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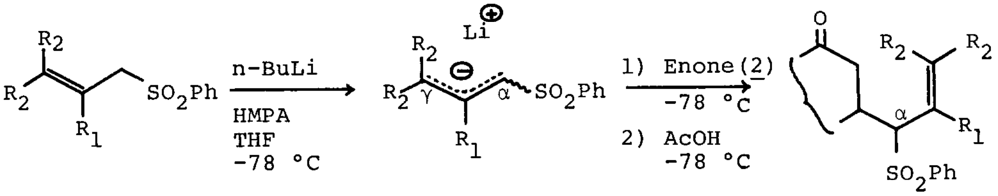
# REGIOSELECTIVE CONJUGATE ADDITION OF SULFONYLALLYL CARBANIONS TO α,β-UNSATURATED KETONES

Masahiro Hirama
Suntory Institute for Bioorganic Research
Shimamoto-cho, Mishima-gun, Osaka 618, Japan

Summary: Ambident lithium carbanions of allyl phenyl sulfones add 1,4-α to both acyclic and cyclic enones exclusively if HMPA is present in the medium; in contrast, 1,2-α addition to cyclic enone is the major kinetic course in the absence of HMPA, which is followed by rearrangement to the 1,4-γ adduct.

Two aspects in regioselectivity come into play simultaneously when conjugated enones are reacted with the ambident nucleophile, sulfonylallyl carbanion.[1] Namely, these are the problems of 1,2- or 1,4-addition[2] to the enone, and α- or γ-substitution[3] of the carbanion. For instance, the conjugate addition of n-butyllithium-generated allyl sulfone anions to enones was reported recently, but the regioselectivity was opposite between 2-cyclohexenone(1,4-γ) and 3-penten-2-one(1,4-α).[4] During the course of a synthetic project, it became necessary to develop conditions which would lead to selective 1,4-α conjugate additions. Exploratory studies have led to the finding that clean 1,4-α additions to both acyclic and cyclic enones can be realized when the lithium carbanions(1 mol) are reacted in the presence of 2 mol of hexamethylphosphoramide(HMPA) at -78 °C.

The results of the reaction of allyl(1a), β-methallyl(1b) and prenyl phenyl



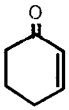
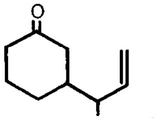
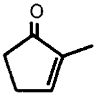
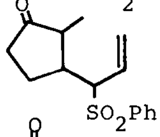
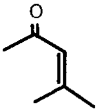
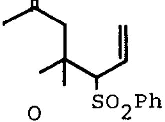
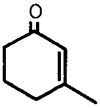
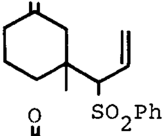
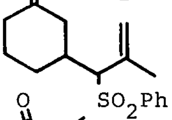
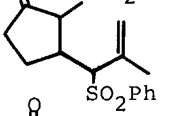
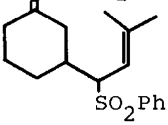
1a, $R^1=R^2=H$

1b, $R^1=CH_3$, $R^2=H$

1c, $R^1=H$, $R^2=CH_3$

3

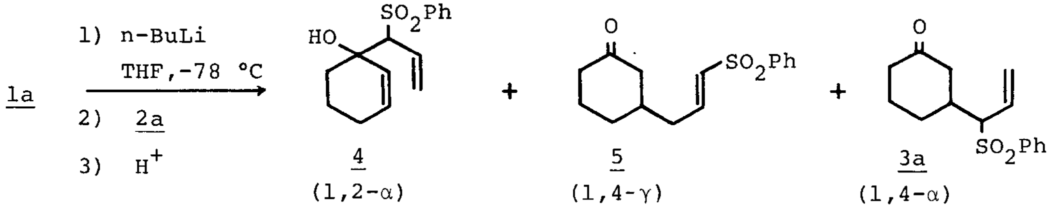
Table 1. 1,4-α Addition of Sulfonylallyl Carbanions to Enones.

| sulfone | enone | | 1,4-α adduct | | % yield |
|---|---|---|---|---|---|
| 1a |  | 2a |  | 3a | 89 |
| 1a |  | 2b |  | 3b | 94 |
| 1a |  | 2c |  | 3c | 70 |
| 1a |  | 2d |  | 3d | 71 |
| 1b | 2a | |  | 3e | 91 |
| 1b | 2b | |  | 3f | 79 |
| 1c | 2a | |  | 3g | 76 |

sulfones(1c) with several enones(2a-2d) are shown in Table 1.[5] All yields quoted are those of chromatographically isolated products. This rapid and exclusive 1,4-α addition of lithium anion of 1a to 2a was found to be complete within 2 min.[6] It is also noteworthy that, in contrast to the recent observation,[4] smooth additions took place even with β,β-disubstituted substrates such as 2c and 2d.

On the other hand, when the reaction is carried out in THF at -78 °C in the absence of HMPA, the lithium anion of 1a reacts with 2a to give the 1,2-α adduct (4) as the major kinetic product, which in turn is transformed mainly to the 1,4-γ adduct(5), slowly at -78 °C or quickly at 0 °C(Table 2[5a]). The thermodynamically controlled formation of 1,4-γ adduct(5) from 1,2-α one(4) was confirmed by the treatment of isolated 4 with n-butyllithium at -78 °C in THF, followed by warming to 0 °C for 40 min; this afforded 5[7] and 3a in yields of 83% and 17%, respectively.

Table 2. Product Distribution as a Function of Reaction Time, Temperature and Additive(HMPA) in the Reaction of Anion of 1a with 2a in THF.



| reaction condition | 4 | 5 | 3a | total yield % |
|---|---|---|---|---|
| -78 °C, 2.5 min | 69 | 22 | 8 | 95 |
| -78 °C, 10 min | 65 | 27 | 8 | 100 |
| -78 °C, 50 min | 43 | 46 | 11 | 89 |
| -78 °C, 10 min ⟶ 0 °C, 40 min | 0 | 83 | 17 | 81 |
| -78 °C, 10 min ⟶ with HMPA(2 equiv.) -78 °C, 40 min | 14 | 44 | 42 | 75 |

However, a considerable amount of 1,4-α(3a) was produced, in addition to 1,4-γ(5) and recovered 4, when 2 equiv. of HMPA was added to the reaction mixture at -78 °C, 10 min after the addition of 2a to the anion of 1a, and subsequent maintenance of the mixture at the same temperature for 40 min(Table 2). This HMPA-induced transformation of 4 to 3a was also demonstrated by treating isolated 4 with n-butyllithium in THF-HMPA(2 equiv.) at -78 °C for 40 min; this afforded 3a in 73% yield, but in both cases, 14% and 25% respectively, of unreacted 4 was still present. Therefore, it can be concluded that the rapid and highly regioselective formation of 1,4-α adduct in the THF-HMPA(2 equiv.) system shown in Table 1 results from a direct conjugate addition rather than a kinetically controlled 1,2-α addition and subsequent rearrangement.

The HMPA-induced control of regioselectivity leading to 1,4-α adducts is currently being utilized in syntheses of carbocyclic natural products.

A typical experimental procedure(Table 1) is as follows. To a solution of 182 mg(1.0 mmol) of 1a and 0.348 ml(2.0 mmol) of HMPA in 4.0 ml of dry THF was dropwise added 0.70 ml(1.0 mmol) of 1.43 M n-butyllithium in hexane at -78 °C under $N_2$ and the mixture was stirred at the same temperature for 10 min. To the deep yellow solution was quickly added 0.116 ml(1.2 mmol) of 2a at -78 °C. Addition of 2a resulted in a rapid discharge of the color. After 30 min at -78 °C, the mixture was quenched by the addition of 0.070 ml of acetic acid and then saturated aqueous $NH_4Cl$ was added at -78 °C. The mixture was allowed to warm to room temperature and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography(hexane/ether = 1/1) to yield 247 mg(89% yield from 1a) of 3a as a colorless solid mixture of racemic diastereoisomers.

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## References and Notes

1) For the versatility of allyl sulfones as synthetic intermediates, see: B. M. Trost, N. R. Schmuff and M. J. Miller, *J. Am. Chem. Soc.*, **102**, 5979(1980) and references cited threrin.
2) For regioselective 1,4-addition of acyl anion equivalents, see: P. C. Ostrowski and V. V. Kane, *Tetrahedron Lett.*, 3549(1977); C. A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 100(1979); J. Lucchetti, W. Dumont and A. Krief, *Tetrahedron Lett.*, 2695(1979).
3) For regioselectivity in the reactions of ambident nucleophiles, see: D. Seyferth, G. J. Murphy and B. Mauzé, *J. Am. Chem. Soc.*, **99**, 5317(1977); Y. Yamamoto, H. Yatagai and K. Maruyama, *J. Org. Chem.*, **45**, 195(1980); F. E. Ziegler and C. Chan Tam, *Tetrahedron Lett.*, 4717(1979).
4) G. A. Kraus and K. Frazier, *Synth. Commun.*, **8**, 483(1978).
5) (a) All new compounds were fully characterized by NMR(360 MHz), IR and MS (high resolution).
   (b) The 1,4-α adducts are the mixtures of racemic diastereoisomers, the ratios of which were determined by 360 MHz $^1$H-NMR as follows: 3a(3:1), 3b(3:1), 3d(3:1), 3e(3:1), 3f(2:2:1), 3g(2:1).
6) A very small amount of two other isomers was detected in the reaction mixture by 360 MHz $^1$H-NMR; namely, peak intensities led to a ratio of 97:2:1 for 1,4-α(3a):1,4-γ(5):1,2-α(4).
7) Although oxy-Cope rearrangements of lithium alkoxides are normally slow [see, D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765(1975)], it is conceivable that the transformation of 4 into 5 is accelerated by the sulfone group.

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