Kurzmitteilungen

One-Flask Pyridylethylation of Amines by 2-(2-Pyridyl)-ethanol

Einstufige Pyridylethylierung von Aminen mit 2-(2-Pyridyl)ethanol

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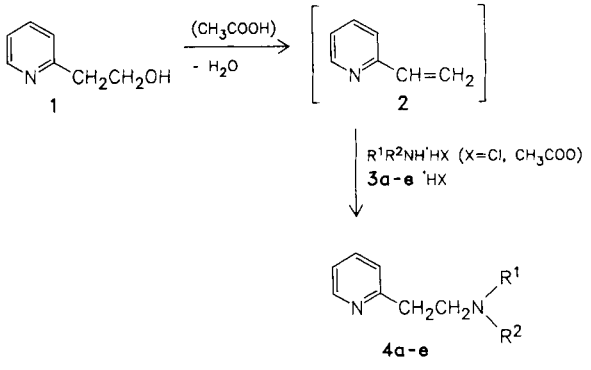
The known methods for pyridylethylation of primary and secondary amines make use of 2-(2-halogenoethyl)-pyridine[1] or 2-vinylpyridine[2-6] as alkylating agents. The reaction of 2-vinylpyridine, which is catalyzed by protic acids, is carried out with the hydrochlorides or acetates of the amines in alkoholic or aqueous media[2-4]. Although the yields are thus good enough, the use of 2-vinylpyridine has some disadvantages due to its easy polymerization and high toxicity. 2-(2-Pyridyl)-ethanol (**1**) has been applied for pyridylethylation of some carboxylic acids with the aim of introducing a protecting group[7]. On the other hand, it is well known that **1** readily eliminates water to give 2-vinylpyridine (**2**) under both acidic and basic catalysis[9-11].

We tried now to find conditions for direct pyridylethylation of primary and secondary amines by the alkohol **1**. Our first stimulating result was registered after a 21 h reflux of aqueous solution of methylamine hydrochloride (**3a** · HCl) with **1** to give 2-(2-methylaminoethyl)-pyridine (**4a**; betahistine, a cerebral vasodilator) in 11% yield. In this case a significant amount of unreacted **1** was recovered and the reaction was accompanied by slow evolution of methylamine gas. Other experiments, carried out in pyridine or dimethylformamide as solvents, failed. However, the reaction succeeded in glacial acetic acid by heating **1** with the corresponding amine salt **3a-e** · HX (scheme) in a molar ratio of 1:3 at 100-120°C for 15-30 h. The substituted 2-(2-aminoethyl)-pyridines **4a-e** were prepared in 17-64% yield (table 1). All products, known to be oily substances, were characterized as picrates[2,3]. A trial for pyridylethylation of aniline remained unsuccessful because of its more rapid N-acetylation.

As expected, the pyridylethylation by means of **1** in acetic acid occurs through the formation of 2-vinylpyridine (**2**) as an intermediate. This was confirmed by a 12 h reflux of **1** in glacial acetic acid to afford 70% yield of **2**.

The use of glacial acetic acid as a reaction medium allows both steps – elimination and addition – to be realized as one-flask procedure.



3, 4	a	b	c	d	e
R^1	CH_3	C_2H_5	C_3H_7	C_2H_5	CH_2CH_2>O
R^2	H	H	H	C_2H_5	CH_2CH_2

Experimental Part

M.p.'s: Büchi 510 (Switzerland), uncorrected. - TLC: silica gel 60 precoated plates (Merck, W.Germany), layer thickness 0.25 mm, eluted by 2-propanol/25% aq. ammonia 9:1 (vol. parts); detection: UV 254 nm and I_2 vapour.

Table 1: N-Substituted 2-(2-aminoethyl)-pyridines **4a-e** and 2-vinylpyridine (**2**)

Product	Amine salt used	React. time, h	Yield,[a] %	B.p.°C/hPa[b]	R_f	...picrate, m.p. °C[b] (ethanol)
4a	methylamine · HCl	15	64	118-120/35[c]	0.42	di.., 191-194
4a	methylamine acetate	27	38	82-84/8[c]	0.42	di.., 191-194
4b	ethylamine acetate	16	41	102-104/12	0.55	di.., 153-154
4c	propylamine · HCl	15	43	117/14	0.64	di.., 158-160
4d	diethylamine · HCl	25	20	112-114/12	0.67	di.., 162-164
4e	morpholine · HCl	20	17	154/11	0.62	mono.., 142-145 di.., 180-182
2	–	12	70	89-90/67	0.74	mono.., 156-156.5

Notes: [a]Yield of distilled TLC homogeneous product. - [b]B.p.'s of bases and m.p.'s of picrates are in good agreement with lit. data[2,3]. - [c]Dihydrochloride (hygroscopic!): m.p. 148-150°C (lit.[8] m.p. 148-149°C).

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General procedure

A mixture of 12.3 g (0.1 mol) of **1** and 0.3 mol of the corresponding amine (as hydrochloride or base) in 125 ml of glacial acetic acid is refluxed for periods as shown in table 1. The solvent is then evaporated *in vacuo* to dryness. (If an amine hydrochloride is employed, the residue is triturated with 50 ml of 2-propanol, the separated crystals of the unreacted salt filtered off and the filtrate concentrated *in vacuo* to dryness). The residue is then treated with 50 ml of water and extracted with chloroform (5 x 20 ml). The aqueous layer is made alkaline with 50 ml of 4N NaOH and extracted with chloroform (8 x 25 ml). The latter extract is dried over Na_2SO_4, the chloroform evaporated and the oily residue distilled fractionally *in vacuo*. For further details cf. table 1.

2-Vinylpyridine

A solution of 12.3 g (0.1 mol) of **1** in 150 ml of glacial acetic acid is refluxed for 12 h. The solvent is removed *in vacuo*, 50 ml of water are added to the residue which is extracted with chloroform (4 x 50 ml). The extract is washed with water (4 x 25 ml), dried over Na_2SO_4 and distilled: Yield 7.3 g (see table 1).

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