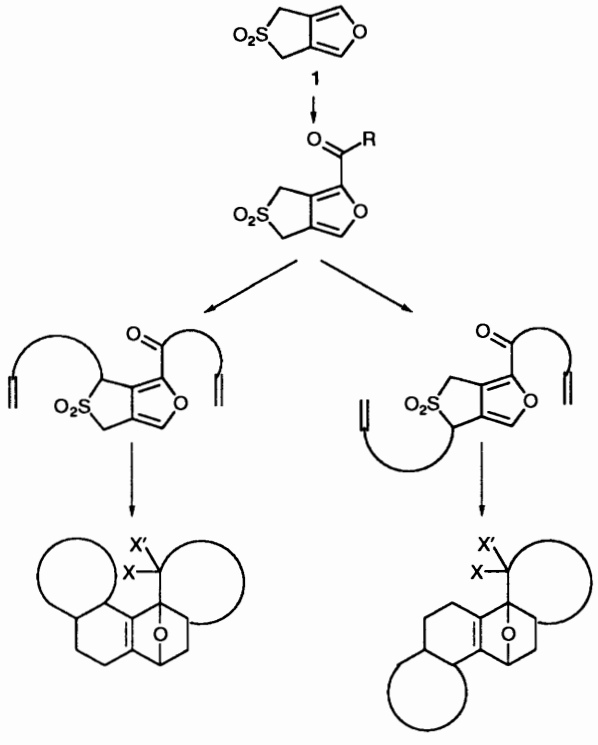
Regioselective Alkylation of 1(3)-Acetyl-4*H*,6*H*-thieno[3,4-*c*]furan 5,5-Dioxide

Katsuhiro Konno, Yoh Kawakami, Takaaki Hayashi and Hiroaki Takayama*
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

Reaction of the title compound **2** with a variety of alkylating agents regioselectively gave, depending on the reaction conditions used, 4-alkylated compound **3** or 6-alkylated compound **4**, which were further alkylated to afford the dialkylated compounds **5**–**7** in similar ways.

4*H*,6*H*-Thieno[3,4-*c*]furan 5,5-dioxide **1** has potential as a novel building block for the synthesis of polycyclic ring systems by way of Diels–Alder reactions and substitution of the furan and the sulfolene moieties. Thus, compound **1** reacts readily with a variety of dienophiles under Diels–Alder conditions to give four types of cycloadducts.[1] It is also alkylated at the 4-position of the sulfolene moiety under basic conditions to furnish products which lead to fused ring furans in good yield.[2] Further, under Friedel–Crafts' reaction conditions, the furan moiety of **1**, gives 1(3)-acylated derivatives,[3] which, followed by sequential Diels–Alder reactions, affords tricyclic and tetracyclic compounds in high yield.[4] 1(3)-Acylated derivatives of **1** when further alkylated regioselectively at the α- or α'-position of the SO_2 group and subsequently cyclised by a tandem Diels–Alder reaction could give pentacyclic compounds (Scheme 1). Here, we



Scheme 1

describe the successful regioselective alkylation of 1(3)-acetyl 4*H*,6*H*-thieno[3,4-c]furan 5,5-dioxide **2** as a model substrate.

After numerous attempts, we found that **2** gave, depending on the reaction conditions used, either the 4- or 6-monoalkylated compound with complete regioselectivity (see Table 1). Thus, with tetrabutylammonium fluoride (TBAF) as base in THF at room temperature (Method A), the 4-alkylated product **3** was obtained in good to high yield with no detectable 6-alkylated compound **4**, whereas the reaction took place exclusively at the 6-position when **2** was alkylated in the presence of lithium hexamethyldisilazide (LiHMDS) in hexamethylphosphoric triamide (HMPA)–THF at −78 °C (Method B). Under both sets of conditions, the only by-product was the 4,4- or 6,6-dialkylated compound (5–15%).

Table 1 Monoalkylation of 1(3)-acetyl-4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **2**

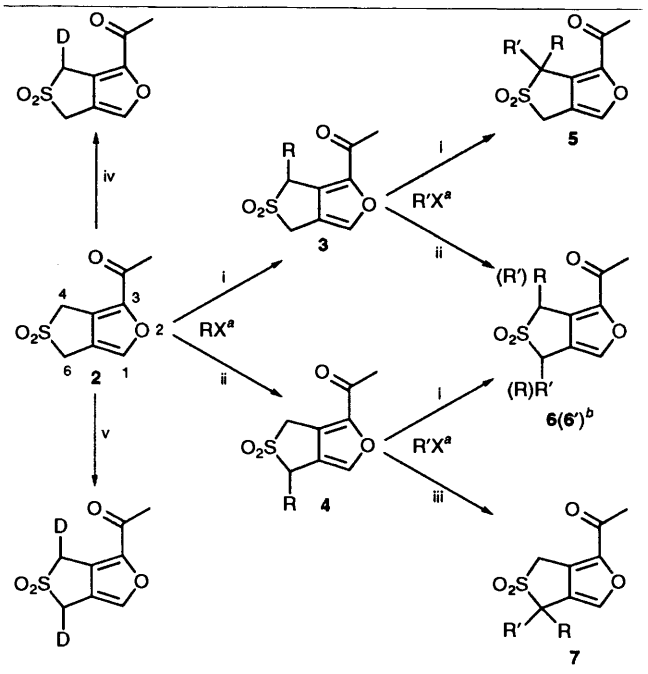
Entry	RX	Method[a]	**3** (%)	**4** (%)
1	MeI	A	72	0
2	CH_2=$CHCH_2Br$	A	71	0
3	$PhCH_2Br$	A	74	0
4	BuI	A	77	0
5	BuBr	A	58	0
6	Pr^iI	A	56	0
7	MeI	B	0	76
8	CH_2=$CHCH_2Br$	B	0	77
9	$PhCH_2Br$	B	0	79
10	BuI	B	0	75
11	BuBr	B	0	28
12	Pr^iI	B	0	26

[a] *Reaction conditions*: Method A: RX (1.2 equiv. for entries 1–3 and 2 equiv. for entries 4–6) and TBAF (3 equiv. for entries 1–3 and 6 equiv. for entries 4–6) in THF (room temp., 15 min), Method B: RX (1.2 equiv. for entries 7–9 and 2 equiv. for entries 10–12) and LiHMDS (4 equiv.) in HMPA (4 equiv.)–THF (−78 °C, 10 min).

The presence of the 4,4- or 6,6-dialkylated compound as a by-product prompted us to further investigate regioselective alkylation of **3** and **4**, since it could, ultimately, lead to incorporation of a substituent into the ring junction of the pentacyclic compound (see Tables 2 and 3). The alkylation of **3** proceeded in a similar way to the monoalkylation of **2**: the 4,4-dialkylated compound **5** or the 4,6-dialkylated compound **6** was obtained by Method A or B, respectively, again with complete regioselectivity. The 4,6-dialkylated compound **6'** was also produced from **4** by Method A although the isomer ratio was different from that in the case of **6**.† In contrast, the alkylation of **4** at the 6-position was ineffective by Method B, giving the 6,6-dialkylated product **7** only in poor yield. It was found, however, that the forced conditions using LiHMDS in THF at −20 °C (Method C) greatly improved the reaction rate and gave **7** in satisfactory yield. With the procedures described in Tables 2 and 3, there was no by-product produced although starting material was recovered (10–20%).

The high regioselectivity of these reactions may arise from the properties of the anions generated. In Method A, the weak base employed ensures that a carbanion is formed only at the 4-position, the protons at this site being more acidic than those

† For the stereoselectivity of the 4,6-dialkylated products **6** and **6'**, our assumption, based on our previous results on the alkylation of 3-sulfolene, is that, in Method A, the *cis*-isomer is predominant, while the *trans*-isomer is the major product in Method B.[5]



Scheme 2 *Reagents and conditions*: i, TBAF–THF, room temp., 15 min.; ii, LiHMDS–HMPA–THF, −78 °C, 10 min.; iii, LiHMDS–THF, −20 °C, 10 min.; iv, TBAF–THF, room temp., 5 min then D_2O; v, LiHMDS–THF, −78 °C, 5 min then D_2O. [a] See Tables 1–3 for RX and RX'. [b] Compounds **6** and **6'** (in parenthesis) denote the products from **3** and **4**, respectively (see Tables 2 and 3).

Table 2 Dialkylation of 4-monoalkylated compound **3**

Entry	R	R'X	Method[a]	**5** (%)	**6**[b] (%)
1	Bu	MeI	A	74	0
2	Me	BuI	A	72	0
3	Me	BuI	B	0	55 (1:2)
4	Bu	Me_2SO_4	B	0	72 (1:3)
5	Me	Me_2SO_4	B	0	79 (1:2)
6	Bu	BuI	B	0	70 (1:2)

[a] *Reaction conditions*: Method A: R'X (1.2 equiv. for MeI and 2 equiv. for BuI) and TBAF (3 equiv. for R'X = MeI and 6 equiv. for R'X = BuI) in THF (room temp., 15 min), Method B: R'X (2.4 equiv. for Me_2SO_4 and 2 equiv. for BuI) and LiHMDS (4 equiv.) in HMPA (4 equiv.)–THF (−78 °C, 10 min). [b] Obtained as a *cis–trans* mixture and the ratio is shown in parenthesis.

Table 3 Dialkylation of 6-monoalkylated compound **4**

Entry	R	R'X	Method[a]	**6'**[b] (%)	**7** (%)
1	Bu	MeI	A	75 (1:1)	0
2	Me	BuI	A	61 (3:2)	0
3	Me	MeI	A	77 (1:1)	0
4	Bu	BuI	A	76 (5:2)	0
5	Bu	MeI	C	0	65
6	Me	BuI	C	0	79

[a] *Reaction conditions*: Method A: R'X (1.2 equiv. for MeI and 2 equiv. for BuI) and TBAF (3 equiv. for R'X = MeI and 6 equiv. for R'X = BuI) in THF (room temp., 15 min), Method C: R'X (1.2 equiv. for MeI and 2.2 equiv. for BuI) and LiHMDS (3 equiv.) in THF (−20 °C, 10 min). [b] Obtained as a *cis–trans* mixture and the ratio is shown in parenthesis.

at the 6-position as a result of the 3-acyl group; thus, only the 4-alkylated product is obtained. In Method B, however, the strong base generates anions both at the 4- and the 6-position (4,6-dianion), the latter being much more reactive than the former as a result of conjugate stabilisation for the 4-anion by the 3-acyl group; this results in exclusive formation of 6-alkylated product. Quenching experiments with D_2O established the generation of the 4-monoanion and the 4,6-dianion: the 4-monodeuteriated product was obtained after treatment of **2** with TBAF (3 equiv.) in THF (room temp. 5 min), followed by the addition of an excess of D_2O, whereas quenching of the solution of **2** and LiHMDS (2 equiv.) in THF (−78 °C, 5 min) with D_2O yielded the 4,6-dideuteriated product.

Application of the procedures described here to synthesis of pentacyclic compounds as projected in Scheme 1 is in progress.

Experimental

Typical Procedure for Alkylation of **2** *at C-4* (*Method A, Entry* 4 *in Table* 1).—To a stirred solution of **2** (200 mg) and BuI (0.23 cm^3, 2 equiv.) in THF (4 cm^3) was added 1 mol dm^{-3} TBAF–THF (6 cm^3, 6 equiv.) and the mixture stirred at room temperature under argon for 15 min. After this the reaction mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a brown oily residue which was purified by silica gel flash chromatography (15 g, 1% AcOEt–benzene) to give the 4-alkylated compound **3** (R = Bu) (197 mg, 77%) as colourless needles, m.p. 105–106 °C (recrystallized from 1:1 AcOEt–hexane); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.89 (t, 3 H, *J* 7.3), 1.30–1.42 (m, 2 H), 1.42–1.52 (m, 2 H), 2.01–2.18 (m, 2 H), 2.50 (s, 3 H), 4.03 (dd, 1 H, *J* 1.5, 15.3), 4.13 (dd, 1 H, *J* 1.2, 15.3), 4.32 (dd, 1 H, *J* 4.9, 7.6) and 7.47 (dd, 1 H, *J* 1.2, 1.5); ν_{max}(Nujol)/cm^{-1} 1674, 1622, 1541, 1312, 1200 and 1107; *m/z* 256 (M^+) and 192 ($M^+ - SO_2$) (Found: M^+, 256.0793. $C_{12}H_{16}O_4S$ requires *M*, 256.0769).

Typical Procedure for Alkylation of **2** *at C-6* (*Method B, Entry* 10 *in Table* 1).—To a stirred solution of **2** (500 mg), BuI (0.57 cm^3, 2 equiv.) and HMPA (1.74 cm^3, 4 equiv.) in THF (20 cm^3) was added 1 mol dm^{-3} LiHMDS–THF (10 cm^3, 4 equiv.) at −78 °C and the mixture stirred at −78 °C for 10 min under argon. The reaction was quenched by the addition of aq. NH_4Cl to the mixture which was then extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a pale yellow oily residue which was purified by silica gel flash chromatography (20 g, 1–2% AcOEt–hexane) to give the 6-alkylated compound **4** (R = Bu), (482 mg, 75%) as colourless plates, m.p. 77–79 °C (recrystallized from 1:1 AcOEt–hexane); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.93 (t, 3 H, *J* 7.3), 1.36–1.48 (m, 2 H), 1.48–1.64 (m, 2 H), 1.68–1.80 (m, 1 H), 2.06–2.18 (m, 1 H), 2.48 (s, 3 H), 4.04 (dt, 1 H, *J* 1.5, 7.3), 4.32 (s, 2 H) and 7.48 (d, 1 H, *J* 1.2); ν_{max}(Nujol)/cm^{-1} 1672, 1541, 1312, 1227 and 1140; *m/z* 256 (M^+) and 192 ($M^+ - SO_2$) (Found: M^+, 256.0782. $C_{12}H_{16}O_4S$ requires *M*, 256.0770).

Typical Procedure for Alkylation of **3** (*Method B, Entry* 4 *in Table* 2).—To a stirred solution of **3** (R = Bu) (30 mg), Me_2SO_4 (0.03 cm^3, 2.4 equiv.) and HMPA (0.08 cm^3, 4 equiv.) in THF (1 cm^3) was added 1 mol dm^{-3} LiHMDS–THF (0.05 cm^3, 4 equiv.) at −78 °C and the mixture stirred at −78 °C for 10 min undr argon. The reaction was quenched by the addition of aq. NH_4Cl to the mixture which was then extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a pale yellow oily residue which was purified by silica gel TLC (2:3 AcOEt–hexane) to give two isomers of the dialkylated compound **6** (R = Bu, R' = Me) in 72% yield [4 mg (18%) of less polar isomer and 17 mg (54%) of more polar isomer].

Compound **6** (R = Bu, R' = Me), *less polar isomer*: white solid; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.88 (t, 3 H, *J* 7.2), 1.30–1.50 (m, 4 H), 1.62 (d, 1 H, *J* 7.0), 1.96–2.15 (m, 2 H), 2.48 (s, 3 H),

4.07 (dq, 1 H, *J* 1.5, 6.9), 4.36 (dd, 1 H, *J* 5.5, 7.6) and 7.43 (d, 1 H, *J* 1.5); ν_{max}(Nujol)/cm^{-1} 1674, 1541 and 1312; *m/z* 270 (M^+) and 206 ($M^+ - SO_2$) (Found: M^+, 270.0921. $C_{13}H_{18}O_4S$ requires *M*, 270.0926).

Compound **6** (R = Bu, R′ = Me), *more polar isomer*: white solid; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.92 (t, 3 H, *J* 7.3), 1.34–1.64 (m, 4 H), 1.60 (d, 1 H, *J* 7.0), 1.90–2.02 (m, 1 H), 2.28–2.38 (m, 1 H), 2.50 (s, 3 H), 4.10 (dq, 1 H, *J* 1.5, 7.0), 4.28 (dd, 1 H, *J* 3.7, 9.5) and 7.46 (d, 1 H, *J* 1.5); ν_{max}(Nujol)/cm^{-1} 1672, 1540 and 1312; *m/z* 206 ($M^+ - SO_2$) (Found: $M^+ - SO_2$, 206.1286. $C_{13}H_{18}O_2$ requires $M^+ - SO_2$, 206.1297).

Typical Procedure for Alkylation of **4** (*Method A, Entry* 2 *in Table* 3).—To a stirred solution of **4** (R = Me), (40 mg) and BuI (0.05 cm^3, 2 equiv.) in THF (1 cm^3) was added 1 mol dm^{-3} TBAF–THF (1.1 cm^3, 6 equiv.) and the mixture stirred at room temperature for 15 min under argon. The reaction mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. The brown oily residue was purified by silica gel TLC (2:3 AcOEt–benzene) to give two isomers of the dialkylated compound **6′** (R = Me, R′ = Bu) in 61% yield [19 mg (37%) of less polar isomer and 12 mg (24%) of more polar isomer]. The spectral data of these products were identical with those of **6** (R = Bu, R′ = Me).

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