The solid-state diastereoselective formation of oxazolidines

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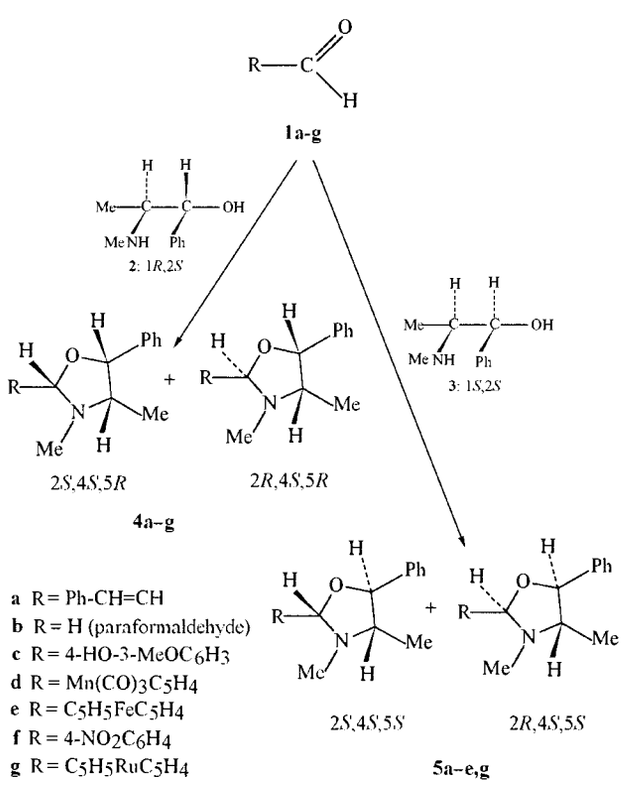
A number of organic and organometallic aldehydes have been converted into optically active oxazolidines by solid-state interaction with (−)-ephedrine and (+)-pseudoephedrine. The stereoselectivity of the solid-state reaction is compared with that in boiling ethanol solution.

The best known solid-state reactions in organic chemistry are those in which unsaturated compounds are photochemically di- and polymerised.[1] Although thermal solid-state reactions seem to be much less studied, nevertheless, they include a broad spectrum of reaction types which sometimes have practical importance because of their higher selectivity together with a different reactivity for the starting compounds in the solid state as compared with in solution.[2] Recently we have found a new example of such reactions which involves the formation of oxazolidines by allowing solid mixtures of aldehydes and β-amino alcohols to react.[3] The use of optically active (−)-ephedrine or (+)-pseudoephedrine leads, in the case of prochiral aldehydes, mainly to one of the two possible diastereoisomers of the product. Since chiral oxazolidines are widely used in asymmetric transformations[4] the solid-state synthesis of these compounds is of both theoretical and practical interest. In the present paper we report on the solid-state synthesis of oxazolidines from (−)-ephedrine, (+)-pseudoephedrine and several organic and organometallic aldehydes (Scheme 1).



Scheme 1

We have also made a comparable study of the diastereoselectivity in the formation of the chiral C-2 centre of oxazolidines by the solid-state and solution synthesis.

Although the synthesis of oxazolidines from aldehydes and β-amino alcohols is usually carried out in different solvents,[5] it appears that the presence of solvent is unnecessary for the reaction. In fact, in the earliest papers by Knorr and Rossler on oxazolidine synthesis it was reported that simple mixing of liquid aldehydes and 1,2-amino alcohols resulted in a spontaneous reaction.[6] We have shown that liquid cinnamaldehyde **1a** reacts in the absence of solvent with the solid amino alcohols **2** or **3** to give, within a few hours, the crystalline oxazolidines **4a** and **5a**, respectively. Moreover, even when both starting compounds are solids effective oxazolidine formation occurs. Thus, equimolar mixtures of solid **2** or **3** with one of the aldehydes **1c–g** or paraformaldehyde **1b** at room temperature when periodically stirred gives quantitative formation of the corresponding oxazolidines **4** or **5**. The time for complete conversion of the reactants depends both on the aggregate state of the reaction mixtures at different stages of the synthesis and on the intensity of mechanical stirring (Table 1). Thus, during the interaction of **1b** with **2** or **3** which leads in both cases to the formation of the liquid oxazolidines **4b** and **5b** the reaction is complete within 1 h. The products of the reaction of cymantrenecarbaldehyde **1d** with **2** or **3**, ferrocenecarbaldehyde **1e** with **2** and 4-nitrobenzaldehyde **1f** with **2** are crystalline compounds, namely **4d**, **5d**, **4e** and **4f**. However, in these cases mobile oils are formed during the reaction which is complete in 20–40 h. Vanillin **1c** and **2** when mixed react to form an oil which is almost solid. This precludes the possibility of it being mechanically stirred at room temperature and thereby reagent diffusion is inhibited; thus even after 2 months an NMR spectrum of a sample of the reaction mixture showed the presence of measurable amounts of starting compounds as well as the product **4c**.

The interaction of **1g** with **2** and **1c**,**e**,**g** with **3** can be considered as real solid-state reactions, since in these cases the reaction mixtures appeared to be dry solid powders at all stages. The formation of oxazolidines from the coloured organometallic aldehydes **1e** and **1g** is accompanied with a colour change from bright orange to pale yellow in the case of **1e** and from yellow to nearly white in the case of **1g**. The conversion times from the starting reagents to the oxazolidines **4g**, and **5c**,**e**,**g** were in the range 3 days to 3 weeks and depended on the intensity of the stirring. Use of a vibration ball mill for mixing and activating the reagents accelerates the interaction significantly. Thus, in a vibration mill, the reaction of ferrocene carbaldehyde **1e** with **3** is complete within 5 min, the oxazolidine **5e** being formed in quantitative yield. Therefore, the solid-state inter-

Table 1 The solid-state reaction of **1a–g** with **2** and **3**

Entry	Aldehyde	β-Amino alcohol	Product	Time[a]	De (%)[b,c]
1	**1a**	**2**	**4a**	5 h	95[d]
2	**1a**	**3**	**5a**	5 h	98[d]
3	**1b**	**2**	**4b**	1 h	—
4	**1b**	**3**	**5b**	1 h	—
5	**1c**	**2**	**4c**	60 days	94
6	**1c**	**3**	**5c**	10 days	100
7	**1d**	**2**	**4d**	30 h	88[d]
8	**1d**	**3**	**5d**	48 h	95[d]
9	**1e**	**2**	**4e**	20 h	92
10	**1e**	**3**	**5e**	72 h	98[d]
11	**1f**	**2**	**4f**	48 h	53
12	**1g**	**2**	**4g**	10 days	100
13	**1g**	**3**	**5g**	21 days	100

[a] Full conversion of starting reagents and 100% yield of the products. [b] Diastereomeric excess after full conversion. [c] Determined from integrals of the ^{1}H NMR spectra. [d] Optically pure compounds after one crystallization from hexane.

action of the aldehydes with 1,2-amino alcohols is a practical and preparative method for the synthesis of oxazolidines.

In all the observed solid-state syntheses a new chiral centre at C-2 of the heterocyclic ring is formed with a high degree of diastereoselectivity (Table 1). Analysis of the NMR spectra of the reaction products after complete reaction shows the preferential formation of one of two possible diastereoisomers. In order to compare this diastereoselectivity for solid-state reactions with that for those carried out in solution we allowed all the aldehydes studied to react with **2** or **3** in boiling ethanol.[7] As was expected, product formation in solution was accompanied by high asymmetric induction. In fact, the diastereoisomeric selectivity and absolute configuration of the oxazolidines formed in ethanol solution and in the solid state appeared to be identical. Nevertheless a different stereochemical result was observed for the reaction of cymantrenecarbaldehyde **1d** with (−)-ephedrine. While at all stages of the solid-state syntheses of the oxazolidines **4c**,**e**,**g** and **5c–e**,**g** the predominant diastereoisomer is the same, in the solid-state reaction of **1d** with **2** this was not so. At the stage of 70–80% of conversion (4–5 h) the 2*R*-enantiomer of the oxazolidine **4d** predominated (ratio of diastereoisomers 2*R*:2*S* = 3:1) whilst at the completion of the reaction (~30 h) this situation was reversed with 2*R*:2*S* = 1:7 for the solid-state reaction and 2*R*:2*S* = 1:4 for the reaction in ethanol solution.[7] However, when kept for a week the crystalline mixture of the reaction products obtained from **1d** and **2** both in the solid state and in ethanol solution gave clean formation of (2*S*)-**4d** with no detection of the other diastereoisomer. Thus, the formation of (2*R*,4*S*,5*R*)-**4d** appeared to be the result of kinetic control of the reaction between **1d** and **2** in the solid state. This diastereoisomer then undergoes irreversible isomerisation to the thermodynamically more stable (2*S*,4*S*,5*R*)-**4d**.

Probably stereoisomerisation of (2*R*)-**4d** in the solid state is catalysed by water which is formed during the reaction. This would explain the formation of the thermodynamically less stable (2*R*)-**4d** diastereoisomer in the presence of a drying agent. We found that running of the solid-state reaction of **1d** with **2** in the presence of a large excess of anhydrous $MgSO_4$ does not change the diastereoisomeric result, although addition of water to the mixture after the completion of the reaction leads to complete isomerisation of (2*R*)-**4d** to its (2*S*)-isomer. Although this result confirms the influence of water on the diastereoselectivity of formation of the oxazolidine **4d** during the solid-state synthesis, the question as to what induces the change of stereoselectivity remains unanswered.

Another example of the difference in the diastereoisomeric course of the reaction in the solid state and in solution is the interaction of 4-nitrobenzaldehyde **1f** with (−)-ephedrine **2**. It was observed previously by Agamy and Risk that in the reaction of these compounds in $CDCl_3$ or in MeOH at complete conversion mainly (2*S*)-**4f** is formed (85–100%).[8] We found that the solid-state interaction of **1f** with **2** at the stage of full conversion (48 h) gives the oxazolidine **4f** with the ratio of diastereoisomers 2*R*:2*S* = 1:1. On prolonged storage of the reaction mixture, there is a very slow isomerisation of (2*R*)-**4f** to its 2*S*-isomer: after 3 months the ratio 2*R*:2*S* = 7:11. While this example of solid-state reaction is not a diastereoselective one it is interesting in terms of the instability in solution of (2*R*)-**4f** and of the possibility of its isolation.

While the heating of the starting compounds in refluxing benzene with azeotropic distillation of water is often used in the synthesis of oxazolidines[5,9] in some cases the reaction fails to take place in this solvent.[4g] We have found that for all mixtures of the starting compounds as reported in Scheme 1 there is no reaction in benzene solutions at room temperature even after 2–3 days. Therefore in monitoring the course of the solid-state syntheses of oxazolidines by recording the NMR spectra of the reaction mixtures, samples were taken in C_6D_6.

Experimental

^{1}H NMR spectra were recorded in C_6D_6 on a Bruker WP-200 SY spectrometer. Chemical shifts (δ) are reported in ppm downfield from TMS as internal standard; *J* values are given in Hz. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in benzene and are recorded as 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a capillary melting-point apparatus and are uncorrected. Mass spectra were recorded on a Kratos MS 890 spectrometer. Compounds **1d**,[10] **1e**[11] and **1g**[12] were prepared as reported. Other starting materials were purchased from commercial sources and used without purification.

General procedure for the solid-state synthesis of oxazolidines

After an enantiomerically pure β-amino alcohol (1 mmol) had been mixed with the appropriate aldehyde (1 mmol) the mixture was kept in the dark at room temperature and periodically stirred. The course of the reaction was monitored regularly by recording the NMR spectra of samples of the reaction mixture.

In all cases the yield of the products was 100% (70% for entry 5; based on the NMR data). The reaction times and diastereomeric excess (de) of the products are summarized in Table 1.

General procedure for the synthesis of oxazolidines in ethanol solution

A solution of the aldehyde (1 mmol) and the β-amino alcohol (1 mmol) in EtOH (5 ml) was refluxed for 2 h after which the mixture was evaporated. The NMR spectrum of the product was taken without further purification.

The solid-state synthesis of 5e in a vibration ball mill

In a stainless-steel reactor (volume 70 cm^3) **1e** (0.214 g, 1 mmol) was combined with **3** (0.165 g, 1 mmol). 25 Steel balls (12.4 mm diam., 190 g) were used as the activating filling. The reactor was vibrated (f = 12 Hz; A = 11 mm) for 5 min. An NMR spectrum of the reaction mixture was recorded without purification.

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-styryloxazolidine 4a.[9b] Colourless crystals; mp 89–90 °C (from hexane); $[\alpha]_D^{21}$ −75.1 (*c* 1.15) (Found: C, 81.7; H, 7.5; N, 4.9. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); δ_H 0.62 (3H, d, *J* 6.5, 4-Me), 2.05 (3H, s, NMe), 2.60 (1H, m, 4-H), 4.31 (1H, d, *J* 6.7, 5-H), 5.00 (1H, d, *J* 7.8, 2-H), 6.50 (1H, dd, *J* 7.8 and 14.9) and 6.73 (1H, d, 14.7) (olefinic H) and 7.00–7.48 (10H, m, 2 Ph).

(4*S*,5*S*)-3,4-Dimethyl-5-phenyl-2-styryloxazolidine 5a. Colourless crystals; mp 73–74 °C (from hexane); $[\alpha]_D^{21}$ +10.9 (*c* 0.55) (Found: C, 82.15; H, 7.7; N, 4.7. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); δ_H 1.00 (3H, d, *J* 6.5, 4-Me), 2.09 (3H, s, NMe), 2.30 (1H, m, 4-H), 4.60 (1H, d, *J* 6.9, 5-H), 4.75 (1H, d, *J* 7.7, 2-H), 6.45 (1H, dd, *J* 7.7 and 15.4) and 6.72 (1H, d, 15.4) (olefinic H) and 7.00–7.45 (10H, m, 2 Ph).

(4*S*,5*R*)-3,4-Dimethyl-5-phenyloxazolidine 4b.[13] Colourless liquid; $[\alpha]_D^{21}$ +5.6 (*c* 0.36); δ_H 0.61 (3H, d, *J* 6.4, 4-Me), 2.09 (3H, s, NMe), 2.59 (1H, m, 4-H), 3.94 (1H) and 4.82 (1H) (each d, *J* 3.2, CH_2), 5.00 (1H, d, *J* 7.7, 5-H) and 7.06–7.42 (5H, m, Ph).

(4*S*,5*S*)-3,4-Dimethyl-5-phenyloxazolidine 5b.[13] Colourless liquid; $[\alpha]_D^{21}$ +50.8 (*c* 0.56); δ_H 1.05 (3H, d, *J* 6.3, 4-Me), 2.13 (3H, s, NMe), 2.35 (1H, m, 4-H), 4.25 (1H, d, *J* 3.2, 2-H), 4.63 (1H, d, *J* 7.6, 5-H), 4.82 (1H, d, *J* 3.2, 2-H) and 7.17–7.46 (5H, m, Ph).

(4*S*,5*R*)-3,4-Dimethyl-2-(4-hydroxy-3-methoxyphenyl)-5-phenyloxazolidine 4c. Colourless oil; $[\alpha]_D^{21}$ −24.6 (*c* 0.64); δ_H 0.72 (3H, d, *J* 7.2, 4-Me), 2.03 (3H, s, NMe), 2.70 (1H, m, 4-H), 3.29 (3H, s, CH_3O), 4.66 (1H, s, 2-H), 5.05 (1H, d, *J* 8.1, 5-H) and 7.00–7.57 (8H, m, Ph and C_6H_3); *m/z* 299 (M^+) and 298 ($M^+ - 1$).

(4*S*,5*S*)-3,4-Dimethyl-2-(4-hydroxy-3-methoxyphenyl)-5-phenyloxazolidine 5c. Colourless crystals; mp 117–118 °C (from hexane); $[\alpha]_D^{21}$ +56.4 (*c* 0.56) (Found: C, 72.15; H, 7.2; N, 4.6. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.0; N, 4.7%); δ_H 1.00 (3H, d, *J* 6.4, 4-Me), 1.97 (3H, s, NMe), 2.35 (1H, m, 4-H), 3.16 (3H, s, CH_3O), 4.79 (1H, d, *J* 8.5, 5-H), 4.84 (1H, s, 2-H) and 7.00–7.49 (8H, m, Ph and C_6H_3).

(4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyloxazolidine 4e. Yellow powder; mp 60–62 °C (without crystallization); $[\alpha]_D^{21}$ −216.3 (*c* 0.41) (Found: C, 70.1; H, 6.4; Fe, 15.4; N, 3.7. $C_{21}H_{23}FeNO$ requires C, 69.8; H, 6.4; Fe, 15.5; N, 3.9%); δ_H 0.63 (3H, d, *J* 6.4, 4-Me), 2.10 (3H, s, NMe), 2.65 (1H, m, 4-H), 4.10 (2H, m, C_5H_4-β-H), 4.22 (5H, s, C_5H_5), 4.29 (1H, m, C_5H_4-α-H), 4.55 (1H, s, 2-H), 4.74 (1H, m, C_5H_4-α-H), 5.00 (1H, d, *J* 8.4, 5-H) and 7.10–7.58 (5H, m, Ph).

(4*S*,5*S*)-3,4-Dimethyl-2-ferrocenyl-5-phenyloxazolidine 5e. Yellow crystals; mp 113–114 °C (from hexane); $[\alpha]_D^{21}$ +38.3 (*c* 0.86) (Found: C, 69.8; H, 6.4; Fe, 15.2; N, 3.7. $C_{21}H_{23}FeNO$ requires C, 69.8; H, 6.4; Fe, 15.5; N, 3.9%); δ_H 1.03 (3H, d, *J* 6.4, 4-Me), 2.13 (3H, s, NMe), 2.34 (1H, m, 4-H), 4.09 (2H, m, C_5H_4-β-H), 4.26 (1H, m, C_5H_4-α-H), 4.28 (5H, s, C_5H_5), 4.66 (1H, m, C_5H_4-α-H), 4.78 (1H, d, *J* 8.1, 5-H), 4.88 (1H, s, 2-H) and 7.13–7.47 (5H, m, Ph).

(4*S*,5*R*)-3,4-Dimethyl-2-(4-nitrophenyl)-5-phenyloxazolidine 4f. Yellow crystals, mixture of two diastereoisomers (2*S*/2*R* = 53:47) (Found: C, 69.1; H, 6.3; N, 9.5. $C_{17}H_{18}N_2O_3$ requires C, 68.4; H, 6.1; N, 9.4%). (2*S*,4*S*,5*R*)-**4f**: δ_H 0.74 (3H, d, *J* 6.4, 4-Me), 1.93 (3H, s, NMe), 2.70 (1H, m, 4-H), 4.54 (1H, s, 2-H), 5.07 (1H, d, *J* 7.9, 5-H), 7.30–7.50 (7H) and 7.96 (2H) (each m, Ph and C_6H_4). (2*R*,4*S*,5*R*)-**4f**: δ_H 0.62 (3H, d, *J* 6.4, 4-Me), 1.99 (3H, s, NMe), 3.36 (1H, m, 4-H), 5.19 (1H, s, 2-H), 5.42 (1H, d, *J* 4.7, 5-H), 7.30–7.50 (7H) and 8.05 (2H) (each m, Ph and C_6H_4); the ^{1}H NMR data for (2*S*,4*S*,5*R*)-**4f** in $CDCl_3$ were identical with those reported.[8]

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-ruthenocenyloxazolidine 4g. Pale yellow crystals; mp 142–144 °C (from hexane); $[\alpha]_D^{21}$ −165.0 (*c* 0.28) (Found: C, 62.0; H, 5.5; N, 3.5. $C_{21}H_{23}NORu$ requires C, 62.05; H, 5.7; N, 3.45%); δ_H 0.59 (3H, d, *J* 6.6, 4-Me), 2.13 (3H, s, NMe), 2.60 (1H, m, 4-H), 4.46 (1H, s, 2-H), 4.51 (2H, m, C_5H_4-β-H), 4.56 (5H, s, C_5H_5), 4.86 (1H, m, C_5H_4-α-H), 4.92 (1H, d, *J* 8.3, 5-H), 5.07 (1H, m, C_5H_4-α-H) and 7.09–7.47 (5H, m, Ph).

(4*S*,5*S*)-3,4-Dimethyl-5-phenyl-2-ruthenocenyloxazolidine 5g. Pale yellow crystals; mp 111–112 °C (from hexane–benzene); $[\alpha]_D^{21}$ +17.6 (*c* 0.34) (Found: C, 61.9; H, 5.6; N, 3.5. $C_{21}H_{23}NORu$ requires C, 62.05; H, 5.7; N, 3.45%); δ_H 0.97 (3H, d, *J* 6.2, 4-Me), 2.16 (3H, s, NMe), 2.30 (1H, m, 4-H), 4.50 (2H, m, C_5H_4-β-H), 4.58 (5H, s, C_5H_5), 4.65 (1H, d, *J* 8.1, 5-H), 4.79 (1H, s, 2-H), 4.86 (1H) and 4.99 (1H) (each m, C_5H_4-α-H) and 7.06–7.37 (5H, m, Ph).

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