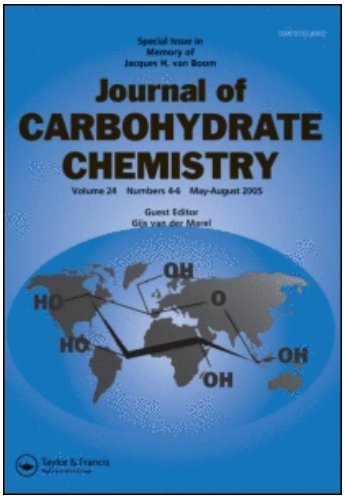


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# Attempted Methylenation of 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconolactone Using Benzothiazol-2-ylmethylsulfone Under Julia Conditions Yields an Unusual Product

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# Attempted Methylenation of 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconolactone Using Benzothiazol-2-ylmethylsulfone Under Julia Conditions Yields an Unusual Product

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Reaction of 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconolactone with benzothiazol-2-ylmethyl-sulfone under Julia Kocienski conditions yielded an unusual product whose strucure was elucidated using $^{1}H$, $^{13}C$-NMR and 2-D spectral data and finally confirmed by single crystal X-ray diffraction data.

**Keywords** D-Gluconolactone, Benzothiazol-2-ylmethylsulfone, Julia olefination, methylenation

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconate **1** containing three isopropylidene groups protecting five hydroxyl and a carboxyl group is an interesting crystalline derivative of D-gluconolactone. With its convenient availability on a

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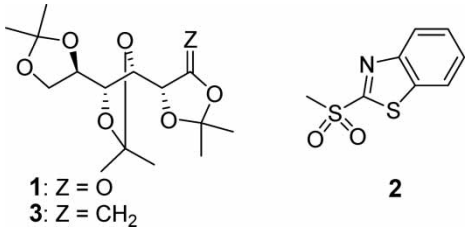



**Figure 1:** Benzothiazol-2-ylmethylsulfone **2** for methylenation of lactone **1**.



multigram scale by a procedure due to Jarosz,[1] it has surfaced as an interesting chiral building block for many synthetic endeavors.[2] Our own interest in homologation of sugar derivatives for synthetic endeavors toward higher carbon sugars prompted possible methylenation of **1** using **2** under Julia Kocienski conditions (Fig. 1). Although Julia Kocienski olefination, also called modified or one-pot Julia olefination, has emerged as a powerful tool for C-C double bond formation in many natural products synthesis,[3] the use of benzothiazol-2-ylmethyl sulfone **2** for methylenation of carbonyl compounds has been limited. The first report constituted a brief study by Julia and coworkers[4] and a second study by Najera's group.[5] In both these studies the carbonyl compounds have been restricted to aldehydes and ketones. In fact, the first use of **2** for the methylenation of a lactone carbonyl has appeared only very recently.[6] We explored the use of methyl-sulfone **2** for possible conversion of **1** to **3**. The other reason for this investigation was the sensitivity and the cost of the Tebbe reagent, which is being presently used for the synthesis of the exo-methylene derivative **3.**[7] Presented herein are the results of this study, which led to a highly unusual product.

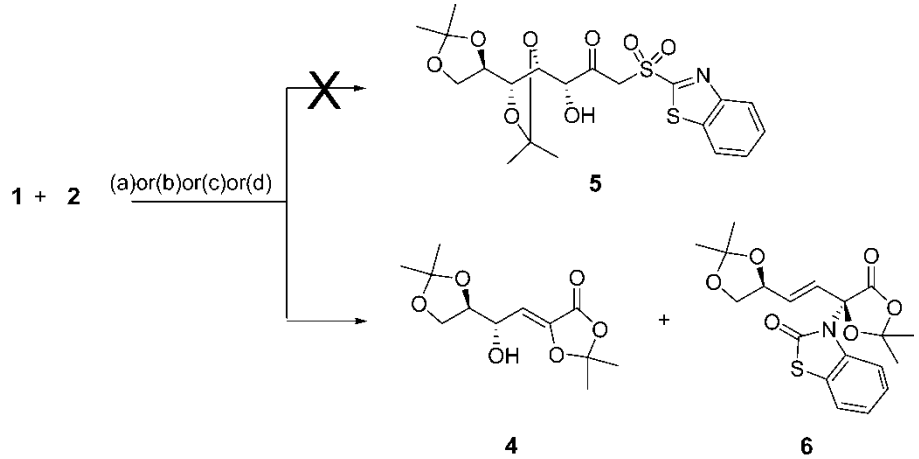
Knowing well that pre-$\alpha$-metalated BT-alkyl sulfones do have a propensity for degradation by an intermolecular *ipso* nucleophilic attack pathway on the heteroaryl moiety, it was obvious to use a Barbier-type procedure. Our first attempt constituted heating of **1** (0.5 mmol) and **2** (0.55 mmol) along with DBU (3 equiv) in THF as a solvent at 60°C. No significant reaction ensued, even after 36 h of heating, and the starting lactone **1** remained intact [$R_f$ (Diethyl-ether/Hexane, 4:7) = 0.44]. This was rather surprising, because with there being an acidic proton at the C-2 carbon in lactone **1,** it could have suffered an elimination reaction. On subsequent addition of DMF as a polar solvent, some partial reaction ensued; however, reaction continued to show recalcitrant behavior. On workup and silica gel chromatography, it furnished two new products along with the recovery of starting lactone in 70% yield. One of the new compounds [10%; $R_f$ (Diethyl-ether/Hexane, 4:7) = 0.11] was confirmed to be the anticipated elimination reaction product **4.**[8] The other product [20%; $R_f$ (Diethyl-ether/Hexane, 4:7) = 0.18] was neither the desired

compound **3** nor the other logically anticipated product **5** resulting from the opening of lactone ring.

Interestingly, the yield of this product increased to 45% and was also the only reaction product when DMF alone was used as the solvent for the reaction (Sch. 1). A clean $^1$H NMR spectrum indicated the presence of benzothiazole moiety and a fragment X in the structure (Fig. 2). The presence of the structural fragment X in the compound was unambiguously established using COSY, HSQC and HMBC spectral data (Fig. 3) (Table 1). This was highly intriguing along with a strong absorption at 1800 $cm^{-1}$ in the IR spectrum, which indicated the presence of a lactone carbonyl. This information led to the structure **6** for this new compound. However, the compound eluded its confirmed structural identity until the obtainment of X-ray crystal structure data, which indeed confirmed it to be **6** (Table 2).

The obtainment of the compound **6** can be easily rationalized invoking the known ability of aza-aromatic sulfones to undergo nucleophilic substitutions.[9] In fact, the ability to undergo nucleophilic substitution particularly peaks in the case of benzothiazol-2-sulfonyl derivatives.[4,10] The free hydroxyl group in the elimination product **4**[11] reacts with methyl-sulfone **2** under the basic reaction conditions and produces, through an ipso-substitution, an intermediate **7** with concomitant expulsion of methyl sulfinate (Sch. 2). The intermediate **7** under the thermal conditions undergoes a facile [3, 3] sigmatropic shift and explains the formation of the product **6**.






**Scheme 1**

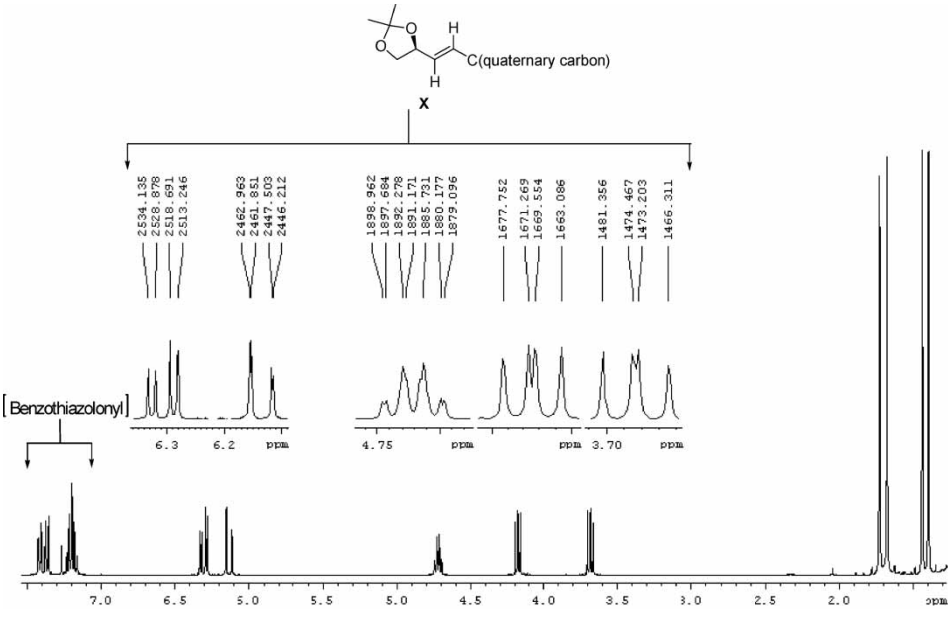
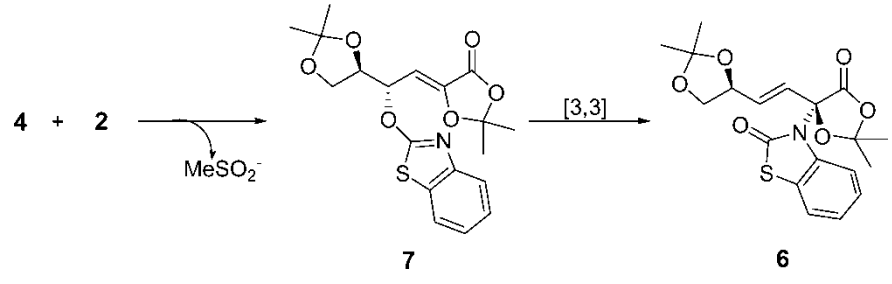



**Figure 2:** A clean $^{1}$H-NMR spectrum of the unusual product obtained.

In the light of these results, we conclude that for the obtainment of compound **3**, the literature-reported methylenation of **1** using Tebbe reagent should continue to remain as the most effective method, despite its cost. Titanocene methylidene complex ($Cp_2Ti{=}CH_2$) generated from Petasis reagent[12] could be another potential alternative for the desired objective.




**Scheme 2**

## EXPERIMENTAL

All solvents were distilled and dried using the usual recommended procedures. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded using deuteriochloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as a reference. For monitoring reactions, TLCs were performed on precoated silica gel

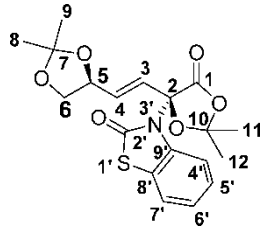


**Figure 3:** Structure of the unusual product as evidenced by $^{1}H$- and $^{13}C$-NMR spectral data.

plates followed by dipping in a solution prepared by adding ammonium ceric sulfate (1 g) and ammonium molybdate (21 g) to concentrated sulfuric acid (31 mL) and made up to 500 mL with distilled water. The TLC plates were later heated up to 100°C for development.



**Table 1:** $^{1}H$ and $^{13}C$ NMR Spectral Data of **6**.

| Position | $^{13}C$ | Carbon type[a] | $^{1}H$[b] | COSY (H–H) | HMBC (H → C/ C → H) |
|---|---|---|---|---|---|
| 1 | 169.5 | S | — | — | — |
| 2 | 86.2 | S | — | — | H-3, H-4 |
| 3 | 128.3 | D | 1H, 6.11–6.15 (dd, 15.6, 1.1) | H-4 | H-4, H-5, C-2 C-3, C-4, C-5 |
| 4 | 134.9 | D | 1H, 6.28–6.33 (dd, 15.6, 5.4) | H-3,H-5 | H-3, H-6 C-2, C-3, C-5 |
| 5 | 74.9 | D | 1H, 4.69–4.74 (m) | H-4,H-6 | C-3, H-4, H-3 |
| 6 | 68.7 | T | 2H, 6a: 3.66–3.70 (dd,8.2,6.9) 6b: 4.15–4.19 (dd,8.2,6.5) | H-5 | C-5, C-4, C-7, H-5 |
| 7 | 110.0 | S | — | — | H-6, H-8, H-9 |
| 8 | 25.7 | Q | 3H, 1.39 (s) | — | C-7, C-9, H-9 |
| 9 | 26.1 | Q | 3H,1.44 (s) | — | C-7, C-8, H-8 |
| 10 | 111.4 | S | — | — | H-11, H-12 |
| 11 | 26.5 | Q | 3H, 1.67 (s) | — | C-10, C-12, H-12 |
| 12 | 28.1 | Q | 3H,1.73 (s) | — | C-10, C-11, H-11 |
| 2′ | 165.5 | S | — | — | — |
| 4′ | 122.7[c] | D | 1H, 7.38–7.40[c] (m) | H-5′ | H-5′ |
| 5′ | 125.8[c] | D | 1H, 7.16–7.36[c] (m) | H-4′ | H-4′ |
| 6′ | 123.9[c] | D | 1H, 7.16–7.36[c] (m) | H-7′ | H-7′ |
| 7′ | 114.8[c] | D | 1H, 7.36–7.38[c] (m) | H-6′ | C-6′, H-6′ |
| 8′ | 122.9 | S | — | — | |
| 9′ | 135.2 | S | — | — | H-4′, H-5′ |

[a]S = quaternary carbon, D = CH, T = $CH_2$, Q = $CH_3$, multiplicities and assignments made by DEPT, HSQC, and HMBC techniques.
[b]Multiplicities and coupling constants in Hz in parentheses.
[c]Data interchangeable.

## 3-{(S)-4-((E)-2-((S)-2, 2-Dimethyl-(1, 3) dioxolan-4-yl)-vinyl)-2, 2-dimethyl-5-oxo-(1, 3) dioxolan-4-yl}-3H-benzothiazol-2-one (6)

Compound **6** was obtained under the four reaction conditions: (i) DBU, THF, 60°C; (ii) DBU, DMF, 70°C; (iii) $Cs_2CO_3$, DMF/THF (1:3), 70°C; and (iv) $K_2CO_3$, DMF/THF (1:3), 70°C.

In general, to the reaction flask containing triacetonide **1** (0.316 mmol), methyl sulfone **2** (0.411 mmol), and a base (0.949 mmol), the corresponding anhydrous solvents (totally 3 mL) as mentioned above was added under nitrogen atmosphere. In case of reaction conditions, (i) and (ii) base were added after the addition of solvent. The reaction mixture was subjected to heating for 36 h under nitrogen atmosphere at 70°C. After this period the reaction mixture was allowed to cool, followed by the addition of aqueous saturated ammonium chloride solution (10 mL) and extraction with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water and then



**Table 2:** Summary of crystal data and data collection parameters for 3-{(S)-4-((E)-2-((S)-2, 2-Dimethyl-(1, 3) dioxolan-4-yl)-vinyl)-2, 2-dimethyl-5-oxo-(1, 3) dioxolan-4-yl}-3H-benzothiazol-2-one.

| | |
|---|---|
| Chemical formula | $C_{19}H_{21}NSO_6$ |
| Formula weight | 391.43 |
| Crystal system | Orthorhombic |
| Space groups | P $2_1$ $2_1$ $2_1$ |
| Unit cell dimensions | |
| *a* (Å) | 6.7282 (2) |
| *b* (Å) | 15.1078 (3) |
| *c* (Å) | 18.9808 (4) |
| $\alpha$, $\beta$, $\gamma$ (°) | 90.00, 90.00, 90.00 |
| *V* (Å)$^3$ | 1929.37 (8) |
| *Z* | 4 |
| $D_{calcd}$ (mg m$^{-3}$) | 1.348 |
| Absorption coefficient $\mu$ (mm$^{-1}$) | 0.203 |
| F(000) | 824 |
| Index ranges | $-5 \leq h \leq 8$, $-20 \leq k \leq 20$, $-25 \leq l \leq 25$ |
| Crystal size (mm) | 0.3 × 0.2 × 0.2 |
| Measured data | 23737 |
| Unique data | 4762 |
| Parameters | 245 |
| Restraints | 0 |
| R (all data) | 0.0676 |
| $wR_2$ | 0.1021 |
| Goodness-of-fit | 0.970 |
| Mean and maximum shift/esd | 0.000, 0.000 |
| Maximum and minimum difference electron density (e Å$^{-3}$) | 0.307 and −0.297 |

dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified using silica gel column chromatography with diethyl ether-hexane (1:10) as eluent. The pure product was obtained as colorless needle-like crystals. m.p.: 110–112°C; $R_f = 0.17$ (Diethyl-ether/Hexane, 4:7); $[\alpha]_D^{25} = +8.79$ (c = 1, $CHCl_3$); HRMS calcd for $C_{19}H_{21}NO_6S$: 391.1168. Found: 392.1158 $[M+H]^+$.

## X-ray diffraction analysis of compound 6

X-ray diffraction data for compound **6** were collected on a Bruker X8 kappa APEX II diffractometer equipped with graphite monochromated Mo-K$\alpha$ radiations. Unit cell parameters and orientation matrix were obtained using 36 reflections collected by random search routines from different zones and indexed by method of short vectors followed by least-squares refinement. The intensity data were collected by $\omega$-2$\theta$ scan technique at 293°K. Structure was solved by the direct method technique using the SIR92 (WINGX) program.[14] The nonhydrogen atoms were anisotropically refined. Hydrogen atoms were fixed at geometrically meaningful positions and were given riding model refinement. Full-matrix least-squares refinement using $F^2$ was continued until maximum shift/esd converged to zero. The SHELXL97 (WINGX)[15] program was used for refinement. The x-ray diffraction data of compound **6** is deposited in the Cambridge Crystallographic Data Centre (12, Union Road, Cambridge, CB2 1EZ, UK) and the data deposition number is CCDC 630597 (Fig. 4).



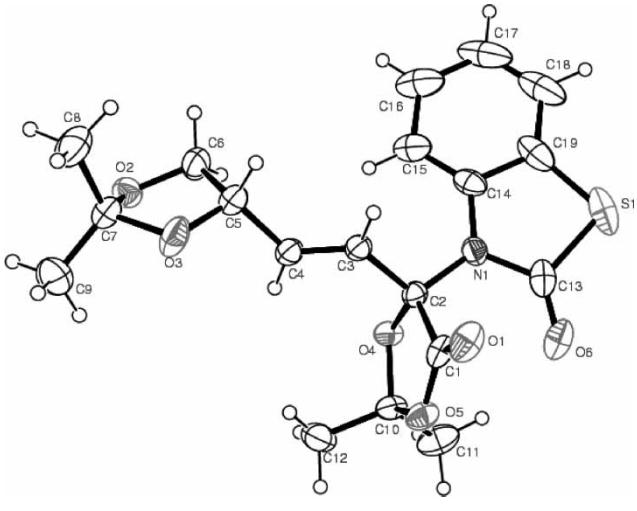



**Figure 4:** ORTEP plot[13] of compound **6** with thermal ellipsoids drawn at 50% probability level (Johnson, 1976).

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[11] It is highly intriguing and interesting to note that compound **4** is not formed when the starting tri-isopropylidene lactone **1** is heated alone with bases such as $Cs_2CO_3$,; $K_2CO_3$; DBU; NaOAc; $Et_3N$ under the reaction conditions, THF/DMF; 70°C or DMF/70°C that led to the formation of unusual product **6**.

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