Reactions of benzyloxy- and benzhydryloxyethoxyalkynes with heterocyclic amines

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A new series of heterocyclic oxyethoxyalkynylamines was synthesized and the aminomethylation reactions of benzyloxy- and benzhydryloxyethoxyalkynes with piperidine, 4-benzylpiperidine, morpholine, piperazine, 1-benzylpiperazine and 1-benzhydrylpiperazine were explored; the influence of temperature and the nature of the amines on the course of the reaction was determined.

Key words: amines, oxyethoxyalkynes, morpholine, piperidine, piperazines

INTRODUCTION

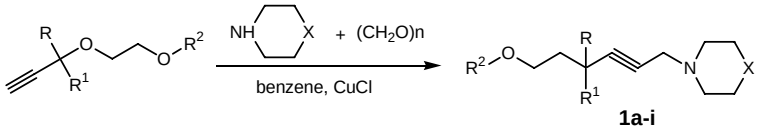
The piperidine nucleus is a structural fragment of many natural as well as synthetic physiologically active substances [1]. It is also known that some benzylpiperazine derivatives are biologically active and may be used as preparations for dilating blood vessels [2]. As a continuation of the analysis of chemical properties of benzyl- and benzhydryloxyalkynes [3], some oxyethoxyalkynylpiperidines and morpholines were synthesized [4]. The goals of this work were as follows: to synthesize new acetylenic analogues of the above-mentioned physiologically active substances; to explore the aminomethylation reactions of benzyl- and benzhydryloxyethoxyalkynes with piperidine, morpholine, 4-benzylpiperidine, piperazine, 1-benzylpiperazine and 1-benzhydrylpiperazine; to work out the isolation procedure of the heterocyclic amines from the reaction mixture.

RESULTS AND DISCUSSION

In aminomethylation reactions of benzyl- and benzhydryloxyethoxyalkynes with piperidine, morpholine and 4-benzylpiperidine, a new series of heterocyclic oxyethoxyalkynylamines was synthesized. Though the rate of the reaction in benzene was lower than in dioxane, however, less tar was formed in benzene and the optimal reaction temperature was established to be 50–60 °C. Because of the extremely high boiling temperature of heterocyclic amines **1 f–i** (Scheme 1) and the inability to isolate them by distillation, the traditional method of purifying amines with 10% HCl and NaOH solutions was used. During reactions with benzylpiperidine a ~10% surplus of oxyethoxyalkyne was used in order to avoid any amine remaining in the reaction mixture.

Heterocyclic oxyethoxyalkynylamines **1 a–e** were also isolated as hydrochlorides, and the isolation hydrochlorides of amines **1 f–i** (obtained from 4-benzylpiperidine and the corresponding oxyethoxyalkyne) in the crystalline form was unsuccessful, as they softened in the air forming a glassy mass. Thus, when piperidine, morpholine and 4-benzylpiperidine were reacted with benzyl- and benzhydryloxyethoxyalkynes in benzene, using an equivalent amount of paraformaldehyde and a catalytic amount of CuCl, after 15–20 h at 50–60 °C of stirring, 57–74% of heterocyclic oxyethoxyalkynylamines **1 a–i** (Scheme 1) were isolated.

Scheme 1

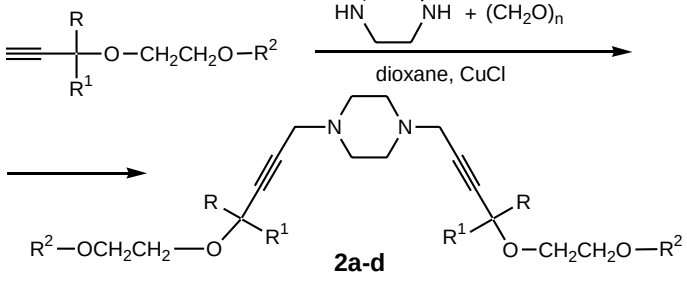


1a-i

R = H(**1 a, f, h**), CH_3 (**1 b–e, g, i**); R^1 = H (**1 f, h**), CH_3 (**1 a, b, d, i**), CH_2H_5 (**1 c, e, g**);
R = $CH_2C_6H_5$ (**1 a–c, f, g**), CH $(C_6H_5)_2$ (**1 d, e, h, i**);
X = CH_2 (**1 a, d, e**), O (**1 b, c**), $CHCH_2C_6H_5$ (**1 f–i**).

Aminomethylation of resin-bound alkynes with piperazines [5] and of 3-methoxy-1-propyne with 4-phenylpiperazine [6] is known. Piperazine easily polymerises in the presence of paraformaldehyde [7], and the polymer of piperazine and paraformaldehyde was synthesized during the Munich reaction [8]; we have established that this polymer does not further reacts with the corresponding alkynes. While carrying out the reactions of benzyl- and benzhydryloxyethoxyalkynes with piperazine using dioxane as a solvent, we established the term of reaction at a temperature of 20 °C and 50 °C. Thus, during the reaction of alkynes with piperazine, using an equivalent amount of paraformaldehyde and a catalytic amount of CuCl, after 15–20 h at ~50 °C (or 100–120 h at ~20 °C) of stirring, 43–52% of the corresponding 1,4-bis-alkynylpiperazines **2 a–d** (Scheme 2) were obtained.

Scheme 2

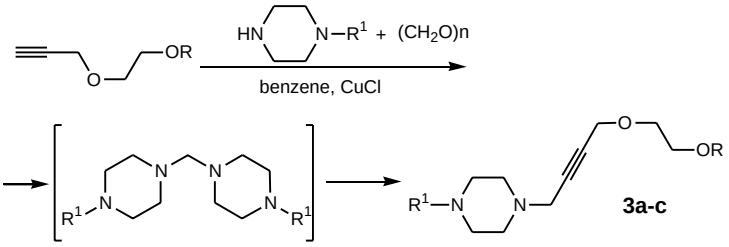


2a-d

R = H(**2 a, c**), CH_3(**2 b, d**); R^1 = H (**2 a, c**), CH_3 (**2 b, d**); R^2 = $CH_2C_6H_5$ (**2 a, c**), $CH(C_6H_5)_2$ (**2 b, d**).

In the aminomethylation reactions of 1-benzylpiperazine and 1-benzhydrylpiperazine, the condensation products with paraformaldehyde were isolated: 1-benzhydryl-4-[(4-benzhydryl-1-piperazinyl)methyl]piperazine – NMR ^{1}H data (δ ppm): 2.47 m (16H, piperazine), 2.96 s (2H, NCH_2N), 4.24 s (2H, 2CH), 7.32 m (20H, benzene) and 1-benzyl-4-[(4-benzyl-1-piperazinyl)methyl]piperazine – NMR ^{1}H data (δ ppm): 2.55 m (16H, piperazine), 2.98 s (2H, NCH_2N), 3.59 s (4H, $2CH_2$), 7.42 m (10H, benzene). These intermediate products further reacted with the corresponding alkynes. Therefore, reactions of 1-benzylpiperazine and 1-benzhydrylpiperazine with benzyloxy- and benzhydryloxyethoxyalkynes (a 5% surplus of oxyethoxyalkynes was used in order to avoid any amine remaining in the reaction mixture) were carried out using benzene as a solvent. After 10–15 h at 35–45 °C of stirring, 46–48% of the corresponding alkynylpiperazines **3 a–c** (Scheme 3) were isolated. When dioxane was used as a solvent, tar was formed and made the isolation of the products more difficult.

Scheme 3



3a-c

R = $CH_2C_6H_5$ (**3 a, c**), $CH(C_6H_5)_2$ (**3b**); R^1 = $CH_2C_6H_5$ (**3 a, b**), $CH(C_6H_5)_2$ (**3 c**).

EXPERIMENTAL

During the synthesis of all heterocyclic amines **1 a–i, 2 a–d, 3 a–c** the course of the reaction was followed chromatographically on a Silufol plate, using the following carrier: 1-butanol : ethyl acetate: 2-propanol: water = 5 : 3 : 2 : 1. ^{1}H NMR spectra were recorded on a Tesla BS-567A NMR spectrometer at 80 MHz with *TMS* as internal standard.

Synthesis of heterocyclic oxyethoxyalkynylamines (1 a–e). 900 mg (30 mmol) of paraformaldehyde, 400 mg of CuCl, and 30 mmol of corresponding oxyethoxyalkyne were added to 150 cm^3 of benzene; during 1 h, 30 mmol of a corresponding amine dissolved in 20 cm^3 of benzene was added dropwise at ~30 °C. Then the temperature was gradually increased to 50–60 °C; the stirring continued for 15–20 h following chromatographically the course of the reaction. After the completion of the reaction, the mixture was cooled to room temperature and treated with a saturated solution of NH_4Cl (2 × 50 cm^3). The benzene layer was separated, washed with water (3 × 100 cm^3) and dried with $MgSO_4$. After the solvent was distilled and thoroughly vacuumed off, the oil-like oxyethoxyalkynylamine was dissolved in 50 cm^3 of dry ethyl ether; gaseous HCl was added to the solution (while stirring and cooling) to pH ≈ 4. The oxyethoxyalkynylamines hydrochlorides crystallized in a refrigerator were filtered off and washed with 50 cm^3 of dry ethyl ether, recrystallized from the mixture of dry ethyl alcohol and ethyl ether and finally dried in vacuo ($CaCl_2$). The corresponding hydrochlorides were obtained in 63–82% yields; their melting points were established. Part of hydrochlorides were treated with 10% NaOH solution to pH ≈ 8, the product was extracted with benzene, washed with water to pH = 7 and dried with $MgSO_4$. After the sol-

vent was distilled and vacuumed off, the corresponding oxyethoxyalkynylamines were obtained as an oil-like mass; their ^{1}H NMR spectra in $(CD_3)_2CO$ were recorded and the elemental analysis was carried out. Data on heterocyclic oxyethoxyalkynylamines **1 a–e** are listed in Table 1.

Synthesis of benzyloxyethoxyalkynylpiperidines (1 f–i). 990 mg (33 mmol) of paraformaldehyde, 400 mg of CuCl and 33 mmol of a corresponding oxyethoxyalkyne were added to 130 cm^3 of benzene; during 1 h, 5250 mg (30 mmol) of 4-benzylpiperidine dissolved in 20 cm^3 of benzene was added dropwise at ~30 °C. Then the temperature was gradually increased to 50–60 °C; stirring continued for 15–20 h following chromatographically the course of the reaction. On the reaction completion, the mixture was

Table 1. **Data on benzyl- and benzhydryloxyethoxyalkynylamines 1 a–i**

Cpd. No	Yield, %	Mp, °C HCl	Found / requires, %			Formula	NMR ^{1}H data (δ ppm; *J* Hz)
			C	H	S		
1a	63	82–84	75.59 75.71	9.13 9.02	4.58 4.67	$C_{19}H_{27}NO_2$	1.5 (3H, CH_3, d, ^3J = 7), 1.59 (6H, $3CH_2$, m), 2.58 (4H, CH_2NCH_2, t, ^3J=7), 3.38 (2H, CCH_2, d, ^5J = 2), 3.81 (4H, OCH_2CH_2O, m), 4.42 (1H, CCH, k, ^3J = 7, ^5J = 2), 4.67 (2H, OCH_2, s), 7.46 (5H, C_6H_5, m).
1b	65	115–116	7.65 71.89	8.71 8.57	4.31 4.41	$C_{19}H_{27}NO_3$	1.57 (6H, $2CH_3$, s), 2.6 (4H, CH_2NCH_2, t, ^3J = 7), 3.43 (2H, CCH_2, s), 3.74 (4H, CH_2OCH_2, t, ^3J = 7), 3.82 (4H, OCH_2CH_2O, m), 4.67 (2H, OCH_2, s), 7.46 (5H, C_6H_5, m).
1c	68	84–85	72.31 72.47	8.95 8.81	4.08 4.22	$C_{20}H_{29}NO_3$	1.16 (3H, CH_3, t, ^3J = 7), 1.55 (3H, CH_3, s), 1.82 (2H, CH_2, q, ^3J = 7), 2.63 (4H, CH_2NCH_2, t, ^3J = 7), 3.46 (2H, CCH_2, s), 3.77 (4H, CH_2OCH_2, t, ^3J = 7), 3.85 (4H, OCH_2CH_2O, m), 4.7 (2H, OCH_2, s), 7.47 (5H, C_6H_5, m).
1d	82	98–100	79.61 79.75	8.61 8.49	3.49 3.57	$C_{26}H_{33}NO_2$	1.57 (6H, CH_3, s), 1.60 (6H, $3CH_2$, m), 2.59 (4H, CH_2NCH_2, t, ^3J = 7), 3.45 (2H, CCH_2, s), 3.83 (4H, OCH_2CH_2O, m), 5.67 (1H, CHO, s), 7.50 (10H, $2C_6H_5$, m).
1e	70	71–73	79.78 79.95	8.79 8.69	3.38 3.45	$C_{27}H_{35}NO_2$	1.15 (3H, CH_3, t, ^3J = 7), 1.52 (3H, CH_3, s), 1.61 (6H, $3CH_2$, m), 1.81 (2H, CH_2, q, ^3J = 7), 2.59 (4H, CH_2NCH_2, t, ^3J = 7), 3.41 (2H, CCH_2, s), 3.79 (4H, OCH_2CH_2O, m), 5.76 (1H, CHO, s), 7.51 (10H, $2C_6H_5$, m).
1f	57	–	79.45 79.53	8.35 8.27	3.59 3.71	$C_{25}H_{31}NO_2$	1.35–1.85 (5H, CH_2CHCH_2, m), 2.63 (2H, CCH_2C, d, ^3J = 6), 2.84–3.11 (4H, CH_2NCH_2, m), 3.39 (2H, CCH_2N, t, ^5J = 2), 3.78 (4H, OCH_2CH_2O, m), 4.31 (2H, CCH_2O, t, ^5J = 2), 4.65 (2H, OCH_2, s), 7.32–7.45 (10H, $2C_6H_5$, m).
1g	68	–	80.01 80.14	9.01 8.88	3.25 3.33	$C_{28}H_{37}NO_2$	1.12 (3H, CH_3, t, ^3J = 7), 1.5 (3H, CH_3, s), 1.35–1.85 (5H, CH_2CHCH_2, m), 1.77 (2H, CH_2, q, ^3J = 7), 2.63 (2H, CCH_2C, d, ^3J = 6), 2.85–3.25 (4H, CH_2NCH_2, m), 3.42 (2H, CCH_2N, s), 3.81 (4H, OCH_2CH_2O, m), 4.67 (2H, OCH_2, s), 7.33–7.45 (10H, $2C_6H_5$, m).
1h	61	–	81.94 82.08	7.89 7.77	2.93 3.08	$C_{31}H_{35}NO_2$	1.35–1.85 (5H, CH_2CHCH_2, m), 2.63 (2H, CCH_2C, d, ^3J = 6), 2.85–3.10 (4H, CH_2NCH_2, m), 3.41 (2H, CCH_2N, t, ^5J = 2), 3.81 (4H, OCH_2CH_2O, m), 4.37 (2H, CCH_2O, t, ^5J = 2), 5.63 (1H, CHO, s), 7.36–7.54 (15H, $3C_6H_5$, m).
1i	67	–	82.15 82.28	8.29 8.16	2.79 2.90	$C_{33}H_{39}NO_2$	1.58 (6H, $2CH_3$, s), 1.35–1.85 (5H, CH_2CHCH_2, m), 2.64 (2H, CCH_2C, d, ^3J = 6), 2.87–3.02 (4H, CH_2NCH_2, m), 3.40 (2H, CCH_2N, s), 3.79 (4H, OCH_2CH_2O, m), 5.66 (1H, CHO, s), 7.36–7.52 (15H, $3C_6H_5$, m).

cooled and treated with a saturated solution of NH_4Cl (2 × 50 cm³). The benzene layer was separated, washed with water (3 × 100 cm³) and dried with $MgSO_4$. After the solvent was distilled and thoroughly vacuumed off, the oil-like oxyethoxyalkynylamine was dissolved in 50 cm³ of dry ethyl ether and gaseous HCl was added to the solution (while stirring and cooling) to pH ≈ 4. All hydrochlorides of amines **1 f–i** could not be isolated as crystals; therefore, after cooling ethyl ether was decanted and the oil-like mass was further washed with 50 cm³ of dry ethyl ether. Then the oil-like mass was treated with NaOH solution (1200 mg NaOH / 25 cm³ H_2O) and extracted with benzene. The benzene layer was separated, washed with water to pH = 7 and dried with $MgSO_4$. After the solvent was distilled and thoroughly vacuumed off, 61–68% of corresponding amines **1 f–i** as an oil-like mass were isolated; their ^{1}H NMR spectra in $(CD_3)_2CO$ were recorded and the elemental anaysis was carried out. The data on benzyloxyethoxyalkynylpiperidines **1 f–i** are listed in Table 1.

Synthesis of 1,4-bis-alkynpiperazines (2 a–d). 20 mmol of corresponding oxyethoxyalkynes, 600 mg (20 mmol) of paraformaldehyde and 300 mg of CuCl were added to 100 cm³ of dioxane; during 8 h, 860 mg (10 mmol) of piperazine was added while stirring at ~20 °C. On the following day the temperature was increased to ~50 °C and stirring continued for another 15–20 h (or 100–120 h at ~20 °C), following chromatographically the course of the reaction. On the reaction completion, 100 cm³ of saturated solution of NH_4Cl and 150 cm³ of benzene were added; after 10–15 min of stirring the benzene layer was separated, washed with water (2 × 100 cm³) and dried with $MgSO_4$. Benzene was distilled and vacuumed off, the remainder was dissolved in 25 cm³ of ethyl ether and acidified with HCl solution (2 cm³ HCl / 20 cm³ 2-propanol) to pH ≈ 5 and left in a refrigerator. Then the hydrochlorides crystallized were filtered off and washed with 50 cm³ of dry ethyl ether, recrystallized from the mixture of 2-propanol and ethyl ether, 43–52% of corresponding hydrochlorides were obtained; their melting points were established. Part of hydrochlorides were treated with 10% solution of NaOH to pH ≈ 9 and extracted with benzene. The benzene layer was separated, washed with water to pH = 7 and dried with $MgSO_4$. After the solvent was distilled and vacuumed off, the corresponding 1,4-bis-alkynylpiperazines **2 a–d** were obtained as an oil-like mass; their ^{1}H NMR spectra in $(CD_3)_2CO$ were recorded and the elemental anaysis was carried out. Data on 1,4-bis-alkynylpiperazines **2 a–d** are listed in Table 2.

Synthesis of benzyl- and benzhydryloxyethoxyalkynylpiperazines (3 a–c). 750 mg (25 mmol) of paraformaldehyde and 300 mg of CuCl were added to

Table 2. **Data on (1,4-bis-alkynylpiperazines) 2 a–d and (benzyl- and benzhydrylpiperazinalkynes) 3 a–c**

Cpd. No	Yield, %	Mp, °C HCl	Found / requires, %			Formula	NMR ^{1}H data (δ ppm; *J* Hz)
			C	H	S		
1	2	3	4	5	6	7	8
2a	46	142–144	73.31 73.44	7.89 7.80	5.63 5.71	$C_{30}H_{38}N_2O_4$	2.66 (8H, $2CH_2NCH_2$, s), 3.43 (4H, $2CCH_2N$, t, ^5J = 2), 3.78 (8H, $2OCH_2CH_2O$, m), 4.35 (4H, $2CCH_2O$, t, ^5J = 2), 4.67 (4H, $2CH_2O$, s), 7.46 (10H, $2C_6H_5$, m).
2b	43	159–161	74.45 74.69	8.56 8.48	5.03 5.12	$C_{34}H_{46}N_2O_4$	1.56 (12H, $4CH_3$, s), 2.65 (8H, $2CH_2NCH_2$, s), 3.42 (4H, $2CCH_2N$, s), 3.77 (8H, $2OCH_2CH_2O$, m), 4.66 (4H, $2CH_2O$, s), 7.46 (10H, $2C_6H_5$, m).
2c	52	138–140	78.38 78.47	7.29 7.21	4.28 4.35	$C_{42}H_{46}N_2O_4$	2.68 (8H, $2CH_2NCH_2$, m), 3.43 (4H, $2CCH_2N$, t, ^5J = 2), 3.80 (8H, $2OCH_2CH_2O$, m), 4.35 (4H, $2CCH_2O$, t, ^5J = 2), 5.64 (2H, 2CHO, s), 7.44 (20H, $4C_6H_5$, m).
2d	43.5	149–151	75.01 75.13	7.61 7.53	3.73 3.81	$C_{46}H_{54}N_2O_4$	1.53 (12H, $4CH_3$, s), 2.63 (8H, $2CH_2NCH_2$, s), 3.41 (4H, $2CCH_2N$, s), 3.78 (8H, $2OCH_2CH_2O$, m), 5.64 (2H, 2CHO, s), 7.44 (20H, $4C_6H_5$, m).
3a	46	180–183	76.02 76.15	8.03 7.98	7.31 7.40	$C_{24}H_{30}N_2O_2$	2.61 (8H, $2CH_2NCH_2$, m), 3.42 (2H, CCH_2N, t, ^5J = 2), 3.59 (2H, CH_2N, s), 3.78 (4H, $2OCH_2CH_2O$, m), 4.33 (2H, CCH_2O, t, ^5J = 2), 4.66 (2H, CH_2O, s), 7.2–7.65 (10H, $2C_6H_5$, m).
3b	48	155–158	79.15 79.26	7.62 7.53	6.09 6.16	$C_{30}H_{34}N_2O_2$	2.62 (8H, $2CH_2NCH_2$, m), 3.43 (2H, $2CH_2NCH_2$, t, ^5J = 2), 3.60 (2H, CH_2N, s), 3.80

Table 2 (continued)

1	2	3	4	5	6	7	8
3c	47	142–145	79.09 79.26	7.56 7.53	6.03 6.16	$C_{30}H_{34}N_2O_2$	(4H, $2OCH_2CH_2O$, m), 4.36 (2H, CCH_2O, t, ^5J=2), 5.63 (1H, CHO, s), 7.24–7.66 (15H, $3C_6H_5$, m). 2.57–2.64 (8H, $2CH_2NCH_2$, m), 3.43 (2H, $2CH_2NCH_2$, t, ^5J = 2), 3.80 (4H, $2OCH_2CH_2O$, m), 4.35 (2H, CCH_2O, t, ^5J = 2), 4.38 (1H, CHN, s), 4.67 (2H, CH_2N, s), 7.2–7.7 (15H, $3C_6H_5$, m).

100 cm^3 of benzene; during 1 h, 4400 mg (25 mmol) of 1-benzylpiperazine or 6300 mg (25 mmol) of 1-benzhydrylpiperazine dissolved in 25 cm^3 of benzene was added dropwise at ~25 °C. Then, during 1 h, 26 mmol of corresponding oxyethoxyalkyne dissolved in 25 cm^3 of benzene was added dropwise at ~25 °C upon stirring. The temperature was gradually increased to 40–45 °C; the stirring continued for 10–15 h following chromatographically the course of the reaction. When the reaction was complete, 100 cm^3 of saturated solution of NH_4Cl was added. The benzene layer was separated, washed with water and dried with $MgSO_4$. The benzene was distilled and vacuumed off, the remainder was acidified with HCl solution (5 cm^3 HCl / 25 cm^3 2-propanol) to pH ≈ 5 and left in a refrigerator; if the product failed to crystallize, ethyl ether was added. The hydrochlorides were filtered off, washed with ethyl ether, recrystallized from the mixture of dry ethyl alcohol and ethyl ether; 46–50% of corresponding amine hydrochlorides were obtained; their melting points were established. Part of hydrochlorides were treated with 10% solution of NaOH to pH ≈ 9, extracted with benzene, washed with water to pH = 7 and dried with $MgSO_4$. After the solvent was distilled and vacuumed off, the corresponding benzyl- and benzhydryloxyethoxyalkynylpiperazines **3 a–c** were obtained; their ^{1}H NMR spectra in $(CD_3)_2CO$ were recorded and the elemental analysis carried out. Data on benzyl- and benzhydryloxyethoxyalkynylpiperazines **3 a–c** are shown in Table 2.

CONCLUSION

A series of new heterocyclic oxyethoxyalkynylamines was synthesized. The aminomethylation reactions of benzyloxy- and benzhydryloxyethoxyalkynes with heterocyclic amines and the isolation procedure of heterocyclic amines from the reaction mixture were explored.

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BENZILOKSI- IR BENZHIDRILOKSIETOKSIALKINŲ REAKCIJOS SU HETEROCIKLINIAIS AMINAIS

S a n t r a u k a

Ištirta benziloksi- ir benzhidriloksietoksialkinų aminometilinimo reakcija su piperidinu, 4-benzilpiperidinu, morfolinu, piperazinu, 1-benzilpiperazinu bei 1-benzhidrilpiperazinu; nustatyta temperatūros ir amino prigimties įtaka šiai reakcijai. Susintetinti nauji heterocikliniai oksietoksialkinilaminai ir nustatytos jų išskyrimo iš reakcijos mišinio sąlygos.