NUCLEOPHILIC ADDITION OF DILITHIATED AMIDES TO 3-SUBSTITUTED PYRIDINES

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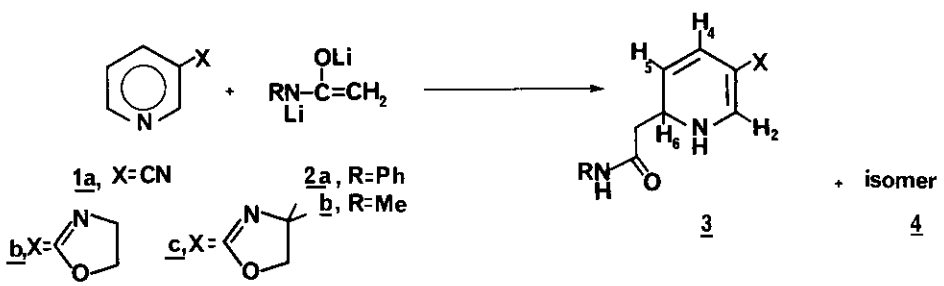
Abstract — Dilithiated amides (2), derived from N-phenyl or N-methyl-acetamide and n-BuLi, react with 3-cyanopyridine (1a), 3-(1,3-oxazol-2-in-2-yl)pyridine (1b) or 3-(4,4-dimethyl 1,3-oxazol-2-in-2yl)pyridine (1c) to give dihydropyridines. The major isomer obtained in each case is the 1,6-dihydropyridine (3a-f).

The chemistry of pyridines and dihydropyridines has attracted much attention for many years and many reasons, not the least of which is the biological importance of the NAD(P)H - NAD(P) redox system. Several methods have been developed for the synthesis of dihydropyridines[1] with recent interest directed towards photochemical routes[2], reinvestigations of the Hantzsch condensation[3] and nucleophilic addition to pyridines[4-7] and pyridinium salts[8]. Following the original studies of Ziegler[9] in 1930 on the addition of organolithiums to pyridine, recent studies [4-7] have examined the influence of electron withdrawing groups, in particular the oxazolinyl moiety, at the 3-position of pyridine in directing nucleophilic substitution to the 2-, 4- or 6-position, as shown schematically below:

With the exception of lithioacetonitrile and 2-lithio-1,3-dithiane[6], these studies have for the most part used simple alkyl- or aryllithiums, devoid of any further functionality, and generally show a preference for the formation of the 1,4-dihydropyridine except with

sterically demanding nucleophiles, such as ^{t}BuLi, which shows varying amounts of 1,6- and, in some instances, 1,2-addition; choice of solvent and temperature can also effect the mode of addition. We have recently had occasion to examine the reactivity of stabilized carbanions, in particular dianions derived from N-phenyl and N-methylacetamide (2)[10], with 3-substituted pyridines; our preliminary results are the subject of this Communication. The monoanion obtained from lithiation of N-methyl-N-phenylacetamide failed to react under the conditions described, giving instead N-methylaniline as the major product; the dianions gave no observed reaction product with pyridine itself. Addition products obtained from reaction of dilithiated acetamides (2a,b) with pyridines (1a-c) are listed in Table 1; a general

Table 1



pyridine[a]	amide	reaction conditions (°C, h)	ratio 3:4 (^{1}H nmr)	product[b,c]	mp (°C)	yield (%)
1a	2a	0, 0.5	>10:1	3a	155	49
		RT, 1.5				
1a	2b	RT, 1.0	2:1	3b	134-5	40
1b	2a	RT, 1.0	3:1	3c	144-5	30
1b	2b	RT, 1.0	>10:1	3d	160-5	30
1c	2a	0, 0.5	>10:1	3e	177-8	53
		RT, 1.0				
1c	2b	RT, 1	>10:1	3f	154-6	43

[a] Oxazolinylpyridines were prepared according to literature procedures: references 4 and 11.

[b] Products were isolated by trituration with or recrystallization from ethyl acetate, ether or methylene chloride.

[c] All products gave satisfactory analytical data; combustion analyses were performed either on the dihydropyridine or the corresponding pyridine obtained by oxidation.

experimental procedure is outlined below. In all cases the crude product, recovered in greater than 90% yield, was predominantly dihydropyridine(s) by ^{1}H nmr with small amounts of unreacted starting materials and/or oxidation products of the dihydropyridines being present. The isolated yields reflect to a certain extent the instability of the dihydropyridines during purification; once isolated as crystalline solids they may be stored for prolonged periods with minimal decomposition. The structure of the major adduct was assigned on the basis of the low field position (4.67-4.83δ) of the proton at the site of addition which suggested a 1,2- or 1,6-isomer rather than a 1,4-dihydropyridine due to the deshielding effects of an adjacent nitrogen atom[13]. Distinction between the 1,6- and 1,2-isomers was made on the basis of (a) proton-proton spin decoupling experiments which showed coupling (ca. 5Hz) between H_5 and the proton at the site of nucleophilic addition (H_6), or (b) chemical oxidation ($KMnO_4$, acetone) to a pyridine which showed no evidence of a H_6 proton by nmr[12]. Chemical shifts (δ, $CDCl_3$) for the dihydropyridine ring hydrogens are given in Table 2. The minor isomer accompanying 3b has been tentatively assigned the

Table 2

Compound	H_2	H_4	H_5	H_6
3a	6.90	5.94	5.06	4.83
3b	6.90	5.89	4.99	4.74
3c	7.17	6.45	5.17	4.80
3d	7.11	6.43	5.08	4.70
3e	7.10	6.46	5.15	4.78
3f	7.04	6.40	5.06	4.67

1,2-dihydropyridine structure on the basis of low field signals (6.67 and 6.52δ) attributed to H_4 and H_6 of this isomer; the minor isomer accompanying 3c, however, has been assigned the 1,4-dihydropyridine structure on the basis of low field (7.00 and 6.04δ) signals for H_2 and H_6 and a high field signal (4.05δ) for the hydrogen at the position of nucleophilic addition (H_4)[13].

In view of the utility of pyridine derivatives in the synthesis of natural products, we are examining further the reactions of stabilized carbanions with substituted pyridines.

General procedure: The amide (8 mmoles) was dissolved under a nitrogen atmosphere in dry tetrahydrofuran (25 mL) then cooled in an ice bath. ^{n}BuLi (18 mmol, 2.5 M in hexanes) was added dropwise by syringe and then the reaction mixture was stirred for 1 h (0° C to room temperature). A solution of the substituted pyridine (7 mmol) in dry THF (15 mL) was added dropwise to the reaction mixture (at 0° C or room temperature) with a yellow-orange

colour forming immediately followed by an orange precipitate. After 1-2 h the reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL) and the product was isolated by extraction with CH_2Cl_2 (2x50 mL). The organic solution was dried (Na_2SO_4), filtered and evaporated to dryness to give the crude product as a viscous oil or an amorphous solid, which was purified by trituration or recrystallization.

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13. See references 4-6 for representative chemical shifts of 1,2-, 1,4- and 1,6-dihydropyridines.

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