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# THE DUAL BEHAVIOUR OF N,N-DIALKYLPYRIDYLCARBOXYLIC AMIDES IN THE REACTION WITH LITHIUM DIISOPROPYLAMIDE[1]

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The dual behaviour of N,N-diisopropylpyridylcarboxylic amides in the reaction with $iPr_2NLi$ depending upon temperature and structure of a given amide, is described.

The direct metallation of pyridine has, until recently, been precluded from the arsenal of substitution methods mainly because most strong bases act as nucleophiles and add to the heteroaromatic nucleus[2]. In the last few years a number of elegant regioselective techniques have been reported which allow direct generation of metallated species[3,4,5,6,7].

As part of a wide-ranging investigation of pyridylcarboxylic amides 1, 2 and 3 in the reaction with strong bases, we studied the reaction of the N,N-dialkylamides with $iPr_2NLi$. N,N-Diisopropylamides 1a, 2a and 3a reacted with $iPr_2NLi$, readily formed at -78° in $Et_2O$ organolithiums 1b, 2b and 3b, which gave expected products with carbonyl-electrophiles[4].

However, different behaviour of studied amides in the reaction with $iPr_2NLi$, depending upon temperature and structure of a given amide, was observed, as is explained in the present paper.

Amides 1a, 2a and 3a reacted with one equivalent of $iPr_2NLi$ ($Et_2O$/-78°/1hr.-/MeOD)[8] and demonstrated a very low extent of transformation into lithiated reactive intermediates; 1b (98% - 5%D), 2b (98% - 17%D) and 3b (99% - 24%D), and a notable increase of such intermediates with an excess of base (two equivalents of $iPr_2NLi$) respectively 1b (97% - 13%D), 2b (97% - 60%D) and 3b (98% - 48%D). A longer reaction time (5hrs.) did not improve the lithiation reaction; in both cases of molar ratio 1:1 and 1:2; 1b (95% - 5%D) and (82% - 16%D)[9], 2b (95% - 18%D) and (97% - 64%D) and 3b (95% - 23%D) and (98% - 51%D) respectively.

On the other hand, reaction of amides 1a, 2a and 3a with iPr$_2$NLi and PhCONMe$_2$ which acted as an electrophile trap (molar ratio 1:1:1, amide/Et$_2$O/-78°-iPr$_2$NLi/0.25hr./PhCONMe$_2$/0.75hr./MeOH) gave comparatively higher yields of the corresponding ketoamides[10] 1c (52%), 2c (47%) and 3c (36%), than those which would have been expected from incorporation of deuterium (MeOD quenching). The remainder of the materials being recovered as starting amides, and some amount (~5%) of product derived from the reaction of PhCONMe$_2$ with iPr$_2$NLi, which was formed via dipole-stabilized carbanion[11,12].

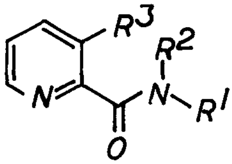
The obtained results may suggest that the lithiated reactive intermediates 1b, 2b and 3b are formed in reversible reactions.

Together with an increase of temperature (amide/Et$_2$O/-78°/iPr$_2$NLi/1hr.-/→0°/10min./MeOD) different courses of reactions of studied amides with iPr$_2$NLi were observed.

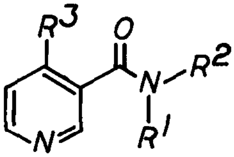
Thus, the picolinamide 1a gave ketoamide 4 (93%)[10]. In the case of isonicotinamide 3a lithiated amide 3b (47% - 26%D) and ketoamide 5 (15%)[10] were obtained. The observed ketoamides 4 and 5 were formed as products of self reactions of 1b with 1a and 3b with 3a respectively. Nicotinamide 2a beasides the lithiated amide 2b (12% - 53%D) produced isomeric bipyridines. The usual workup afforded 2,4′-bipyridine 6 (6%)[10] and 4,4′-bipyridine 7 (59%)[10], which were identified after aromatization (KMnO$_4$/acetone/20°/1hr.) of unstable hydro-compounds.

Although the results obtained cannot be unequivocally explained, it is interesting to consider the following: i. Ashby[13] has shown that iPr$_2$NLi is an efficient one-electron donor to molecules which have favorable reduction potential. ii. Recently, Newkome[14] has described that in the reaction of iPr$_2$NLi with pyridine leading to 2,4′- and 4,4′-bipyridines, pyridine radical-anion has been involved at 0° in HMPTA. Complex ESR signal corresponded to both $C_5H_5N^{\dot{-}}$ and iPr$_2$N$^{\bullet}$ was obtained. On the other hand, in THF at -60° the strong signal characteristic of iPr$_2$N$^{\bullet}$ was observed, and no signal for $C_5H_5N^{\dot{-}}$. iii. Other workers[15] have shown that the pyridine radical-anion dimerizes instantly in ethereal solvents. iv. It has been reported[16], that the calculated order of stability for pyridyl anions is 3>4>2.

A probable explanation of the observed dual behaviour of amides 1a, 2a and 3a in the reaction with iPr$_2$NLi may be presented as follows: a. At low temperature in a reversible reaction stable lithiated reactive intermediates are formed. It seems to be, that together with an increase of temperature, depending upon the stability order of pyridyl anions, picolinamide and isonicotinamide are retained in their carbanionic forms of the type A, but nicotinamide is transferred into corresponding radical-anion B, as the consequence of either disproportionation of lithiated species or the reaction of iPr$_2$NLi with amide.
b. On the other hand, a number of examples of lithiohydrocarbons undergoing nucleophilic addition to the pyridine nucleus of nicotinic acid derivatives are known (see below). If so, nucleophilic addition of 2b to 2a, with the consequential formation of bipyridines 6 and 7, cannot be excluded[11].


1

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a, | iPr | iPr | H |
| b, | iPr | iPr | Li |
| c, | iPr | iPr | COPh |
| d, | H | Ph | H |
| e, | Li | Ph | Li |
| f, | H | Ph | Me |
| g, | Me | Ph | Me |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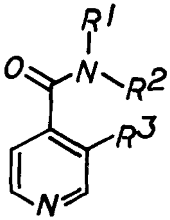
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a, | iPr | iPr | H |
| b, | iPr | iPr | Li |
| c, | iPr | iPr | COPh |
| d, | H | Ph | H |
| e, | H | Ph | Me |
| f, | H | Ph | nBu |
| g, | H | Ph | Ph |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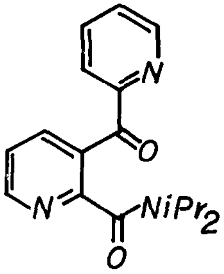
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a, | iPr | iPr | H |
| b, | iPr | iPr | Li |
| c, | iPr | iPr | COPh |
| d, | H | Ph | H |
| e, | Li | Ph | Li |
| f, | H | Ph | Me |
| g, | Me | Ph | Me |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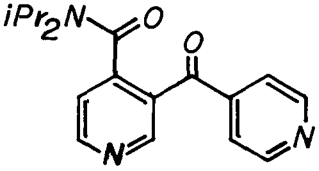
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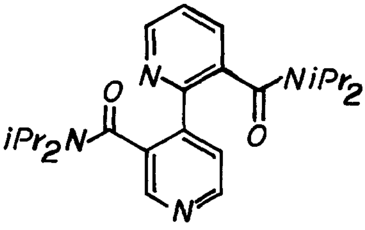
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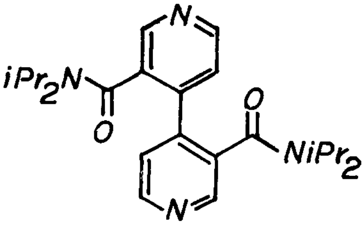
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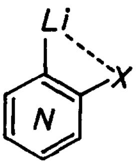
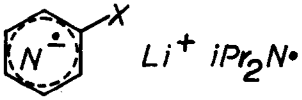

A


B

A and B - X=$CONiPr_2$

In consideration of unsuccessful attempts at alkylation by alkyl halides (MeI) of N,N-diisopropylamides 1a, 2a and 3a after reaction with $iPr_2NLi$[17], and that, the preparation of alkylated derivatives of pyridylcarboxylic acids and their repetitive lithiation sequence, provide the basis for rational regioselective synthesis a wide variety of 2,3- and 3,4-disubstituted pyridines, we extended our study for N-substituted pyridylcarboxylic amides 1d, 2d and 3d.

Amides 1d and 3d upon reaction with two equivalents of nBuLi (THF/-78°/0.5hr.-/MeOD) gave bis(N- and 3-)lithiated amides 1e (97% - 98%D) and 3e (96% - 99%D). The lithiated amides 1e and 3e reacted with one equivalent of MeI (THF/-78°/0.5hr.-/ 20°/0.5hr./$H_2O$) afforded corresponding 3-methylated amides[10] 1f (31%) and 3f (75%). Reaction with an excess of MeI (three equivalents) produced mono- and dimethylated derivatives. Thus, the picolinamide gave 1f (62%) and 1g (18%). In the case of isonicotinamide only 3g (87%) was formed.

In contrast with the amides 1d and 3d, the nicotinamide 2d reacted with MeLi, nBuLi and PhLi gave 1,4-adducts to the pyridine ring. This reaction has previously been observed in the cases of 2-(3-pyridyl)-4,4-dimethyloxazoline[18], N,N-diethylnicotinamide[18] and N,N-diisopropylnicotinamide[17]. Thus, the 4-substituted nicotinamides 2e, 2f and 2g were obtained in the sequence of reactions; addition to the pyridine nucleus of MeLi, nBuLi and PhLi (THF/-78°/1hr./ 20°/1hr.) and aromatization ($KMnO_4$/acetone/20°/1hr.) of 1,4-dihydro adducts in total yields of 59%, 91% and 74% respectively.

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8. Percentages of lithiated reactive intermediates (MeOD quenching) were calculated by $^1H$ NMR spectra of isolated amides. Values are within ±5% of reported data. In parentheses are given total recovery of amides - extent of deuteration
9. In the reaction of amide 1a (molar ratio 1:2/5hrs.) 12% of ketoamide 4 was yielded.
10. Satisfactory analytical and spectral data were obtained for all compounds. Yields were given for analytically pure products.
11. As will be discussed in the full paper.
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