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Solid-Liquid Phase Transfer Catalytic Synthesis. VII The Synthesis of α-Substituted-2-pyridylmethyl-amine via the Alkylation of Benzaldehyde Imine

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SYNTHETIC COMMUNICATIONS, 22(2), 265-269 (1992)

SOLID—LIQUID PHASE TRANSFER CATALYTIC SYNTHESIS Ⅶ: THE SYNTHESIS OF α—SUBSTITUTED-2—PYRIDYLMETHYLAMINE VIA THE ALKYLATION OF BENZALDEHYDE IMINE

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ABSTRACT: The anion derived from the benzaldehyde imine 2 reacts with alkyl halide to form alkylated products 3; Hydrolysis of 3 gives α—alkyl—2 pyridylmethylamine in 34—53% overall yield.

α—Substituted—2—pyridylmethylamine derivatives are of important physiological activity[1] and potentially procursors to medicinal agents[2]. Previous synthetic routes to these targets were in three steps: α—cyanopyridine reacted with Grignard reagents to form α—acylpyridine[3], followed by oximation and reduction[4] to afford α—alkyl—2—pyridylmethylamine.

In recent years we have reported a series of solid—liquid phase transfer catalytic alkylation, Michael addition, carbonyl addition and dipolar cycloaddition[5—11]. Here we would like to report an inexpensive, simple synthesis of α—alkyl—2—pyridylmethylamine in 34—53%

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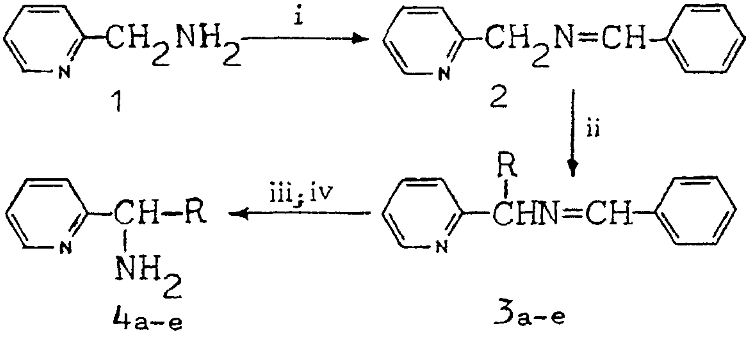
overall yield under solid—liquid phase transfer catalytic conditions. The synthetic route is as follow:



i. PhCHO, molecular sieve, CH_2Cl_2, r. t.; ii. KOH, TBAB, RX, 50℃; iii. 1N HCl—EtOH—H_2O; iv. 2N NaOH.

The condensation of 2—pyridylmethylamine with benzaldehyde in CH_2Cl_2 in the presence of 4Å molecular sieve for 1. 5h gave aldimine, which was directly alkylated without isolation and purification because it was not so stable.

The alkylation of 2 was achieved by treatment with potassium hydroxide(2 equiv.), 4Å molecular sieve and alkyl halide(1. 2 equiv.) in the presence of a catalytic amount(0. 05 to 1 equiv.) of tetrabutylammonium bromide(TBAB) in dichloromethane.

Then hydrolysis of 3 with 1N hydrochloric acid at room temperature, followed by isolation and purification gave α—alkyl—2—pyridylmethylamine. The purified yield were ranging from 34—53%(Table 1, The overall yield is based on 1 via three steps: condensation, alkylation and hydrolysis). The products 4_{a-e} were characterised(Table 2).

The procedure described above provided a simple, inexpensive and new method for synthesis of α—alkyl—2—pyridylmethylamine. This method can also be easily adapted to large—scale synthesis.

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Table 1. Synthesis of α—substituted—2—pyridylmethylamine

product	alkyl halide	alkylation time(h)	hydrolysis time(h)	overall yield(%)[a]
4a	phCH_2Cl	6	1	53
4b	p—$CH_3OC_6H_4CH_2Cl$	6	2	53
4c	p—$ClC_6H_4CH_2Br$	3	2[b]	41
4d	$CH_3CH_2CH_2CH_2Br$	12	1	44
4e	CH_2=$CHCH_2Br$	8	1	34

a. overall yield based on 1.

b. hydrolyzed with 2. 4—dinitrophenylhydrazine.

Experimental

General Considerations: IR spectra were recorded on a Microlab MX 620 infrared spectrometer; ^{1}H—NMR Spectra were recorded on a Varian FT—80A spectrometer using TMS as an internal standard; MS data were obtained using a VG 7070E instrument; CH_2Cl_2 was dried by 3Å molecular sieve; 4Å molecular sieve was dried at 500℃ for 3h.

General Procedure for the Preparation of α—Alkyl—2—Pyridylmethylamine: A mixture of 2—pyridylmethylamine(1. 08g, 10mmol), benzaldehyde(1. 06g, 10mmol), 4Å molecular sieve(5g) and CH_2Cl_2 was stirred at r. t. for 1. 5h. Then potassium hydroxide(1. 12g, 20mmol), tetrabutylammonium bromide(0. 16g, 0, 5mmol) and benzyl chloride(1. 52g, 12mmol) were added in order. The mixture was stirred at 50℃ and the reaction was monitored by TLC(Et_2O/MeOH, 9:1) till completion. Filtered and the solvent was evaporated. The residue was taken up in 10ml EtOH and then stirred with 2N aq HCl(10ml) at r. t. for 1—2h. The solution was poured into water(40ml) and extracted with ether(4× 40ml). The aqueous fraction was neutralized with 2N sodium hydroxide

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Table 2. Analytical data of compounds 4.

Product 4a—e	IR (cm^{-1})	1H—NMR($CDCl_3$)δ,J(Hz)	Ms m/z(%)
4a	3380 3298	8.48(1H,d,J=4.2Hz), 7.60—6.75(3H,m),7.13(5H,s), 4.15(1H,m),2.92(2H,m), 1.90(2H,s,—NH_2).	199(M^++1) 107(100)
4b	3348 3242	8.51(1H,d,J=4.2Hz), 7.64—6.54(3H,m),7.00(2H,d, J=10Hz),4.10(1H,m),3.72(3H,s), 2.90(2H,m),2.01(2H,s,—NH_2).	219(M^++1) 107(100)
4c	3350 3272	8.42(1H,d,J=4.2Hz), 7.90—6.70(7H,m),4.10(1H,t, J=5.0Hz),3.18(2H,s,—NH_2), 2.90(2H,d,J=5.0Hz).	233(M^++1) 235(M^++3) 107(100)
4d	3355 3285	8.48(1H,d,J=4.2Hz), 7.70—6.78(3H,m),3.88(1H,m)1.93 (2H,s,—NH_2),2.25—0.87(6H, m),0.86(3H,t,J=7.0Hz).	165(M^++1) 107(100)
4e	3355 3283 3261	8.47(1H,d,J=4.2Hz), 7.64—6.55(3H,m),5.90—4.60 (3H,m,—CH=CH_2),3.85(1H,m), 2.35(2H,m),2.35(2H,m), 2.08(2H,s,—NH_2).	149(M^++1) 107(100)

and extracted with ether(4 × 40ml). This second ether extract was dried and evaporated to give the crude 4a. The product was purified by flash chromatography(silica gel,eluent:EtOH). yield:1. 05g(53%).

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