2-butenolide **14** to 2-trimethylsilyl-4-trimethylsilyloxyfuran **15**. (Ph.D. thesis of D. Tobia,UCSB). This seems reasonable based on our own experience. The transformation should be more favorable than phthalide, as the aromaticity of the benzene ring is not disrupted.



14 **15**

5. One -Pot Procedure: Phthalide **4b** (6.2 mmol) in THF was added to LDA (6.9 mmol) at -78°C whereby the solution turned yellow. After 30 minutes chlorotrimethylsilane (22.0 mmol) was added and the solution warmed to 0°C for 1.5 hours. The solution was reduced to one-third its original volume *in vacuo* while warming gently. The solution was cooled to -78°C and LDA (6.9 mmol) was added

whereby the solution became dark red. After 1.5 hours chlorotrimethylsilane (22.0 mmol) was added and the solution warmed to 0°C for 1.5 hours while the solution lightened considerably. Evaporation *in vacuo* gave molecule **7** with the spectra reported. Compound **7** ^{1}H NMR ($CDCl_3$) : δ 0.35 (s, 9H), 0.38 (s, 9H), 6.58 (dd, J=9 Hz, J=6.4 Hz), 6.75 (dd, 1H, J=9 Hz, J=6.4 Hz), 7.22 (dd, 2H, J=9 Hz, J=6.4 Hz). Compound **7** is very unstable to moisture and rapidly reverts to **6** when exposed to air.

6. Kessar, S.V.; Singh, P.;Kaur, N.P.; Chawla, U.; Shakla, K.; Aggarwal, P.; Venugopal, D. *J. Org. Chem.* ***1991***, *56*, 3908-3912.

7. Compound **8** ^{1}H NMR ($CDCl_3$) : δ 0.21 (s, 9H), 0.31 (s, 9H), 3.71 (s, 3H), 3.78 (s, 3H), 7.01 (t, 1H, J=7.8 Hz), 7.08 (t, 1H, J=7.5 Hz), 7.26 (d, 1H, J=7.5 Hz), 7.41 (d, 1H, J=7.8 Hz) : MS m/z (%) : 421(3), 420(9), 362(30), 361(100), 301(60), 257(94). Compound **8** is stable for several weeks at room temperature provided the compound is in a closed vial.

8. Bird, C.W.; Wong, C.K.; Koh, F.L.K. *Tetrahedron*, **1976**, *32*, 269-274. (6% yield reported)

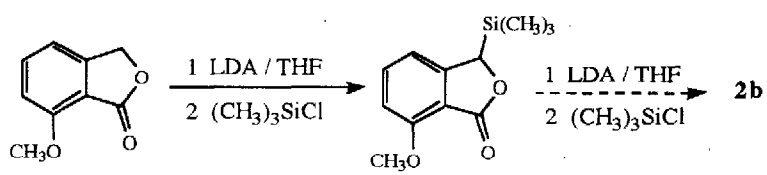
Compound **9** was prepared by treating the isobenzofuran **7** prepared as above, while still in solution, with DMAD (6.8 mmol) and stirred at room temperature overnight (14 hours). The solution was evaporated to remove excess solvents whereby trifluoroacetic acid (5 mL) was added and the solution stirred for another hour giving the desired compound **9** in 82% overall yield from **4b**.

9. Tobia, D.; Ph.D. Dissertation, University of California Santa Barbara, **1987**.

10. The first attempts at the preparation of the bis-trimethylsilylated isobenzofuran **10** using the LTMP system and isolation *via* the N-phenylmaleimide adduct did not result in a characterized derivative; however, if triethylsilyl chloride were used with the LTMP system, then the bis-triethylsilated derivative was formed, which afforded a characterized N-phenylmaleimide derivative. We believe that our bis-trimethylsilylated system offers advantages in that the formation of LTMP is not required, the inexpensive commercially available LDA is used. Use of TMSCl rather than TESCl is advantageous from both availability and particular cost factors.

11. (a) Naito, K.; Rickborn, B. *J. Org. Chem*, **1980**, *45*, 4061-4062. (b) Makhlouf, M.A.; Rickborn, B. *J. Org. Chem*, **1981**, *46*, 2734-2739. (c) Mirsadeghi, S.; Rickborn, B. *J. Org. Chem*, **1987**, *52*, 787-792.

12. 3-Trimethylsilyl-7-methoxyphthalide **17** was prepared from 7-methoxyphthalide **16** and LDA / chlorotrimethylsilane.



Compound **17** ^{1}H NMR ($CDCl_3$) : δ 0.47 (s, 9H), 3.92 (s, 3H), 5.15 (s, 1H), 6.77 (t, 2H, J=7.8 Hz), 7.51 (t, 1H, J=7.8 Hz). Work is currently under way to prepare **2b** and react it with the appropriate chloroquinones.

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