# Selective Synthesis of α-Sulphenyl-, α-Sulphinyl-, and α-Sulphonyl-α,β-unsaturated Carbonyl Compounds by the Knoevenagel Reaction

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Simple treatment of aldehydes with the carbonyl compounds (**1**) [$R^2COCH_2S(O)_nAr$; $n = 0, 1, 2$] and piperidine stereoselectively produces the condensation products (**7**), the stereochemistry of which is controlled by the steric requirements of two functional groups $COR^2$ and $S(O)_nAr$ in a sulphur-stabilized carbanion intermediate.

Carbonyl, sulphenyl, sulphinyl, and sulphonyl groups exert a strong stabilizing effect on carbanions. In aldol condensations the sodium and lithium enolates of methyl phenylsulphenylacetate (**1**; $R^2$ = OMe, Ar = Ph, $n$ = 0) and ethyl phenylsulphinylacetate (**1**; $R^2$ = OEt, Ar = Ph, $n$ = 1) are too stable to react with aldehydes (**6**) whereas the use of magnesium and zinc salts drives the equilibrium of the condensations towards products.[1,2] When a leaving group is β to the above functional groups in β-elimination reactions, elimination probably proceeds by the *E*1*cb* mechanism sometimes in a stereoconvergent manner to give the most thermodynamically stable isomer of the olefin.[3,4] Julia *et al.* treated the sulphones (**2a, b**) with a base and found that *threo*- and *erythro*-(**2a**) underwent stereospecific elimination to yield *Z*- and *E*-isomers of the sulphone (**3**), respectively, while both *threo*- and *erythro*- (**2b**) afforded only the *E*-isomer of (**3**).[5] On the other hand, we have found that treatment of a diastereoisomeric mixture (*threo* : *erythro*, 55 : 45)[1] of the sulphide (**4a**)

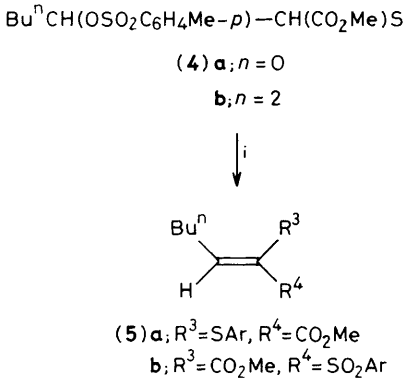
**Table 1.** Preparation of (7) by the Knoevenagel reaction.

| Compound (7) | $R^1$ | $R^2$ | Ar | *n* | Temp./ °C | Time/ h | Yield/ % | Configuration |
|---|---|---|---|---|---|---|---|---|
| **a** | $\mathrm{Bu^n}$ | OMe | $C_6H_4Cl$-*p* | 2 | 0 | 24 | 80 | *E* |
| **b** | $\mathrm{Bu^n}$ | OMe | $C_6H_4Cl$-*p* | 1 | 0 | 24 | 70 | *E* |
| **c** | $\mathrm{Bu^n}$ | $\mathrm{OBu^t}$ | Ph | 1 | 0 | 24 | 67 | *E* |
| **d** | $\mathrm{Pr^i}$ | OMe | $C_6H_4Cl$-*p* | 1 | 20 | 24 | 90 | *E* |
| **e** | Ph | OMe | Ph | 1 | 60 | 6 | 85 | *E* |
| **f** | $\mathrm{Bu^n}$ | Ph | Ph | 0 | 60 | 6 | 73 | *Z* |
| **g** | $\mathrm{Bu^n}$ | Ph | Ph | 1 | 0 | 10 | 61 | *E* |
| **h** | $\mathrm{Bu^n}$ | Me | Ph | 0 | 60 | 6 | 63 | *Z* |
| **i** | $\mathrm{Bu^n}$ | Me | Ph | 1 | 0 | 6 | 68 | *Z* |
| **j** | $\mathrm{Bu^n}$ | Me | Ph | 2 | 0 | 24 | 60 | *E* |

$R^2COCH_2S(O)_nAr$
(**1**)

$\mathrm{Bu^n}CHX\text{-}CH(Me)SO_2Ph$ $\mathrm{Bu^n}CH{=}C(Me)SO_2Ph$
(**2**) **a**; $X = OSO_2C_6H_4Me$-*p* (**3**)
**b**; $X = OAc$

**Scheme 1.** Ar = $C_6H_4Cl$-*p*; i, DBU, $CH_2Cl_2$, room temp.

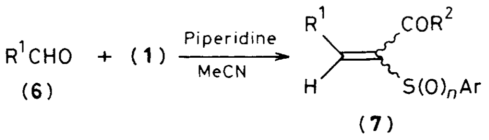


(**4**) **a**; *n* = 0
**b**; *n* = 2

(**5**) **a**; $R^3 = SAr$, $R^4 = CO_2Me$
**b**; $R^3 = CO_2Me$, $R^4 = SO_2Ar$

or the sulphone (**4b**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) leads to the *Z*-sulphide (**5a**) (87% yield) or the *E*-sulphone (**5b**) (89% yield), respectively (Scheme 1).

These results suggest that the combined stabilizing effect of both a carbonyl group and a sulphur atom on a carbanion should result in stereoconvergent elimination, regardless of the leaving group. Using this assumption α-sulphenyl-, α-sulphinyl-, and α-sulphonyl-α,β-unsaturated carbonyl compounds (**7**) were prepared stereoselectively from (**6**) and the carbonyl compounds (**1**). Dressler and Graham have reported the Knoevenagel condensations of aromatic aldehydes and (**1**; $R^2 = OEt$, Ar = Ph, *n* = 2), but the stereochemistry remained uncertain.[6]



(**6**) (**7**)

A solution of (**6**) (1.2 equiv.), (**1**), and piperidine (0.1 equiv.) in MeCN was kept at 0—60 °C. Chromatography on silica gel gave one isomer of (**7**). The yields of the other diastereoisomers were lower than 3%, for example, the *E*:*Z* ratio in (**7b**) was 99:1 in the reaction mixture (by h.p.l.c.). Treatment of the sulphoxides [*e.g.*, (**7b**)] with NaI and $(CF_3CO)_2O$ in acetone[7] gave the corresponding sulphides [*e.g.*, *E*-isomer of (**5a**)] in quantitative yields with retention of configuration. The structural assignments were confirmed by the comparison of the olefinic proton signals in $^1H$ n.m.r. spectra with those of the conjugated sulphides (**7**; *n* = 0), in which the signal *cis* to a carbonyl group is shifted markedly downfield. Typical results from reactions of (**1**) and (**6**) are shown in Table 1.

Similar treatment of butanal with methyl benzoylacetate gave the condensation product in 77% yield, but with low stereoselectivity (*E*:*Z* 40:60). It may be concluded then that a sulphur atom plays an important role in stabilizing the intermediate carbanion, and the steric requirements of the functional groups decrease in the order $SO_2Ar > COMe > S(O)Ar > COAr > CO_2Me > SAr$.

The present synthetic method has the following advantages: (1) reagents are readily available, (2) the procedure is simple, and (3) the applications of stereospecific oxidation (using *m*-chloroperbenzoic acid) and reduction [NaI–$(CF_3CO)_2O$] make it possible to prepare stereoselectively *E*- and *Z*-isomers of (**7**), which may be used as Michael acceptors[8,9] and as Diels–Alder dienophiles.

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