Synthesis of long-chain 2-alkadiynylpyridines

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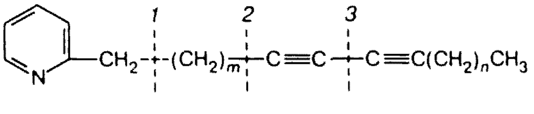
Four pathways of synthesis of 1-(2-pyridyl)heptacosa-12,14-diyne, using 10-bromodecan-1-ol and acetylene or tetradec-1-yne and 2-methylbut-3-yn-2-ol along with α-picoline as initial compounds, were studied and compared. It was shown that direct introduction of a completely formed unsaturated hydrocarbon chain into an α-picoline molecule by alkylation of its lithium derivative is the most appropriate method for preparation of long-chain 2-alkadiynylpyridines.

Key words: long-chain 2-alkadiynylpyridines, synthesis, Langmuir—Blodgett films.

Amphiphilic long-chain pyridine derivatives form Langmuir—Blodgett (LB) films.[1-6] In ordered supramolecular systems (LB films or crystals), these compounds, if they have the diacetylene group in the side chain, are able to polymerize under the action of light, heat, and other types of radiation to form extended conjugation regions with retention and strengthening of the general structural organization.[4,5,7-10] Pyridine rings, which are grouped and oriented on the surface and at the boundaries between layers in LB films, remaining relatively free and accessible, can exhibit basic, complex-forming, catalytic, electron-accepting, and other properties that are typical of pyridine. In addition, these properties of the heterocycle are used in synthesis of amphiphilic monomers containing the modified pyridine group, for example, in the form of the pyridinium-tetracyanoquinodimethane complex,[1,8] followed by preparation of LB multilayers. All this initiates a challenge to apply these films in novel technologies. Natural unsaturated long-chain pyridine derivatives with a wide spectrum of biological activity are also of interest.[11] The syntheses of pyridyl-substituted long-chain diacetylenes ((4-pyridyl)alkadiynes and *N*-alkadiynylpyridinium salts) are described.[4,5,7,8]

This work is devoted to a search for a reasonable pathway for preparing 2-alkadiynylpyridines. Possible variants were studied and compared using as an example the synthesis of 1-(2-pyridyl)heptacosa-12,14-diyne (**1**).



1: $n = 11$, $m = 10$

An alkadiynylpyridine molecule can be connected by bonds *1*, *2*, and *3*. Assembling the molecule *via* these bonds in different sequences made it possible to realize four pathways for the synthesis of compound **1**, in which 10-bromodecan-1-ol (**3**) and acetylene (pathways I, II, and IV) or 2-methylbut-3-yn-2-ol (**4**) and tetradec-1-yne (**5**) (pathway III) along with α-picoline (**2**) were used as initial compounds (Table 1).

The first and second pathways (Scheme 1) involve the linear growth of the molecular chain of **1** and differ by the sequence of bonding synthons. The sequence of the formation of C—C bonds is *1*, *2*, *3* and *2*, *1*, *3*, respectively.

In the both cases, the final stage is the same: condensation of 13-(2-pyridyl)tridec-1-yne (**6**) with 1-bromotetradec-1-yne (**7**) according to Cadiot and Chodkiewicz. This reaction is the main method for coupling of two terminal acetylene groups to the nonsymmetrically substituted diacetylene group.[12] When the polarity of synthons corresponding to the cleavage of target product

Table 1. Comparative characteristics of variants of synthesis of 1-(2-pyridyl)heptacosa-12,14-diyne (**1**)

Variant of synthesis	Yields of compound **1** (%) calculated on the basis of the initial compounds			Total number of stages
	2	**3**	**5**	
I	13.3	18.2	18.5	6
II	10.5	25.5	18.5	5
III	34.7	47.6	51.0(19.1)*	7
IV	31.1	56.3	29.0	5

* Without regeneration of diyne **13**.

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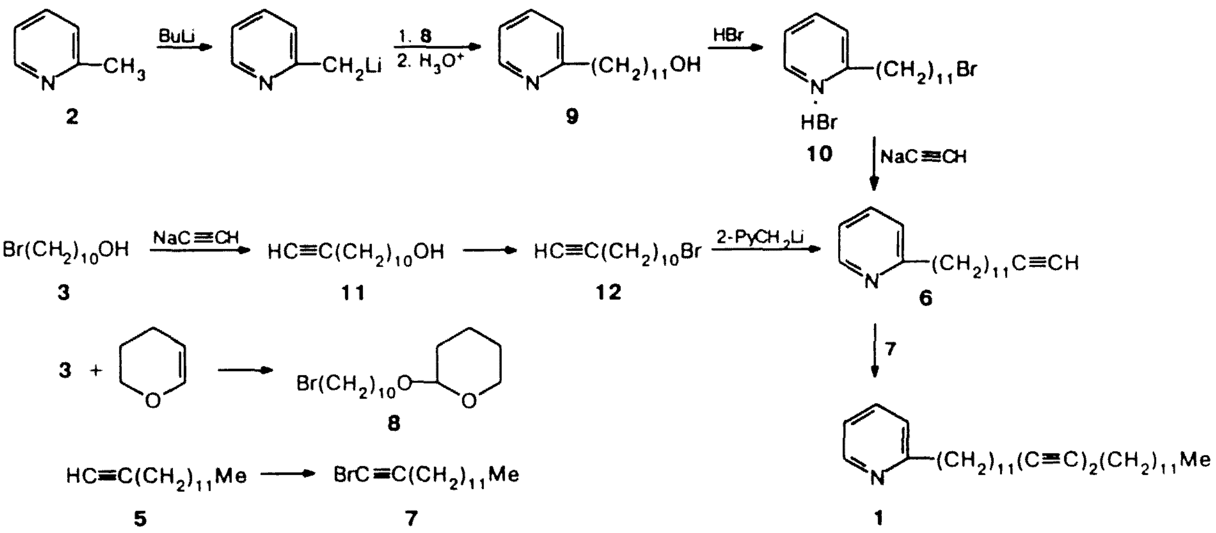
Scheme 1

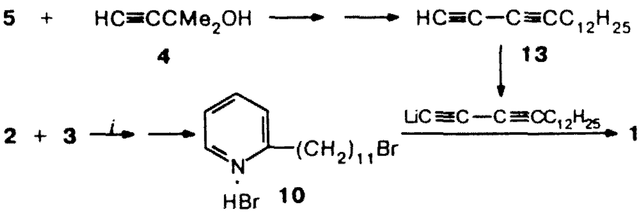


1 by bond *3* changes to the opposite one, tetradec-1-yne (**5**) and 1-halo-13-(2-pyridyl)tridec-1-yne could be formed instead of compounds **6** and **7**. We performed both variants of condensation, but the yield of **1** at the final stage did not exceed 40 % even in the first, best variant. In addition, the incomplete transformation of pyridyltridecyne **6** under the reaction conditions created difficulties for isolation of compound **1**, because the properties of the initial and final compounds, both of which are bases, are close. It is noteworthy that the yield of the target product also was only 34 % in the previously described synthesis of 1-(4-pyridyl)heneicosa-6,8-diyne by the same method.[8]

It is known that the nature of functional substituents and the length of the carbon chain in initial acetylenes affect yields in the Cadiot—Chodkiewicz reaction.[12,13] However, the reasons for this dependence are not quite clear. It cannot be excluded that a low yield in condensation of pyridylacetylenes is related to the ability of pyridines to form complexes with Cu^{I} cations, which are the catalysts of the reaction. It is possible that the formation of complexes of a cooper acetylenide intermediate is accompanied by steric blocking of the reaction center by the long hydrocarbon chain, which retards the condensation. According to this assumption, alkynylpyridinium salts, which are unable to form complexes with Cu^{I}, condense with noticeably higher yields than pyridylacetylenes.[7,8]

Unlike the first and second pathways of preparation of **1**, the third pathway (Scheme 2) is the convergent synthesis and provides independent assembling of two intermediate products, bromide **10** and hexadeca-1,3-diyne (**13**) *via* bonds *1* and *3*. Diyne **13** was synthesized by the developed three-stage method from tetradec-1-yne (**5**) and 2-methylbut-3-yn-2-ol (**4**) in a yield of 68 %.[14] At the final stage of the synthesis of **1** (formation of bond *2*), 1,3-diyne **13** was alkylated by bromide **10** (Scheme 2).

Scheme 2



i. Scheme 1

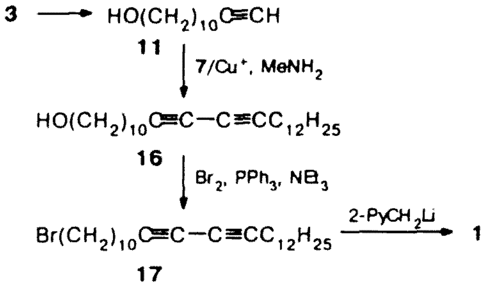
A threefold excess of **13** was used for the alkylation. This provided the complete reaction of bromide **10**. In the absence of compound **10**, pyridylacetylene **1** was readily separated from unreacted hydrocarbon **13** *via* pyridinium salt or by chromatography (a yield of **1** was 84 %; regenerated **13** was repeatedly used).

It is noteworthy that under these conditions alka-1,3-diynes can be successfully alkylated by analogs of 2-(ω-bromoalkyl)pyridines having another position of the side chain in the heterocycle as well. For example, 1-(4-pyridyl)octacosa-13,15-diyne (**15**) was synthesized in a yield of 90 % from 12-(4-pyridyl)dodecyl bromide hydrochloride (**14**) and 1,3-diyne **13**.

The fourth pathway of synthesis of **1** (Scheme 3), as the first and second pathways, is linear, but differs basically in the primary formation of the side chain, which is then attached to an α-picolyl residue. The sequence of bond formation is *2*, *3*, *1*.

The absence of the pyridine cycle upon assembling of the hydrocarbon chain made it possible to perform reactions, including the Cadiot—Chodkiewicz condensation, without difficulties. A total yield of 1-bromohexacosa-11,13-diyne (**17**) from alcohol **3** was about 60 %. The alkylation of α-picoline **2** by long-chain bromide **17** at the final stage of synthesis of

Scheme 3



pyridylacetylene **1** occurred with a yield higher than 90 %.

The total yields of final pyridylalkadiyne **1** calculated per main initial compounds of all four variants of the synthesis considered are presented in Table 1 for comparison. It can be seen that variants III and IV are characterized by higher and comparable parameters. The convergent synthesis (III) allows one to obtain compound **1** in the highest yield calculated per tetradecyne **5**, but its yield calculated per expensive bromodecanol **3** is lower and the number of stages is higher than in the fourth variant. An advantage of this variant is its certain versatile character. Substitution of α-picolyllithium for other alkylated organolithium compounds at the final stage (Scheme 3) allows one to synthesize a series of monomers with various terminal aromatic and heterocyclic groups ("exchangeable functional heads" of the monomer), which are related to pyridylalkadiynes, by the same method based on the same key intermediate bromodiacetylene.

Experimental

IR spectra were recorded on a UR-20 spectrophotometer in $CHCl_3$, and ^1H NMR spectra were recorded on a Jeol FX90Q spectrometer (90 MHz) in $CDCl_3$.

10-Bromodecan-1-yl tetrahydro-2-pyranyl ether (8). Concentrated HCl (0.25 mL) was carefully added with shaking to a mixture of compound **4** (10.0 g, 42 mmol) and freshly distilled 2-dihydropyran (7.1 g, 84 mmol) in 25 mL of anhydrous ether, and the mixture was left to stand for 6 h. The reaction mixture was diluted with ether, thoroughly washed with water, and dried over Na_2SO_4, and the solvent was distilled off *in vacuo*. Compound **8** (12.3 g, yield 90.8 %) was isolated by chromatography on SiO_2 (ASKG trade mark) using benzene as eluent. ^1H NMR, δ: 1.15—2.0 (m, 22 H, CH_2); 3.40 (t, 2 H, CH_2Br); 3.50—4.0 (m, 4 H, CH_2O); 4.47—4.62 (br.m, 1 H, CHO_2).

11-(2-Pyridyl)undecan-1-ol (9). A 1.83 *N* solution of butyllithium (28.5 mL, 51 mmol) in hexane was added dropwise with stirring to compound **2** (4.8 g, 51 mmol) in 40 mL of THF at −20 °C in an argon atmosphere, and after 15 min of stirring compound **6** (11.0 g, 34 mmol) in 20 mL of THF was added. A mixture was stirred for 30 min at −20 °C and then at room temperature for 8 h, carefully decomposed with water, and extracted with ether. After removal of the solvent, dilute (1 : 1) HCl (20 mL) was added to a residue, and a mixture was let to stay for 12 h. Admixtures were extracted from an aqueous solution with ether, the solution was alkalized with Na_2CO_3, and product **9** was extracted with ether. An extract was washed with water and dried over $MgSO_4$. Compound **7** (6.3 g, 74.0 %) was obtained after reprecipitation from ether with hexane, m.p. 43.0—43.5 °C (from hexane). Found (%): C, 77.00; H, 10.94; N, 5.33. $C_{16}H_{27}NO$. Calculated (%): C, 77.06; H, 10.91; N, 5.62. IR, ν/cm^{-1}: 3625 (O—H). ^1H NMR, δ: 1.15—1.80 (m, 18 H, CH_2); 1.90, (br.s, 1 H, OH); 2.75 (t, 2 H, CH_2Py); 3.60 (t, 2 H, CH_2O); 6.95—7.15 (m, 2 H, β-H); 7.45—7.65 (m, 1 H, γ-H); 8.40—8.55 (m, 1 H, α-H).

1-Bromo-11-(2-pyridyl)undecane hydrobromide (10). A mixture of compound **9** (4.0 g, 16 mmol) and 46.8 % HBr (20 mL) in 150 mL of benzene was refluxed for 5 h with a Dean—Stark trap until complete cessation of water separation and then for 3 h more. A reaction mixture was concentrated *in vacuo* to a volume of 50 mL, and hydrobromide **10** was filtered off. Compound **10** was obtained in a 84.3 % yield (5.3 g), m.p. 96—97 °C (from a toluene—hexane (5 : 2) mixture). Found (%): C, 49.14; H, 7.21; Br, 40.47. $C_{16}H_{26}NBr \cdot HBr$. Calculated (%): C, 48.87; H, 6.92; Br, 40.64. ^1H NMR, δ: 1.30 (s, 14 H, CH_2); 1.60—2.05 (m, 4 H, CH_2CBr, CH_2CPy); 3.25 (t, 2 H, CH_2Py); 3.40 (t, 2 H, CH_2Br); 7.60—7.90 (m, 2 H, β-H); 8.20—8.50 (m, 1 H, γ-H); 8.62—8.80 (m, 1 H, α-H).

Dodec-11-yn-1-ol (11). Freshly distilled DMF (30 mL) and compound **4** (2.4 g, 10 mmol) in 30 mL of DMF were added to sodium acetylenide prepared from Na (0.7 g, 30 mmol) in 100 mL of liquid NH_3. After removal of ammonia, the mixture was stirred for 2 h at 50 °C, decomposed upon cooling with ice-cold water (NH_4Cl (2 g) and water (50 mL)), and extracted with benzene. An extract was thoroughly washed with water and filtered through a thin layer of Al_2O_3 (II activity grade). Chromatographically pure alcohol **11** (1.7 g, 93.4 %) was obtained.[15]

12-Bromododec-1-yne (12). A solution of Br_2 (1.13 mL (0.22 mmol) in 27 mL of CCl_4) was added dropwise to a suspension of PPh_3 (5.7 g, 22 mmol) in 100 mL of anhydrous CCl_4 in an argon atmosphere at 0 °C. A mixture was stored for 30 min at 20 °C and cooled to 5 °C, and acetylene alcohol **11** (3.0 g, 16.7 mmol) in 4 mL of NEt_3 was added. A reaction mass was stirred for 24 h at ~20 °C, filtered, evaporated *in vacuo* to 30 mL, diluted with 40 mL of hexane, and filtered again. After removal of the solvent, bromide **12** (3.5 g, 86.0 %) was isolated from the filtrate by chromatography of a residue on SiO_2 (hexane as an eluent).[16]

13-(2-Pyridyl)tridec-1-yne (6). A. Compound **6** was synthesized from sodium acetylenide (1.1 g, 46.5 mmol of Na) and hydrobromide **10** (3.7 g, 9.3 mmol) as described above for compound **11**. The yield of compound **6** was 2.0 g (83.7 %), n_D^{26} = 1.4936. Found (%): C, 83.87; H, 10.77; N, 5.24. $C_{18}H_{27}N$. Calculated (%): C, 83.99; H, 10.57; N, 5.44. IR, ν/cm^{-1}: 2125 (C≡C); 3325 (≡CH). ^1H NMR, δ: 1.15—1.80 (m, 18 H, CH_2); 1.92 (t, 1 H, HC≡); 2.13 (br.t, 2 H, CH_2C≡); 2.75 (t, 2 H, CH_2Py); 6.95—7.15 (m, 2 H, β-H); 7.45—7.65 (m, 1 H, γ-H); 8.40—8.5 (m, 1 H, α-H).

B. Compound **2** (5.4 g, 58.5 mmol) was alkylated by compound **12** (4.8 g, 19.5 mmol) under the conditions of synthesis of compound **9**; the yield of compound **6** was 4.1 g (80.9 %).

Hexacosa-11,13-diyn-1-ol (16). A solution of compound **11** (1.7 g, 9.3 mmol) in 7 mL of THF was added dropwise with intense stirring to a mixture of CuCl (0.046 g, 0.47 mmol), $NH_2OH \cdot HCl$ (0.55 g, 9.3 mmol), 25 % aqueous $MeNH_2$ (1 mL), and THF (5 mL) in an argon atmosphere. Then bromotetradecyne **7** [17] (5.1 g, 18.6 mmol), obtained in a yield of 96.0 % by the previously described method,[18] in 7 mL of THF was slowly added. After 30-min stirring, a reaction mass was diluted with 40 mL of water and thoroughly extracted with ether. An extract was washed with water and dried over $MgSO_4$. A residue was chromatographed on SiO_2 (ASKG trade mark, benzene as an eluent) to isolate alcohol **16** (2.6 g, 47.5 %) with m.p. 56—57 °C (from hexane). Found (%): C, 83.14; H, 12.12. $C_{26}H_{46}O$. Calculated (%): C, 83.35; H, 12.38. ^1H NMR, δ: 0.88 (t, 3 H, CH_3); 1.30 (s, 32 H, CH_2); 1.40—1.60 (m, 4 H, $CH_2CC\equiv$); 2.25 (t, 4 H, $CH_2C\equiv$); 3.65 (t, 2 H, CH_2O).

1-Bromohexacosa-11,13-diyne (17) was obtained similarly to compound **12** from alcohol **16** (0.75 g, 2 mmol) in a yield of 0.76 g (86.7 %), m.p. 33—34 °C (from hexane). Found (%): C, 71.16; H, 10.32; Br, 18.12. $C_{26}H_{45}Br$. Calculated (%): C, 71.37; H, 10.37; Br, 18.26. ^1H NMR, δ: 0.88 (t, 3 H, CH_3); 1.30 (s, 30 H, CH_2); 1.40—1.60 (m, 4 H, $CH_2CC\equiv$); 1.83 (quintet, 2 H, CH_2Br); 2.25 (t, 4 H, $CH_2C\equiv$); 3.40 (t, 2 H, CH_2Br).

1-(2-Pyridyl)heptacosa-12,14-diyne (1). A. Pyridyltridecyne **6** (0.5 g, 2 mmol) and bromotetradecyne **7** (1.1 g, 4 mmol) were condensed in the presence of CuCl (0.2 g, 2 mmol) and i-$PrNH_2$ (0.85 mL, 10 mmol) under the conditions of preparation of compound **16**. The yield of product **1** was 0.35 g (38.5 %), m.p. 37—38 °C. Found (%): C, 85.68; H, 11.33; N, 2.93. $C_{32}H_{51}N$. Calculated (%): C, 85.46; H, 11.43; N, 3.11. ^1H NMR, δ: 0.88 (t, 3 H, CH_3); 1.3 (s, 32 H, CH_2); 1.40—1.60 (m, 4 H, $CH_2CC\equiv$); 1.70 (quintet, 2 H, CH_2CPy); 2.25 (t, 4 H, $CH_2C\equiv$); 2.75 (t, 2 H, CH_2Py); 6.95—7.15 (m, 2 H, β-H); 7.45—7.65 (m, 1 H, γ-H); 8.40—8.55 (m, 1 H, α-H).

B. A 1.86 *N* solution of butyllithium (3.1 mL, 5.1 mmol) in hexane and hydrobromide **10** (0.5 g, 1.27 mmol) were added at an interval of 15 min to a solution of hexadecadiyne **13** [14] (0.8 g, 3.8 mmol) in 10 mL of THF in an argon atmosphere at −35 °C. The mixture was stirred for 1 h at the same temperature and for 12 h at 20 °C. The reaction mass was diluted with 20 mL of hexane, and NH_4Cl (0.5 g) and water (0.5 mL) were added. The organic layer was decanted and filtered through a thin layer of Al_2O_3. Unreacted initial hexadecadiyne (0.52 g) and product **1** (0.48 g, 84.2 %) were isolated by chromatography on SiO_2 (ASKG trade mark, benzene and $CHCl_3$ as eluents).

C. A 1.8 *N* solution of butyllithium in hexane (1.7 mL) was added dropwise with stirring to 10-bromodecanol **3** (0.28 g, 3.0 mmol) in 5 mL of THF in an argon atmosphere at −10 °C. In 15 min pyridylundecanol **9** (0.44 g, 1 mmol) in 5 mL of THF was added. The mixture was stirred for 30 min at −5 °C and diluted with pentane (25 mL), and NH_4Cl (0.5 g) and water (20 mL) were added. The aqueous solution was extracted with pentane. The extract was washed with water and dried over $MgSO_4$. After removal of the solvent and chromatography of a residue on SiO_2 (ASKG trade mark) using $CHCl_3$ as an eluent, compound **1** (0.42 g, 93.3 %) was obtained.

1-(4-Pyridyl)octacosa-13,15-diyne (15) was obtained by the reaction of hexadecadiyne **13** (0.49 g, 2.2 mmol) and 4-(12-bromododecyl)pyridine hydrochloride **14** (0.14 g, 0.37 mmol) under the conditions of synthesis of **1** by method **B**. Compound **15** was obtained in a yield of 0.15 g (89.0 %), m.p. 44.0—44.5 °C (from methanol). Found (%): C, 85.22; H, 11.60; N, 3.19. $C_{33}H_{53}N$. Calculated (%): C, 85.46; H, 11.52; N, 3.02. ^1H NMR, δ: 0.88 (t, 3 H, CH_3); 1.25 (s, 34 H, CH_2); 1.40—1.70 (m, 4 H, $CH_2CC\equiv$); 1.82 (m, 2 H, CH_2CPy); 2.25 (t, 4 H, $CH_2C\equiv$); 2.57 (t, 2 H, CH_2Py); 7.10 (d, 2 H, β-H); 8.35—8.55 (br.m, 2 H, α-H).

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