Chemistry of Heterocyclic Compounds, Vol. 37, No. 3, 2001

INTERACTION OF (*Z*)-1-HYDROXY-3-METHYLPENT-2-EN-4-YNE WITH CH_2O–SECONDARY AMINE SYSTEM. NEW ROUTE TO FORM α-(1,3-BIS-N,N-DIALKYLAMINOPROP-2-YL)FURANS

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The aminomethylation of (Z)-1-hydroxy-3-methylpent-2-en-4-yne with paraformaldehyde and secondary amines has been studied. The reaction was established to begin with the formation of vinylacetylenic monoadducts, which under the action of the aminomethylating agent are heterocyclized into the corresponding α-(1,3-bis-N,N-dialkylaminoprop-2-yl)-β-methylfurans.

Keywords: aminoalkylation, bis(dialkylamino)furans, *(Z)*-vinylacetylenic alcohol, heterocyclization.

We reported previously [1] the synthesis of α-(1,3-bis-N,N-dialkylaminoprop-2-yl)-substituted furans (**1**), which are the products of the Mannich reaction of (*Z*)-1-hydroxy-3-methylpent-2-en-4-yne (**2**) with diisopropylamine and diethylamine. In a more detailed study of the aminomethylation reaction vinylacetylenic alcohol **2** was established to react with the secondary amines **3a-k** in the presence of CuBr (or CuCl), irrespective of the reactant ratios, to form the furan compounds **1a-k** in addition to the linear monoadducts **4a-k**.

Boiling the reactants in dioxane at alcohol–amine ratio of 1:2 (method A) is optimal for the formation of product **1**. Separation of the resulting mixture was carried out by column chromatography on Al_2O_3. Yields as a rule were not high (12-62%) (Table 1). Competing reactions are undoubtedly the reason for the moderate yields of furan derivatives. The yields are not increased on varying the temperature or the duration of the process. In the case of amines **3b,f**, in addition to the amine bases **1b,f** and **4b,f**, both (1-diethylamino-2-propen-2-yl)-3-methylfurans **5a,b** and 3-methylhexa-2,4,5-trienol **6** were detected in yields of 8-10 and 4-8% respectively. The formation of products **5a,b** and **6** occurs by elimination of dialkylamino group from the target amines **1** and **4**. A similar conversion with the formation of allene is known for other examples [2]. In addition, an oxidative coupling reaction of the initial acetylene derivative **2** takes place, as a result of which 3,8-dimethyldeca-2,8-diene-4,6-diyne-1,10-diol (**7**) was obtained in 8-12% yield [3]. The structures of the products mentioned were in agreement with their spectral characteristics (see Experimental).

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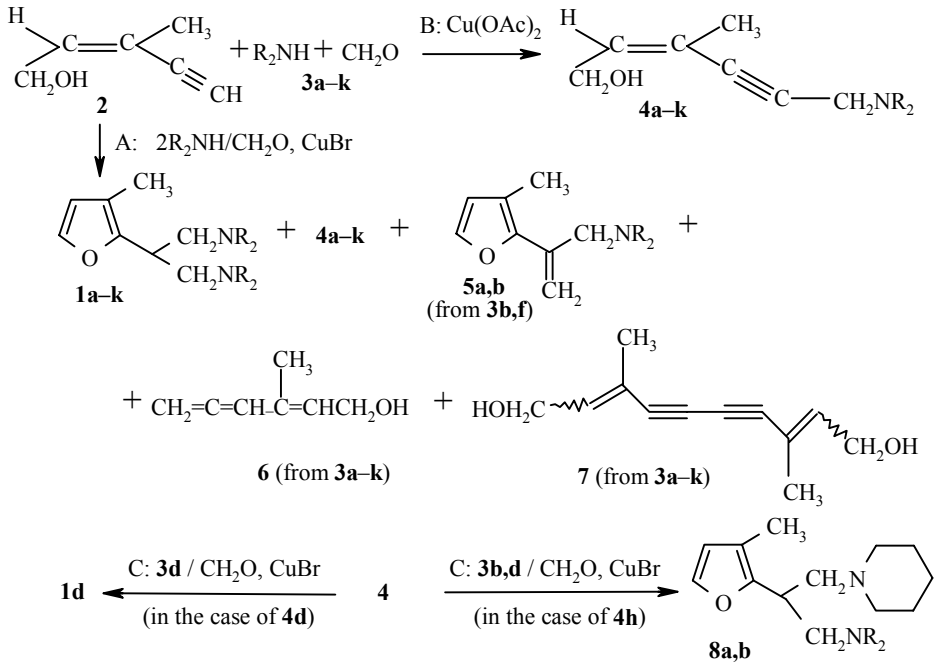
 0009-3122/01/3703-0276$25.00

Scheme 1



1,3,4a R = CH_3; **b** R = C_2H_5; **c** R = C_3H_7-*i*; **d** R = C_4H_9-*n*; **e** R = C_5H_{11}-*i;*
f R = C_6H_{11}-*c*; **g** RR = $(CH_2)_4$; **h** RR = $(CH_2)_5$; **i** RR = $(CH_2CH_2)_2O$; **j** RR = $(CH_2)_6$;
k R = $(CH_2CH_2)_2NCOC_6H_5$; **5a** R = C_2H_5; **b** R = C_6H_{11}-*c*; **8a** R = C_2H_5; **b** R = C_4H_9-*n*

We discovered that only the linear amino alcohols **4a-k** were readily formed in the reaction of vinylacetylenic alcohol **2** catalyzed by copper acetate monohydrate (procedure B). It became clear that furan compounds of symmetrical (**1d**) or mixed (**8a,b**) structure may be obtained from amino alcohols **4d** or **4h** respectively on treatment of the latter with secondary amines under conditions of the Mannich reaction (procedure C).

The products obtained (**1** and **8**), which were uncrystallizable oils, had the characteristic odor of amines and were characterized by good solubility in the usual solvents. Attempts to obtain crystalline derivatives, hydrochlorides or quaternary salts as iodomethylates, proved to be in vain. The composition and structure of the compounds were completely in agreement with the results of elemental analysis and spectral data (Tables 1,2,3).

The considered type of transformation of vinylacetylenic alcohol **2** into dialkylamino derivatives of furan has not been described in the literature and is fairly general. Based on the structure established for the furan derivatives it is possible to suggest a mechanism for their formation which comprises combination of Mannich reaction, heterocyclization, and aminomethylation by a type of Prince reaction.

It is known [4] that the carboimmonium cation **9** is an active aminomethylating agent (see Scheme 2).

Scheme 2

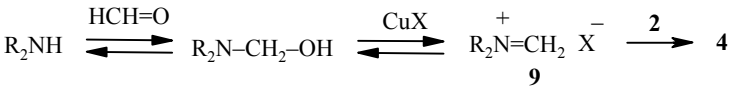


TABLE 1. Characteristics of α-(1,3-Bis-N,N-dialkylaminoprop-2-yl)furans **1a-k**, **8a-b**

Compound	Empirical formula	Found, % / Calculated, %			R_f	n_D^{20}	Yield, % by method A (by method C)
		C	H	N			
1a	$C_{12}H_{22}N_2O$	68.53	10.54	13.32	0.67		12
1b	$C_{16}H_{30}N_2O$	72.21 / 72.13	11.28 / 11.35	10.63 / 10.52	0.68	1.4695	27
1c	$C_{20}H_{38}N_2O$	74.54 / 74.48	11.73 / 11.82	8.91 / 8.69	0.69	1.4680	36
1d	$C_{24}H_{46}N_2O$	76.61 / 76.13	12.23 / 12.25	6.88 / 7.40	0.61	1.4642	26 (71)
1e	$C_{28}H_{54}N_2O$	77.94 / 77.35	12.71 / 12.52	6.31 / 6.44	0.63	1.4463	28
1f	$C_{32}H_{54}N_2O$	79.77 / 79.61	11.17 / 11.27	5.98 / 5.80	0.64		21
1g	$C_{16}H_{26}N_2O$	73.31 / 73.24	10.06 / 9.99	10.74 / 10.68	0.65		32
1h	$C_{18}H_{30}N_2O$	74.38 / 74.43	10.87 / 10.41	9.55 / 9.65	0.66	1.4986	62
1i	$C_{16}H_{26}N_2O_3$	65.19 / 65.28	9.05 / 8.90	10.06 / 9.52	0.64	1.5005	34
1j	$C_{20}H_{34}N_2O$	75.54 / 75.42	10.68 / 10.76	8.57 / 8.80	0.65		20
1k	$C_{30}H_{36}N_4O_3$	72.05 / 71.97	7.14 / 7.25	11.45 / 11.19	0.64		20
8a	$C_{17}H_{30}N_2O$	73.41 / 73.33	10.73 / 10.86	10.27 / 10.06	0.68	1.5069	(55)
8b	$C_{21}H_{38}N_2O$	75.58 / 75.39	11.39 / 11.45	8.58 / 8.37	0.65		(25)

The linear vinylacetylenic monoadduct **4** may be subjected to intramolecular cyclization under the reaction conditions with the formation of the exocyclic vinyl ether **10**, as has been described repeatedly for acetylene derivatives in which the nucleophilic center is in convenient position for cyclization [5] (in our case *cis* hydroxyl group). Its stabilization into the corresponding furan **11** is not observed, but probably addition of immonium ion occurs at the double bond with subsequent aromatization (Scheme 3). Two variants are possible in this case. In the first (A) simple stabilization of the transition state takes place and aromatization occurs with the formation of furan. If the radicals R and R^1 are identical in the amine then symmetrical type **1** amino derivatives of furan are obtained. If the radicals are different then mixed compounds of type **8** are formed.

TABLE 2. ^{1}H NMR Spectral Characteristics of the Synthesized α-(1,3-Bis-N,N-dialkylaminoprop-2-yl)furans **1, 8**, δ, ppm, CC, *J*, Hz

Compound	5-H, 1H, d, *J* = 1.2	4-H, 1H, d, *J* = 1.2	2-CH_3, 3H, s	C'H(C"H_2NR_2)$_2$
1	2	3	4	5
1a	7.18	6.09	1.98	2.13 (12H, s, 4CH_3); 2.38-2.58 (4H, m, 2C"H_2); 3.08 (1H, quintet, *J* = 6.4, C'H)
1b	7.19	6.12	1.97	0.96 (12H, t, *J* = 6.4, 4CH_3); 2.31-2.54 (8H, m, 4CH_2N); 2.56-2.78 (4H, m, 2C"H_2); 3.02 (1H, quintet, *J* = 6.4, C'H)
1c	7.25	6.25	2.02	0.89 (12H, d, *J* = 6.4, 4CH_3); 1.02 (12H, d, *J* = 6.4, 4CH_3); 2.58 (2H, q AB system, 2C"H); 2.75-2.86 (3H, m, C'H, 2C"H); 2.97 (4H, heptet, *J* = 6.4, 4CHN)
1d	7.2	6.12	1.98	0.80-0.95 (12H, m, 4CH_3); 1.15-1.53 (16H, m, 8CH_2); 2.25-2.50 (8H, m, 4CH_2N); 2.50-2.70 (4H, m, 2C"H_2); 3.12 (1H, t, *J* = 6.4, C'H)

TABLE 2 (continued)

1	2	3	4	5
1e	7.18 (br. s)	6.12 (br. s)	1.98	0.81-0.92 (24H, m, $8CH_3$); 1.18-1.90 (12H, m, $4CH_2$, 4CH); 2.05-2.78 (12H, m, $2C''H_2$, $4CH_2N$); 3.00 (1H, m, C'H)
1f	7.22	6.17	2.00	1.00-1.40 and 1.50-1.90 (40H, two m, $20CH_2$); 2.40-2.90 (9H, br. m, C'H, $2C''H_2$, 4CH ring)
1g	7.20	6.15	1.97	1.65-1.86 (8H, two m, $4CH_2$); 2.35-2.60 (8H, two m, $4CH_2N$); 2.60-2.95 (5H, two m, C'H, $2C''H_2$)
1h	7.20	6.13	1.97	1.30-1.60 (12H, two m, $6CH_2$); 2.20-2.40 (8H, m, $4CH_2N$); 2.47 and 2.62 (4H, two q AB system, $2C''H_2$); 3.18 (1H, quintet, J = 6.4, C'H)
1i	7.18	6.10	1.95	2.28-2.75 (12H, m, $2C''H_2$,$4CH_2N$); 3.12 (1H, quintet, J = 6.4, C'H); 3.52-3.75 (8H, m, $4CH_2O$)
1j	7.20	6.15	2.00	1.55 (16H, br. s, $8CH_2$); 2.50-2.65 (8H, m, $4CH_2N$); 2.65-2.88 (4H, m, $2C''H_2$); 3.08 (1H, quintet, J = 6.4, C'H)
1k	7.15	6.10	1.95	2.10-2.50 and 3.20-3.80 (16H, br. m, $8CH_2N$); 2.54 and 2.60 (4H, two q AB system, $2C''H_2$); 3.13 (1H, quintet, J = 6.4, C'H); 7.35 (10H, s, $2C_6H_5$)
8a	7.20	6.12	1.98	0.93 (6H, t, J = 6.4, $2CH_3$); 1.30-1.70 (6H, m, $3CH_2$); 2.25-2.78 (12H, m, $2C''H_2$, $4CH_2N$); 3.0 (1H, quintet, J = 6.4, C'H)
8b	7.21	6.12	1.98	0.88 (6H, t, J = 6.4, $2CH_3$); 1.10-1.50 (14H, m, $7CH_2$); 2.25-2.45 (8H, m, $4CH_2N$); 2.25-2.78 (4H, m, $2C''H_2$); 3.05 (1H, quintet, J = 6.4, C'H)

Although the initial attack in the second variant (B) is facilitated, stabilization of the transition states and aromatization is not possible. The trisubstituted furan **12** was not detected among the reaction products.

Scheme 3

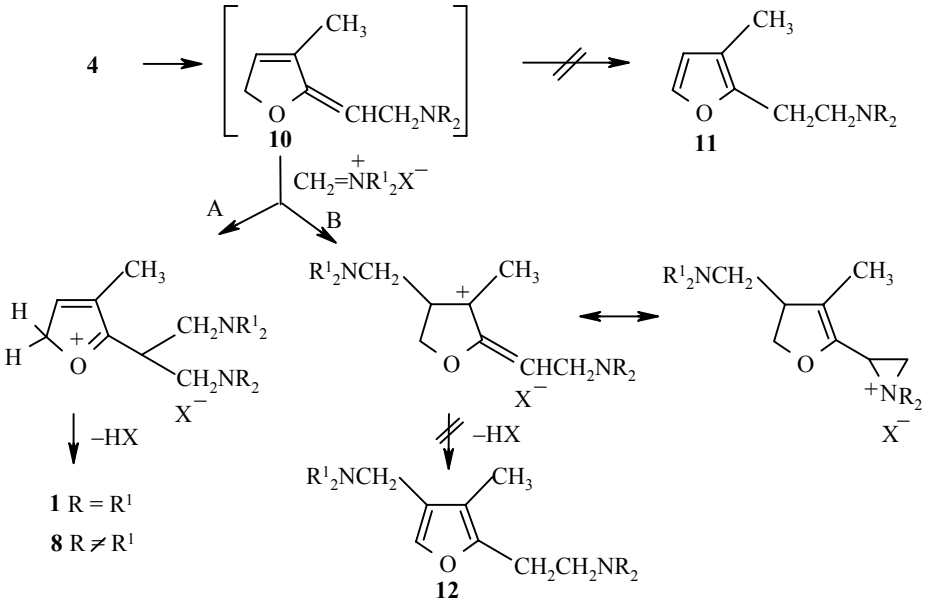


TABLE 3. Characteristics of the Synthesized 6-(N,N-Dialkylamino)-3-methylhex-2-en-4-yn-1-ols (**4a-k**)

Compound	Empirical formula	Found, % / Calculated, %			R_f	^{1}H NMR spectrum, δ, ppm, CC (*J*), Hz						Yield, % by method B (by method A)
		C	H	N		=CH, 1H, t, *J* = 6.4	CH_2O, 2H, d, *J* = 6.4	CH_2N, 2H, s	OH, 1H, w. s	CH_3, 3H, br. s	NR_2	
4a	$C_9H_{15}NO$	70.43 / 70.55	9.91 / 9.87	9.48 / 9.14	0.35	5.68	4.12	3.25	4.78	1.73 unres. d	2.15 (6H, s, $2CH_3$)	30 (20)
4b	$C_{11}H_{19}NO$	72.94 / 72.88	10.36 / 10.57	8.01 / 7.73	0.34	5.78	4.18	3.53	4.64	1.75	0.96 (6H, t, *J* = 6.4, $2CH_3$); 2.28-2.40 (4H, m, $2CH_2$)	50 (33)
4c	$C_{13}H_{23}NO$	74.50 / 74.59	10.89 / 11.08	6.98 / 6.69	0.38	5.73	4.18	3.51	3.02	1.80	1.07 (12H, d, *J* = 6.4, $4CH_3$); 3.14 (2H, q, *J* = 6.4, 2CH)	12
4d	$C_{15}H_{27}NO$	75.55 / 75.89	11.54 / 11.47	6.04 / 5.90	0.36	5.75	4.20	3.48	3.90	1.80	0.85 (6H, t, *J* = 6.4, $2CH_3$); 1.10-1.50 (8H, m, $4CH_2$); 2.25-2.60 (4H, m, $2CH_2N$)	60 (20)
4e	$C_{17}H_{31}NO$	77.01 / 76.92	11.64 / 11.77	5.39 / 5.28	0.41	5.81	4.28	3.48	*	1.86	0.86 (12H, degen. t, $4CH_3$); 1.20-1.75 (4H, m, $2CH_2$); 2.00-2.60 (6H, dm, $2CH_2N$, 2CH)	56
4f	$C_{19}H_{31}NO$	78.91 / 78.84	11.02 / 10.80	5.16 / 4.84	0.44	5.80	4.27	3.60	*	1.86	0.90-1.90 (20H, dm, $10CH_2$); 2.65-2.82 (2H, m, 2CHN)	50
4g	$C_{11}H_{17}NO$	73.83 / 73.70	9.78 / 9.56	8.01 / 7.81	0.45	5.80	4.23	3.52	1.85	2.75	1.60-1.90 (4H, m, $2CH_2$); 2.40-2.65 (4H, m, $2CH_2N$)	35
4h	$C_{12}H_{19}NO$	74.67 / 74.57	9.83 / 9.97	7.47 / 7.25	0.42	5.85	4.30	3.41	1.87	2.33	1.35-1.70 (6H, two m, $3CH_2$); 2.51 (4H, t, *J* = 6.4, $2CH_2N$)	70
4i	$C_{11}H_{17}NO_2$	67.51 / 67.66	8.83 / 8.78	7.21 / 7.17	0.39	5.82	4.28	3.42	2.60	1.83	2.30-2.55 (4H, m, $2CH_2N$); 3.55-3.80 (4H, m, $2CH_2O$)	40
4j	$C_{13}H_{21}NO$	75.29 / 75.31	10.41 / 10.21	6.94 / 6.74	0.34	5.85	4.32	3.54	2.45	1.90	1.55-1.80 (8H, m, $4CH_2$); 2.72 (4H, t, *J* = 6.4, $2CH_2N$)	36
4k	$C_{18}H_{22}N_2O_2$	72.51 / 72.45	7.38 / 7.43	9.57 / 9.39	0.33	5.87	4.30	3.50	*	1.88	2.30-2.80 (4H, m, $2CH_2N$); 3.30-3.90 (4H, m, $2CH_2NCO$); 7.30-7.50 (5H, m, C_6H_5)	40

* Very broad signal.

We note that the scheme proposed enables the structures to be obtained which are practically impossible to synthesize by standard methods. Tertiary 1,3-diaminopropanes carrying furan ring are of interest as potentially biologically active compounds with a wide spectrum of action.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) instrument in $CDCl_3$ or DMSO relative to TMS. The IR spectra were drawn on a Specord M 80 instrument.

The synthesis of alcohol **2** was described previously [6]. For elemental analysis compounds **1**, **4**, and **8** were redistilled at a pressure of 0.5-1 mm Hg from a collared flask at bath temperature of 180-220°C. A check on the course of reactions and the purity of compounds was effected by TLC on Silufol UV-254 plates, eluent was ether–hexane–ethyl acetate–methanol 3:2:1:1 with conc. NH_4OH (one drop). Visualization was realized with iodine vapor and with acidified $KMnO_4$ solution.

α-(1,3-Bis-N,N-dialkylaminoprop-2-yl)-β-methylfurans (1a-k), 6-N,N-Dialkylamino-3-methylhex-2-en-4-yn-1-ols (4a-k), 2-(3-Dialkylaminoprop-2-en-2-yl)-3-methylfurans (5a,b), 3-Methylhexa-2,4,5-trienol (6), and 3,8-Dimethyldeca-2,8-diene-4,6-diyne-1,10-diol (7). A. CuBr (0.29-0.43 g, 2-3 mmol) was added to solution of alcohol **2** (0.55 g, 6 mmol), paraformaldehyde (0.45 g, 15 mmol), and the appropriate amine **3** (12-13 mmol) in dioxane (15 ml). The mixture was boiled for 1-3 h until disappearance of initial alcohol, evaporated to 2/3 to 1/2 of volume, and poured into 2 N HCl solution. The neutral products were extracted with ether (then treated as below).

Aqueous ammonia solution was added to the aqueous layer containing amine products to pH ~8 and the solution extracted with ether (3 × 25 ml). The extract was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated. The residue, a dark oil, was dissolved in hexane (1-2 ml) and separated on Al_2O_3 column (25 × 2.5 cm) eluting initially with petroleum ether, then with petroleum ether–ether (10-50% of ether by volume). The furan compounds have a high mobility under the conditions of chromatography.

The eluates of diamines **1a,d,e,g,h,j** and amino alcohols **4a,b,d** were evaporated, redistilled, and pure products were obtained. The eluates of diamines **1b,c,f,i,k** were evaporated, and were chromatographed once more on silica gel L 40/160; eluent was pentane and then pentane–ether (10-20% of ether by volume). In the case of product **1b** furan **5a** (80 mg) was isolated as an oil. R_f ~0.8. Yield ~10%. IR spectrum, ν, cm^{-1}: 1620, 1565, 1515, 1210. UV spectrum (EtOH): 263 nm (8400). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.03 (6H, t, *J* = 7, $2CH_3$); 2.17 (3H, s, CH_3); 2.55 (4H, q, *J* = 7, $2CH_2$); 3.4 (2H, s, CH_2N); 5.35 (2H, br. s, CH_2=); 6.22 (1H, d, *J* = 1.2, 4-H furan); 7.27 (1H, d, *J* = 1.2, 5-H furan). Found, %: C 74.63; H 9.95; N 7.31. $C_{12}H_{19}NO$. Calculated, %: C 74.57; H 9.91; N 7.25.

In a similar manner furan **5b** (40 mg) was isolated as an oil in the case of product **1f**. R_f ~0.74. Yield ~6%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.00-1.35 (12H, m, $6CH_2$ ring); 1.65-1.80 (8H, m, $4CH_2$ ring); 2.50-2.65 (2H, m, 2CH); 2.18 (3H, s, CH_3); 3.55 (2H, br. s, CH_2N); 5.28 (1H, d, *J* = 1.2, CH=); 5.58 (1H, d, *J* = 1.2, CH=); 6.27 (1H, d, *J* = 1.2, 4-H furan); 7.28 (1H, d, *J* = 1.2, 5-H furan). The eluates of amino alcohols **4c,e-k** (yields ~13-24%) contained small amounts of contaminants, additional purification was not carried out.

The ether extract containing the neutral products was washed sequentially with saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and ether evaporated. The solid residue was filtered off, and recrystallized from ethyl acetate–methanol, 3:1 mixture, and diol **7** (0.12 g, ~8%) of mp 134-135°C was obtained. IR spectrum: 2100 cm^{-1}. ^{1}H NMR spectrum (DMSO), δ, ppm, *J* (Hz): 1.80 (6H, s, $2CH_3$); 4.13 (4H, d, *J* = 6.4, $2CH_2O$); 5.96 (2H, t, *J* = 6.4, 2CH=). The filtrate was chromatographed on SiO_2 (eluent pentane–ether, 4:1), and an oil (25 mg) was obtained containing the extremely unstable allene **6**. IR spectrum: 1940 cm^{-1}.

6-N,N-Dialkylamino-3-methylhex-2-en-4-yn-1-ols (4a-k). B. Secondary amine **3a-k** (6 mmol) was added to solution of alcohol **2** (5 mmol), paraformaldehyde (10 mmol), and a catalytic amount of copper acetate in dioxane (15 ml). The mixture was boiled for 1.5-3 h until the disappearance of the starting material. The reaction mixture was evaporated to half volume, acidified with 2 N HCl, and extracted with ether (3 × 25 ml). Products **4a-k** were isolated from the extract by procedure A. The characteristics of the isolated compounds are given in Table 3.

2-(1-Dialkylaminomethyl-3-piperidinoprop-2-yl)-3-methylfurans (8a,b). C. Secondary amine **3b,d** (6 mmol) was added to solution of amino alcohol **4** (5.0 mmol), paraformaldehyde (3.7 mmol), and CuBr (2-3 mmol) in dioxane (15 ml). The mixture was boiled for 1-2 h until disappearance of the starting material **4**. Processing of the reaction mixture and isolation of the products was carried out according to procedure A. The characteristics of the compounds **8a,b** obtained are given in Table 1.

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