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Dedicated to Full Member of the Russian Academy of Sciences M.G. Voronkov on his 90th anniversary

Microwave-Initiated Hydroamination of 2-Ethoxypropenal with Secondary Amines

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Abstract—Reactions of 2-ethoxyprop-2-enal with cycloaliphatic secondary amines (morpholine, piperidine, pyrrolidine) follow 1,4- or 1,2-addition pattern with subsequent condensation of the adduct with the initial amine to produce isomeric 2-ethoxyprop-2-ene-1,1-diamines and 2-ethoxyprop-1-ene-1,3-diamines. These reactions are accelerated by a factor of 15–30 under microwave irradiation and in the presence of water. The regioselectivity of primary nucleophilic attack varies over a wide range, depending on the amine basicity and reactant ratio. The reaction of 2-ethoxyprop-2-enal with pyrrolidine and water at a ratio of 1 : 10 : 10 was characterized by increased regioselectivity of 1,4-addition (up to 75%). Unlike cycloaliphatic amines, 2-ethoxyprop-2-enal reacted with *N*-methylaniline under microwave irradiation at a lower rate to give 2-ethoxy-N^1,N^1,N^3-trimethyl-N^1,N^1,N^3-triphenylpropane-1,1,3-triamine.

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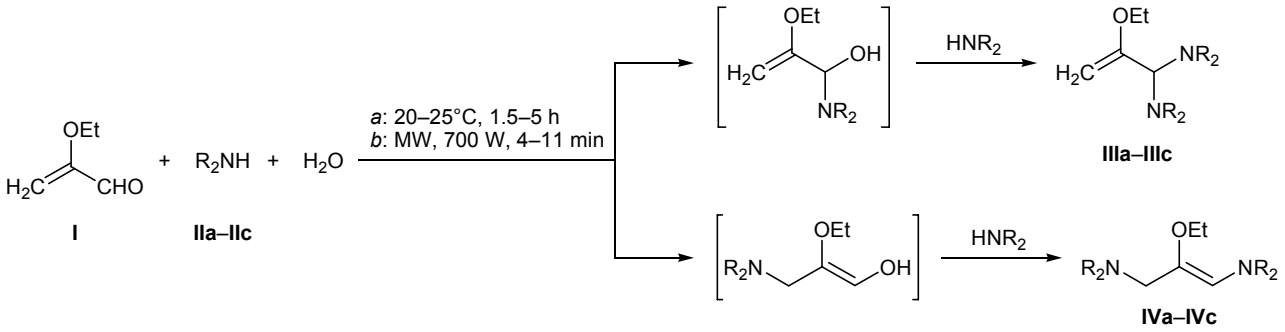
Unlike most propenals, 2-alkoxypropenals tend to take up water, thiol, and alcohol molecules at the C=C bond to give the corresponding Markovnikov adducts [1]. However, the direction of attack by thiols in alkaline medium changes, and they act as nucleophiles to afford exclusively thia-Michael adducts [2]. Reactions of 2-alkoxypropenals with other nucleophiles (amines and CH acids) were studied very poorly. α-Alkoxy-substituted acrylic systems, in particular, α-alkoxyacroleins, occur in animal and plant tissues [3]. It is believed that these compounds react with nucleophilic HO, HS, and HN groups of enzymes, amino acids, proteins, DNA, and RNA [4]. Conjugate addition of amines to α,β-unsaturated carbonyl compounds is now extensively studied as synthetically important field of organic chemistry [5]. Products of conjugate addition of amines, specifically β-amino carbonyl compounds and their derivatives, are used as peptide analogs or precursors of optically active amino acids, amino alcohols, diamines, and lactams, many of which are medical agents [6].

As shown previously, secondary amines (such as morpholine and piperidine) are capable of adding to α-ethoxyacrolein at both *1,2* and *1,4* positions (Michael reaction), yielding isomeric mixtures of 2-ethoxyprop-2-ene-1,1-diamines and 2-ethoxyprop-1-ene-1,3-diamines [7]. These reactions were carried out by heating the reactants in boiling benzene with simultaneous removal of water and without it (reaction time 2–6 h) and were accompanied by formation of *N*-formyl derivative of the initial amine as by-product (up to 30%). Over the subsequent 20 years microwave irradiation has opened new prospects in the development of many thermally possible processes. As a rule, microwave irradiation considerably accelerates chemical reactions, improves their yield and selectivity, and ensures solvent-free processes. Moreover, some reactions that could not be performed under conventional thermal conditions successfully occur under microwave irradiation [8].

Michael reaction is one of the most extensively studied reactions in organic synthesis, and its potential can be increased with the use of microwave irradiation [9, 10]. Furthermore, studies on Michael addition in aqueous solution have been initiated since 1990s [11]. With a view to elucidate the effects of microwave irradiation (MW) and aqueous medium in the present work we continued our studies on the addition of secondary amines to α-ethoxyacrolein [7].

Scheme 1.



R_2N = morpholino (**a**), piperidino (**b**), pyrrolidin-1-yl (**c**).

It should be noted that numerous addition reactions of secondary amines to activated α,β-unsaturated carbonyl compounds were performed with α,β-unsaturated esters, acids, amides, nitriles, and ketones [10, 12–14], whereas conjugated aldehydes were seldom used as Michael acceptors [13, 15]. Reactions with the latter are strongly complicated by side processes, in particular by 1,2-addition with subsequent condensation, as well as by polymerization [13, 16].

In the reaction of 2-ethoxyprop-2-enal (**I**) with piperidine and morpholine at room temperature in aqueous medium (2 equiv of water), the conversion of initial aldehyde **I** was 75–80% in 3–5 h, while the same conversion of **I** in analogous reaction under microwave irradiation was attained in 6–11 min (according to the ^{1}H NMR data; see table); in both cases, mixtures of isomeric ethoxypropenediamines **III** and **IV** were formed (Scheme 1). Unlike morpholine and piperidine, the reaction with pyrrolidine as stronger nucleophile was much faster. The conversion of aldehyde **I** was complete in 1.5 h at room temperature or in 4 min under microwave irradiation (^{1}H NMR). The addition of cycloaliphatic amines **IIa**–**IIc** both in the presence and in the absence of water was characterized by similar rates.

Previous attempts to accomplish conjugate addition of secondary aromatic amines to α,β-unsaturated aldehydes in the presence of a number of catalysts were unsuccessful [14, 17]. Up to now, catalysts have been proposed (e.g., nickel, magnesium, and zinc perchlorate complexes [18] and bismuth trifluoromethanesulfonates) which ensured selective conjugate addition of aliphatic amines to α,β-unsaturated carbonyl compounds in up to 70% yield [19]. Insofar as such catalysts are difficultly accessible and expensive, we tried to initiate the addition of an aromatic amine (*N*-methylaniline) to aldehyde **I** with the aid of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) which is successfully used in analogous processes [20]. However, we failed to obtain the corresponding 1,4-addition product according to the procedure described in [20], and no reaction occurred.

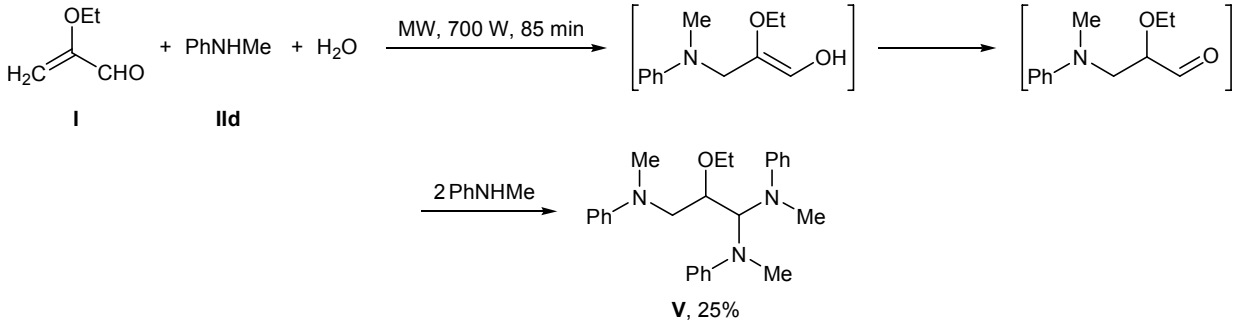
The reaction of *N*-methylaniline with 2-ethoxyprop-2-enal (**I**), initiated by microwave irradiation, was much slower than the reactions of **I** with morpholine and piperidine and especially with pyrrolidine. The conversion of aldehyde **I** was only 50% after irradiation for 85 min at a maximal power (700 W; see table), and the presence of water was necessary. The final product in the reaction of *N*-methylaniline with 2-eth-

Reaction of 2-ethoxyprop-2-enal with secondary amines at room temperature and under microwave irradiation

Amine	pK_a	Room temperature		Microwave irradiation, 700 W	
		reaction time, h	conversion of **I**,[a] %	reaction time, min	conversion of **I**,[a] %
Morpholine	8.33	3	80	8	80
Piperidine	11.12	5	75	11	75
Pyrrolidine	11.31	1.5	100	4	100
N-Methylaniline	4.85	–	–	85–120	50

[a] According to the ^{1}H NMR data.

Scheme 2.



oxyprop-2-enal (**I**) was 2-ethoxy-N^1,N^1,N^3-trimethyl-N^1,N^1,N^3-triphenylpropane-1,1,3-triamine (**V**) (yield 25%; Scheme 2). The structure of **V** was determined by ^{1}H and ^{13}C NMR spectroscopy using HSQC-GP and HMBC-GP ^{1}H–^{13}C two-dimensional techniques.

Thus reactions of 2-ethoxypropen-2-al with cycloaliphatic secondary amines in aqueous solution under microwave irradiation are characterized by high conversion (75–100% in 4–11 min) and selectivity (no by-products were detected). *N*-Methylaniline as weakly basic aromatic amine can also be involved in conjugate addition to unsaturated aldehyde **I**, but this process is followed by formation of aminal **V**, presumably due to prolonged irradiation. Depending on the reaction conditions, amine nature, reactant ratio, and amount of polar solvent, mixtures of 1,2- and 1,4-addition products are generally formed at a ratio of 2:1 to 7.6:1 for morpholine, 1:2 to 1:2.5 for piperidine, and 1.5:1 to 1:3 for pyrrolidine. Considerably increased regioselectivity toward formation of 1,4-addition product **IVc** (75%, according to the ^{1}H NMR data) was achieved in the reaction of aldehyde **I** with pyrrolidine and water at a ratio of 1:10:10. Selective conjugate addition (66%, ^{1}H NMR) was also observed in the reaction of 2-ethoxyprop-2-enal with piperidine and water at a ratio of 1:1.5:1.5. These findings indicate that the presence of an ethoxy group in the α-position of Michael acceptor does not prevent Michael reaction under the given conditions and provide additional information on the effect of substituents in α,β-unsaturated carbonyl compounds [10].

To conclude, microwave irradiation and the presence of water strongly accelerates addition of secondary amines to α-ethoxy-substituted α,β-unsaturated aldehyde. The regioselectivity of the process depends on the basicity of the medium; therefore, in the reaction with pyrrolidine and water taken in a large excess with respect to aldehyde **I** the yield of the 1,4-addition product attains 75%.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and Bruker AV-400 spectrometers at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference; the chemical shifts were measured with an accuracy of 0.01 and 0.02 ppm, respectively. GC–MS analysis was performed on a Hewlett–Packard HP 5890 gas chromatograph (Ultra-2 column, injector temperature 250°C, oven temperature programming from 70 to 280°C at a rate of 20 deg/min) coupled with an HP 5971A mass-selective detector (electron impact, 70 eV). Microwave-assisted reactions were performed in an LG MS-1904H microwave furnace (700 W). Silica gel 60 (0.063–0.200 mm, Merck) was used for chromatographic purification.

Condensation of 2-ethoxyprop-2-enal (I) with morpholine and piperidine (*general procedure***).** *a*. A mixture of 1 g (10 mmol) of aldehyde **I**, 20 mmol of morpholine or piperidine, and 0.36 g (20 mmol) of water was stirred for 2–5 h at room temperature (^{1}H NMR monitoring). The mixture was extracted with diethyl ether, the extract was dried over $MgSO_4$, and the solvent and unreacted initial compounds were removed to obtain isomer mixture **IIIa**/**IVa** or **IIIb**/**IVb** in an overall yield of 80% (^{1}H NMR).

b. An ampule was charged with 1 g (10 mmol) of aldehyde (**I**), 20 mmol of the corresponding amine, and 0.36 g (20 mmol) of water, and the mixture was irradiated in a microwave furnace at a power of 700 W over a period of 8–11 min (in 1-min pulses followed by cooling to room temperature). The mixture was extracted with diethyl ether, the extract was dried over $MgSO_4$, and the solvent and unreacted initial compounds were removed to obtain isomer mixture **IIIa**/**IVa** (overall yield 87%) or **IIIb**/**IVb** (84%; according to the ^{1}H NMR data). The products were identified by comparing their spectral parameters with those reported in [7].

The reaction can also be carried out under analogous conditions but without addition of water.

2-Ethoxy-3,3-dimorpholinoprop-1-ene (IIIa). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, CH_3, J = 7.0 Hz), 2.42 m (6H, CH_2), 2.52 m (2H, CH_2), 2.94 s (1H, CH), 3.63 m (8H, CH_2), 3.74 q (2H, C**H**$_2$CH$_3$, J = 7.0 Hz), 3.97 d and 4.10 d (1H each, =CH_2, J = 1.7 Hz). Mass spectrum (retention time 10.68 min), m/z (I_{rel}, %): 256 (22) $[M]^+$, 170 (100) $[M - N(CH_2CH_2)_2O]^+$, 140 (65), 112 (9), 100 (98), 84 (9) $[M - 2N(CH_2CH_2)_2O]^+$, 70 (9), 56 (33), 42 (19), 29 (23) $[Et]^+$.

2-Ethoxy-1,3-dimorpholinoprop-1-ene (IVa). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3, J = 7.0 Hz), 2.52 m (8H, CH_2), 3.02 s (2H, CH_2), 3.63 m (8H, CH_2), 3.87 q (2H, OCH_2, J = 7.0 Hz), 4.90 s (1H, =CH). Mass spectrum (retention time 10.97 min), m/z (I_{rel}, %): 256 (23) $[M]^+$, 170 (100) $[M - N(CH_2CH_2)_2O]^+$, 140 (71), 112 (9), 100 (78), 84 (7) $[M - 2N(CH_2CH_2)_2O]^+$, 70 (10), 56 (20), 41 (12), 29 (11) $[Et]^+$.

2-Ethoxy-3,3-dipiperidinoprop-1-ene (IIIb). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3, J = 7.0 Hz), 1.41 m (8H, CH_2), 1.45 m (8H, CH_2), 2.34 m (4H, CH_2), 2.90 s (1H, CH), 3.72 q (2H, OCH_2, J = 7.0 Hz), 3.89 d and 3.98 d (1H each, =CH_2, J = 2.8 Hz).

2-Ethoxy-1,3-dipiperidinoprop-1-ene (IVb). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, J = 7.0 Hz), 1.53 m (12H, CH_2), 2.42 m (8H, CH_2), 2.78 s (1H, CH_2), 3.88 q (2H, OCH_2, J = 7.0 Hz), 4.85 s (1H, =CH).

2-Ethoxy-3,3-bis(pyrrolidin-1-yl)prop-1-ene (IIIc). The procedure was the same as above, method *b*. A mixture of 2 g (20 mmol) of aldehyde **I** and 2.84 g (40 mmol) of pyrrolidine was irradiated in a microwave furnace (700 W) over a period of 4 min (in 1-min pulses followed by cooling to room temperature). According to the ^{1}H NMR data, the conversion was 100%. Vacuum distillation gave a mixture of isomers **IIIc** and **IVc** at a ratio of 1.5:1. Yield 2.88 g (64%), dark red liquid, bp 25–35°C (35 mm). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3, J = 7.0 Hz), 1.75 m (8H, 3-H, 4-H), 2.60 m (8H, 2-H, 5-H), 2.94 s (1H, NCH), 3.75 q (2H, OCH_2, J = 7.0 Hz), 3.94 d and 4.03 d (1H each, =CH_2, J = 1.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.43 (CH_3), 49.78, 51.88, 62.39 (OCH_2), 84.52 (NCH), 84.91 (CH_2=), 158.81 (=C–O).

2-Ethoxy-1,3-bis(pyrrolidin-1-yl)prop-1-ene (IVc). ^{1}H NMR spectrum, δ, ppm: 1.73 t (3H, CH_3, J = 7.0 Hz), 1.75 m (8H, 3-H, 4-H), 2.63 m (8H, 2-H, 5-H), 2.97 s (2H, CH_2), 3.72 q (2H, CH_2O), 5.25 s (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 23.43 (CH_3), 49.78, 52.72 (NCH_2), 53.76, 64.80 (OCH_2), 123.46 (=CHN), 133.03 (O–C=). Found for isomer mixture **IIIc**/**IVc**, %: C 69.52; H 10.78; N 12.38. $C_{13}H_{24}N_2O$. Calculated, %: C 69.64; H 10.71; N 12.50.

When the reaction was carried out at a **I**–**IIc**–H_2O ratio of 1:10:10 (MW, 5 min), a mixture of isomers **IIIc** and **IVc** was obtained at a ratio of 1:3.

2-Ethoxy-*N*^{1},*N*^{1},*N*^{3}-trimethyl-*N*^{1},*N*^{1},*N*^{3}-triphenylpropane-1,1,3-triamine (V) was synthesized as described above in *b*. A mixture of 2 g (20 mmol) of aldehyde **I**, 4.28 g (40 mmol) of *N*-methylaniline, and 0.72 g (40 mmol) of water was subjected to microwave irradiation (700 W) over a period of 85 min (in 1-min pulses followed by cooling to 20°C). The mixture was extracted with diethyl ether (3×15 ml), the extracts were combined and dried over $MgSO_4$, the solvent and unreacted initial compounds were removed, and the residue was subjected to chromatography on silica gel using hexane–diethyl ether (3:1) as eluent. Yield 1.33 g (25%, calculated on the initial amine), dark brown liquid. Compound **V** was isolated as a mixture of two diastereoisomers at a ratio of 1:1. ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.68 s (3H, CH_3N), 2.81 s (3H, CH_3N), 2.89 s (3H, CH_3N), 3.19 d and 3.32 d (1H, CH_2, J = 9 Hz), 3.29 d and 3.32 d (1H, CH_2, J = 4.3 Hz), 3.52 q and 3.61 q (1H each, OCH_2, J = 7.0 Hz), 3.91 m (1H, CH), 5.03 d (1H, CH, J = 8.2 Hz), 6.54 d (2H, *o*-H, J = 8.1 Hz), 6.56 t (2H, *m*-H, J = 8.0 Hz), 6.68 m (3H, *p*-H), 6.84 d (2H, *o*-H, J = 8.1 Hz), 7.00 d (2H, *o*-H, J = 7.6 Hz), 7.08 t (2H, *m*-H, J = 7.6 Hz), 7.20 m (2H, *m*-H). ^{13}C NMR spectrum, δ_C, ppm: 15.42 (**C**H$_3$CH$_2$), 31.01 (CH_3N), 33.40 (CH_3N), 39.11 (CH_3N), 54.43 (CH_2N), 62.86 (CHN), 65.04 (CH_2O), 72.58 (CH_2O), 111.20 (C^m), 112.59 (C^o), 112.97 (C^o), 116.24 (C^p), 117.38 (C^p), 118.06 (C^p), 127.82 (C^m), 128.07 (C^o), 128.86 (C^m), 146.73 (C^i), 147.72 (C^i), 150.18 (C^i). Found for isomer mixture, %: C 77.54; H 8.14; N 9.89. $C_{26}H_{33}N_3O$. Calculated, %: C 77.42; H 8.19; N 10.42.

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