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SYNTHESIS OF ALKYL HETERYL ETHERS FROM ACETATES UNDER INTERPHASE CATALYSIS CONDITIONS IN A LIQUID/SOLID SYSTEM

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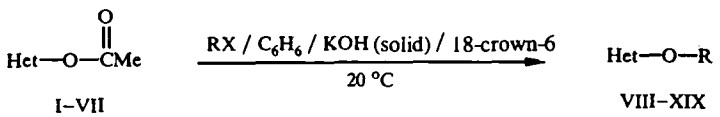
The reaction of acetates of heterocyclic alcohols with alkyl halides in the two-phase catalytic system of solid KOH/C_6H_6/18-crown-6 at room temperature leads selectively to the formation of the corresponding heterocyclic ethers in 32-93% yield.

Heterocyclic ethers are of interest as potential agents for muscular relaxation [1] and have lipid lowering activity [2]. Compounds of this class are usually obtained by the reaction of the corresponding heteryl halide with alkali metal alkoxides [3, 4] or with alkali metals in alcohol [5], and also by the reaction of heterocyclic alcohols with alkyl halides in the presence of NaH in ether [6] or dimethylformamide [7], or KOH in dimethylsulfoxide [8].

The use of interphase catalytic methods [9] simplifies the etherification significantly, however, only a few publications are known which are devoted to the synthesis of heterocyclic ethers [10, 11].



I–VII VIII–XIX

I Het = (2-furyl)CH_2; II Het = (2-thienyl)CH_2; III Het = (2-pyridyl)CH_2; IV Het = (6-methyl-2-pyridyl)CH_2; V Het = 3-pyridyl; VI Het = (3-pyridyl)CH_2; VII Het = (4-pyridyl)CH_2; VIII Het = (2-furyl)CH_2, R = Me; IX Het = (2-furyl)CH_2, R = CH_2Ph; X Het = (2-thienyl)CH_2, R = Me; XI Het = (2-thienyl)CH_2, R = CH_2Ph; XII Het = (2-pyridyl)CH_2, R = CH_2Ph; XIII Het = (6-methyl-2-pyridyl)CH_2, R = Me; XIV Het = (6-methyl-2-pyridyl)CH_2, R = CH_2Ph; XV Het = 3-pyridyl, R = Me; XVI Het = 3-pyridyl, R = CH_2Ph; XVII Het = (3-pyridyl)CH_2, R = CH_2Ph; XVIII Het = (4-pyridyl)CH_2, R = Me; XIX Het = (4-pyridyl)CH_2, R = CH_2Ph.

A new one-step method has been developed by us for the synthesis of alkyl heteryl ethers from the corresponding acetates of heterocyclic alcohols (I)-(VII) in the two-phase catalytic system of solid KOH/C_6H_6/18-crown-6 at room temperature. Under these mild conditions, products (VIII)-(XIX) were isolated by vacuum distillation in 32-93% yield (Table 1).

The formation of ethers (VIII)-(XIX) from acetates (I)-(VII) seemingly occurs through the intermediate heteryl carbinols. However the formation of such intermediates was not confirmed chromato-mass spectroscopically due to the rapid conversion. The ethers (VIII)-(XIX) obtained in this work were identified by PMR and mass spectrometry.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH 90/DS spectrometer in $CDCl_3$, internal standard was TMS. The mass spectra were obtained on a Kratos MS 25 chromato-mass spectrometer, energy of ionizing electrons was 70 eV. GLC analysis

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TABLE 1. Characteristics of Alkyl Heteryl Ethers (VIII)-(XIX)

Acetate	Alkylating agent (RX)	Reaction time, h	Reaction product	bp, °C/10 mm Hg	Yield, %	Literature
I	MeI	14	VIII	65...67	80	[7]
I	$PhCH_2Br$	3	IX	130	84	[12]
II	MeI	4	X	74...76	73	[13]
II	$PhCH_2Br$	4	XI	152...153	93	
III	$PhCH_2Br$	5	XII	172...173	87	[5]
IV	MeI	2	XIII	81...83	88	
IV	$PhCH_2Br$	2	XIV	162...164	82	
V	MeI	8	XV	92...94	32	[14]
V	$PhCH_2Br$	4	XVI	140...141	57	[14]
VI	$PhCH_2Br$	4	XVII	166...168	68	[15]
VII	MeI	4	XVIII	78...79	57	[5]
VII	$PhCH_2Br$	4	XIX	178...179	87	[5]

TABLE 2. PMR Spectra of Heterocyclic O-Ethers (VIII)-(XIX)

Compound	Chemical shifts, ppm
VIII	3.36 (3H, s, OCH_3); 4.40 (2H, s, CH_2); 6.33 (2H, m, 3-H and 4-H); 7.38 (1H, m, 5-H)
IX	4.42 and 4.49 (4H, s and s, CH_2OCH_2); 6.29 (2H, m, 3-H and 4-H); 7.24 (5H, m, Ph); 7.33 (1H, m, 5-H)
X	3.36 (3H, s, OCH_3); 4.58 (2H, s, CH_2); 6.93 (2H, m, 4-H and 5-H); 7.22 (1H, m, 3-H)
XI	4.53 and 4.71 (4H, s and s, CH_2OCH_2); 6.96 (2H, m, 4-H and 5-H); 7.24 (1H, m, 3-H); 7.31 (5H, m, Ph)
XII	4.62 and 4.64 (4H, s and s, CH_2OCH_2); 7.09 (1H, m, 5-H); 7.31 (5H, m, Ph); 7.47 (1H, m, 3-H); 7.62 (1H, m, 4-H); 8.51 (1H, m, 6-H)
XIII	2.44 (3H, s, CH_3 on pyridine ring); 3.44 (3H, s, OCH_3); 4.53 (2H, s, CH_2); 7.0-7.2 (2H, m, 3-H and 5-H); 7.55 (1H, m, 4-H)
XIV	2.53 (3H, s, CH_3 on pyridine ring); 4.55 and 4.64 (4H, s and s, CH_2OCH_2); 7.0-7.6 (8H, m, Ph, 3-H, 4-H, and 5-H)
XV	3.40 (3H, s, CH_3); 7.20 (2H, m, 4-H and 5-H); 8.16 (1H, m, 6-H); 8.42 (1H, m, 2-H)
XVI	5.09 (2H, s, CH_2); 7.17 (2H, m, 4-H and 5-H); 7.36 (5H, m, Ph); 8.20 (1H, m, 6-H); 8.38 (1H, m, 2-H)
XVII	4.53 and 4.56 (4H, s and s, CH_2OCH_2); 7.17 (1H, m, 5-H); 7.31 (5H, m, Ph); 7.62 (1H, m, 4-H); 8.53 (2H, m, 2-H and 6-H)
XVIII	3.42 (3H, s, OCH_3); 4.47 (2H, s, CH_2); 7.24 (2H, m, 3-H and 5-H); 8.53 (2H, m, 2H and 6-H)
XIX	4.53 and 4.60 (4H, s and s, CH_2OCH_2); 7.31 (7H, m, Ph, 3-H, and 5-H); 8.56 (2H, m, 2-H and 6-H)

was carried out on a Chrom 5 chromatograph with a flame-ionization detector and a glass column packed with 5% OV-101 on chromosorb W-HP (80-100 mesh), analysis temperature was 170-250°C. 3-Hydroxypyridine, 18-crown-6, benzyl bromide (all Fluka), methyl iodide, 6-acetoxymethyl-2-methylpyridine (IV), and 2-acetoxymethylfuran (I) (Reakhim) were used without further purification. 2-Thienylmethanol and 2-, 3-, and 4-pyridylmethanol were obtained by reducing the corresponding aldehydes (Fluka) with sodium borohydride in methanol [16].

General Procedure for Obtaining Heterylcarbinol Acetates (II), (III), (V)-(VII). 2-Acetoxymethylthiophen (II). A solution of acetyl chloride (3.60 ml, 50.5 mmole) in benzene (10 ml) was added dropwise to a solution of 2-thienylmethanol (3.6 g, 31.6 mmole) and triethylamine (7.97 ml, 56.8 mmole) in dry benzene (25 ml). The mixture was stirred for 3 h at room temperature, water (30 ml) added, the organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvent was distilled from the filtrate under reduced pressure, and the residue distilled under vacuum. Compound (II) was obtained of bp 90°C/10 mm Hg. PMR spectrum, ppm: 2.11 (3H, s, CH_3); 5.36 (2H, s, CH_2); 7.11 (1H, m, 4-H); 7.24 (1H, m, 5-H); 7.44 (1H, m, 3-H). Yield was 71%.

TABLE 3. Mass Spectra of Heterocyclic O-Ethers (VIII)-(XIX)

Compound	m/z (I_{rel}, %)
VIII	112 (36, M^+), 95 (5), 81 (100), 53 (34), 41 (8)
IX	188 (3, M^+), 97 (17), 91 (75), 81 (100), 65 (13), 53 (22), 39 (14)
X	128 (37, M^+), 111 (7), 97 (100), 85 (17), 69 (7), 53 (12), 45 (27), 39 (13)
XI	204 (2, M^+), 113 (26), 97 (100), 92 (70), 85 (29), 77 (21), 65 (24), 51 (22), 45 (28), 39 (27)
XII	199 (22, M^+), 91 (100), 80 (4), 65 (17), 53 (7), 39 (24)
XIII	137 (<1, M^+), 122 (2), 107 (100), 92 (10), 79 (9), 65 (10), 39 (12)
XIV	313 (14, M^+), 107 (31), 91 (100), 65 (13), 53 (10)
XV	109 (100, M^+), 94 (13), 66 (55), 44 (19), 39 (45), 28 (49)
XVI	185 (15, M^+), 91 (100), 65 (15), 51 (8), 39 (16)
XVII	198 (2, M^+-1), 108 (37), 92 (100), 79 (28), 65 (42), 51 (25), 39 (36)
XVIII	123 (50, M^+), 108 (87), 93 (100), 80 (69), 65 (46), 51 (44), 45 (40), 39 (60)
XIX	198 (<1, M^+-1), 107 (16), 93 (100), 79 (29), 65 (38), 51 (27), 39 (32)

The acetates (III) and (V)-(VII) were obtained similarly.

2-Acetoxymethylpyridine (III) was obtained from 2-pyridylmethanol. Reaction time was 3 h. Bp 81-82°C/10 mm Hg. PMR spectrum, ppm: 217 (3H, s, CH_3); 5.33 (2H, s, CH_2); 7.38 (2H, m, 3-H and 5-H); 7.82 (1H, m, 4-H); 8.76 (1H, m, 6-H). Yield was 74%.

3-Acetoxypyridine (V) was obtained from 3-hydroxypyridine. Reaction time was 3 h. Bp 79-80°C/10 mm Hg. PMR spectrum, ppm: 3.38 (3H, s, CH_3); 7.42 (1H, m, 5-H); 7.60 (1H, m, 4-H); 8.64 (2H, m, 2-H and 6-H). Yield was 70%.

3-Acetoxymethylpyridine (VI) was obtained from 3-pyridylmethanol. Reaction time was 3 h. Bp 84-85°C/10 mm Hg. PMR spectrum, ppm: 2.18 (3H, s, CH_3); 5.24 (2H, s, CH_2); 7.51 (1H, m, 5-H); 7.91 (1H, m, 4-H); 8.80 (2H, m, 2-H and 6-H). Yield was 77%.

4-Acetoxymethylpyridine (VII) was obtained from 4-pyridylmethanol. Reaction time was 3 h. Bp 104-105°C/10 mm Hg. PMR spectrum, ppm: 2.22 (3H, s, CH_3); 5.22 (2H, s, CH_2); 7.40 (2H, m, 3-H and 5-H); 8.78 (2H, m, 2-H and 6-H). Yield was 59%.

General Procedure for Obtaining Heterocyclic Ethers (VIII)-(XIX). 2-Furylmethyl Methyl Ether (VIII). Finely powdered KOH (4.48 g, 80 mmole) was added to a solution of 2-acetoxymethylfuran (2.52 g, 20 mmole), methyl iodide (4.48 ml, 80 mmole), and 18-crown-6 (0.26 g, 1 mmole) in benzene (20 ml). The mixture was stirred at room temperature, following the progress of the reaction by GLC. The mixture was filtered, the excess of MeI and the solvent were distilled from the filtrate under reduced pressure, and the residue was distilled in vacuum. Compound (VIII) (1.57 g, 80%) was obtained having bp 67°C/10 mm Hg.

Ethers (X), (XIII), (XV), and (XVIII) were obtained similarly. In the synthesis of ethers (IX), (XI), (XII), (XIV), (XVI), (XVII), and (XIX), one equivalent of alkylating agent relative to the initial acetate was used. The characteristics of compounds (VIII)-(XIX) are given in Tables 1-3.

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