Chemistry of Heterocyclic Compounds, Vol. 34, No. 4, 1998

SYNTHESIS AND ALKYLATION OF PYRIDYLACETYLENES UNDER PHASE TRANSFER CATALYSIS CONDITIONS IN A LIQUID/SOLID SYSTEM

É. Abele, R. Abele, K. Rubina, A. Gaukhman, and E. Lukevics

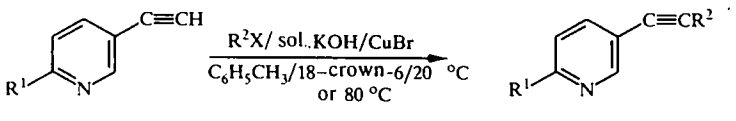
We have investigated the alkylation of 2-methyl-5-ethynylpyridine by butyl bromide in liquid/liquid and liquid/solid two-phase catalytic systems. We have shown that the catalytic system solid KOH/18-crown-6/CuBr/toluene is the most active in this reaction; using this system, we obtained alkylation products of ethynylpyridines in 34-43% yields.

Pyridylacetylenes and their derivatives are widely used as synthons in organic synthesis [1-9]. Usually pyridylacetylenes are obtained from the corresponding vinylpyridines by addition of bromine followed by treatment of the intermediate with potassium hydroxide [1, 10]. We also know of synthesis methods for these compounds from acetylpyridines [11], halopyridines, and trimethylsilylacetylene [4] or from pyridinecarbaldehydes by reaction with chloromethylene(triphenyl)phosphine ylide followed by treatment with potassium *tert*-butoxide [12].

We have developed a new phase transfer catalysis (PTC) method for synthesis of 2- and 3-ethynylpyridines from vinylpyridines, based on bromination of vinylpyridines in the system HBr/H_2O_2/triethylbenzylammonium chloride (TEBAC)/CCl_4 followed by treatment of the intermediate (α,β-dibromoethylpyridinium bromide) with powdered KOH and K_2CO_3 in the system Allyquot/18-crown-6/benzene. Under these conditions, 2- and 3-ethynylpyridines are obtained in 23% and 24% yields.

The synthesized ethynylpyridines were used in phase transfer catalysis of alkylation. The application of the phase transfer catalysis method in alkylation of terminal aromatic acetylenes is described in several publications [13-15], but alkylation of ethynylpyridines under phase transfer catalysis conditions has not been studied before. First we studied in detail the reaction of alkylation of 2-methyl-5-ethynylpyridine (I) (as the most stable pyridylacetylene) by *n*-butyl iodide in different phase transfer catalysis systems (Table 1).

We established that the phase transfer catalysis system solid KOH/18-crown-6/CuBr/toluene is the most active in alkylation of 6-methyl-3-ethynylpyridine by butyl bromide. In the presence of this system product, IVc was obtained in 42% yield. The use of copper monobromide as the second catalyst in alkylation of terminal acetylenes was also demonstrated in [14]. In the absence of the copper salt, the product is obtained in 33% yield. Using KOH in 50% aqueous solution and also solid KF and K_2CO_3 proved to be quite ineffective.



I,II IIIb-d, IVa-d

I R^1 = H; II R^1 = Me; IIIb R^1 = H, R^2 = Et; IIIc R^1 = H, R^2 = n-Bu; IIId R^1 = H, R^2 = $CH_2CH{=}CH_2$; IVa R^1 = Me, R^2 = Me; IVb R^1 = Me, R^2 = Et; IVc R^1 = Me, R^2 = n-Bu; IVd R^1 = Me, R^2 = $CH_2CH{=}CH_2$

Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 518-521, April, 1998. Original article submitted November 1, 1997.

0009-3122/98/3404-0459$20.00

TABLE 1. Alkylation of 2-Methyl-5-ethynylpyridine (I) by Butyl Bromide Under Phase Transfer Catalysis Conditions at 80°C

Base	Catalyst	Reaction time, h	Yield of IVc, % (from GLC data)
KOH	18-crown-6	18	33
KOH	18-crown-6/CuBr (20 mol.%)	18	42
K_2CO_3	18-crown-6	12	0
KF	18-crown-6	12	0
50% KOH	Oct_4NBr	12	0
50% KOH	$BnEt_3NBr$	12	0

The catalytic system powdered KOH/18-crown-6/CuBr/toluene (as the most active) was used in alkylation of ethynylpyridines I and II by different alkyl and allyl halides. All the reaction products (34-43% yield) are unstable and easily turn to tar as the temperature is raised and on contact with air.

Alkylation of the most active 3-ethynylpyridine (I) occurs at room temperature, while alkylation of 2-methyl-5-ethynylpyridine (II) was possible at 80°C. All attempts to obtain the alkylation products of 2-ethynylpyridine, and also to carry out phase transfer catalysis for alkylation of 3-ethynylpyridine by methyl iodide, ended in the compound not being isolated due to the reaction mixture turning entirely to tar.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90/DS spectrometer in $CDCl_3$, internal standard TMS. Mass spectra were obtained on a Hewlett Packard HP-6890. GLC analysis was done on a Chrom-5 chromatograph with flame ionization detector and a glass column filled with 5% OV-101 on Chromosorb W-HP (80-100 mesh), temperature 150-200°C. 18-Crown-6, TEBAC, Allyquot (Fluka), alkyl iodides, and allyl bromide (Reakhim) were used without additional purification. The vinylpyridines were distilled under vacuum before use. 2-Methyl-5-ethynylpyridine II was obtained according to the procedure described in [10].

General Procedure for Obtaining Ethynylpyridines. 2-Ethynylpyridine. TEBAC (0.4 g, 1.8 mmoles) was added to a solution of 11.7 g (0.11 moles) 2-vinylpyridine in 40 ml carbon tetrachloride; then 40 ml of concentrated HBr and 24 ml 30% H_2O_2 were added with cooling (0°C). The reaction mixture, spontaneously warming up to room temperature, was stirred for 1 h. The oil falling out of solution was decanted, the aqueous layer was evaporated, and the remainder was added to the oil. The oil obtained (the intermediate, α,β-dibromoethylpyridinium bromide) was recrystallized in a desiccator over P_2O_5. Yield, 21.0 g (54%).

Allyquot (2.9 g, 7.2 mmoles), 12.3 g (0.22 moles) finely ground KOH, and 30.4 g (0.22 moles) powdered K_2CO_3 were added to a suspension of α,β-dibromopyridinium bromide, 25.0 g (72 mmoles) in 300 ml benzene. The mixture was stirred for 8 h at 30°C, then a second portion of base was added: 8.0 g (0.14 moles) KOH and 20.0 g (0.14 moles) K_2CO_3, and this was stirred for 6 h at 50°C. Finally, 8.0 g (0.14 moles) KOH and 0.19 g (0.72 mmoles) 18-crown-6 was added and this was stirred for 6 h at 80°C. The mixture obtained was filtered and evaporated under reduced pressure. The residue was distilled under vacuum and 2-ethynylpyridine was obtained. T_{bp} 41°C/2.2 mm Hg. Yield, 1.40 g (24%).

3-Ethynylpyridine (I) was similarly obtained from 3-vinylpyridine. T_{bp} 33-34°C/1 mm Hg. Yield, 1.70 g (23%).

General Procedure for Alkylation of 2-Methyl-5-ethynylpyridine (II) by Butyl Iodide Under Phase Transfer Catalysis Conditions. In a Pierce microreactor, 10 mmoles (for solid KOH, KF, and K_2CO_3) or 0.5 ml 50% aqueous KOH was added to a solution of 0.236 g (2 mmoles) of 2-methyl-5-ethynylpyridine II, 0.68 ml (6 mmoles) *n*-butyl iodide, and 0.1 mmoles of the catalyst in 1.5 ml toluene. This was stirred at 80°C for 12-18 h (monitored by GLC).

General Procedure for Alkylation of 3-Ethynylpyridine (I) by Alkyl Halides. 3-(1-Butynyl)pyridine (IIIb). Powdered KOH (0.28 g, 5 mmoles) and 0.013 g (0.2 mmoles) CuBr were added to a solution of 0.103 g (1 mmoles) 3-ethynylpyridine I, 0.24 g (3 mmoles) ethyl iodide, and 0.013 g (0.05 mmoles) 18-crown-6 in 0.8 ml toluene. This was stirred for 13 h at room temperature and then filtered. The filtrate was evaporated down on a rotary evaporator. The residue was purified by column chromatography (eluent, benzene—ethylacetate, 1:1). Yield, 0.055 g (42%). PMR spectrum: 1.18 (3H, t,

J = 7.4 Hz, CH_3); 2.38 (2H, q, J = 7.4 Hz, CH_2); 7.18 (1H, m, 5-H); 7.49 (2H, m, 4-H and 6-H); 8.47 ppm (1H, m, 2-H). Mass spectrum, m/z ($I_{rel.}$, %): 131 (56, M^+), 130 (100), 116 (10), 103 (13), 89 (17), 77 (12), 63 (16), 51 (21), 39 (10).

Compounds IIIc, d are obtained similarly.

3-(1-Hexynyl)pyridine (IIIc). Obtained by reaction of 3-ethynylpyridine with butyl iodide for 9 h. PMR spectrum: 0.87 (3H, m, CH_3); 1.51 (4H, m, $CH_2(CH_2)_2CH_3$); 2.38 (2H, m, CCH_2); 7.00 (1H, m, 5-H); 7.22 (1H, m, 4-H); 7.42 (1H, m, 6-H); 8.42 ppm (1H, m, 2-H). Mass spectrum, m/z (I_{rel}, %): 159 (31, M^+), 144 (35), 130 (100), 117 (80), 103 (13), 89 (34), 78 (18), 63 (24), 51 (20), 39 (17). Yield, 43%.

3-(1-Pentyn-4-enyl)pyridine (IIId). Obtained by reaction of 3-ethynylpyridine (I) with allyl bromide for 4 h. PMR spectrum: 1.22 (2H, m, CH_2); 5.02 and 5.96 (3H, m and m, $CH=CH_2$); 6.98 (1H, m, 5-H); 7.35 (1H, m, 4-H); 7.51 (1H, m, 6-H); 8.47 ppm (1H, m, 2-H). Mass spectrum, m/z (I_{rel}, %): 143 (100, M^+), 117 (64), 89 (25), 63 (32), 51 (34), 39 (32). Yield, 41%.

General Procedure for Alkylation of 2-Methyl-5-ethynylpyridine (II) by Alkyl Halides. 2-Methyl-5-(1-propynyl)pyridine (IVa). Powdered KOH (0.56 g, 10 mmoles) and 0.026 g (0.4 mmoles) CuBr were added to a solution of 0.236 g (2 mmoles) 2-methyl-5-ethynylpyridine II, 0.36 ml (6 mmoles) methyl iodide and 0.026 g (0.1 mmoles) 18-crown-6 in 1.5 ml toluene. This was stirred for 11 h at 80°C and then filtered. The filtrate was evaporated down on a rotary evaporator. The residue was purified by column chromatography (eluent, benzene–ethylacetate, 1:1). Yield, 0.11 g (42%). PMR spectrum: 1.17 (3H, s, CCH_3); 2.49 (3H, s, CH_3 on ring); 6.98 (1H, m, 3-H); 7.44 1H, m, 4-H); 8.42 ppm (1H, m, 6-H). Mass spectrum, m/z (I_{rel}, %): 131 (100, M^+), 116 (8), 103 (29), 89 (14), 77 (22), 63 (27), 51 (19), 39 (12).

Compounds IVb-d were obtained similarly.

2-Methyl-5-(1-butynyl)pyridine (IVb). Obtained by reaction of II with ethyl iodide in 17 h. PMR spectrum: 1.16 (3H, t, J = 7.2 Hz, CH_3); 2.36 (2H, q, J = 7.2 Hz, CH_2); 2.36 (1H, s, CH_3 on ring); 6.98 (1H, m, 3-H); 7.47 (1H, m, 4-H); 8.42 ppm (1H, m, 6-H). Mass spectrum, m/z (I_{rel}, %): 145 (100, M^+), 130 (57), 115 (17), 103 (22), 91 (10), 77 (32), 63 (28), 51 (24), 39 (17). Yield, 34%.

2-Methyl-5-(1-hexynyl)pyridine (IVc). Obtained by reaction of II with butyl iodide in 18 h. PMR spectrum: 0.87 (3H, m, CH_3), 1.47 (4H, m, $CH_3(CH_2)_2CH_3$); 2.40 (2H, m, CCH_2); 2.89 (1H, s, CH_3 on ring); 7.00 (1H, m, 3-H); 7.53 (1H, m, 4-H); 8.51 ppm (1H, m, 6-H). Mass spectrum, m/z (I_{rel}, %) 173 (33, M^+), 158 (100), 144 (54), 130 (80), 117 (24), 103 (13), 89 (12), 77 (44), 63 (29), 51 (19), 39 (18). Yield, 37%.

2-Methyl-5-(1-pentyn-4-enyl)pyridine (IVd). Obtained by reaction of II with allyl bromide in 7 h. PMR spectrum: 1.18 (2H, m, CCH_2); 2.42 (3H, s, CH_3); 5.29 and 6.16 (3H, m and m, $CH=CH_2$); 6.98 (1H, m, 3-H); 7.40 (1H, m, 4-H); 8.27 ppm (1H, m, 6-H). Mass spectrum, m/z (I_{rel}, %): 157 (100, M^+), 142 (16), 130 (26), 115 (45), 89 (14), 77 (19), 63 (27), 51 (19), 39 (23). Yield, 35%.

REFERENCES

1. A. P. Gray, H. Kraus, D. E. Heitmeier, and R. H. Shiley, J. Org. Chem., **33**, No. 8, 3007 (1968).
2. G. G. Abbot and D. Leaver, J. Chem. Soc., Chem. Commun., No. 5, 150 (1973).
3. T. Tsuchiya, H. Sashida, and A. Konoshita, Chem. Pharm. Bull., **31**, No. 12, 4568 (1983).
4. T. Sakomoto, Y. Kondo, M. Shiraiwa, and H. Yamanaka, Synthesis, No. 3, 245 (1984).
5. L. Della Ciana and A. Haim, J. Heterocycl. Chem., **21**, No. 2, 607 (1984).
6. K. Berger, N. Sewald, E. Huber, and R. Offlinger, Z. Naturforsch. B: Chem. Sci., **44**, No. 10, 1298 (1989).
7. M. Inouye, T. Miyake, M. Farusyo, and H. Nakazumi, J. Am. Chem. Soc., **117**, No. 50, 12416 (1995).
8. S. A. Nye and K. T. Potts, Synthesis, No. 5, 275 (1988).
9. P. Ziessel and J. Suffert, Tetrahedron Lett., **37**, No. 12, 2011 (1996).
10. D. Leaver, W. K. Gibson, and J. D. R. Vass, J. Chem. Soc., No. 12, 6053 (1963).
11. I. L. Kotliarevskii, L. G. Fedonok, and L. N. Korelenok, Izv. Siber. Otdel., Akad. Nauk SSSR. Ser. Khim., **2**, 111 (1969).
12. J. Gonzalo Rodriguez, R. Martin-Villamil, F. H. Cano, and I. Fonseca, J. Chem. Soc., Perkin Trans. I, No. 5, 709 (1997).

13. M. Lissel, Tetrahedron Lett., **26**, No. 15, 1843 (1985).
14. V. V. Grushin and H. Alper, J. Org. Chem., **57**, No. 7, 2188 (1992).
15. E. V. Dehmlow and U. Fastabend, Gazz. Chim. Ital., **126**, No. 1, 53 (1996).