3. R. Pews and Z. Lysenko, J. Org. Chem., 50, 5115 (1985).
4. P. Martin, E. Steiner, E. Streth, T. Winkler, and D. Bellus, Tetrahedron, 41, 4057 (1985).
5. M. Asscher and D. Vofsi, J. Chem. Soc,. No. 3, 1887 (1963).
6. O. Seide, Berichte, 57, 1802 (1924).
7. M. Cava and N. Bhattacharua, J. Org. Chem., 23, 1614 (1958).

ALKYLATION OF 4-PICOLINIUM SALTS UNDER PHASE TRANSFER CONDITIONS

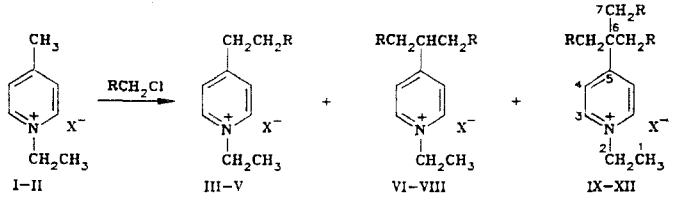
R. V. Butkene, G. V. Mikul'skene,
O. S. Éikher-Lorka, and G.-K.
K. Kupyatis

UDC 547.821.411.4:541.128.1

Alkylation of 1-ethyl-4-methylpyridinium bromide by allyl, benzyl and propargyl chlorides has been effected under conditions of phase transfer catalysis in a solid phase–liquid system (K_2CO_3–$CHCl_3$). Using the example of alkylation by allyl chloride, the effect of the concentration and the nature of the catalyst, the concentration of the base, and the temperature on the yield of mono-, di-, and trisubstituted products has been studied. The reactivity of the alkyl chlorides increases in the order allyl < benzyl < propargyl. When the reaction is carried out in a liquid–liquid system (25% aqueous NaOH–$CHCl_3$) the Br^- anion of the starting material is replaced by Cl^-, in contrast to the K_2CO_3–$CHCl_3$ system.

Alkylation of picolines is most frequently carried out with organolithium compounds [1] but these are time-consuming and expensive. Phase transfer catalysis has recently become widely used for the alkylation of CH-acids but this reaction has been little studied for picolines and only the quaternary salts of 2- and 4-methyl-, 2,6-dimethyl, and 2,4,6-trimethylpyridines have been alkylated by methyl iodide in an aqueous NaOH–CH_2Cl_2 system with tetrabutylammonium hydroxide as catalyst [2].

Extending the work into a series of unsaturated pyridine compounds [3], we carried out the alkylation of 1-ethyl-4-methylpyridinium bromide [1] by allyl, benzyl, and propargyl chlorides. To optimize the reaction conditions, we studied the effect of concentration and catalyst type, the concentration of the base, and the temperature on the yield in the alkylation of compound I by allyl chloride in a solid phase–liquid system. Chloroform was chosen as the solvent and anhydrous K_2CO_3 as the base.



I, III–XI X=Br; II, XII X=Cl; III, VI, IX R=CH=CH_2; IV, VII, X R=C≡CH; V, VIII, XI, XII R=C_6H_5

As can be seen from Fig. 1, alkylation will also occur without a phase transfer catalyst but the presence of a catalyst (dicyclohexano-18-crown-6, DCH-18-C-6) leads to an increasing yield of the product of complete alkylation IX as the catalyst concentration increases. It was established earlier [4] that crown ethers and quaternary ammonium salts do not transfer CO_3^{2-} into the organic phase. We suggest that in the process which we have studied, deprotonation of the salt I takes place on the surface of the solid carbonate and the anion so formed is transferred to the organic phase in the form of an ion pair with the crown ether complex and a potassium cation. After more than 20% DCH-18-C-6 has been added, there is no further significant increase in the yield of IX which is evidence of the cyclic nature of the formation and breakdown of the ion pair with the crown ether complex [4].

Institute of Chemistry and Chemical Technology, Academy of Sciences of the Lithuanian SSR, Vilnius 232600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 520-524, April, 1989. Original article submitted May 25, 1987; revision submitted March 28, 1988.

0009-3122/89/2504-0433$12.50

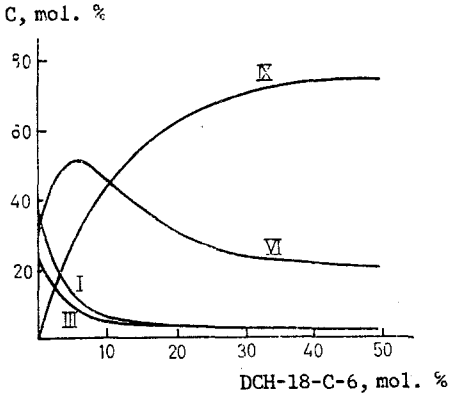


Fig. 1

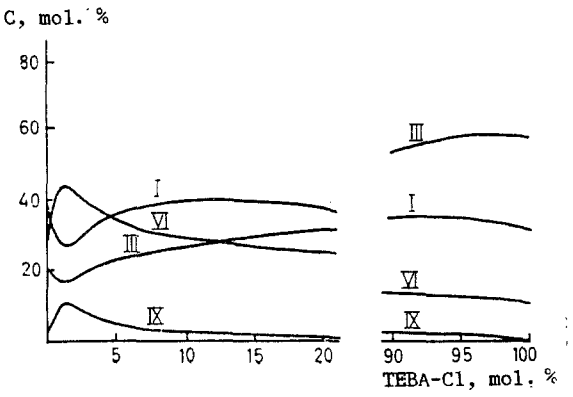


Fig. 2

Fig. 1. Effect of concentration of catalyst (dicyclohexano-18-crown-6-) on the concentration of products in the reaction mixture (38 mmole K_2CO_3, 45°C, 3 h).

Fig. 2. Effect of TEBA-Cl catalyst concentration on product concentration in the reaction mixture (38 mmole K_2CO_3, 45°C, 3 h).

TABLE 1. Dependence of Composition of Reaction Mixture on Alkyl Chloride Type (45°C, 3 h, 38 mmole K_2CO_3, 2.5 mmole DCH-18-C-6, 15 ml $CHCl_3$)

R	Concentration of compounds in reaction mixture, mol. %			
	I	III–V	VI–VIII	IX–XI
CH_2=CH	4,1	3,4	29,7	62,8
CH_2=CH*	0	1,5	25,1	73,4
C_6H_5	0	1,28	49,1	49,6
CH≡C	0	0	3,3	96,7
CH≡C†	20,6	39,7	30,4	9,3

*Reaction carried out in 15 ml acetonitrile.
†Reaction carried out without catalyst at 30°C.

The initial quaternary pyridinium salt I can, in principle, act as a phase transfer catalyst. Experiments with pyridinium salts not containing functional groups on the pyridine ring showed that they display very low catalytic activity [4]. Only 2- and 4-dialkylaminopyridinium salts proved to be effective catalysts [4, 5]. In the reactions which we studied, the starting material did not display any marked catalytic activity, otherwise in the course of the catalytic reaction (Starks cycle) [6] partial exchange of Br^- by Cl^- would have taken place in the starting material and in the reaction products III, VI, and IX. That this did not occur was demonstrated by means of TLC.

With a different phase transfer catalyst, triethylbenzylammonium chloride (TEBA-Cl, QCl), the dependence of the yield of alkylated product on the catalyst concentration takes on a different form (Fig. 2). Addition of small quantities of QCl (up to 1 mol. %) increases the alkylation rate. Because, according to [7], onium salts do not transfer doubly charged ions, this can be explained, as in [4], by transfer of the deprotonated anion HCO_3^-, which is formed in the reaction, from the surface of the crystal into the organic phase; the surface of the carbonate is then liberated for subsequent deprotonation reactions. Subsequent addition of QCl up to 5 mol. % leads to a fall in the deprotonation reaction rate which is seen as an increase in the concentration of the starting material I in the reaction mixture. This, apparently, occurs as a result of partial blocking of the surface of the carbonate by the bulky onium cation. Further addition of QCl up to 100 mol. % does not produce any significant change in the concentration of I although the concentration of the monoalkylated derivative increases at the expense of a reduction in the concentration of di- and tri-alkylated products. This can occur, as in the case of extractive alkylation [6], on account of an increase in the transfer by onium cations Q^+ of anions A^- from the surface of the carbonate into the bulk of the organic phase and by the lining up of the concentrations of ion pairs QA and allyl chloride in the organic phase associated with this, which determines the high probability of monoalkylation in comparison with di- and trialkylation.

TABLE 2. Carbon-13 and Proton NMR Spectra of Compounds I-XII

Compound	Chemical shift, ^1H, δ, ppm (J, Hz)							Chemical shift, ^{13}C, ppm							
	C_1, t	C_2,q	C_3,d (7)	C_4,d (7)	C_8	C_7	R	C_1	C_2	C_3	C_4	C_5	C_6	C_7	R
I	1,49	4,56	8,76	7,83	2,54 s	—	—	16,45	57,20	143,96	129,55	160,62	22,17	—	—
II	1,48	4,48	8,61	7,77	2,53 s	—	—	—	—	—	—	—	—	—	—
III	1,49	4,67	8,99	7,89	2,93 t	2,53 ... 2,20	5,71 m; 4,90 d (16); 4,86 d (11)	16,42	57,20	143,81	128,99	163,81	34,45	33,41	137,58; 117,85
IV	1,48	4,63	8,89	7,88	3,01 t	2,56 t	2,23 t	16,64	57,39	144,04	129,58	161,41	34,27	18,66	83,83; 72,37
V	1,49	5,11	8,69	7,82	3,33 ... 2,80		7,51 ... 7,11	16,46	57,20	143,74	127,36	162,86	37,22	35,39	140,75; 129,56; 129,56; 128,95
VI	1,51	4,69	8,90	7,78	3,09 t	2,52 ... 2,23	5,58 m; 4,86 d (16); 4,82 d (11)	16,42	57,28	143,96	128,58	165,92	45,48	39,20	136,23; 118,49
VII	1,48	4,60	8,71	7,78	3,57 ... 3,22	2,68 d	2,27 t 7,13 ... 6,91	16,64	57,39	144,04	128,46	162,34	43,01	23,40	81,89; 73,53
VIII	1,37	4,44	8,69	7,64	3,73 ... 3,31	3,04 ... 2,84	5,53 m; 4,96 d (16); 4,93 d (11)	16,42	57,28	143,81	127,46	165,07	49,77	41,14	139,48; 129,99; 129,47; 128,32
IX	1,51	4,61	8,90	7,97	—	2,48 d (8)	2,31 t	16,46	57,17	143,85	127,79	167,34	46,41	41,14	133,66; 120,25
X	1,50	4,58	8,84	8,07	—	2,84 d (2)	7,27 ... 6,98;	16,64	57,39	144,04	127,68	162,75	45,74	27,36	80,34; 74,42
XI—XII	1,36	4,41	8,44	7,64	—	3,18 s	6,89 ... 6,58	16,88	57,59	143,79	127,79	165,83	48,22	43,29	137,33; 131,50; 129,10; 129,10

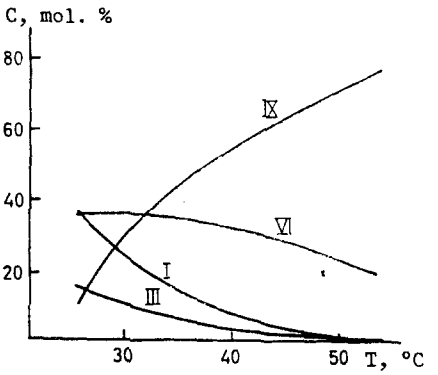


Fig. 3. Effect of temperature on the concentration of products in the reaction mixture (2.5 mmole DCH-18-C-6, 38 mmole K_2CO_3, 3 h).

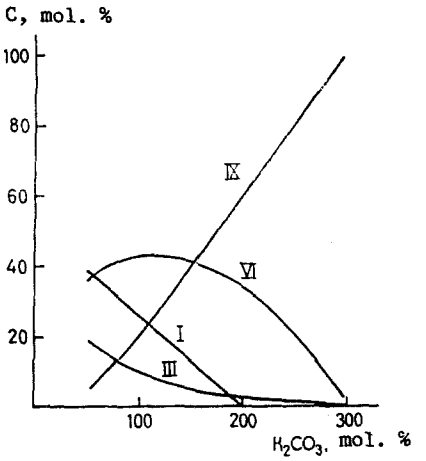


Fig. 4. Effect of K_2CO_3 concentration of products in reaction mixture (2.5 mmole DCH-18-C-6, 45°C, 5 h).

In a study of the effect of temperature on the alkylation, it was noted that on increasing the temperature from 25 to 55°C the yield of trialkylated product IX increased (Fig. 3); this means that the reaction rate also increases. However, because of resin formation the overall yield of alkylated products falls from 97 to 65% (calculated on compound I reacted). The same sort of relationship is also observed for the concentration of K_2CO_3 (Fig. 4): at 300 mol. % K_2CO_3 and a reaction time of 5 h the yield of trialkylated product IX has already reached 85%.

In addition to allyl chloride, propargyl chloride and benzyl chloride were used as alkylating agents. Mono- and dipropargyl substituted compounds IV and VII could be obtained only when the reaction was carried out at lower temperatures without a catalyst (Table 1). It can be seen from Table 1 that the activity of the alkyl chlorides for the first two stages of the alkylation reaction increases in the order allyl < benzyl < propargyl, but the yield of tribenzyl substituted product XI is lower than that of the triallyl substituted product IX, probably because of steric factors. The use of acetonitrile as solvent instead of chloroform resulted in a small increase in reaction rate (Table 1).

Reaction of compound I with benzyl chloride in a liquid—liquid system results in the tribenzyl derivative XII. Of the different conditions tested, the greatest yield of XII was obtained by using 25% aqueous NaOH as the second liquid phase with TEBA-Cl catalyst in an atmosphere of nitrogen. The yield in this case, however, amounted to 31%. The bromide anion of the starting material I had been exchanged for chloride in the final product. The formation of compound XII was confirmed by a synthesis starting from the salt II which has a Cl^- anion.

It was established by a special experiment that the initial compound I and the products of alkylation V, VIII, and XI in aqueous solution with sodium chloride exchange the Br^- anion for Cl^-. Sodium chloride is formed in the course of the alkylation reaction.

In the IR spectra of all the compounds, there were bands at 1640-1635 cm^{-1} ($C{=}N^+$ of the pyridine ring). In the spectra of the allyl compounds, this band overlapped the absorption band of the isolated ethylene bond. In the spectra of compounds IV, VII, and X there is an absorption band at 2050 cm^{-1} assigned to $C{\equiv}C$.

Lines in the carbon-13 NMR spectra (Table 2) were assigned to the corresponding carbon atoms on the basis of the additive effect of the substituents on the chemical shifts [9] together with such methods as off resonance, GD, and APT. From the results of Table 2 it follows that on the introduction of the first two identical substituents into the methyl group the chemical shifts of $C_{(6)}$ change by the same amount while the introduction of the third substituent has an insignificant effect on this chemical shift. On the basis of the chemical shifts of the compounds studied, we calculated the increment of 4-substituted pyridine for an ethyl group added at the nitrogen. For the C_α atom the increment was 50.51 ppm, for C_β, 9.74 ppm. Elemental analyses were carried out only on the crystalline compounds VIII, XI, and XII; the remaining compounds were very hygroscopic, oily substances.

EXPERIMENTAL

Infrared spectra were run on a Specord 71 IR instrument in KBr disks, PMR spectra on a Hitachi R-22 (90 MHz) in 4:1 CD_3CN–D_2O, carbon-13 NMR spectra on a Tesla BS-567A (25.142 MHz) in D_2O, with HMDS internal standard. The concentration of the reaction products was determined by HPLC on a KhZh-1304 instrument with a 300 × 4 mm column of Silasorb 600 silica gel (15 μm), visualization was by UV light (218 nm), and the eluent 0.01 M NH_4ClO_4 in 93% C_2H_5OH with the addition of 1 ml/liter 0.1 M NaOH. Monitoring of the progress of the reaction and the purity of the compounds was effected by TLC on Silufol UV-254 plates in 10:10:6:1 dichloroethane-acetonitrile-ethanol-water. Compound I was prepared by the method of [10].

The results of the elemental analyses for compounds VIII, XI, and XII for C, H, N corresponded to the calculated values.

1-Ethyl-4-methylpyridinium Chloride (II). A mixture, cooled to 5°C, of 25.9 g (280 mmole) 4-picoline, 26.9 g (420 mmole) ethyl chloride, and 43 ml acetonitrile was placed in a cooled metal autoclave of 100 ml capacity. The autoclave was heated for 5 h at 80°C. The reaction product was purified on a silica gel column (5:1 acetone-water). Yield 41.9 g (95%) of the chloride II.

General Method for the Alkylation of 1-Ethyl-4-methylpyridinium Halides (I-II). A. Into a three-necked flask, fitted with a mechanical stirrer (~1000 rpm), a thermometer, and a re-

flux condenser and immersed in a thermostat at the required temperature, was placed 12.5 mmole halide I or II, 105 mmole alkyl chloride, 15 ml chloroform, and the required quantity of catalyst and potassium carbonate, and the mixture was stirred for 3 or 5 h. The solid deposit was filtered off and washed with chloroform. The filtrate was evaporated in vacuum and the individual compounds isolated by chromatographing the residue on a column of silica gel with 6:6:1 chloroform–acetonitrile–water. The ratio of the reaction products was determined by liquid chromatography after removing resinous substances from the reaction mixture on a short column of silica gel. Salt VIII, $C_{22}H_{24}NBr$, mp 144-145°C. XI, $C_{29}H_{30}NBr$, mp 236-237°C.

B. To a mixture of 2.53 g (12.5 mmole) halide I, 12.1 ml (105 mmole) benzyl chloride, and 0.142 g (0.625 mmole) TEBA-Cl in a current of nitrogen was added 18 ml 25% NaOH. This was stirred (~1000 rpm) for 3 h in a thermostat at 45°C. The aqueous layer was extracted with chloroform, the extract combined with the organic layer and evaporated in vacuum. The residue was recrystallized from water. Yield 1.7 g compound XII, $C_{29}H_{30}NCl$, mp 205-206°C.

LITERATURE CITED

1. P.-L. Compagnon, T. Kimny, and F. Gasquer, Bull. Soc. Chim. Belges, 90, 803 (1981).
2. L. S. Hart, C. R. J. Killen, and K. D. Saunders, J. Chem. Soc., Chem. Commun., No. 1, 24 (1979).
3. O. S. Eikher-Lorka, and G.-K. K. Kupyatis, Khim. Geterotsikl. Soedin., No. 10, 1357 (1986).
4. E. V. Dehmlow and S. S. Dehmlow, Phase Transfer Catalysis, Verlag Chemie, Deerfield Beach, Fla. (1983).
5. D. I. Brunelle and D. A. Singleton, Tetrahedron Lett., No. 32, 3383 (1984).
6. S. S. Yufit, Mechanism of Interphase Catalysis [in Russian], Moscow, Nauka, (1984).
7. A. Brändström, Adv. Phys. Org. Chem., 15, 267 (1977).
8. S. S. Yufit and I. A. Esikova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 47 (1983).
9. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, NMR Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1983).
10. T. Takahashi and K. Sato, Yakugaku Zasshi, 78, 461 (1958); Chem. Abs. 52, 17257 (1958).

REACTION OF ETHYL 9-THIOACRIDONYL-10-ACETATE WITH HYDRAZINE

A. A. Martynovskii, I. V. Mel'nik,
N. A. Klyuev, V. L. Rusinov, and
A. I. Panasenko

UDC 547.835.1.04:543.422

The reaction of ethyl 9-thioacridonyl-10-acetate with hydrazine hydrate gives the corresponding ethyl hydrazonoacridonyl-10-acetate, which readily undergoes a reaction with aldehydes and on heating in DMF reacts with hydrazine hydrate to form 9-ylidenehydrazonoacridonyl-10-acetic acid hydrazide. The latter undergoes a condensation reaction with aldehydes to form ylidenehydrazides of acridonyl-10-acetic acid 9-ylidenehydrazones. The structures of these compounds have been confirmed by UV, IR, PMR, and mass spectrometry.

Among acridine derivatives there are compounds which exhibit high antimicrobial [1], anti-inflammatory [2], and antitumor [3] activity.

With the aim of trying to find compounds with potential antimicrobial activity we have studied the reactivity of ethyl 9-thioacridonyl-10-acetate (I) towards hydrazine hydrate. It transpired that hydrazine attacks the $C_{(9)}$ atom and not the carbethoxy group:

Zaporozh'e Medical Institute, Zaporozh'e 330074.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 525-527, April, 1989. Original article submitted July 23, 1987; revision submitted January 22, 1988.

0009-3122/89/2504- 0438$12.50