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New Approach to the Synthesis of 2,3-Substituted γ-Aminobutyric Acids and Their Derivatives

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Abstract—A new approach to the synthesis of 2,3-substituted γ-aminobutyric acids is proposed. This method consists of the selective catalytic reduction of substituted 3-cyanopropanoic acid esters, which are generated in high yield in the reaction of disubstituted cyclopropenes with sodium cyanide in the corresponding alcohol.

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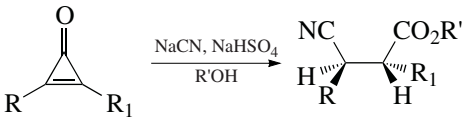
γ-Aminobutyric acid derivatives have a wide spectrum of physiological activity and are mainly used as antiepileptic, anxiolythic, and other psychotropic drugs. In this context, a search for new approaches to the synthesis of these compounds is important.

In our previous work,[1] we discovered a new reaction of substituted cyclopropenes with sodium cyanide in nucleophilic solvents, such as alcohols and water. This reaction generates esters of 2,3-substituted 3-cyanopropanoic acids (Scheme 1). The reaction conditions and the composition of products are specified in the table.



1 **2, 3**

R = Ph, R_1 = Ph (**1a**), Me (**1b**)

Scheme 1.

This reaction was chosen to be the key stage in the synthesis of γ-aminobutyric acid derivatives. Because methanol as a nucleophilic solvent provides for the best yield and diastereoselectivity of the process, we chose compound **2b** to carry out further transformations. One-stage recrystallization of compound **2b** from toluene produced 2,3-diphenyl-3-cyanopropanoate as the pure RR,SS diastereomer pair.

The catalytic hydrogenation of compound **2b** was studied (Scheme 2). Over a 10% Pd/carbon supported catalyst, the process yielded a complex product mixture, which contained, in addition to the desired compound, twinning products and the unreacted cyano ester. Reduction with hydrogen over skeletal nickel avoided the generation of byproducts. For example, the hydrogenation of compound **2b** in THF in the presence of aqueous ammonia at 60°C and 12 atm hydrogen pressure produced a 1 : 1 mixture of 2,3-diphenylbutyrolactame **4** and methyl 2,3-diphenyl-4-aminobutyrate **5**. Compounds **4** and **5** were separated and characterized separately. When the reaction temperature was increased to 80°C, selective and virtually quantitative preparation of product **4** became possible. Below 50°C, hydrogenation did not occur; therefore, we have not found parameters to ensure the selective preparation of amino ester **5**.

In summary, we have discovered a fundamentally new approach to synthesize lactames of 2,3-substituted γ-aminobutyric acids. In view of the high yields of all intermediate stages and the final hydrogenation stage, this method can be considered as preparative. We are planning to extend this method to free amino acids and then to asymmetric and α-unsubstituted γ-aminobutyric acids.

EXPERIMENTAL

2,3-Diphenylbutyrolactame (4). To an autoclave (stainless steel), added were diastereomerically pure methyl 2,3-diphenyl-3-cyanopropanoate (0.5 g, 20 mmol) in THF (20 mL), 25% aqueous ammonia (1 mL), and freshly prepared skeletal nickel (10 mol %). Hydrogenation was carried out at 80°C and the 30 atm hydrogen pressure until gas absorption stopped (for 5–7 h). The reaction mixture was filtered from the catalyst and concentrated.

[1] Yu. V. Skornyakov, D. S. Tereshchenko, A. V. Ignatenko, M. V. Proskurnina, and N. S. Zefirov, Izv. Akad. Nauk, Ser.: Khim., 2005, vol. 9, p. 2066.

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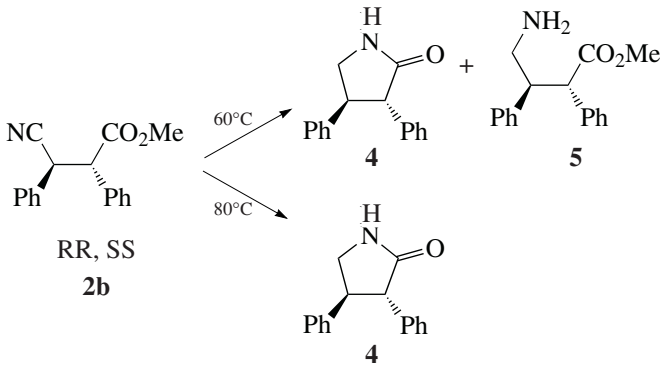


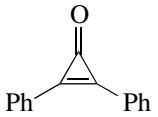
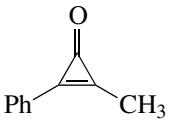
Scheme 2.

Crystalline 2,3-diphenylbutyrolactame **4** obtained in quantitative yield did not require further purification.

^{1}H NMR spectrum ($CDCl_3$), ppm: 7.15–7.40 (m, 10H, 2Ph), 6.89 (s, 1H, NH), 3.8 (t, 1H), 3.54 (t, 1H, CH_2N), 3.67–3.83 (m, 2H, CH–CH).

^{13}C NMR spectrum, ppm: 177.63 (C=O), 140.06, 137.67, 128.84, 128.75, 128.48, 127.35, 127.30 (2Ph), 55.45 (CH–C=O), 50.38 (CH–CH–C=O), 47.66 (CH_2).

Reaction conditions and product yields

Cyclopropenone	R'OH	Conditions	Product	RR, SS fraction, %	Yield, %
	H_2O	Dioxane, refluxing	**2a**	65	45
	MeOH	20°C	**2b**	90	90
	EtOH	20°C	**2c**	65	86
	i-PrOH	Refluxing	**2d**	58–60	75
	n-PrOH	Refluxing	**2e**	60	75
	$PhCH_2OH$	60°C	**2f**	63	80
	MeOH	20°C	**3b**	70	88
	EtOH	20°C	**3c**	60–63	80
	i-PrOH	Refluxing	**3d**	55–58	75
	n-PrOH	Refluxing	**3e**	60	75