1,2-Asymmetric induction in nucleophilic Michael addition reactions of amines under microwave irradiation

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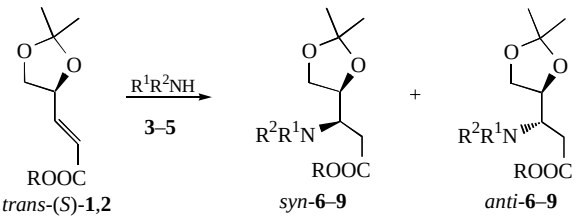
1,2-Asymmetric induction of up to 76% is observed in the reactions of several amines with the β-substituted acrylic acid ester (*S*)-**1** containing a γ-asymmetric carbon atom in the absence of solvent after 12 min microwave irradiation.

The development of methods for preparing β-amino acids and their derivatives[1] which have biological activity dependent on the stereochemistry of the isomers, is one of the most urgent problems in fine organic synthesis. Stereocontrolled Michael addition of amines to the double bond of α,β-unsaturated carboxylic acids could be a convenient and cheap method for the solution of this chemical problem, which is simultaneously associated with the selection of conditions for asymmetric induction and control of stereochemistry at the newly formed chiral centres.[2]

We have shown for the first time that microwave irradiation (MW) can be successfully used to activate the reactions of amines with esters of crotonic acid.[3] Under these conditions, the chemical yields of target esters of β-aminobutyric acid reach 84%, the rate of their formation increases by several orders of magnitude, and the reaction duration is 10–25 min (*cf.* 50 h in ref. 4). An insignificant stereoselectivity was observed when either the amine or the ester group contained a chirality source. In the reaction with methyl crotonate, the action of the α-ethylphenyl chiral centre of the amine through two σ-bonds resulted in a weak asymmetric induction (diastereoisomer ratio 54:46); 1,5-asymmetric induction in the reactions of achiral amines (piperidine, morpholine and benzylamine) with *sec*-butyl crotonate is completely absent.[3]

In this work, we studied (under MW conditions) the stereoselectivity of conjugated addition of amines to esters of an α,β-unsaturated carboxylic acid with a stereogenic centre in the γ-position. The ethyl ester of β-substituted acrylic acid *trans*-(*S*)-**1**,[5] which is widely used as a starting object along with the methyl ester of *trans*-(*S*)-**2** and which can easily be obtained from D-(+)-mannitol, was used as a substrate with a chiral source in various addition reactions at the double bond.[4,6–8] The reactions of the ester of *trans*-(*S*)-**1** with amines **3**–**5** were carried out in a commercial microwave oven (Funai MO 785 VT) in the absence of solvent for 12 min at a power of 510 W and the temperature of the reaction mixture not higher than 60 °C. The reaction run was monitored by thin layer chromatography on silica gel, and reaction products were isolated by column chromatography on silica gel using a heptane–ethyl acetate (2:1) mixture as the eluent. The chemical and optical yields of amino esters **6**–**8** are presented in Table 1.

The *syn*- and *trans*-diastereoisomers of β-amino esters **6**–**8** obtained were isolated as mixtures, and the analysis of their ^{1}H NMR† spectra made it possible to determine the ratio of diastereoisomers in amino esters **6**–**8**.



trans-(*S*)-**1**,**2** *syn*-**6**–**9** *anti*-**6**–**9**

1 R = Et
2 R = Me

3,**6** R = Et, R^1 = H, R^2 = CH_2Ph
4,**7** R = Et, (R^1 + R^2) = –$(CH_2)_5$–
5,**8** R = Et, R^1 = H, R^2 = (*S*)-CH(Me)Ph
9 R = Me, R^1 = H, R^2 = CH_2Ph

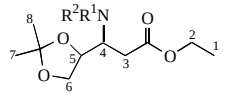
Table 1 Chemical and optical yields of esters of β-amino acids **6**–**8**.

	Time/min	Reaction conditions	Yield (%)	Diastereoisomer ratio (%)
6	12	MW	79	88:12
7	12	MW	95	64:36
8	12	MW	28	85:15

It is shown in ref. 4 that the observed *syn*-stereoselectivity of the conjugated addition of benzylamine **3** to the methyl ester of *trans*-(*S*)-**2** depends on the reaction temperature: a diastereoisomeric excess of *syn*-isomer **9** reaches a maximum (100%) at –50 °C and decreases to 80% when the temperature increases to 0 °C and the reaction duration is 50 h.

The published data on the stereoselectivity of the reactions of esters of *trans*-(*S*)-**1** and *trans*-(*S*)-**2** with *N*-[6] and C-nucleophiles[7] performed under conditions different from those used in the current work indicate that in these cases, the predominant diastereoisomers have a *syn*-configuration. For example, in the reaction with hydroxylamine (room temperature, 24 h, $ZnCl_2$, 79%), the *syn*:*anti* ratio is 20:1;[6] in the reaction with nitromethane (temperature from –30 °C to 34 °C, 12–4 h, TBAF, yield *ca.* 70%), the *syn*:*anti* ratio varies from 19:1 to 7:1.[7]

† The ^{1}H NMR spectra were recorded on a VXR-400 Varian spectrometer (400 MHz) in a $CDCl_3$ solution at 28 °C using TMS as the internal standard. Protons in the ^{1}H NMR spectra are numbered as follows:



The reverse assignment of the signals of H-A and H-A′ is also possible. The spectra of predominantly formed diastereoisomers are given.

For **6**, δ: 1.25 (t, 3H, Me-1, $J_{Me\text{-}1,CH_2\text{-}2}$ 7.18 Hz), 1.33 (s, 3H, Me-7), 1.39 (s, 3H, Me-8), 2.45 (dd, 1H, H-3, $J_{H\text{-}3,H\text{-}3'}$ 14.93 Hz, $J_{H\text{-}3,H\text{-}4}$ 6.20 Hz), 2.49 (dd, 1H, H-3′, $J_{H\text{-}3',H\text{-}3}$ 14.93 Hz, $J_{H\text{-}3',H\text{-}4}$ 6.20 Hz), 3.14 (q, 1H, H-4, $J_{H\text{-}4,H\text{-}3}$ = $J_{H\text{-}4,H\text{-}3'}$ = $J_{H\text{-}4,H\text{-}5}$ 6.20 Hz), 3.81 (dd, 1H, H-6, $J_{H\text{-}6,H\text{-}6'}$ 8.40 Hz, $J_{H\text{-}6,H\text{-}5}$ 6.78 Hz), 3.99 (dd, 1H, H-6′, $J_{H\text{-}6',H\text{-}6}$ 8.40 Hz, $J_{H\text{-}6',H\text{-}5}$ 7.13 Hz), 4.13 (q, 2H, CH_2-2, $J_{CH_2\text{-}2,Me\text{-}1}$ 7.18 Hz), 4.20 (ddd, 1H, H-5, $J_{H\text{-}5,H\text{-}6}$ 6.78 Hz, $J_{H\text{-}5,H\text{-}6'}$ 7.13 Hz, $J_{H\text{-}5,H\text{-}4}$ 6.20 Hz); R^1: 1.8 (s, 1H, NH); R^2: 3.90 (s, 2H, CH_2), 7.20–7.35 (m, 5H, Ph).

For **7**, δ: 1.31 (t, 3H, Me-1, $J_{Me\text{-}1,CH_2\text{-}2}$ 7.15 Hz), 1.34 (s, 3H, Me-7), 1.40 (s, 3H, Me-8), 2.33 (dd, 1H, H-3, $J_{H\text{-}3,H\text{-}3'}$ 14.53 Hz, $J_{H\text{-}3,H\text{-}4}$ 6.32 Hz), 2.52 (dd, 1H, H-3′, $J_{H\text{-}3',H\text{-}3}$ 14.53 Hz, $J_{H\text{-}3',H\text{-}4}$ 8.79 Hz), 3.20 (dt, 1H, H-4, $J_{H\text{-}4,H\text{-}3}$ = $J_{H\text{-}4,H\text{-}5}$ 6.32 Hz, $J_{H\text{-}4,H\text{-}3'}$ 8.79 Hz), 3.75 (dd, 1H, H-6, $J_{H\text{-}6,H\text{-}6'}$ 7.91 Hz, $J_{H\text{-}6,H\text{-}5}$ 6.32 Hz), 3.96 (t, 1H, H-6′, $J_{H\text{-}6',H\text{-}6}$ = = $J_{H\text{-}6',H\text{-}5}$ 7.91 Hz), 4.17 (dq, 1H, H-2, $J_{H\text{-}2,H\text{-}2'}$ 14.0 Hz, $J_{H\text{-}2,Me\text{-}1}$ 7.15 Hz), 4.19 (dq, 1H, H-2′, $J_{H\text{-}2',H\text{-}2}$ 14.0 Hz, $J_{H\text{-}2',Me\text{-}1}$ 7.15 Hz), 4.25 (dt, 1H, H-5, $J_{H\text{-}5,H\text{-}6}$ = $J_{H\text{-}5,H\text{-}4}$ 6.32 Hz, $J_{H\text{-}5,H\text{-}6'}$ 7.91 Hz); R^1 + R^2: 1.38 (m, 2H), 1.48 (m, 4H), 2.48 (m, 4H).

For **8**, δ: 1.25 (t, 3H, Me-1, $J_{Me\text{-}1,CH_2\text{-}2}$ 7.19 Hz), 1.30 (s, 3H, Me-7), 1.37 (s, 3H, Me-8), 2.41 (dd, 1H, H-3, $J_{H\text{-}3,H\text{-}3'}$ 15.16 Hz, $J_{H\text{-}3,H\text{-}4}$ 5.19 Hz), 2.52 (dd, 1H, H-3′, $J_{H\text{-}3',H\text{-}3}$ 15.16 Hz, $J_{H\text{-}3',H\text{-}4}$ 6.29 Hz), 2.84 (ddd, 1H, H-4, $J_{H\text{-}4,H\text{-}3}$ 5.19, $J_{H\text{-}4,H\text{-}3'}$ 6.29 Hz, $J_{H\text{-}4,H\text{-}5}$ 5.10 Hz), 3.76 (dd, 1H, H-6, $J_{H\text{-}6,H\text{-}6'}$ 7.39 Hz, $J_{H\text{-}6,H\text{-}5}$ 6.61 Hz), 3.90 (dd, 1H, H-6′, $J_{H\text{-}6',H\text{-}6}$ 7.39 Hz, $J_{H\text{-}6',H\text{-}5}$ 6.61 Hz), 4.08 (dt, 1H, H-5, $J_{H\text{-}5,H\text{-}6}$ = $J_{H\text{-}5,H\text{-}6'}$ 6.61 Hz, $J_{H\text{-}5,H\text{-}4}$ 5.10 Hz), 4.12 (q, 2H, CH_2-2, $J_{CH_2\text{-}2,Me\text{-}1}$ 7.19 Hz); R^1: 1.89 (s, 1H, NH); R^2: 1.33 (d, 3H, Me, $J_{Me\text{–}CH}$ 6.7 Hz), 3.88 (q, 1H, CH, $J_{CH\text{–}Me}$ 6.7 Hz), 7.20–7.35 (m, 5H, Ph).

The comparison of the stereochemical results obtained in refs. 4, 6 and 7 with the preliminary data obtained in this work suggests that in the variant of the Michael reaction used, MW has no effect on the order of magnitude of 1,2-asymmetric induction and the predominantly formed diastereoisomers of amino esters **6**–**8** most likely have the *syn*-configuration as well.

Thus, the diastereoselectivity of the Michael addition of amines under MW conditions is due (as in the absence of MW[4,6,7]) to asymmetric induction of the γ-chiral centre in the starting ester of *trans*-(*S*)-**1**, which is located near the prochiral centre in the β-position, and the stereochemistry of nucleophilic addition is determined by the structure of the amine used. A high level of asymmetric induction was achieved when benzylamine **3** was used as the nucleophile. It is noteworthy that the stereoselectivity of reaction of the cyclic amine, piperidine **4**, as compared to the primary benzylamine **3**, in the reaction with ester **1** under MW conditions is approximately four times lower, which is most likely related to the relatively higher nucleophilicity of piperidine. This decreases the role of steric preference of the nucleophilic attack of amine from the *pro-S* or *pro-R* side of the double bond of ester **1** to the prochiral centre at the β-position. The diastereoisomeric excess (70%) in the case of amine **8** is most likely the result of the overall stereochemical effect of two chirality sources: in the γ-position of the starting *trans*-(*S*)-ester-**1** (1,2-asymmetric induction) and in amine (*S*)-**5** (1,3-asymmetric induction).

This work was financially supported by the Russian Foundation for Basic Research (grant no. 96-03-32157) and MOPO RF (grant no. 01.0170f from the Interuniversity Science Technical Program ‘General and Technical Chemistry’).

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Received: Moscow, 23rd April 1998
Cambridge, 21st May 1998; Com. 8/03093F