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# SYNTHESIS OF CERTAIN DIPYRIDYLACETYLENES USING PALLADIUM-CATALYZED CROSS-COUPLING OF ETHYNYL- AND HALOPYRIDINES

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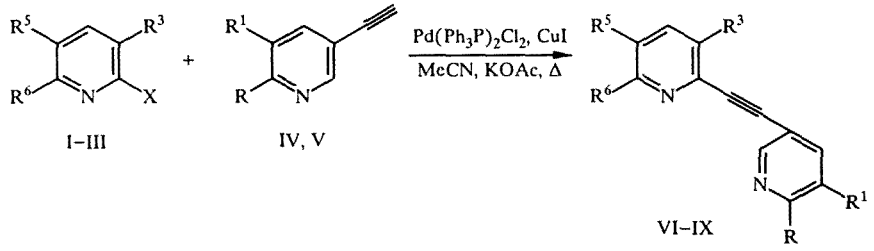
*A series of dipyridylacetylenes were obtained by reacting ethynylpyridines with chloro- and bromopyridines during catalysis with phosphino complexes of palladium in the presence of copper iodide and a base.*

It has been found in the last few years that dipyridylacetylenes have various useful properties and may be of interest as starting materials for preparing liquid crystals [1] and materials used in nonlinear optics [2], and also as potential biologically active substances (see, for example, [3]).

The known methods of preparation of this class of compounds are based on the use of bromi-nation – dehydrobromination of dipyridylethylenes [4], the synthesis of which constitutes an independent problem. During the 1980s-1990s, methods of synthesis of dipyridylethylenes were developed, based on the reaction of arylmethylphosphonates with arylcarbaldehydes (the Wadsworth–Emmons reaction) [5] or on the coupling of arylcarbaldehydes in the presence of compounds of low-valence titanium (the McMurry reaction) [6]; data have been reported on the use of a modified Horner–Emmons reaction in preparing 4-pyridylphenylacetylene from 4-pyridylcarbaldehyde [7]. However, all these methods of preparing this class of compounds from carbonyl derivatives of pyridine are multistage ones, and in addition, they cannot be considered universal, since various carbaldehydes of the pyridine series are difficult to obtain.

A more promising synthetic scheme of obtaining dipyridylacetylenes can, in our view, be based on the use of the reaction of cross-coupling of halogen derivatives of pyridine with ethynylpyridines during catalysis by the $Pd^0/Cu^1$ system. Although reactions of halopyridines with terminal acetylenes are known [8-10], analysis of literature data shows that the iodine and bromine derivatives are used most widely in these reactions. Chloropyridines (especially β-chloro derivatives of the pyridine series) are considerably less active in various palladium-catalyzed reactions [11]. The presence of acceptor substituents such as the nitro-, cyano-, and N-oxide groups increases the reactivity of chloropyridines in cross-coupling reactions. This fact is of considerable importance, since chloropyridines, particularly the α derivatives, are more accessible (both commercially and synthetically) and more stable than the corresponding bromine and iodine derivatives.

We were able to introduce into the cross-coupling reaction not only bromo- but also chloropyridines while using bis(triphenylphosphino)palladium and cuprous iodide as catalysts (1 mole % of each) and obtain the series of dipyridylacetylenes VI-IX, XII, XIII, XV, XX. The reaction was carried out in acetonitrile while heating to 50-80°C; the base used was potassium acetate, since the yields of the coupling products are extremely low in the reaction of nitrochloropyridines with ethynylpyridines under conditions described previously [8] for reactions of halopyridines with terminal acetylenes (with triethylamine as the solvent).




I–III IV, V VI–IX

I $R^3=R^5=R^6=H$, X=Br; IIa $R^3=R^6=H$, $R^5=NO_2$, X=Cl; IIb $R^3=R^6=H$, $R^5=NO_2$, X=Br;

III $R^3=R^6=Me$, $R^5=NO_2$, X=Br; IV $R^1=H$, R=Me; V R, $R^1$= 

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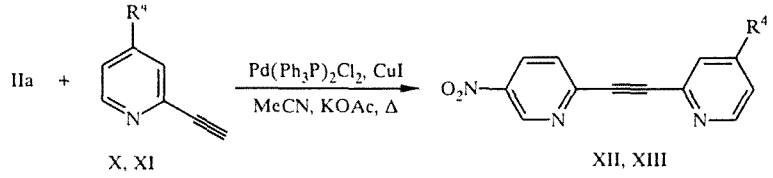
TABLE 1. Conditions of Cross-Coupling Reactions, Constants, and Yields of Dipyridylacetylenes

| Reactant | | Reaction condi-tions* | Reaction time, h | Reaction product | Empricial formula | mp, °C (solvent) | Yield†, % |
|---|---|---|---|---|---|---|---|
| halo-pyridine | ethyl-pyridine | | | | | | |
| I | IV | A | 10 | VI | $C_{13}H_{10}N_2$ | 75 (benzene–hexane) | 80 |
| IIa | IV | B | 3 | VII | $C_{13}H_9N_3O_2$ | 190 (MeCN) | 60 |
| | | A | 10 | | | | Trace |
| IIb | IV | B | 1 | | | | 80 |
| IIa | V | B | 3 | VIII | $C_{16}H_9N_3O_2$ | 198 (EtOH) | 80 |
| | | A | 15 | | | | 68 |
| III | IV | B | 4 | IX | $C_{15}H_{13}N_3O_2$ | 152...154 ($CCl_4$) | 70 |
| IIa | X | B | 3 | XII | $C_{12}H_7N_3O_2$ | 192 (acetone) | 72 |
| IIb | | B | 0,5 | | | | 85 |
| IIa | XI | B | 3 | XIII | $C_{13}H_9N_3O_2$ | 195 (acetone) | 78 |
| XIV | IV | B | 5 | XV | $C_{21}H_{15}N_3$ | 223 (benzene–hexane) | 65 |

*Triethylamine, 30°C (A); acetonitrile, KOAc, boiling (B).

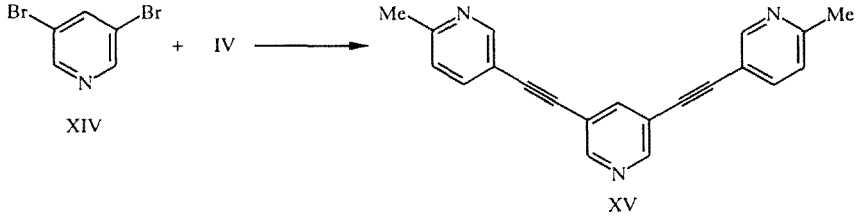
**After column chromatography.

Ethynylpyridine was introduced into the reaction mixture gradually, since the addition of the entire amount of reactant at the start of the reaction with chloronitropyridine showed an appreciable increase in formation of the product of homocoupling of terminal acetylene. For example, in the reaction of 2-chloro-5-nitropyridine (IIa) with 3-ethynyl-6-methylpyridine (IV), the byproduct of the reaction is formed in 40% yield (determined chromato-mass-spectrometrically). A lowering of the total yield of the conversion products of the initial compounds was also noted in this case. This is probably due to the occurrence of oxidation–reduction side reactions involving $Pd^0$ and nitro groups, which successfully compete with the main direction of the process, particularly in the case of the chlorine derivative, since the carbon–chlorine bond exhibits low activity at the stage of oxidative addition of $Pd^0$.



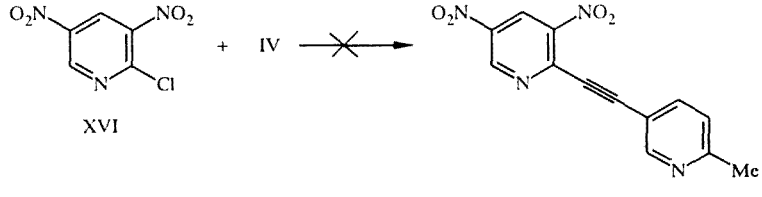

X, XI XII, XIII

X, XII R=H; XI, XIII $R^4$=Me




XIV XV

The reaction of 3,5-dinitro-2-chloropyridine (XVI) with acetylene IV was accompanied by the formation of a difficult-to-identify mixture in which the expected acetylene XVII was not observed.




XVI XVII

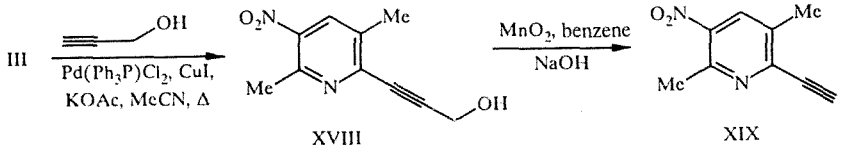
TABLE 2. Spectral Characteristics of Dipyridylacetylenes

| Compound | IR spectrum, $cm^{-1}$ | | Mass spectrum (70 eV), m/z ($I_{rel}$, %) | PMR spectrum, δ, ppm (solvent) |
|---|---|---|---|---|
| | C≡C | $NO_2$ | | |
| VI | 2228 | — | 194 ($M^+$, 100), 193 (32), 192 (10), 179 (8), 167 (5), 166 (6), 140 (3), 139 (3), 128 (3), 97 (3), 83 (5), 78 (4), 63 (3), 51 (4) | 6-Methylpyridyl-3: 7.54 (1H, d, J = 8.20 Hz, 5-H); 7.77 (1H, d.d, J = 2.40; 8.20 Hz, 4-H); 8.73 (1H, d, J = 2.40 Hz, 2-H); pyridyl-2; 7.17 (1H, m, 3-H); 7.27 (1H, m, 5-H); 7.70 (1H, m, 4-H); 8.64 (1H, m, 6-H) ($CDCl_3$). |
| VII | 2230 | 1525, 1356 | 239 ($M^+$, 100), 193 (22), 166 (35), 116 (11), 75 (11), 51 (13) | 6-Methylpyridyl-3; 2.62 (3H, s, $CH_3$); 7.39 (1H, d.d, J = 0.80; 8.05 Hz, 5-H); 7.87 (1H, d.d, J = 2.23; 8.03 Hz, 4-H); 8.74 (1H, d.d, J = 0.79; 2.19 Hz, 2-H); 5-nitropyridyl-2: 8.50 (1H, d.d, J = 0.67; 8.58 Hz, 3-H); 8.67 (1H, d.d, J = 2.68; 8.60 Hz, 4-H); 9.44 (1H, d.d, J = 0.68; 2.65 Hz, 6-H) ($CDCl_3$). |
| VIII | 2229 | 1525, 1362 | 275 ($M^+$, 100), 229 (18), 202 (26), 175 (5), 152 (4), 114 (3), 101 (10), 87 (9), 75 (4), 51 (5) | Quinolyl-3: 7.65-7.96 (2H, m); 8.05-0.09 (2H, m); 8.57 (1H, br. s, 4-H); 9.04 (1H, br. s, 2-H); 5-nitropyridyl-2: 7.95 (1H, d, J = 8.50 Hz, 5-H); 8.54 (1H, d.d, J = 2.70; 8.50 Hz, 4-H); 9.39 (1H, d, J = 2.71 Hz, 6-H) ($CD_3CN$). |
| IX | 2232 | 1525, 1358 | 243 ($M^+$, 100) | 3,6-Dimethyl-5-nitropyridyl-2: 2.59 (3H, s, $CH_3$); 2.86 (3H, s, 6-$CH_3$); 8.19 (1H, s, 4-H); 6-methylpyridyl-3: 2.62 (3H, s, 6-$CH_3$); 7.21 (1H, d, J = 7.86 Hz, 5-H); 7.81 (1H, d.d, J = 7.96; 2.20 Hz, 4-H); 8.76 1H, d.d, J = 2.04 Hz, 2-H) ($CDCl_3$). |
| XII | 2239 | 1520, 1360 | 225 ($M^+$, 100), 179 (37), 152 (78), 78 (72) | Pyridyl-2: 7.45 (1H, d.d.d, J = 1.25; 4.83; 7.65 Hz, 5-H); 7.72 (1H, m, 3-H); 7.84 (1H, m, 4-H); 8.67 (1H, m, 6-H); 5-nitropyridyl-2: 7.89 (1H, d.d, J = 0.74; 8.61 Hz, 3-H); 8.58 (1H, d.d, J = 2.70; 8.61 Hz, 4-H); 9.40 (1H, d.d, J = 0.74; 2.70 Hz, 6-H) ($CD_3CN$ and DMSO-$D_6$). |
| XIII | 2229 | 1530, 1350 | 239 ($M^+$, 100), 193 (27), 181 (6), 166 (42), 154 (18), 92 (22), 65 (17), 57 (7), 51 (9), 41 (14), 40 (13) | 4-Methylpyridyl-2: 2.42 (3H, s, $CH_3$); 7.32 (1H, d.d, J = 1.71; 5.00 Hz, 5-H); 7.62 (1H, d.d, J = 0.41; 1.71 Hz, 3-H); 8.53 (1H, d.d, J = 0.66; 5.00 Hz, 6-H); 5-nitropyridyl-2: 7.99 (1H, d.d, J = 0.70; 8.60 Hz, 3-H); 8.68 (1H, d.d, J = 2.68; 8.61 Hz, 4-H); 9.42 (1H, d.d, J = 0.68; 2.66 Hz, 6-H) (acetone-$D_6$). |
| XV | 2226 | — | 309 ($M^+$, 100) | 7.96 (1H, t, J = 1.96 Hz, 4-H); 8.96 (2H, d, J = 1.90 Hz, 2 and 6-H); 6-methylpyridyl-3: 2.56 (6H, s, $CH_3$); 7.19 (2H, d, J = 8.00 Hz, 5-H); 7.74 (2H, d.d, J = 2.16; 8.00 Hz, 4-H); 8.66 (2H, d, J = 2.00 Hz, 2-H) ($CD_2Cl_2$). |

This is probably due to the formation of a chelate complex with the participation of a nitro group in the ortho position in the organopalladium intermediate, which is inactive at the transmetalation stage. A similar picture was observed in the cross-coupling of 2-chloropyrazine N-oxide with terminal acetylenes [11]. However, the literature has reported instances of conversions of halogen derivatives of pyridine containing a nitro group in the ortho position to the halogen atom, for example, the reaction of 2-chloro-3-nitropyridine with phenylboric acid [12] and of 2,6-dimethyl-3-nitro-4-iodopyridine with trimethylsilylacetylene [13]. A successful course of cross-coupling reactions in these cases is due either to the use of a chelate-forming bidentate phosphino ligand—bis(diphenylphosphino)butane [12], or to the presence of a methyl group in the ortho position to the nitro group [13]; this apparently prevents coordination of the oxygen atom of the nitro group at the palladium atom in the organopalladium intermediate.

It is well known that the cross-coupling reaction of halogen derivatives of pyridine with terminal acetylenes is a convenient method of obtaining not only disubstituted acetylenes but also terminal pyridylacetylenes. In the latter case, use is commonly made of cross-coupling reactions of halopyridines with trimethylsilylacetylene [14] or with 2-methylbut-3-yn-2-ol [15] with subsequent treatment of the coupling product with KOH in methanol or NaOH in toluene, respectively. An attempt to obtain 2-ethynyl-5-nitro-3,6-dimethylpyridine from the corresponding bromine derivative by means of trimethylsilylacetylene proved unsuccessful. The reaction took place with the formation of an unidentified mixture of compounds. It should be emphasized that this lack of success was apparently due to the presence of a nitro group in the pyridine ring, since the coupling

of 2-bromopyridine and 2-bromo-4-methylpyridine took place successfully. We therefore found another method of obtaining nitrothynylpyridine, similar to the one described earlier for the preparation of ethynylbenzenes [16]. The cross-coupling reaction of 2-bromo-5-nitro-3,6-dimethylpyridine (III) with propargyl alcohol formed 2-(hydroxymethylethynyl)-5-nitro-3,6-dimethylpyridine (XVIII) in 60% yield. Treatment of the latter with manganese oxide (IV) formed 2-ethynyl-5-nitro-3,6-dimethylpyridine in 90% yield.




XVIII XIX

## EXPERIMENTAL

The IR spectra were recorded with an UR-20 instrument in vaseline oil. The PMR spectra were recorded with a Varian VXR-400 instrument in different solvents; internal standard, TMS. Assignment of the signals in the PMR spectra of compounds VI-IX, XII, and XIII was based on double-resonance experiments. The mass spectra were obtained with a KRATOS MS-25 RFA instrument.

Data of the ultimate analysis of all the synthesized compounds for C, H, and N correspond to the calculated data.

2-Ethynylpyridine (X) and 3-ethynylquinoline (V) were obtained in accordance with the methods described in [14, 15].

**2-Ethynyl-4-methylpyridine (XI, $C_8H_7N$)** was obtained as in [15] from 2-bromo-4-methylpyridine and 2-methylbut-3-yn-2-ol in two steps with a total yield of 70%, bp 90-92°C (13 torr). IR spectrum: 2120 $cm^{-1}$ (C≡C), 3300 $cm^{-1}$ (≡CH); mass spectrum (70 eV): found: $M^+$ 117, calculated: M 117. 3-Ethynyl-6-methylpyridine (V) was obtained in accordance with the method of [17].

**Cross Coupling Reaction of Halopyridines with Ethynylpyridines (general procedure)**. To a solution of the halogen derivative of pyridine (1 mmole, 0.14 mole/liter) in a suitable solvent (see Table 1) is added 196 mg (2 mmoles) of potassium acetate. The mixture is stirred for 5 min in a stream of argon, and 7 mg (0.01 mmole) of bis(triphenylphosphino)palladium and 2 mg (0.01 mmole) of cuprous iodide are added. To the mixture obtained, a solution of ethynylpyridine (1.2 mmoles, 0.25 mole/liter) is added dropwise with stirring and heating. After the solution of ethynylpyridine has been added, the reaction mixture is stirred with heating for a period of time indicated in Table 1. The solution is then filtered, evaporated under vacuum, and the residue is dissolved in a 10:1 benzene–ethyl acetate mixture (2 ml) and quickly passed through a column with neutral alumina (10 g). The solvent is evaporated off, the residue is purified by flash chromatography on silica gel (20 g), and chloroform is used as the eluent. The reaction conditions, constants, and yields of dipyridylacetylenes are listed in Table 1, and the spectral data are shown in Table 2.

**2-(Hydroxymethylethynyl)-5-nitro-3,6-dimethylpyridine (XVIII, $C_{10}H_{10}N_2O_3$)**. To a solution of 346 mg (1.5 mmoles) of 2-bromo-5-nitro-3,6-dimethylpyridine in 20 ml of acetonitrile are added 40 mg (0.06 mmole) of bis(triphenylphosphino)palladium dichloride, 20 mg (0.1 mmole) of cuprous iodide, and 376 mg (3.8 mmoles) of potassium acetate. Then, 0.1 g (1.8 mmoles) of 2-propynol is added in a stream of argon. The reaction mixture is stirred for 2 h at 60°C then filtered, and the precipitate is washed twice with acetonitrile. The combined filtrate is evaporated to dryness, and the dry residue is extracted with ether. The ether is evaporated off and the residue is recrystallized from a 1:2 benzene–cyclohexane mixture. A yellow crystalline substance is obtained in the amount of 185 mg (60%), mp 121-123°C. IR spectrum: 1370, 1515 ($NO_2$), 2260 (C≡C), 3280 $cm^{-1}$ (OH). PMR spectrum ($CDCl_3$): 2.48 (3H, s, $CH_3$); 2.82 (3H, s, $CH_3$); 4.60 (2H, s, $CH_2$); 5.02 (1H, br. s, OH); 8.15 ppm (1H, s, 4-H).

**2-Ethynyl-5-nitro-3,6-dimethylpyridine (XIX, $C_9H_8N_2O_2$)**. To a solution of 1.03 g (5 mmoles) of 2-(hydroxymethylethynyl)-5-nitro-3,6-dimethylpyridine in 20 ml of benzene are added 1.4 g (25 mmoles) of ground-up potassium hydroxide and 4.35 g (0.05 mole) of manganese dioxide. The mixture is stirred for 30 min at room temperature, filtered, and the manganese dioxide residue is washed several times with ether. The solvent is evaporated off, and the residue is recrystallized from an 8:1 hexane–benzene mixture. A yellow crystalline substance is obtained in the amount of 0.8 g (90%).

mp 98°C. IR spectrum: 1345, 1572 ($NO_2$), 2130 (C≡C), 3310 $cm^{-1}$ (≡CH). PMR spectrum (acetone-$D_6$): 2.53 (3H, s, $CH_3$), 2.73 (3H, s, $CH_3$), 4.30 (1H, s, ≡CH), 8.30 (1H, s, 4-H).

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## REFERENCES

1. K. Seto, H. Shimojitosyo, H. Matsubara, and S. Tokahashi, Chem. Lett., No. 6, 323 (1990).
2. Conjugated Polymeric Materials: Opportunities in Electronics, J. L. Bredas and R. R. Chance (eds.), NATO ASI Ser. 182, Kluwer Academic Publishers, Dordrecht (1990).
3. R. A. Chandraratna, XIII International Symposium on Medicinal Chemistry Book of Abstracts, Paris (1994), ML 29.
4. P.-M. Windsheif and F. Vögtle, Synthesis, No. 1, 87 (1994).
5. G. R. Newcome, J. M. Roper, and J. M. Robinson, J. Org. Chem., **45**, 4380 (1980).
6. J. E. McMurry, Chem. Rev., **55**, 263 (1989).
7. K. Kondo, N. Ohnishi, K. Takemoto, H. Yoshida, and K. Yoshida, J. Org. Chem., **57**, 1622 (1992).
8. K. Sonogashira and N. Hagihara, Tetrah. Lett., **16**, 4467 (1975).
9. H. J. Gibson, M. d'Alarcao, and N. J. Leonard, J. Org. Chem., **50**, 2462 (1985).
10. J. M. Tilley, D. L. Coffen, B. N. Schaer, and J. Lind, J. Org. Chem., **52**, 2469 (1987).
11. N. Sato, A. Hayakawa, and R. Takeuchi, J. Heterocycl. Chem., **27**, 503 (1990).
12. M. B. Mitchell and P. J. Wallbank, Tetrah. Lett., **32**, 2273 (1991).
13. T. Sakamoto, Y. Kondo, and H. Yamanaka, Heterocycles, **22**, 1347 (1984).
14. T. Sakamoto, M. Shiraiva, Y. Kondo, and H. Yamanaka, Synthesis, No. 4, 312 (1983).
15. D. E. Ames, D. Bull, and C. Tokundwa, Synthesis, No. 4, 364 (1981).
16. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, Synthesis, No. 9, 728 (1984).
17. A. N. Kost, P. B. Terent'ev, and L. V. Moshentseva, Methods of Obtaining Chemical Reagents and Preparations [in Russian], Moscow (1964), No. 2, p. 73.