# THE γ-ALKYLATION OF ENONES USING SILYL DIENOL ETHERS:
## THE EFFECT OF CHANGING THE ELECTROPHILE AND OF CHANGING THE SILYL GROUP[1]

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*Summary*: Phenylthiomethyl chloride ( **3** ) and the trimethylsilyl dienol ether ( **2** ) of crotonophenone react to give the lowest level of γ-attack of a range of carbon electrophiles and trimethylsilyl dienol ethers; the γ-selectivity for this reaction can be raised from 45:55 to 85:15 by changing the silyl group from trimethylsilyl to triphenylsilyl.

We reported earlier[2] that trimethylsilyl dienol ethers (**1**) react with a variety of electrophiles to give a high proportion of product resulting from attack at the γ-position ($d^4$ reactivity[3]). When $R^1$ in **1** was $Pr^i_2CHO$ and $R^2$ was Me, we got exclusively γ-attack with most of the
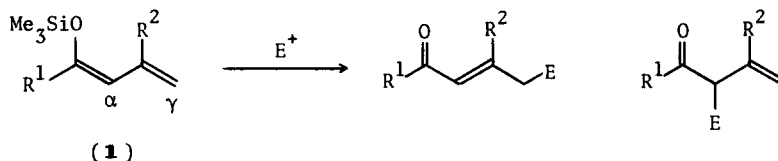


electrophiles that we tried, but when $R^1$ was smaller and $R^2$ was H, several electrophiles gave substantial amounts of α-attack. Since that time, we have sought ways to improve upon these -promising results, and report our progress here.

Our first task was to find which trimethylsilyl dienol ether (**1**) and which electrophile gave the *lowest* proportion of γ-attack relative to α-attack. Our second task would then be to improve this ratio, so that thereafter we could reasonably assume that all other combinations would give a higher proportion of γ-attack. Of the groups $R^1$ which we had tried (H, Ph, OR), phenyl gave the lowest γ:α ratio in phenylthiomethylation (45:55).[2,4] Without searching further,
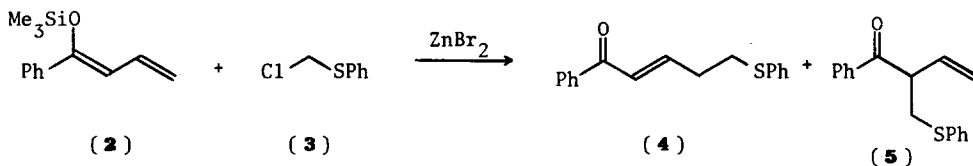


and to keep matters simple, we used the trimethylsilyl dienol ether ( **2** ) with a variety of carbon electrophiles. Those that gave reasonable yields are reported in Table 1; in summary, phenylthiomethylation[4] gave the lowest γ:α ratio.[5,6,7] It is noteworthy that, on the whole, those reagents which give the better-stabilised electrophilic species also give the higher γ:α ratios.[8]

This may be the result of steric, electronic or thermodynamic control, and is reasonable on any of these counts. In the case of phenylthiomethylation, at least, we have been able to show that the γ:α ratio (45:55) is 'kinetic' and not 'thermodynamic': we could see no change in the relative intensities of distinctive p.m.r. signals of the two products (**4** and **5**) as the reaction proceeded. Furthermore, both products, resubmitted to the reaction conditions, were recovered unchanged.[9]

TABLE 1



(**2**)
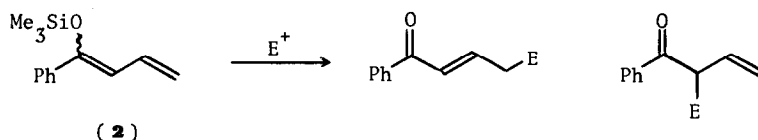
| Electrophilic Reagent | Lewis Acid | Reaction Conditions | γ:α Ratio[10] | Yield[11] |
|---|---|---|---|---|
| $PhSCH_2Cl$ (**3**) | $ZnBr_2$ | $CH_2Cl_2$, r.t., 90 min | $45:55^2$ | $58\%^2$ |
| $MeOCH_2Cl$ | $ZnBr_2$ | $CH_2Cl_2$, r.t., 30 min | 55:45 | 82% |
| $MeCH(OEt)_2$ (**6**) | $ZnBr_2$ | $CH_2Cl_2$, r.t., 2 h | 60:40 | 78% |
| $PhSCHClPr^n$ | $ZnBr_2$ | $CH_2Cl_2$, r.t., 5 min | $66:34^2$ | $85\%^2$ |
| PhCHO | $TiCl_4$ | $CH_2Cl_2$, -23°, 45 min | 100:0 | 48% |
| $Me_2C(OMe)_2$ | $TiCl_4$ | $CH_2Cl_2$, -23°—r.t., 60 min | 100:0 | 78% |
| $(MeO)_3CH$ | $TiCl_4$ | $CH_2Cl_2$, -23°—r.t., 60 min | 100:0 | 52% |

Now that we knew that we were dealing with a kinetically determined ratio, there remained two conspicuous variables with which we could hope to increase the proportion of γ-attack—the silyl group and the Lewis acid. Our results with the first of these variables are summarised in Table 2. The t-butyldimethylsilyl and the triethylsilyl dienol ethers (**7** and **8**) led to an even lower proportion of γ-attack: although larger, these silyl groups are more electron-donating than the trimethylsilyl group, and the electronic effect is evidently greater than the steric. In agreement with this, replacement of each methyl group of the trimethylsilyl ether (**2**) with phenyl groups led progressively to higher and higher proportions of γ-attack, until, with the triphenylsilyl enol ether (**11**), the γ:α ratio was a useful 85:15. Finally, the m-chlorophenyldiphenylsilyl dienol ether (**12**), which has an even more electron-withdrawing group, gave, as far as we could tell (p.m.r.), exclusively the product (**4**) of γ-attack.[12] However, for most purposes, the triphenylsilyl group is both adequate and practical.[13] Thus the reaction of the acetal (**6**) with the triphenylsilyl enol ether (**11**) gave only the product of γ-attack, as we had expected, since this electrophile was already more γ-selective than phenylthiomethyl chloride (Table 1).

These results establish that the silyl group is still in the molecule at the time of reaction. An unattractive but possible mechanism had involved the replacement of the silyl group

by the metal of the Lewis acid as the first step. This may well be a reaction competitive with the alkylation reaction, for we find that the most significant effect of changing the Lewis acid is dramatically to change the overall yield. In most cases, only one Lewis acid is any good, and that not always the same one. In only one case were we able to get tolerable yields with more

TABLE 2
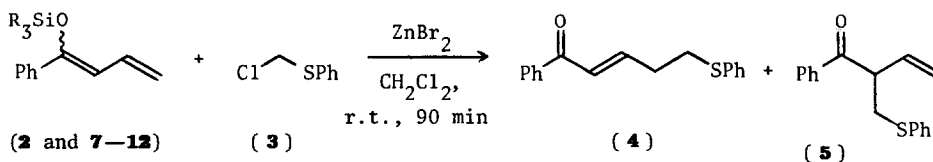


| | Silyl Dienol Ether | Yield of Silyl Dienol Ether | γ:α Ratio[10] | Yield of (4) + (5)[11] |
|---|---|---|---|---|
| (7) | $R_3$ = $Me_2Bu^t$ | 32% | 23:77 | 62% |
| (8) | $R_3$ = $Et_3$ | 52% | 34:66 | 75% |
| (2) | $R_3$ = $Me_3$ | 71% | 45:55[2] | 58%[2] |
| (9) | $R_3$ = $Me_2Ph$ | 48% | 60:40 | 91% |
| (10) | $R_3$ = $MePh_2$ | 68% | 68:32 | 74% |
| (11) | $R_3$ = $Ph_3$ | 59%[13] | 85:15 | 93% |
| (12) | $R_3$ = $m$-$ClC_6H_4Ph_2$ | 26% | 100:0 | 58% |

TABLE 3
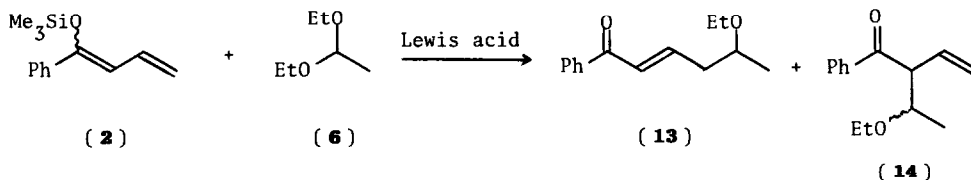


| Lewis Acid | Reaction Conditions | γ:α Ratio[10] | Yield of (13) + (14) |
|---|---|---|---|
| $Me_3SiOSO_2CF_3$ (10 mol %) | $CH_2Cl_2$, -78°, 5 h | 40:60 | 41% |
| $ZnBr_2$ | $CH_2Cl_2$, r.t., 2 h | 60:40 | 78% |
| $TiCl_4$-$Ti(OPr^i)_4$ 1:1 | $CH_2Cl_2$, -50°, 90 min | 80:20 | 79% |

than one Lewis acid: the reaction of the acetal (6) with the trimethylsilyl enol ether (2) worked with zinc bromide,[4,14] with the titanium tetrachloride-titanium tetraisopropoxide mixture,[15] and with trimethylsilyl triflate.[16] The γ:α ratios varied (Table 3), implying that the Lewis acid may still be attached to the acetal at the time of reaction, a state of affairs compatible with what is known[17] of the mechanism of acid-catalysed nucleophilic attack on the acetals of aldehydes.

In summary, we have found that a suitably chosen silyl group should make it possible to get a high degree of γ-alkylation of any enone which can be converted into a linearly conjugated silyl dienol ether. In effect, the more electron-withdrawing the substituents on the silyl group, the more the siloxydiene behaves as one would expect a diene to behave; in contrast, the more electron-donating the substituents, the more it behaves like the corresponding lithium dienolate.

NOTES and REFERENCES:

1. Reprints of this paper are not available.

2. I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Letters*, 3207 and 3209 (1979); for earlier work on the γ-reactivity of silyl dienol ethers, see T. Mukaiyama and A. Ishida, *Chemistry Letters*, 319 and 1201 (1975) and 467 (1977).

3. D. Seebach, *Angew. Chem. Internat. Edn.*, **18**, 239 (1979).

4. For an account of phenylthioalkylation as a method of alkylation or alkylidenation, see I. Paterson and I. Fleming, *Tetrahedron Letters*, 993, 995, and 2179 (1979).

5. This statement needs some qualification. Three electrophiles, t-butyl chloride and adamantyl bromide in the presence of titanium tetrachloride, and m-chloroperbenzoic acid alone, gave products only of α-attack in 21%, 32% (61% based on unrecovered starting material) and 48% yield, respectively. These electrophiles were not used when we sought to improve the γ:α ratio, because the yields were inconveniently low, and the γ:α ratio perhaps misleading. Also, it might be unrealistic at this stage to hope to improve the ratio. It is therefore clear that our solution to the $d^4$ problem using triarylsilyl dienol ethers will not necessarily work with absolutely every electrophile, any more than it can be expected to with every triarylsilyl dienol ether.

6. Electrophiles which we tried without getting any recognisable products were: $MeCOCl$ ($TiCl_4$ or $ZnBr_2$), PhCHMeBr ($ZnBr_2$), $Me_2C=CHCH_2Br$ ($ZnBr_2$), ethylene oxide ($TiCl_4$), mesityl oxide ($TiCl_4$) and 2-nitropropene ($TiCl_4$).

7. Two other electrophiles, NBS and PhSeCl, gave exclusively γ-product in 41% and 83% yield, respectively.

8. In agreement with the trend shown in Table 1, Danishefsky has shown[18] that Eschenmoser's salt ($Me_2N^+=CH_2$), a highly stabilised cation, is a γ-selective electrophile in its reactions with a trimethylsilyl dienol ether.

9. In one other case, that of the reaction of the acetal (**6**) with the silyl dienol ether (**2**), we also resubmitted the products to the reaction conditions and recovered them unchanged.

10. Product ratios were determined by p.m.r. analysis, when there were distinctive signals, and by weighing the separated products; these were consistent within experimental error. The latter are quoted in the Tables. Separations were carried out on silica columns.

11. Yields are the isolated yields, being the sum of the yields of the separated products.

12. The work-up in this reaction was troublesome, and led to the low yield; the silyl group is less readily available than the others used in this work; and the ether (**12**) was difficult to handle, since it hydrolysed rather readily.

13. The yield of the triphenylsilyl dienol ether (**11**) was not optimised (nor were those of the other new silyl dienol ethers); the low yield here is probably not serious, since we have been able to make other triphenylsilyl dienol ethers in high yield.

14. I. Paterson, *Tetrahedron Letters*, 1519 (1979).

15. T. Mukaiyama and A. Ishida, *Chemistry Letters*, 319 (1975).

16. S. Murata, M. Suzuki, and R. Noyori, *J. Amer. Chem. Soc.*, **102**, 3248 (1980) and *Tetrahedron Letters*, 2527 (1980).

17. M. L Sinnott and W. P. Jencks, *J. Amer. Chem. Soc.*, **102**, 2026 (1980).

18. S. Danishefsky and M. Prisbylla, *Tetrahedron Letters*, 805 (1980); see also, S. Danishefsky, A. Guingant, and M. Prisbylla, *ibid.*, 2033 (1980).