DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

ALKYLATION OF 2-HYDROXYMETHYLENE-3-ETHOXYPROPIONITRILE SODIUM ENOLATE BY DIMETHYL SULFATE AND ETHYL BROMIDE IN VARIOUS SOLVENTS

M. M. Litvak[1]

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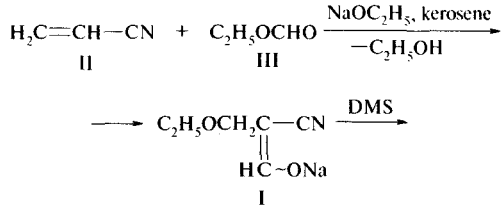
The alkylation of 2-hydroxymethylene-3-ethoxypropionitrile sodium enolate (I) is an important stage in the synthesis of vitamin B_1.

Compound I is obtained from acrylonitrile (II), ethyl formate (III), and powdered $NaOC_2H_5$ in a kerosene medium, after which I is methylated by dimethyl sulfate (DMS) without isolation from the reaction mixture [1, 2]. As seen from the reaction scheme presented below, methylation proceeding in a kerosene – ethanol mixture leads to the formation of target 2-methoxymethylene-3-ethoxypropionitriles (IV) (predominantly in the *cis* and *trans* forms) and an insignificant amount of ethyl esters (V) with an analogous structure. Additional reaction products are the "acryl" (VI, VII) and "acetal" (VIII, IX) impurities [1]



IV: R = CH_3; V: R = C_2H_5 VI: R = C_2H_5, R' = CH_3; VII: R = R' = C_2H_5 VIII: R = C_2H_5, R' = CH_3; IX: R = R' = C_2H_5

As is known, the rate of enolate alkylation and the composition of the alkylation products may significantly depend on the solvent, the nature of the alkylating agent, and the complex-forming agents such as macrocyclic polyesters [3].

The purpose of our work was to compare the efficiency of alkylating compound I by DMS and C_2H_5Br in various solvents with and without a complex-forming agent (dibenzo-18-crown-6, DBC).

The initial sodium enolate I in the form of a light-yellow powder was suspended in a solvent studied (or dissolved in the case of DMF). To this suspension (solution) was added an equimolar amount of DMS or C_2H_5Br and the mixture was stirred at 30 – 35°C. The course of the alkylation process was followed by gas chromatography (GC) (monitoring increase in the content of IV and V in the samples). Our experiments showed that the reaction is virtually completed in all cases within 4 h.

The precipitate was filtered and the filtrate was analyzed for the total content of vinyl esters IV and V by GC using the absolute calibration technique. The ratio of *cis* and *trans* isomers for IV and V was about 1 : 1. In the case of DMS, the content of ethyl ester V in the mixture of methylation products did not exceed 3%.

The results of GC analyses of the methylation products are presented in Table 1. As seen from these experimental data, the best solvents for the methylation of I are acetonitrile and acetone. An analysis of the methylation kinetics showed that the reaction proceeds at a markedly higher rate in acetonitrile, acetone, and (especially) DMF than in all other solvents and is virtually accomplished within 2.5 – 3 h. Introduction of a small (0.25 mol.%) additive of dibenzo-18-crown-6 (an ester capable of forming complexes with sodium ions) accelerates the methylation process, although the yield of vinyl esters remains virtually the same as that in the control.

The ethylation of I by C_2H_5Br is characterized by a slow rate and low yield. Introduction of a small DBC additive accelerates the process, but the yield of the target products is

[1] Belgorod State University, Belgorod, Russia.

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TABLE 1. Efficiency of Alkylating Sodium Enolate I in Various Solvents

Solvent	Alkylating agent	Reaction conditions	Yield of IV and/or V, %
Acetonitrile	DMS	30 – 35°C, 4 h	92
Acetonitrile	DMS	30 – 35°C, 4 h, 0.25 mol.% DBC	92
Acetone	DMS	30 – 35°C, 4 h	91
Kerosene – ethanol (4 : 1 v/v)	"		81
Kerosene	"		71
Ethanol	"		80
Diethyl ether	"		51
DMF	"		46
Benzene	"		25
DMF	C_2H_5Br		79
Acetonitrile	C_2H_5Br		22
Acetonitrile	C_2H_5Br	30 – 35°C, 4 h, 0.25 mol.% DBC	27

still low. Replacing acetonitrile with DMF markedly accelerates the ethylation process and increases the yield of *cis* and *trans* 2-methoxymethylene-3-ethoxypropionitrile isomers (formed in comparable proportions).

It should be noted that the yield of vinyl esters is independent of the isomer composition (*cis* to *trans* ratio) of the initial sodium enolate. This fact was confirmed by using conditions favoring the formation of sodium enolate predominantly in one or the other isomer form [4].

The above results can be of value for the refinement of some technological processes.

EXPERIMENTAL PART

GC analyses were performed on an LKhM-8MD gas chromatograph equipped with a thermal conductivity detector (column: length, 2 m; internal diameter, 2.5 mm; sorbent: Inerton AW, fraction 0.16 – 0.20 mm; impregnating agent, 5% XE-60; carrier gas: helium; gas flow rate, 100 ml/min; thermal regime: column thermostat, 159°C; evaporator, 215°C; detector, 180°C; detector bridge current, 100 mA; recorder chart velocity, 600 mm/h).

The emergence time for *cis* and *trans* 2-methoxymethylene-3-ethoxypropionitrile was 3 min 54 sec and 4 min 48 sec, respectively, and that for *cis* and *trans* 2-ethoxymethylene-3-ethoxypropionitriles was 4 min 36 sec and 5 min 36 sec, respectively.

Alkylation of 2-hydroxymethylene-3-ethoxypropionitrile sodium enolate (general method). To 7.5 g (0.05 mole) of sodium enolate I in 50 ml of a solvent (or a solvent mixture) studied (see Table 1) was added 0.05 mole of an alkylating agent: 5.0 ml of DMS or 4.0 ml of C_2H_5Br; in some cases, 0.25 mol.% of dibenzo-18-crown-6 (complex-forming agent) was added first. The mass was stirred for 4 h at 30 – 35°C (on a glycerol bath).

Upon termination of the process, insoluble products were filtered and the filtrate was concentrated in vacuum, diluted with acetonitrile, and analyzed for the content of vinyl esters IV and V by GC in the absolute calibration mode.

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