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O-SILYLATED DIENOLATES IN ORGANIC SYNTHESIS:
γ-SELECTIVE ALKYLATION OF UNSATURATED CARBONYL COMPOUNDS BY 1,3-DITHIENIUM FLUOROBORATE.

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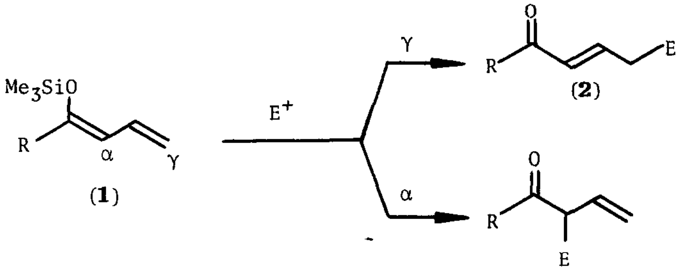
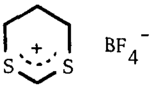
Summary: The alkylation of *O*-silylated dienolates of unsaturated aldehydes, ketones, and esters with 1,3-dithienium fluoroborate shows useful γ-selectivity. The γ-products are selectively protected 1,5-dicarbonyl compounds.

O-Silylated dienolates (**1**) are useful intermediates for the γ-substitution of unsaturated carbonyl compounds.[1-3] We have found, for instance, that the reaction (**1** → **2**) with α-chloroalkyl phenyl sulphides (E = PhSCHR) can be used for γ-alkylation and alkylidenation.[2] The critical γ:α ratio (**2**:**3**) of electrophile attack on **1** was both sensitive to the substrate substitution pattern and the nature of the electrophile.[2-4]



(**1**) (**2**) (**3**)

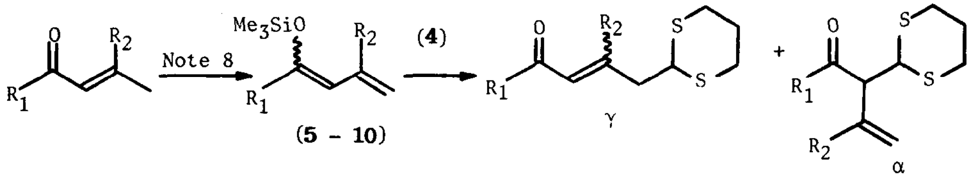


(**4**)

As an extension of this work, we now report that the thiocarbocation electrophile, 1,3-dithienium fluoroborate (**4**), leads to synthetically useful γ-selectivity (γ:α ⩾ 5:1) in the alkylation of a wide range of *O*-silylated dienolates (**1**). The γ-products (**2**,E = 1,3-dithiane-2-yl) are selectively protected 1,5-dicarbonyl compounds, containing the versatile dithioacetal unit[5] for further manipulation.

The readily available electrophile (**4**)[6,7] reacted smoothly and rapidly with *O*-silylated dienolates under identical conditions to those developed for *O*-silylated enolates (CH_3NO_2/CH_2Cl_2, -78°, 10 min).[7] Correspondingly, we feel the γ:α ratios obtained most likely reflect the kinetic selectivities of reaction. The results are summarised in the Table (**5-10**) and in the diagrams **11-23**.

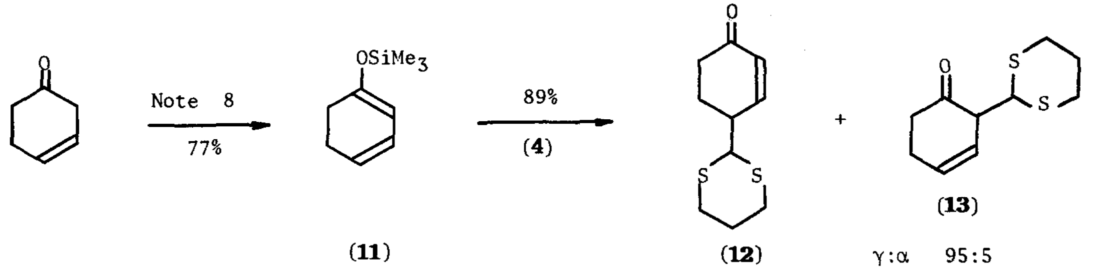
TABLE: Reactions of Acyclic *O*-Silylated Dienolates with 1,3-Dithienium Fluoroborate (**4**) (CH_3NO_2/CH_2Cl_2, 1:3, -78°, 10 min).



	R_1	R_2	γ:α	*E*:*Z* for γ	Yield (γ+α)
(**5**)	EtO	H	53:47	100:0	88%
(**6**)	Bu^tO	H	86:14	100:0	91%
(**7**)	MeO	Me	94:6	45:55	92%
(**8**)	H	H	(100:0)	100:0	30%
(**9**)	H	Me	100:0	40:60	61%
(**10**)	Me	Me	100:0	46:54	87%

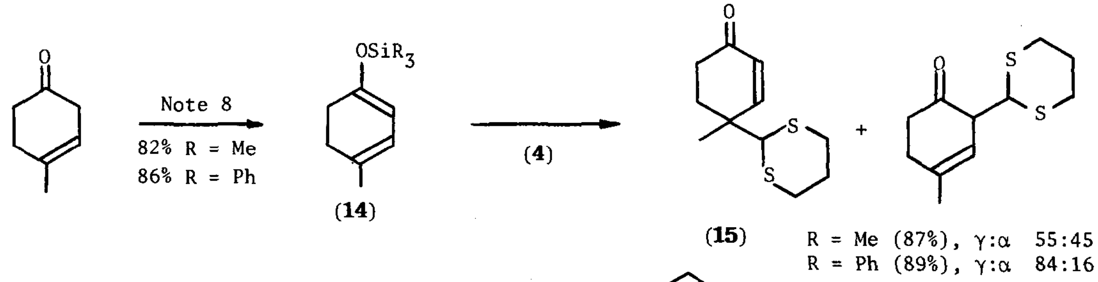
The crotonate-derived *O*-silylated dienolate (**5**) initially showed only low γ-selectivity, however, use of a bulkier alkoxy group, as in **6**, produced a marked improvement in γ-selection.[2] The other α,β-unsaturated ester-derived substrate (**7**) gave a synthetically useful γ:α ratio without this modification. The aldehyde-derived systems (**8** and **9**) gave no identifiable α-products, but the low yield in the reaction of **8** makes this particular result unreliable. The other acyclic substrate examined, **10**, was of enone origin, and gave the γ-product exclusively in high yield. The results for **7**, **9**, and **10** reinforce our earlier finding[2] that an alkyl substituent, R_2, at the β-position enhances γ-selectivity. Interestingly, in these cases, the γ-product was slightly enriched in the *Z*-isomer,[9] whereas in the $ZnBr_2$-catalysed alkylations[2] the *E*-isomer predominated. For R_2 = Me, the aldehyde- and methylketone-derived substrates (**9** and **10**) showed higher γ-selectivity than the corresponding ester derivative (**7**).

We next examined the reaction of some cyclic enone-derived *O*-silylated dienolates (**11**, **14**, **17**, **20**, and **22**) with the 1,3-dithiane cation (**4**). The γ:α ratio was then found to be sensitive to the degree of substitution at the γ-position, as well as at the β-position. The trimethylsilyl dienol ether (**11**) gave the γ-product (**12**) accompanied by only a trace of α-product (**13**), but introduction of a methyl substituent at the γ-position, as in **14** for R = Me, led to the formation of almost equal amounts of the regioisomeric products (**15**) and (**16**).[10] The γ-product (**15**) could be obtained in useful yield, however, by changing to the analogous triphenylsilyl derivative (**14**, R = Ph), as recommended by Fleming and Lee.[4] Alkylation at the tertiary γ-position of **17** was adequately selective with the trimethylsilyl ether itself (**17** → **18**); presumably as there is now an electron-donating alkyl substituent at the β-position encouraging γ-attack. In the case of **20** and **22**, where the γ-position is secondary and also there is a β-substituent, only γ-products were obtained: **21** and **23**,[11] as 5:1 and 8:1 epimeric mixtures respectively.



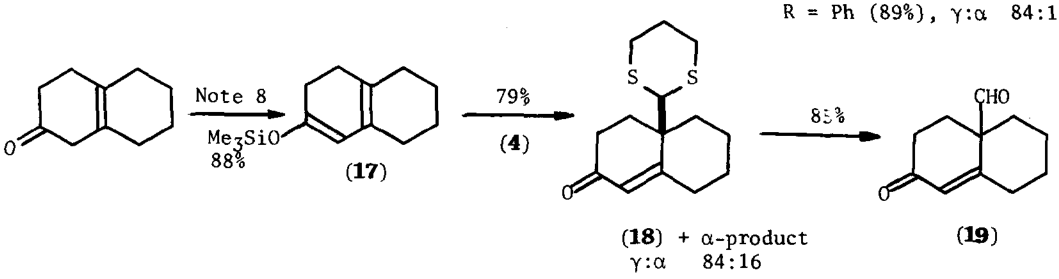
(**11**) (**12**) (**13**)

γ:α 95:5



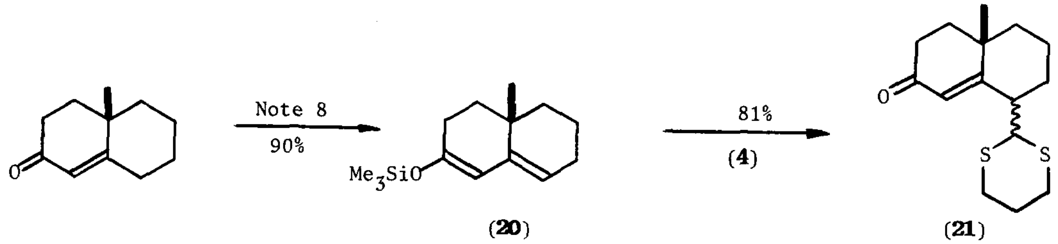
(**14**) (**15**)

R = Me (87%), γ:α 55:45
R = Ph (89%), γ:α 84:16

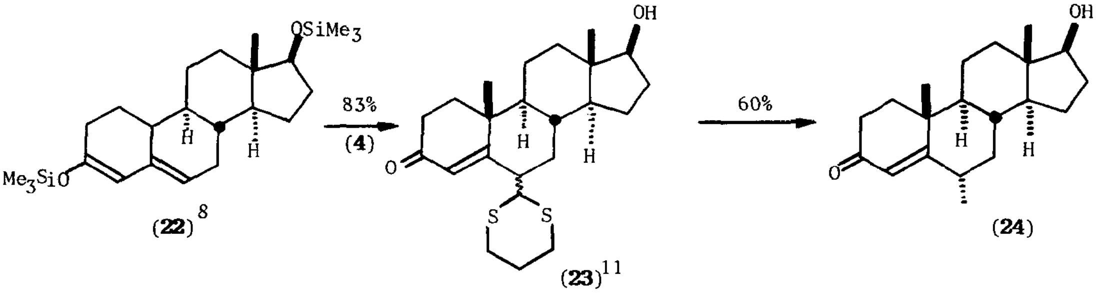


(**17**) (**18**) + α-product (**19**)

γ:α 84:16



(**20**) (**21**)



(**22**)[8] (**23**)[11] (**24**)

Finally, as an illustration of the synthetic potential of these products,[5] hydrolysis of the 1,3-dithiane group in **18** by $HgO\text{-}BF_3{:}OEt_2$ (H_2O-THF)[12] gave the aldehyde (**19**), representing overall γ-formylation. Alternatively, reductive sulphur removal may be used. Treatment of **23** with W-2 Raney nickel (Me_2CO, 20°, 4h)[13] gave 6α-methyltestosterone (**24**),[14] demonstrating a new three-step procedure for the γ-methylation of Δ^4-3-ketosteroids.

In summary, the highly-stabilised thiocarbocation electrophile, 1,3-dithienium fluoroborate, is usually more γ-selective than α-chloroalkyl phenyl sulphides (especially $PhSCH_2Cl$)[2] in its reactions with *O*-silylated dienolates. The introduction of the 1,3-dithiane unit as an electrophilic component into carbonyl compounds[7] should prove a useful addition to its more common nucleophilic role in synthesis.[5]

The *O*-silylated dienolates were prepared as described in note 8. The alkylation reaction with 1,3-dithienium fluoroborate (**4**)[6,7] followed an identical procedure to that described for *O*-silylated enolates (CH_3NO_2/CH_2Cl_2, 1:3, -78°, 10 min),[7] where the α- and γ-alkylation products were separated by flash chromatography on silica gel. The γ:α ratios were measured by 200 MHz ^1H NMR of the crude product mixtures and confirmed by weighing the separated regioisomers.

NOTES and REFERENCES:

[1] T. Mukaiyama and A. Ishida, *Chemistry Letters*, 319 and 1201 (1975), and 467 (1977).

[2] I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Letters*, 3209 (1979).

[3] I. Fleming, J. Goldhill, and I. Paterson, *ibid.*, 3205 (1979).

[4] The γ:α ratio is also influenced by varying the substituents attached to Si, see: I. Fleming and T. V. Lee, *ibid.*, 705 (1981).

[5] B.-T. Gröbel and D. Seebach, *Synthesis*, 375 (1977); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed.*, *4*, 1075 (1965).

[6] E. J. Corey and S. W. Walinsky, *J. Amer. Chem. Soc.*, *94*, 8932 (1972).

[7] See preceding paper.

[8] *O*-Silylated dienolates **5**, **7**, **8**, **9**, **11**, and **14** (R=Me) were prepared as previously described;[2,3] **6** was prepared by the same method as **5** (1. LDA, THF-HMPA 2. Me_3SiCl) in 80% yield; **10** was prepared using 1. KH, THF (20°, 0.5h) 2. Me_3SiCl in 87% yield; **17** was prepared by the same method as **11** (1. LDA, THF 2. Me_3SiCl); **14**, R=Ph was prepared by using 1. LDA, THF 2. Ph_3SiCl; **20** was prepared by using Me_3SiCl, Et_3N, DMF (130°, 6h); **22** was prepared from testosterone using Me_3SiCl, Et_3N, DMAP (catalytic), DMF (130°, 7h) in 91% yield.

[9] It is possible that there is some contribution from a Diels-Alder cycloaddition of acyclic substrates with 1,3-dithienium fluoroborate, a known dienophile,[6] accounting for *kinetic* stereoselectivity for the *Z*-isomer in these particular cases. However, we generally favour direct electrophilic attack for the reactions of these electron-rich dienes.

[10] We previously obtained some indication of this effect in the sulphenylations of **11** and **14** (R = Me), in that **14** gave only a low yield of γ-product, although no α-product was identified.[3]

[11] This reaction (**22** → **23**) was performed at -23°; the major 6α-epimer (**23**) was separated by recrystallisation (m.p. 194-195°; cyclohexane-acetone).

[12] E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, *36*, 366 (1971).

[13] The Ni was partially deactivated by stirring in Me_2CO (20°, 1h) before addition of **23**.

[14] S. Liisberg, W. O. Godtfredsen, and S. Vangedal, *Tetrahedron*, *9*, 149 (1960).

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