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ALKYLATION OF 2-ACETYLPYRROLE AND 1-ALKYL-2-ACETYLPYRROLES UNDER SOLID/LIQUID PHASE-TRANSFER CONDITIONS

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Abstract. The alkylation of 2-acetylpyrrole with alkyl iodides in the benzene/solid KOH system in the presence of 18-crown-6 at room temperature gives the corresponding 1-alkyl derivatives in high yields. The phase-transfer catalysed alkylation of 1-alkyl-2-acetylpyrroles without solvent leads to side-chain di-C-alkylated products, i.e. ketones of the (1-alkyl-2-pyrrolyl)$COCHR_2$ type in satisfactory yields.

Phase-transfer catalysed (PTC) side-chain alkylation of acetylheterocycles (2-acetylfuran,[1] 2- and 3-acetylthiophene,[1,2] 2-, 3- and 4-acetylpyridine[3]) as well as acetophenone[3,4] with alkyl iodides is a simple one-step method for the branching of the CH_3 group in the acetyl fragment. Depending on the starting compound, catalyst and reaction conditions, di- or tri-C-alkylated products can be prepared, which are otherwise difficult to obtain.

The alkylation of 2-acetylpyrrole (1) in the CH_2Cl_2/50% NaOH system in the presence of $Bu_4N^+Br^-$ with dimethyl sulphate occurs N-regiospecifically.[5] We have found that the use of solid/liquid PTC, depending on the reaction conditions, permits one to carry out both N-alkylation of 1 and consecutive side-chain C-alkylation of 1-alkyl-2-acetylpyrroles.

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Reactions of ketone 1 with alkyl iodides R-I in the benzene/solid KOH system in the presence of 18-crown-6 (the molar ratio 1:R-I:KOH:18-crown-6 = 1:5:5:0.01) occur N-regiospecifically at room temperature and give corresponding N-alkyl derivatives in high yields (Table 1). This N-alkylation variant is more convenient compared with the procedure described previously,[5] which demands continuous refluxing and a relatively great amount of catalyst (10 mol. %, in our case - 1%); moreover, the isolation of products in the solid/liquid system is simpler in comparision with the liquid/liquid system.

1-Alkyl-2-acetylpyrroles (2a-c) in the benzene/solid KOH system in the presence of 18-crown-6 and with excess of alkyl iodide do not undergo any transformations. However, when the mixture of ketone 2a-c, alkyl iodide R^1-I, solid KOH and 18-crown-6 (the molar ratio 2:R^1-I:KOH:18-crown-6 = 1:8:4:0.1) in the absence of solvent was stirred at temperature 45-70°C, the side-chain C-alkylation was observed. Alkylation with methyl iodide occurs C-regiospecifically and leads to 1-alkyl-2-pyrrolyl isopropyl ketones (4) in 52-73% isolated yields (Tables 1, 2). According to GC and GC/MS data, the reactions proceed through mono-C-alkylated 1-alkyl-2-pyrrolyl ethyl ketone intermediates (3a,c,d) assigned by mass spectra [m/z 137 (M^+), 151 (M^+) and 165 (M^+), respectively].

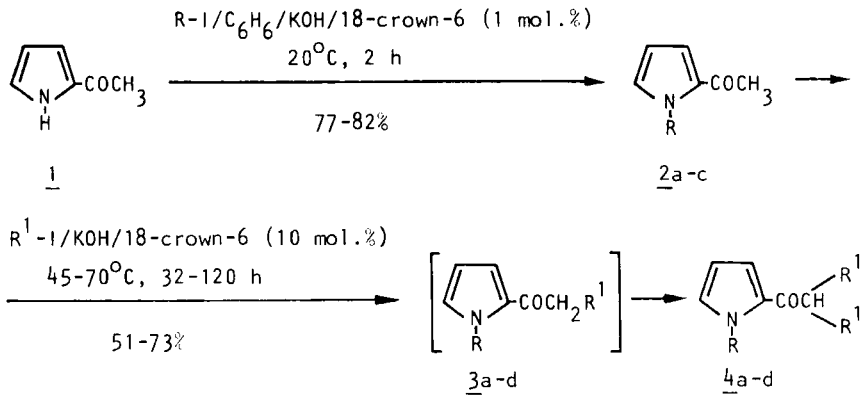

Table 1. PTC Alkylation of 2-acetylpyrrole and 1-alkyl-2-acetylpyrroles

Starting compound	R-I	R^1-I	Temp. (°C)/Time (h)	Product	Yield[a] (%)	b.p. (°C/mm Hg)	Mol. formula[b] or lit. b.p.
1	MeI	-	25/2	2a	82	36-37/1	30-31/0.5[5]
1	EtI	-	25/2	2b	80	82/12	-[c]
1	PrI	-	25/2	2c	77	92-93/12	$C_9H_{13}NO$ (151.2)
2a	-	MeI	45/32	4a	73	62-63/12	$C_9H_{13}NO$ (151.2)
2a	-	EtI	70/38	4b	51	66-67/1	$C_{11}H_{17}NO$(179.2)
2b	-	MeI	45/120	4c	57	88-90/12	$C_{10}H_{15}NO$(165.2)
2c	-	MeI	45/120	4d	52	95-97/12	$C_{11}H_{17}NO$(179.2)

[a] Yield of isolated products.

[b] Satisfactory microanalysis obtained: C ± 0.26, H ± 0.38, N ± 0.31.

[c] Compound 2b was identified by comparision of its ^{1}H NMR[6] and mass spectrum[7] with those described in the literature.

Table 2. Spectral data of synthesized alkyl pyrrolyl ketones 2c, 4a-d[a]

Compound	^{1}H NMR ($CDCl_3$/TMS)[b]; δ (ppm), J (Hz)	MS (70 eV)[c] m/z (%)
2c	0.88 (t,3H,J=7.4,$NCH_2CH_2\underline{CH_3}$), 1.76 (m,2H,$NCH_2\underline{CH_2}CH_3$), 2.42 (s,3H,COMe), 4.27 (t,2H,J=7.4,NCH_2), 6.10 (dd,1H,J_1=2.6,J_2=4.0,H-4), 6.82 (dd,1H, J_1=1.6,J_2=2.6,H-3), 6,93 (dd,1H,J_1=1.6,J_2=4.0,H-5)	151(M^+,43), 136(58), 122(27), 108 (17), 94(100), 80(22)
4a	1.16 (d,6H,J=6.8,$CH(\underline{CH_3})_2$), 3.31(heptet,1H,J=6.8,$\underline{CH}(CH_3)_2$), 3.91 (s,3H, NCH_3), 6.07(dd,1H,J_1=2.6,J_2=4.0,H-4), 6.73(dd,1H,J_1=1.6,J_2=2.6,H-3), 6.92(dd,1H,J_1=1.6,J_2=4.0,H-5)	151(M^+,17), 108(100), 80(8), 53(19), 39(23)
4b	0.86(dist.t,6H,J=7.0,$CH_2\underline{CH_3}$), 1.63(m,4H,$\underline{CH_2}CH_3$), 2.98(m,1H,CHCO), 3.95(s,3H,NCH_3), 6.10(dd,1H,J_1=2.5,J_2=4.0,H-4), 6.81(dd,1H,J_1=1.6, J_2=2.5,H-3), 6.98(dd,1H,J_1=1.6,J_2=4.0,H-5)	179(M^+,7), 151(5), 108(100), 81(10), 53(15), 39(13)
4c	1.18(d,6H,J=6.8,$CH(\underline{CH_3})_2$), 1.35(t,3H,J=7.0,$NCH_2\underline{CH_3}$), 3.33(heptet,1H, J=6.8,$\underline{CH}(CH_3)_2$), 4.36(q,2H,J=7.0,$N\underline{CH_2}CH_3$), 6.13(dd,1H,J_1=2.6,J_2=4.0, H-4), 6.88(dd,1H,J_1=1.5,J_2=2.6,H-3), 6.98(dd,1H,J_1=1.5,J_2=4.0,H-5)	165(M^+.13), 122(100), 94(14), 62(12), 39(7)
4d	0.89(t,3H,J=6.6,$NCH_2CH_2\underline{CH_3}$), 1.16(d,6H,J=7.0,$CH(\underline{CH_3})_2$), 1.69(m,2H, $NCH_2\underline{CH_2}CH_3$), 3.31(heptet,1H,J=7.0,$\underline{CH}(CH_3)_2$), 4.27(t,2H,J=6.6,$NCH_2$), 6.09(dd,1H,$J_1$=2.6,$J_2$=4.0,H-4), 6.82(dd,1H,$J_1$=1.6,$J_2$=2.6,H-3), 6.92 (dd,1H,$J_1$=1.6,$J_2$=4.0,H-5)	179(M^+,3), 136(100), 94(39), 66(13), 41(15)

a ^{1}H NMR[8] and mass spectrum[9] of ketone 2a coincide with those described in the literature; [b]Recorded on a Bruker WH-90 spectrometer and assigned on the basis of data[10]; [c]Recorded on a Kratos MS-25 apparatus.

Ketones 2a-c display lower reactivity than 2-furyl, 2-thienyl, 2-, 3- and 4-pyridyl methyl ketones converting under milder conditions to the corresponding hetaryl isopropyl ketones.[1-3] Compounds 4a,c,d are practically unable to undergo subsequent PTC alkylation to 1-alkyl-2-pyrrolyl tert-butyl ketones: only trace amounts of of trialkylated products were registered (GC/MS) after continuous refluxing of the reaction mixtures containing 4 and excess of MeI and KOH.

Generally, the PTC alkylation of ketone 2a with ethyl iodide (70°C) occurs similarly to that described for MeI: the main product of the reaction is 2-ethyl-1-(1-methyl-1H-pyrrol-2-yl)-1-butanone (4b) isolated in 51% yield results from consecutive side-chain di-C-alkylation through the ketone 3b intermediate (m/z 151, M^+). However, after reaction completion, as judged by the disappearance of the starting compound 2a and 3b intermediate from the solution, the reaction mixture also contained ~18% (GC and GC/MS data) of mono-O- and di-C,O-alkylation products resulting from O-alkylation of ambident 2a and 3b. The main product 4b, owing to lower volatility, can be effectively separated by distillation.

All compounds were identified with the aid of ^{1}H NMR and mass spectra (Table 2).

EXPERIMENTAL

GC analyses were performed on a Chrom-5 instrument equipped with flame-ionization detector using glass columns packed with 5% OV-17/Chromosorb W-HP (80-100 mesh) (Column A, 1.2 m 3 mm) and 10% SE-30 + 2.5% Reoplex-400/Chromosorb W-AW (60-80 mesh) (Column B, 2.4 m 3 mm). 2-Acetylpyrrole and 18-crown-6 were purchased from Fluka.

1-Alkyl-2-acetylpyrroles (2); General procedure.

Finely powdered KOH (22.4 g, 0.4 mol) and R-I (0.32 mol) are added to a solution of 2-acetylpyrrole (1; 4.37 g, 40 mmol) and 18-crown-6 (0.11 g, 0.4 mmol) in benzene (70 ml). The reaction mixture is stirred at room temperature for 2 h (GC control: Column

A, 130°C). After filtration, the benzene and excess of R-I is evaporated at reduced pressure and the residue is distilled in vacuo to give 2a-c (see Tables 1, 2).

Alkyl 1-alkyl-2-pyrrolyl ketones (4a-d); General procedure.

To a solution of 1-alkyl-2-acetylpyrrole (2a-c; 12 mmol) and 18-crown-6 (0.32 g, 1.2 mmol) in MeI or EtI (96 mmol) is added finely powdered KOH (2.69 g, 48 mmol). The reaction mixture is refluxed with stirring for 32-120 h (see Table 1) to achieve complete disappearance of the starting 2a-c and 3a-d intermediate from the solution (GC control: Column B, 150-160°C at alkylation with MeI and Column A, 150°C at alkylation with EtI). After filtration, the excess of MeI or EtI is removed at reduced pressure and the residue is distilled in vacuo to give 4a-d (see Tables 1, 2).

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