Functionalisation of Unsaturated Amides: Synthesis of Chiral α- or β-Hydroxy Acids

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Mercury cyclisation of hemiamidals containing a stereogenic centre affords diastereoisomeric mixtures of tetrahydro-1,3-oxazin-4-ones or oxazolidin-4-ones, which are easily separated by silica gel chromatography and hydrolysed to give chiral α- and β-hydroxy acids.

We recently reported the electrophile promoted cyclisation of allylic α,β or β,γ-unsaturated carbamates containing commercially available (*S*)-1-phenylethylamine as the chiral entity. This strategy gave diastereoisomeric mixtures of heterocyclic compounds, which are useful intermediates for the synthesis of amino-alcohols [1] or vicinal diamines.[2]

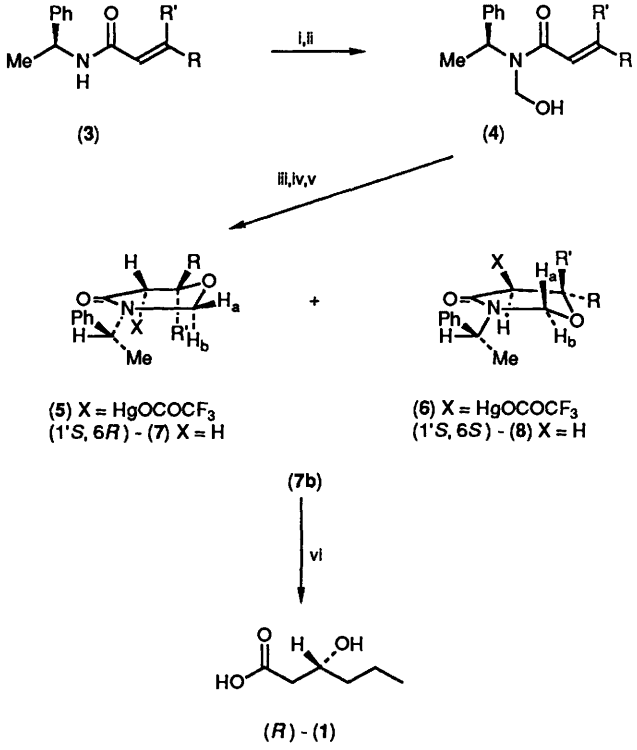
Owing to the preferential conformation of the carbon–hydrogen bond of the stereogenic centre which eclipses the carbonyl group of the newly formed heterocycles, the diastereoisomeric mixtures could be easily separated. Moreover, a comparison of the ^1H and ^{13}C NMR spectra of the two diastereoisomers enabled us to assign the absolute configuration of the new stereogenic centres.

With this earlier work in mind, we have synthesised chiral α- and β-hydroxy acids, useful synthons in organic synthesis, starting from α,β-unsaturated amides of (*S*)-1-phenylethylamine.[3] For this purpose we have modified the procedure of carbamoylmethylation of unsaturated alcohols recently introduced by Harding and co-workers[4] for the synthesis of amino alcohols. Thus we have cyclised with $Hg(OCOCF_3)_2$ the hemiamidals (**4**), obtained by treating the amides (**3**) with MeMgCl and paraformaldehyde. The procedure is outlined in Scheme 1.

In analogy with our previous work,[1,2] the tetrahydro-1,3-oxazin-4-ones (**7**) and (**8**) are easily separated by silica gel chromatography. In contrast, any attempt to separate the diastereoisomeric mixture of oxazolidine-2,4-diones (**10**), obtained utilising the t-butoxycarbonyl group instead of the hydroxymethyl group failed, owing to the presence of two carbonyls next to the carbon–hydrogen bond (Scheme 2).

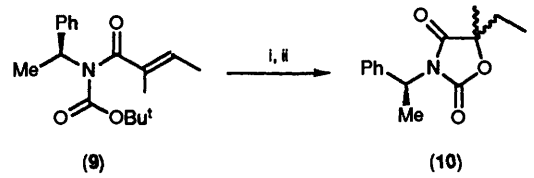
The IR absorption of amide group of six-membered rings at 1 650 cm^{-1} can be used as a diagnostic feature of this kind of molecule. Furthermore, the comparison of ^1H NMR spectra of compounds (**7b**),(**8b**) and (**7c**),(**8c**) allows us to attribute the configuration of the newly formed stereogenic centres (see Experimental section). In fact, owing to the phenyl group shielding, the ^1H NMR spectra of the diastereoisomers (**7b**),(**8b**) and (**7c**),(**8c**) show non-equivalence of H_a, H_b, and R′.

The correct attribution of the stereochemistry is confirmed by the hydrolysis of (**7b**) in 11 M HCl at reflux for 12 h, which affords the (*R*)-3-hydroxyhexenoic acid (**1**) (α −27.2°, *c* 1.2 in $CHCl_3$, in accord with the literature data[6]) and the starting (*S*)-1-phenylethylamine.



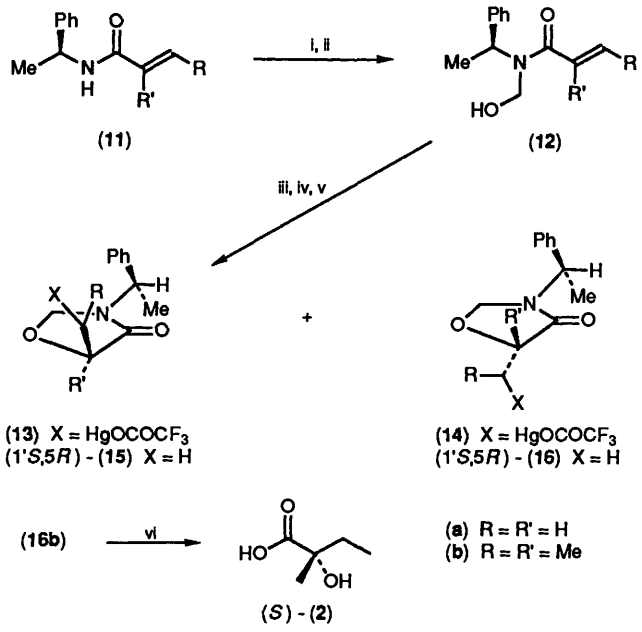
		diastereoisomeric ratio
a; R = R′ = Me	(**5a**):(**6a**)	1:1
b; R = Pr, R′ = H	(**7b**):(**8b**)	2:1
c; R = CH=CHCH$_3$, R′ = H	(**7c**):(**8c**)	1.6:1

Scheme 1. *Reagents and conditions:* i, MeMgCl (1.1 equiv.), THF, 0 °C, 1 h; ii, $(CH_2O)_n$ (2 equiv.), 40 °C, 8 h; iii, $Hg(OCOCF_3)_2$ (1 equiv.), dry CH_2Cl_2, r.t., 1 h; iv, 2 M NaOH, 0.5 M $NaBH_4$ in 2 M NaOH, 0 °C, 30 min; v, silica gel chromatography; vi 11 M HCl, reflux, 12 h.



(9) (10)

Scheme 2. *Reagents and conditions:* i, $Hg(OCOCF_3)_2$ (1 equiv.), THF, r.t., 8 h; ii, 2M NaOH, 0.5M $NaBH_4$ in 2M NaOH, 0 °C, 30 min.



Scheme 3. *Reagents and conditions:* i, MeMgCl (1.1 equiv.), THF, 0 °C, 1 h; ii, $(CH_2O)_n$ (2 equiv.), 40 °C, 8 h; iii, $Hg(OCOCF_3)_2$ (1 equiv.), dry CH_2Cl_2, r.t., 1 h; iv, 2M NaOH, 0.5M $NaBH_4$ in 2M NaOH, 0 °C, 30 min; v, silica gel chromatography; vi, 11M HCl, reflux, 12 h.

Electronic factors stongly influence the regiochemistry of the ring closure, in fact when the hemiamidals (**12a**) and (**12b**) are treated under the conditions above reported, the cyclisation proceeds exclusively through the 5-*exo* mode, to afford 1:1 diastereoisomeric mixtures of oxazolidin-4-ones (**15**) and (**16**) (Scheme 3).

The five-membered rings are easily separated and characterised by means of the ^1H NMR spectra and the IR absorption of the amide group at 1 700 cm^{-1}. Moreover, a comparison of the ^1H NMR spectra of (**15**) and (**16**) allows the absolute configuration at C-5 of the oxazolidin-4-ones to be assigned. Hydrolysis of the oxazolidin-4-one (**16b**) in 11M HCl at reflux affords the (*S*)-2-hydroxy-2-methylbutanoic acid (**2**) (α 8.7°, *c* 2 in $CHCl_3$ in accord with the literature data [7]) together with the starting material (*S*)-1-phenylethylamine.

Thus we have developed a strategy for obtaining chiral functionalised carboxylic acids starting from unsaturated acids, in good yield, under mild conditions and with complete recovery of the chiral auxiliary. Further studies on the cyclisation of hemiamidals are in progress in order to improve the diastereoselectivity of the reaction.

Experimental

Tetrahydro-1,3-oxazin-4-ones (**7**) *and* (**8**).—To a stirred solution of *N*-(1-phenylethyl)amide (**3**) (10 mmol) in dry THF (20 ml) was added MeMgCl (3.0M solution in THF, 11 mmol) at 0 °C. After 30 min at room temperature, paraformaldehyde (20 mmol) was added and the mixture was stirred for further 8 h at 40 °C. Water and ethyl acetate were then added after which the mixture was separated and the organic layer was dried and concentrated. The hemiamidal (**4**) was obtained in quantitative yield and purified by silica gel chromatography or directly cyclised. $Hg(OCOCF_3)_2$ (5 mmol) was added at 0 °C to a stirred solution of the hemiamidal (**4**) (5 mmol) in dry CH_2Cl_2 (30 ml) and the mixture was stirred for 1 h at room temperature. Aqueous NaOH (2M; 5 ml) and aqueous $NaBH_4$ (0.5M in 2M NaOH; (6 ml) were added at 0 °C, and the mixture was stirred, centrifuged, and separated. The organic layer was dried and concentrated and the mixture of (**7**) and (**8**) was separated by silica gel chromatography (overall yield 70%); ν_{max}(film) 1 650 (C=O) cm^{-1}; (**7b**) $\delta_H(CDCl_3)$ 0.90 (t, 3 H, CH_2CH_3), 1.43 (m, 2 H, $CH_2CH_2CH_3$), 1.52 (d, 3 H, $NCHCH_3$), 2.45 (ABX, 2 H, CH_2CHO), 3.75 (m, 1 H, CHO), 4.53 and 4.71 (AB, 2 H, NCH_2O), 6.01 (q, 1 H, $NCHCH_3$), and 7.30 (m, 5 H, Ph); (**8b**) $\delta_H(CDCl_3)$ 0.90 (t, 3 H, CH_2CH_3), 1.46 (m, 2 H, $CH_2CH_2CH_3$), 1.52 (d, 3 H, $NCHCH_3$), 2.40 (ABX, 2 H, CH_2CHO), 3.62 (m, 1 H, CHO), 4.23 and 4.64 (AB, 2 H, NCH_2O), 5.97 (q, 1 H, $NCHCH_3$), and 7.30 (m, 5 H, Ph); (**7c**) $\delta_H(CDCl_3)$ 1.54 (d, 3 H, $NCHCH_3$), 1.62 (d, 3 H, $CH{=}CHCH_3$), 2.58 (ABX, 2 H, CH_2CHO), 4.27 (q, 1 H, CHO), 4.53 and 4.74 (AB, 2 H, NCH_2O), 5.50 (dd, 1 H, $OCHCH{=}CH$), 5.88 (m, 1 H, $CH{=}CHCH_3$), 6.03 (q, 1 H, $NCHCH_3$), and 7.32 (m, 5 H, Ph); (**8c**) $\delta_H(CDCl_3)$ 1.57 (d, 3 H, $NCHCH_3$), 1.72 (d, 3 H, $CH{=}CHCH_3$), 2.56 (ABX, 2 H, CH_2CHO), 4.18 (q, 1 H, CHO), 4.31 and 4.69 (AB, 2 H, NCH_2O), 5.48 (dd, 1 H, $OCHCH{=}CH$), 5.76 (m, 1 H, $CH{=}CHCH_3$), 6.02 (q, 1 H, $NCHCH_3$), and 7.32 (m, 5 H, Ph).

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