Enantioselective Aldol-type Condensation Mediated by Chiral α-Sulphinyl Hydrazones

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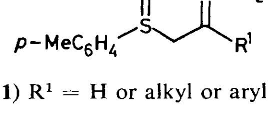
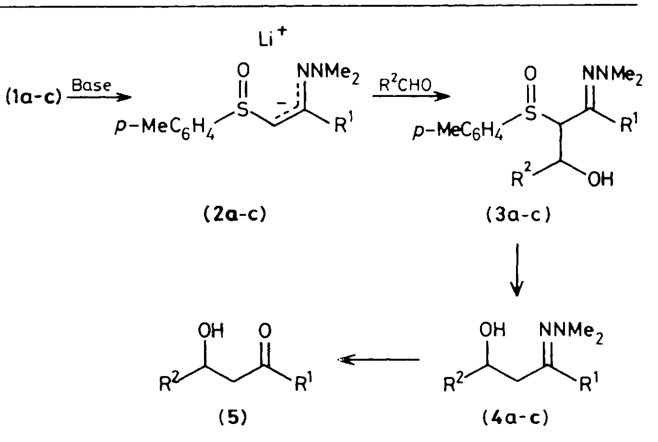
Asymmetric synthesis occurs in the aldol-type condensation of α-sulphinyl hydrazones with aldehydes to give β-hydroxy-hydrazones and -ketones of good enantiomeric purity.

Enantiomerically pure α-sulphinyl hydrazones (**1**), a new class of chiral sulphur-containing derivatives, were recently synthesized by the reaction of diastereoisomerically pure (−)-(*S*)-menthyl toluene-*p*-sulphinate with the appropriate α-lithio-*N*,*N*-dimethylhydrazones.[1] We report here the application of compounds (**1a**—**c**) in enantioselective aldol-type condensations[2] (Scheme 1).

Metallation of (**1a**—**c**) by the action of Bu^nLi or Bu^nLi–HMPA (HMPA = hexamethylphosphoramide) gave (**2a**—**c**), which were treated with aldehydes to afford the adducts (**3a**—**c**) as a mixture of diastereoisomers. Reductive desulphurisation[3] (10% Na–Hg, NaH_2PO_4, MeOH) carried out on the crude products of the condensation reaction, gave optically active β-hydroxy-hydrazones (**4a**—**c**), which were purified by chromatography on silica gel. In the case of compounds (**4a**) and (**4c**) the enantiomeric excess (e.e.) was



(**1**) R^1 = H or alkyl or aryl



(**1a**), (**2a**) R^1 = H
(**1b**), (**2b**) R^1 = Me
(**1c**), (**2c**) R^1 = Ph
(**3a**), (**4a**) R^1 = H, R^2 = Ph
(**3b**), (**4b**), and (**5**) R^1 = Me, R^2 = Ph
(**3c**), (**4c**) R^1 = Ph, R^2 = Et or Pr^i

Scheme 1

Table 1. Enantioselective condensation of (**1a**—**c**) with aldehydes R^2CHO.

Entry	Hydrazones[a]	t_1[b] min	t_2[c] min	R^2	Yield[d] (%)	Enantiomeric excess[e] (%)
A	(**1a**)	5	2	Ph	28	21[f]
B	(**1a**)[g]	5	2	Ph	40	34[f]
C	(**1b**)	3	3	Ph	20	33[f]
D	(**1b**)[g]	3	3	Ph	22	50[f]
E	(**1b**)[g]	3	900	Ph	10	12[f]
F	(**1b**)[g]	420	3	Ph	12	16[f]
G	(**1b**)[h]	60	180	Ph	20	10[i]
H	(**1c**)	3	3	Et	45	7[i]
I	(**1c**)	3	3	$\mathrm{Pr^i}$	21	58[f]
J	(**1c**)[g]	3	3	$\mathrm{Pr^i}$	25	56[f]
K	(**1c**)[h]	60	180	$\mathrm{Pr^i}$	25	88[f]
L	(**1c**)	3	3	Ph	no reaction	
M	(**1c**)[g]	3	3	Ph	no reaction	

[a] All reactions carried out at −90 °C under argon with 0.05 M solution of the hydrazone in tetrahydrofuran and with 1.0 mol. equiv. of $\mathrm{Bu^nLi}$ (1.4 M solution in hexane). [b] Metallation time. [c] Condensation time. [d] Overall yield of (**4a**), (**4c**), and (**5**) starting from (**1a**), (**1c**), and (**1b**) respectively. [e] Determined using (**4a**), (**4c**), and (**5**) (see text). [f] Laevorotatory. [g] Under the conditions described in footnote a and in the presence of 2 mol. equiv. of HMPA. [h] Under the conditions described in footnote a but with 1.5 mol. equiv. of $\mathrm{Bu^nLi}$ and 3.0 mol. equiv. of HMPA. [i] Dextrorotatory.

directly determined by ^1H n.m.r. spectroscopy with the aid of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). The enantiomeric composition of compound (**4b**) could be evaluated in an analogous way after conversion into the corresponding β-hydroxy-ketone (**5**) *via* copper(II) chloride-promoted hydrolysis.[4]

The reaction conditions and e.e.s are reported in Table 1. Although we cannot propose a comprehensive rationalization of the results, we should like to point out some general trends.

It seems reasonable that the increase in enantioselectivity, observed when the steric requirement of the R^1 group in compounds (**1a**—**c**) becomes more demanding (entries A, C, and I),† might be a consequence of the different C=N isomer *E*:*Z* ratio in (**2a**—**c**), which in turn depends on the different C=N isomer *E*:*Z* ratio of the original hydrazones (**1**),[1]‡ and on the reaction conditions. A more crowded compound of type (**2**) should differentiate more between the two enantiofaces of an aldehyde. The presence of HMPA secures better or at least comparable e.e.s with respect to those obtained in its absence (entries A and B, C and D, and I and J).

Longer metallation or condensation times result in lower chemical as well as optical yields (entries D, E, and F).

An increase in the bulk of the R^2 group of the aldehyde is reflected in a marked increase in the e.e. of the β-hydroxy-hydrazones (entries H and I).

More puzzling is the effect of an increase of both the base: substrate molar ratio and of the reaction times (entries G and K). Starting from hydrazone (**1c**) an enhancement of stereoselectivity was obtained, leading to an e.e. of 88%, the best result of aldol-type enantioselection achieved by using a chiral hydrazone reported so far.[6] Conversely, for (**1b**) the use of 1.5 mol. equiv. of base and of longer reaction times led to the β-hydroxy-ketone (+)-(**5**), *i.e.* with the opposite absolute configuration to that of the usually produced (−)-(**5**). Thus, in this case, both enantiomers have been synthesized starting from the same chiral precursor.

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† Unfortunately and surprisingly (**1c**) did not condense with benzaldehyde. However, isobutyraldehyde can be considered a sterically comparable substrate.[5]

‡ *E*:*Z* ratios are 100:0, 75:25, and 15:85 for (**1a**), (**1b**), and (**1c**) respectively.