Solvent-free stereoselective synthesis of β-aryl-β-amino acid esters by the Rodionov reaction using microwave irradiation

Nelly N. Romanova,* Alexander G. Gravis, Pavel V. Kudan and Yuri G. Bundel'

Department of Chemistry, M. V. Lomonosov Moscow State University, 119899 Moscow, Russian Federation.
Fax: +7 095 932 8846; e-mail: rom@org.chem.msu.su

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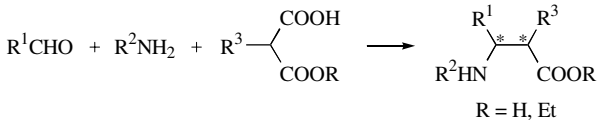
A rapid method for the title synthesis of β-aryl-β-amino acid esters was developed, and the absolute configurations of newly formed C-3 chiral centres in the major and minor diastereomers of the resulting ethyl *N*-[(*S*)-α-methylbenzyl]-β-amino-β-phenylpropionate were determined.

The stereoselective synthesis of β-lactams, which are structure constituents of many natural compounds and pharmaceuticals, is of considerable importance. Homochiral β-lactams can be prepared by cyclisation of enantiomeric esters of β-amino acids that should be stereoselectively synthesised. The preparation of β-amino acid esters by the Michael reaction is performed under severe conditions and does not always result in adequate yields.[1] Previously,[2] it was proposed to activate the Michael reaction using microwave irradiation. This technique made it possible to obtain esters of some β-amino acids in good yields for several minutes. Note that ethyl cinnamate reacted only with morpholine under these conditions.

As an extension of our studies on the rapid synthesis of β-amino acid esters, we examined the effect of microwave irradiation on the chemical yield and stereoselectivity of the Rodionov reaction.[3] This reaction is primarily used for the synthesis of β-amino acids (R = H);[4] however, it was found[5] that β-amino acid esters (R = Et) can also be obtained by this reaction:



Scheme 1

The synthesis of β-amino esters was performed on long heating of the reactants in alcohol; however only ammonia was introduced into condensation with monoethyl malonate and substituted benzaldehydes. In this case, substituted cinnamates were always formed in considerable amounts in addition to β-amino esters.

In this study, monoethyl malonate, its C-alkyl derivatives, aromatic aldehydes, benzylamine, (*S*)-α-methylbenzylamine and the acetates and Schiff bases of these amines were used as substrates.

The conditions of the Rodionov reaction under microwave irradiation were optimised for the synthesis of ethyl *N*-[(*S*)-α-methylbenzyl]-β-amino-β-phenylpropionate. The procedure developed† was used for the syntheses of other esters (Table 1).

Microwave irradiation provides some advantages in the synthesis of β-aminoesters by the Rodionov reaction. Thus, when the synthesis of ethyl *N*-[(*S*)-α-methylbenzyl]-β-amino-β-phenylpropionate was performed under conventional conditions of the Rodionov reaction (on boiling the reactants in ethanol for 10–12 h), only insignificant amounts of the ethyl ester were isolated (Table 1, entries 3 and 5). However, this ester can be obtained in a moderate yield at a similar stereoselectivity under conditions of microwave irradiation in a matter of minutes (Table 1, entry 2).

† An equimolar mixture of an aldehyde, an amine acetate, and a malonic acid derivative (without a solvent) was irradiated in an open glass vessel in a microwave oven (Funai MO785VT, 170 W) for several minutes (until the release of CO_2 was complete). The reaction was monitored by TLC. The reaction products were separated by column chromatography on silica gel with a benzene–ethyl acetate eluent (2:1). Note that an increase in the microwave power up to 350 W resulted in a decrease in the yield of the target amino ester.

Table 1 Chemical and optical yields of ternary Rodionov condensation.[a]

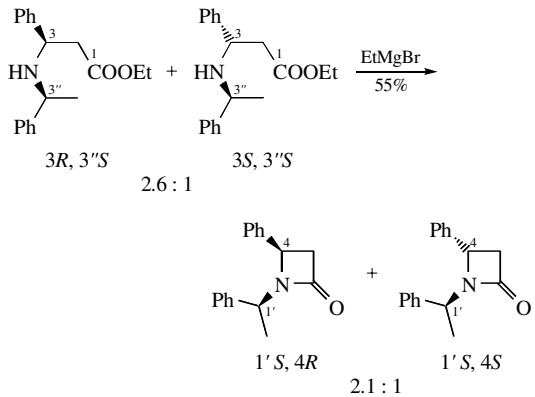
ArCHO + RNH_2·MeCOOH + $HOOCCH_2COOEt$ ⟶ ArCH(NHR)CH_2COOEt (**I**) + ArCH=CHCOOEt (**II**)

Entry	Ar	R	*t*/min	Reaction conditions	Yield of **I** (%)	*d.e.* **I** (%)	Yield of **II** (%)
1	Ph	$PhCH_2$	10	MW	18	—	80
2	Ph	(*S*)-PhCHMe	10	MW	19	35	67
3	Ph	(*S*)-PhCHMe	720	—[b]	2	36	95
4	Ph	(*S*)-PhCHMe	10	MW[c]	17	40	74
5	Ph	(*S*)-PhCHMe	600	—[b,c]	4	32	92
6	Ph	(*S*)-PhCHMe	14	MW[d,e]	17	51	68
7	Ph	(*S*)-PhCHMe	14	MW[d,f]	8	53	85
8	*o*-$O_2NC_6H_4$	(*S*)-PhCHMe	8	MW	21	14	72
9	*p*-$O_2NC_6H_4$	$PhCH_2$	10	MW	23	—	68
10	*p*-$O_2NC_6H_4$	(*S*)-PhCHMe	14	MW	27	27	72
11	*p*-$Me_2NC_6H_4$	(*S*)-PhCHMe	20	MW	0	—	87
12	*p*-$Me_2NC_6H_4$	(*S*)-PhCHMe	16	MW[c]	0	—	28
13	*p*-$MeOC_6H_4$	(*S*)-PhCHMe	15	MW	0	—	34

[a]Microwave experiments (MW) were performed at a power of 170 W. The chemical yields are given for chromatographically pure compounds. The structures of the compounds were supported by IR and ^{1}H NMR spectroscopy and GC–MS. The diastereomeric composition was determined from ^{1}H NMR spectra (400 MHz). [b]Boiling in ethanol. [c]An azomethine was used in the reaction. [d]α-Methylbenzylamine was used in the reaction. [e]The initial amounts of the reactants were 1 mmol. [f]The initial amounts of the reactants were 5 mmol.

On the other hand, malonic acid and monoethyl esters of C-alkyl substituted malonic acids cannot be introduced into the reaction under typical conditions, whereas ethyl malonate underwent almost quantitative conversion.

Note that the replacement of benzylamine with α-methylbenzylamine did almost not decrease the chemical yields of β-amino esters (Table 1, entries 1 and 2 or 9 and 10). At the same time, substituents at the aromatic nucleus of benzaldehyde considerably affected the course of the Rodionov reaction. Electron-donating substituents in the *para*-position of the phenyl ring resulted in that ethyl β-amino-β-arylpropionate was not



Scheme 2

formed at all under microwave conditions (Table 1, entries 11–13). In contrast, the electron-acceptor nitro group in the *ortho*- or *para*-position increased the chemical yields of corresponding β-amino esters with respect to unsubstituted benzaldehyde (Table 1, entries 8 and 2, 9 and 1, 10 and 2).

It should be emphasised that the Rodionov reaction was stereoselective with the use of the above substrates. Thus, for benzaldehyde and α-methylbenzylamine acetate under optimum conditions, *d.e.* was 35% (Table 1, entry 2). The presence of a nitro group at the *para*-position of an aromatic nucleus of benzaldehyde decreased the stereoselectivity (*d.e.* is as low as 27%, Table 1, entry 10). It is likely that the electron-acceptor nitro group decreases the activation energy of the addition of monoethyl malonate to an azomethine, and steric factors become less significant. The nitro group at the *ortho*-position results in a more dramatic decrease in the stereoselectivity (Table 1, entries 8 and 10).

To study the stereochemistry of the synthesis of β-aryl-β-aminopropionates by the Rodionov reaction under microwave irradiation, we chemically determined[6] the absolute configurations of the newly formed C-3 chiral centre for the major and minor diastereomers of ethyl *N*-[(*S*)-α-methylbenzyl]-β-amino-β-phenylpropionate. A mixture of the diastereomers was subjected to cyclisation to form a mixture of the corresponding diastereomers of *N*-[(*S*)-α-methylbenzyl]-4-phenylazetidin-2-one, the ^{1}H NMR spectra of which were published.[7]

A comparison between the ^{1}H NMR spectral data of the prepared β-lactam diastereomers‡ with published data[7] allowed us to conclude that the major and minor diastereomers of ethyl *N*-[(*S*)-α-methylbenzyl]-β-amino-β-phenylpropionate exhibit 3*R*- and 3*S*-configurations, respectively.§

Thus, microwave activation can be successfully used for the stereoselective synthesis of β-amino acid esters by the Rodionov reaction without solvent. The procedure is easy to perform, and the esters can be obtained in moderate chemical and optical yields in 10–14 min.

References

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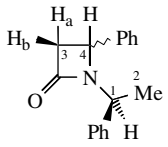
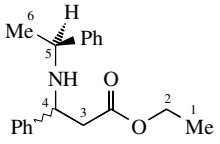
‡ The NMR spectra were recorded on a VXR-400 Varian spectrometer (400 MHz) in a $CDCl_3$ solution at 28 °C using TMS as an internal standard. Protons in the ^{1}H NMR spectra are numbered as follows:



^{1}H NMR, δ: major isomer: 1.76 (d, 3H, Me, $J_{Me,H-1}$ 7.30 Hz), 2.78 (dd, 1H, H_a-3, J_{H_a-3,H_b-3} 14.61 Hz, $J_{H_a-3,H-4}$ 2.56 Hz), 3.24 (dd, 1H, H_b-3, J_{H_b-3,H_a-3} 14.61 Hz, $J_{H_b-3,H-4}$ 5.23 Hz), 4.26 (q, 1H, H-1, $J_{H-1,Me}$ 7.30 Hz), 4.33 (dd, 1H, H-4, J_{H-4,H_a-3} 2.56 Hz, J_{H-4,H_b-3} 5.23 Hz); minor isomer: 1.28 (d, 3H, Me, $J_{Me,H-1}$ 7.25 Hz), 2.79 (dd, 1H, H_a-3, J_{H_a-3,H_b-3} 14.77 Hz, $J_{H_a-3,H-4}$ 5.26 Hz), 3.20 (dd, 1H, H_b-3, J_{H_b-3,H_a-3} 14.77 Hz, $J_{H_b-3,H-4}$ 2.58 Hz), 4.28 (dd, 1H, H-4, J_{H-4,H_a-3} 5.26 Hz, J_{H-4,H_b-3} 2.58 Hz), 5.01 (q, 1H, H-1, $J_{H-1,Me}$ 7.25 Hz).

^{1}H NMR spectra for the major and minor diastereomers correspond to those reported[7] for (1′*S*,4*R*)- and (1′*S*,4*S*)-isomers, respectively.

§



^{1}H NMR, δ: major diastereomer: 1.16 (t, 3H, Me-1, $J_{Me-1,C(2)H_2}$ 7.14 Hz), 1.25 (d, 3H, Me-6, $J_{Me-6,H-5}$ 6.71 Hz), 1.94 (s, 1H, NH), 2.51 (dd, 1H, H_a-3, J_{H_a-3,H_b-3} 15.03 Hz, $J_{H_a-3,H-4}$ 5.14 Hz), 2.61 (dd, 1H, H_b-3, J_{H_b-3,H_a-3} 15.03 Hz, $J_{H_b-3,H-4}$ 9.04 Hz), 3.48 (q, 1H, H-5, $J_{H-5,Me-6}$ 6.71 Hz), 3.80 (dd, 1H, H-4, J_{H-4,H_a-3} 5.14 Hz, J_{H-4,H_b-3} 9.04 Hz), 4.06 [q, 2H, $C(2)H_2$, $J_{C(2)H_2,Me-1}$ 7.14 Hz], 7.15–7.35 (m, 10H, Ph). ^{13}C NMR, δ: 14.12 (Me-6), 25.05 (Me-1), 43.55 (C-3), 55.03 and 56.82 (C-4 and C-5 or reverse), 60.33 (C-2), 126.79–128.49 (Ph-4 and Ph-5), 171.57 (C=O).