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Michael Reactions of Allylic Sulfones with Nitroolefins. Regio- and Stereochemical Control

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Abstract: Michael addition of allylsulfone carbanions to nitroolefins where shown to be sensitive to substitution in both the donor and the acceptor. While sulfone **10** gave predominantly products of γ-addition with aromatic nitroolefins, addition to aliphatic nitroolefins produced almost exclusively α-adducts. In the presence of an OH function in the sulfone (see **13**) only (Z) γ-adducts were observed, while a bromine substituent reversed the regiochemistry.

The Michael addition is a powerful method for the formation of single C-C bonds, hence the current interest to achieve stereocontrol, in reactions of acyclic precursors,[2,3] and regiocontrol, when allylic anions are involved as donors.[4] In this context a recent study on conjugate additions of allylic sulfones to cyclic enones revealed the preferential formation of vinylic sulfone adducts via γ-addition, rationalized by the steric constraints of a cyclic transition state.[5,6] There are no reports, however, on the outcome of analogous reactions with nitroolefins, which are highly effective Michael acceptors.[3]

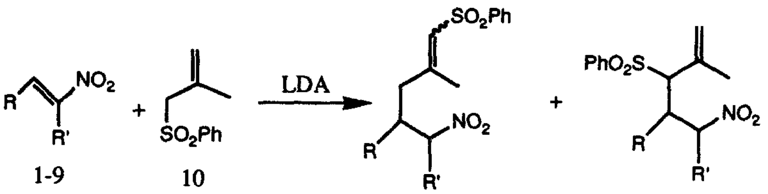
We report herewith some preliminary findings on conjugate additions of allylic sulfones to nitroolefins which emphasize the influence of substitution in both reactants on the stereo- and regiochemical outcome of the reactions. When lithiated methallyl sulfone **10** was reacted with β-nitrostyrene **1** (Table, entry 1)[7] preferential γ-addition occurred (83%) to give vinylic sulfones (**11a,b**), with diastereomeric **12a,b** as the minor products of α-addition.[8] Electron-releasing (p-OMe) or withdrawing (p-Cl) groups caused a varying decrease of regioselectivity (entries 3,4,6). The major vinylic sulfone stereoisomer had an (E) geometry[9] (ratio E/Z: 90-95:10-5), rationalized by the cisoid configuration of the carbanion.[4] When hexamethylphosphoramide (HMPA) was added to the reaction mixture[10] (entries 2 and 5) similar amounts of (E) and (Z) isomers were formed. These results were consistent with a weakening of coordination of the cisoid carbanion with the counterion, which brought as well to the relative increase in α-addition.

A reversal of regiochemical preference occurred when lithiated methallylsulfone **10** was reacted with aliphatic instead of aromatic nitroolefins under identical conditions (Table, entries 8-11).[7] With nitropropene as the acceptor, α-addition occurred exclusively, to give diastereomers **12** in a *syn:anti* ratio of 84:16.[11] The degree of diastereoselectivity at the vicinal centers of allylic sulfone products **12** decreased with increase of the bulk of the aliphatic nitroolefin, but the regioselectivity remained high even with hindered nitroolefins, hence the regioreversal cannot be attributed to steric factors.

Even more dramatic regio- and stereochemical preferences were observed when substituents were introduced in the methyl group of methallyl sulfone. Thus lithiation of hydroxysulfone **13**[12] (2.2 equiv. LDA) and addition of an aromatic nitroolefin[7] led to the formation of a single, regio- and stereohomogeneous product (**15** - **17**, Scheme) by exclusive γ-addition in high yield.[13,14]

Conversely, reaction[15] of bromosulfone **14**[16] with the same nitroolefins occurred regioselectively to give, by α-addition, at the sulfone substituted terminus, the products **18** - **19**, with vinylic sulfones being

TABLE[a]

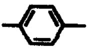
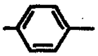
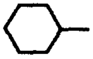


1-9

10

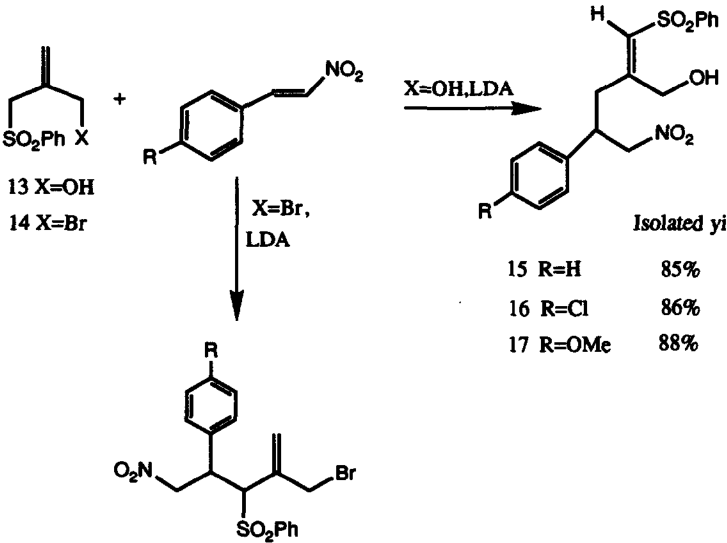
11a (E)
11b (Z)
γ-addition

12a (syn)
12b (anti)
α-addition

Entry	Nitroolefin	11a:11b ratio(%)	12a:12b ratio(%)	Total yield (%)
1	1; R=Ph ; R'=H	79:4	8:9	93
2	1+HMPA	28:40	13:19	89
3	2; R= Cl ;R'=H	72:4	12:12	88
4	3; R= H_3C ; R'=H	69:6	18:7	90
5	3+HMPA	30:27	28:15	97
6	4; R=H_3CO ; R'=H	62:5	9:24	87
7	5; R=Ph ; R'=CH_3[b]	100:0	0	71
8	6; R=CH_3 ; R'=H	0	84:16	90
9	7; R=$CH_3(CH_2)_4$- ; R'=H	8[c]	72:20	82
10	8; R=$(CH_3)_2CH$- ; R'=H	2[c]	71:27	53
11	9; R= ; R'=H	6[c]	63:31	90

[a] The α:γ addition ratio as well as the (E):(Z) and *syn:anti* ratio were determined (a) by ^1H NMR analysis of the crude products and (b) by chromatographic separation and spectral characterization of pure products; [b] Two diastereomers of 11a were formed: erythro:threo:72:28; [c] The minor γ-adduct is the E-isomer.

SCHEME



13 X=OH
14 X=Br

	Isolated yield
15 R=H	85%
16 R=Cl	86%
17 R=OMe	88%

	Isolated yield[a] of α-adducts
18 R=H	66%[b]
19 R=OMe	69%[c]

[a] γ-adducts (<10%) were also formed along with other byproducts; [b] *syn:anti* ratio : 85:15; [c] *syn:anti*:ratio:75:25.

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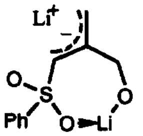
formed only in minor amounts. Exclusive α-addition occurred as well in reactions of **14** with aliphatic nitroolefins (e.g. nitrobutene gave in 72% yield the diastereomeric allylic sulfone adducts).

An attempt to rationalize the regiochemical behavior of some unsymmetrically substituted allyl anions in 1,2 additions to carbonyl groups was previously made either in terms of preference of the electrophile to the harder or softer allylic anion terminus,[18] or by charge distribution and HOMO polarization.[19,20] The complete selectivity achieved presently with sulfone **13** as donor can be rationalized by the intermediacy of the chelated anion (A) which ensures the ultimate-geometry of the double bond in **15** - **17** in a more selective manner than in sulfone **10**. This coordination affects also charge distribution leading to greater preference for γ-attack. A contrary effect could be expected in **14**, in which charge delocalization at the CH_2 terminus, due to the participation of allylic bromine, should enhance attack at the sulfone-substituted carbon, leading to **18** - **19**, respectively. Studies are continuing for the rationalization of the substitution influence, with emphasis on the unprecedented effect of allylic substituents equally distanced from the reactive termini. This should contribute to the exploitation of such reactions for new and selective synthetic routes.



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7. In a typical experiment, to a stirred solution of LDA (0.35 mmol) in THF (2ml) prepared at 0°C and then cooled to -100°C was added dropwise the sulfone **10** (0.32 mmol in 0.5 ml THF) and after 10 min the nitroolefin (0.35 mmol) in 0.3 ml THF. After stirring for 30 min at the above temperature the reaction mixture was quenched (diluted AcOH), extracted (CH_2Cl_2) and chromatographed.
8. The structure of all products has been spectrally confirmed; characteristic ^{1}H NMR vinylic proton shifts of products, entry 1, are as follows ($CDCl_3$, 300 MHz): **11a** (E): δ 5.99 (s, 1H), **11b** (Z): δ 6.17 (s, 1H); **12a** (*syn*): δ 4.57 (bs. 2H); **12b** (*anti*): δ 5.38 (s, 1H), 5.32 (s, 1H).
9. Evidenced by ^{1}H NMR analysis and NOE experiments.
10. For amounts and conditions shown in note 7, 0.5 ml HMPA mixed with 0.5 ml THF was added 10 min prior to the nitroolefin.
11. ^{1}H NMR of the major (*syn*) diastereomer **6**, entry 8: δ 7.86 - 7.49 (m, 5H), 5.01 (dd, J = 13, 5 Hz, 1H) 4.99, (s, 1H), 4.84 (s, 1H), 4.76 (dd, J = 13, 8 Hz), 3.75 (d, J = 9 Hz, 1H), 3.22-3.10 (m, 1H), 1.66 (s, 3H), 1.15 (d, J= 7 Hz, 3H).
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13. Addition of **13** to aliphatic nitroolefins was not regioselective in view of the shown above opposite preference of the donor to γ-addition and the acceptor to α-addition.
14. Representatively, compound **15** had mp 75-76°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.6-7.0 (m, 10 H), 5.9 (s, 1H), 4.61-4.35 (m, 4H), 3.78-3.65 (m, 1H), 2.78-2.42 (m, 3H).
15. Th reaction was quenched after 3 min under otherwise identical conditions,[7] to prevent anion attack on Br.
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17. Representatively, compound **18** (*syn* isomer) had mp 144-145 °C; ^{1}H NMR: δ 7.8 - 7.0 (m, 10H), 5.89 (bs, 2H), 5.02 (dd, J = 12, 3 Hz, 1H), 4.85 - 4.6 (m, 1H), 4.35 (bs, 2H), 4.10 (d, J = 10 Hz, 1H), 3.9 (d, J = 10 Hz, 1H); ^{1}H NMR of the *anti* isomer: δ 7.15 - 7.91 (m, 10H), 5.66 (dd, J = 13, 4 Hz, 1H), 5.49 (s, 1H). 5.43 (s, 1H), 5.02 (dd, J = 13, 10 Hz, 1H), 4.11 - 4.30 (m, 2H), 3.28 (d, J = 11 Hz, 1H), 3.03 (d, J = 11 Hz, 1H).
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