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REACTIONS OF THE N,N-DIALKYLPYRIDYLCARBOXYLIC AMIDES WITH LITHIUM AMIDES. REGIOSELECTIVE LITHIATION OF N,N-DIISOPROPYLPYRIDYLCARBOXYLIC AMIDES, A USEFUL METHOD FOR SYNTHESIS OF 2,3- AND 3,4-DISUBSTITUTED PYRIDINES[1]

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The behaviour of the N,N-dimethyl-, N,N-diethyl- and N,N-diisopropylpyridylcarboxylic amides in the reactions with Et_2NLi and iPr_2NLi, and a convenient way of synthesis of 2,3- and 3,4-disubstituted pyridines, by the direct lithiation of N,N-diisopropylamides leading subsequently to the ortho new C-C bonds formation, are described.

The direct metallation reaction of pyridines has not been extensively studied, except in a few special cases[2]. Recently Meyers observed ortho lithiation of 4-(4,4-dimethyloxazolinyl-2-yl)pyridine by MeLi[3] and 3-(4,4-dimethyloxazolinyl-2-yl)pyridine by 2,2,6,6-tetramethylpiperidine lithium amide[4], which formed 3-lithio and 4-lithio derivatives, respectively. With other organolithium reagents 1,2- or 1,4-additions to the pyridine nucleus were observed[3,4,5]. Ferles[6] reported that ethyl esters of nicotinic and isonicotinic acids were lithiated by iPr_2NLi at 4- and 2-positions, respectively.

In this communication we wish to describe our preliminary study of the behaviour of N,N-dialkylpyridylcarboxylic amides[7] 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b and 3c in the reactions with Et_2NLi and iPr_2NLi.

N,N-Dimethylamides 1a, 2a and 3a upon reaction with Et_2NLi at room temperature in Et_2O (1 hr.) were transfered into N,N-diethylamides[8] 1b, 2b and 3b with yields 75%, 35% and 70%, respectively. No other products were detected. The observed transamidation process probably occurs via intermediate A. Adducts similar to A have been described in reactions of N,N-dialkylamides with lithiohydrocarbons[2,10]. However, N,N-dimethylnicotinamide 2a in addition to the product of the exchange reaction 2a→2b, afforded the regioselectively ortho lithiated amide 2d (14%). Quenching with D_2O or reaction with Ph_2CO converted 2d into amide 2e or lactone[8,9] 5 (11%). Longer reaction time (5 hr.) increased the yield of transformation 2a→2b to 60%, but did not improve the yield of the lithiation reaction, only formation of ketone[8,9] 8a (6%) was observed. N,N-Diethylamide 2b lithiated by Et_2NLi at room temperature in Et_2O (1 hr.) gave 2f, which was converted to 2g (11%) or 5 (9%).

In reaction 2a with Et_2NLi, formation of 2b, 2d or 8a, the fact that 2f was not observed, and the low yield for 2a→2d and 2b→2f suggest that reaction with lithium amide led to unreactive intermediate A. This is in agreement with the observation that increasing molar ratio of reactants from 1:1 to 1:2 did not affect the lithiation process.

N,N-Diethylamides 1b, 2b and 3b reacted with more sterically hindered iPr_2NLi at -45° in Et_2O (1 hr.) gave in good yields the regioselectively lithiated, highly reactive, derivatives 1d, 2f and 3d, which were instantly transferred into the ketones[8,9] 7, 8b and 9.

Good yields in the lithiation reaction and absence of N,N-diisopropylamides 1c, 2c and 3c, which would have been formed in the exchange process, indicate that in this case the intermediate type A was not formed probably for steric reasons.

In contrast with the N,N-diethylamides 1b, 2b and 3b, the N,N-diisopropylamides 1c, 2c and 3c display synthetic utility since the carbonyl groups are sufficiently protected from the above described self reaction.

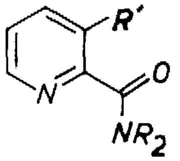
N,N-Diisopropylamides 1c, 2c and 3c lithiated by iPr_2NLi in Et_2O at -78° (2 hr.) afforded the lithiated amides 1e, 2h and 3e, which were formed regioselectively and in good yields. The lithiated amides 1e, 2h and 3e reacted with Ph_2CO gave corresponding carbinols[8,9] 1g, 2j and 3g, which after acidic hydrolysis at room temperature were converted into the lactones[8,9] 4, 5 and 6.

These reactive lithio derivatives could be needed in the realization of synthetic scheme for the preparation of 2,3- and 3,4-disubstituted pyridines bearing functional groups with the C-C bonds easily transformable into other derivatives.

Thus, the lithio-amides 1e, 2h and 3e in the reaction with DMF gave the formylderivatives[9] 1h, 2k and 3h. Obtained aldehydes were reacted, without isolation, with malonic acid in the Doebner modification of the Knoevenagel reaction to give easily isolable unsaturated acids[8,9] 1i, 2l and 3i.

The recent observation by Beak[11], that the N,N-diethylamide function is a very good activating group for ortho-metallation of aromatics, is in agreement with results described herein.

We wish to emphasize that, the N,N-dialkylamide function has a special utility in the pyridine series, since, for the compounds examined by us,



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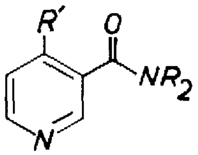

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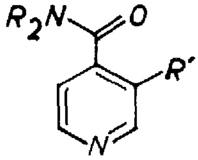
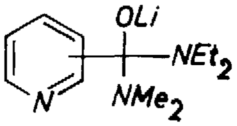


3

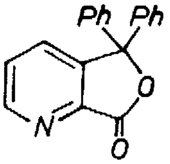
	R	R^1
a,	Me	H
b,	Et	H
c,	iPr	H
d,	Et	Li
e,	iPr	Li
f,	iPr	D (55%)
g,	iPr	CPh_2OH (81%)
h,	iPr	CHO (35%)
i,	iPr	CH=CH-COOH (29%)

	R	R^1
a,	Me	H
b,	Et	H
c,	iPr	H
d,	Me	Li
e,	Me	D
f,	Et	Li
g,	Et	D
h,	iPr	Li
i,	iPr	D (46%)
j,	iPr	CPh_2OH (68%)
k,	iPr	CHO (39%)
l,	iPr	CH=CH-COOH (33%)

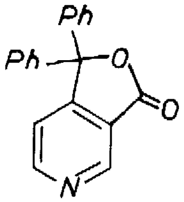
	R	R^1
a,	Me	H
b,	Et	H
c,	iPr	H
d,	Et	Li
e,	iPr	Li
f,	iPr	D (43%)
g,	iPr	CPh_2OH (55%)
h,	iPr	CHO (37%)
i,	iPr	CH=CH-COOH (31%)



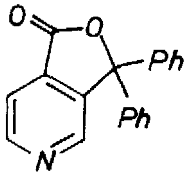
A



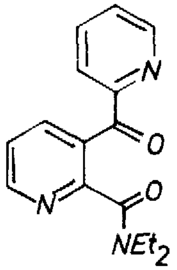
4 (77%)[8,9]



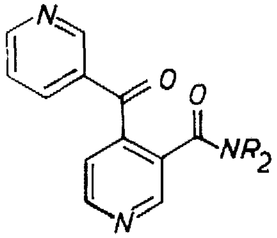
5 (63%)[8,9]



6 (51%)[8,9]



7 (94%)[8,9]



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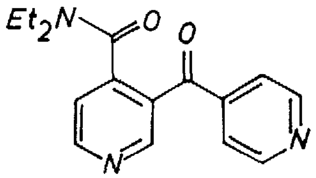

9 (72%)[8,9]

a, R = Me
b, R = Et (68%)[8,9]

no addition to the azomethine bond was observed, even in the reaction with lithiohydrocarbons[12].

The scope and limitation of the methode will be given in a full paper.

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References and Notes

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7. N,N-Dialkylamides 1a, 1b, 1c, 2a, 2c, 3a, 3b and 3c were prepared in the following sequence of reactions: Acids were chlorinated in the reaction with $SOCl_2$ in benzene and after removal of excess chlorinating agent, were reacted, without isolation, with the appropriate amine to afford corresponding amides. The yields of obtained products for pure materials were higher than 65%.
8. Satisfactory analytical and spectral data were obtained for all compounds.
9. Yields of obtained compounds were calculated in proportion to the starting amides; in the cases of aldehydes 1h, 2k and 3h from NMR data, for other products from isolated pure materials.
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12. N,N-Dimethylpyridylcarboxylic amides reacted with lithiohydrocarbons such as MeLi, nBuLi, iPrLi and PhLi gave with good yields respective ketones, and no addition to the pyridine nucleus was observed; J.Epsztajn, Z.Berski, J.Z.Brzeziński and A.Jóźwiak, in preparation.

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