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Lithiation Directed by Amino Alkoxides. Application to the Synthesis of New Disubstituted Dihydrodipyridopyrazines

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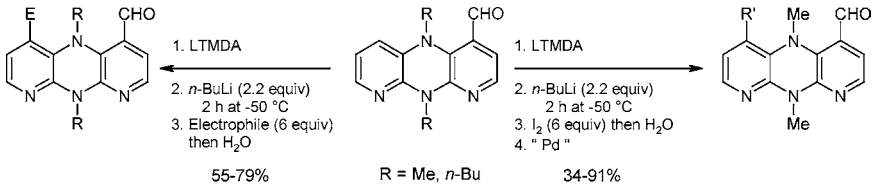
ABSTRACT



The synthesis of new 4,6-disubstituted dihydrodipyridopyrazines starting from corresponding carboxaldehydes via lithiation directed by α-amino alkoxides is described. The *N,N,N′*-trimethylethylenediamine was used as amine component for in situ formation of the α-amino alkoxides. After optimization, this reaction allowed easy access to new interesting starting materials for further applications by palladium-catalyzed reactions.

The directed metalation of heterocycles has been receiving considerable attention[1] and has found wide use in the regioselective introduction of a functional substituent into aromatic and heterocyclic compounds. The ability of certain substituents on heterocyclic systems to direct metalation at a position *ortho* to the substituent (*ortho*-directed metalation) has been observed to be typical in a number of metalation reactions involving organolithium reagents. This phenomenon is of synthetic interest because such a procedure enables one to produce *ortho*-disubstituted products. Metalations of thiophenes, furans, pyrroles, and indoles[2] have been studied extensively, and the synthetic value of this methodology has been determined.[3]

Various *ortho*-directing groups have been utilized to direct lithiation of a variety of heterocycles. The regioselectivity of lithiation can be dependent on the directing group, the heterocycle, and metalation conditions. It appeared that α-amino alkoxide[4] could be formed in situ via the addition of aromatic aldehydes to certain lithium dialkylamides. These heterocyclic α-amino alkoxide could be *ortho*-lithiated, alkylated, and hydrolyzed on workup to provide *ortho*-substituted heterocyclic aldehydes via one-pot reaction. The regioselective control inherent in α-amino alkoxide directed lithiations appeared to have considerable potential for the substitution of various heterocyclic carboxaldehydes.

A few years ago we reported the synthesis of a new family of heterocycles, namely, the dihydrodipyridopyrazines.[5] These heterocycles showed interesting chemical properties,[6] and a few pharmacological investigations attributed potential antitumor activity to these compounds.[7]

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(1) (a) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (b) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957. (c) Snieckus, V. *Pure Appl. Chem.* **1990**, *10*, 2047.
(2) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.
(3) (a) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343. (b) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 5335. (c) Comins, D. L. *Synlett* **1992**, 615.
(4) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979.
(5) Blanchard, S.; Rodriguez, I.; Kuehm-Caubère, C.; Renard, P.; Pfeiffer, B.; Guillaumet, G.; Caubère, P. *Tetrahedron* **2002**, *58*, 3513.

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The convenience and synthetic potential of α-amino alkoxide directed lithiation have prompted us to investigate it in heterocyclic systems such as dihydrodipyridopyrazines. The results of our studies are presented here.

We began our study with 5,10-dimethyl-5,10-dihydrodipyridopyrazine-4-carbaldehyde **1a**,[6] and we attempted to direct metalation on the 3-position (Figure 1).

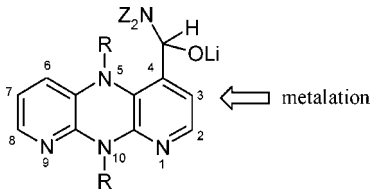
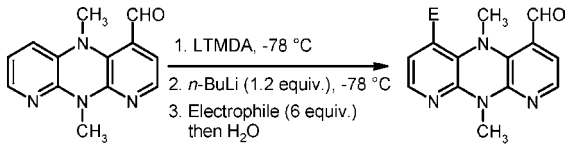


Figure 1.

We performed the metalation reaction using the methodology reported by Comins and co-workers.[2,4] So, the α-amino alkoxide formed in situ at −78 °C, using 1.2 equiv of *N*,*N*,*N*′-trimethylethylenediamine, 1.1 equiv of *n*-butyllithium, and 1 equiv of **1a**, was lithiated with 1.2 equiv of *n*-butyllithium and alkylated using methyl iodide as electrophile. Surprisingly, lithiation occurred on the 6-position; the yield of reaction was rather low (39%), and 13% of starting material was recovered (Table 1, entry 1).

Table 1. Metalation of **1a**



1a **2, 3**

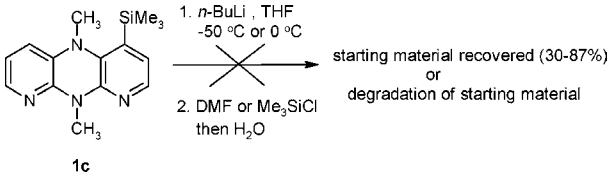
entry	electrophile	E	product	yield (%)
1	CH_3I	CH_3	**2**	39[a]
2	Me_3SiCl	Me_3Si	**3**	54[b]

[a] 13% of starting material was recovered. [b] 24% of starting material was recovered.

Treatment of **1a** with trimethylsilyl chloride as electrophile, under the same conditions, gave access to the 6-substituted product **3** in 54% yield, and starting material was recovered in 24% (Table 1, entry 2).

To elucidate the possibility of metalatation at the 6-position when the 4-position is occupied, **1c** was used as a substrate. Using different conditions (temperature, reaction time, electrophile DMF or Me_3SiCl) no reaction occurred, and only starting material was recovered or degradations were observed (Scheme 1).

Scheme 1



1c

In addition, to verify that the 4,6-disubstituted dihydrodipyridopyrazines **2** and **3** could be further metalated at the 3 position**,** we proceeded to their lithiation using the same conditions. Unfortunately, in the case of **2** the methyl group of the 6-position was attacked, and for compound **3** only degradations of starting material was observed.

From these observations, we concluded that the amino alkoxide intermediate behaves in the same manner as a protecting group and as a directing group, and this unexpected reaction offers a direct method for the synthesis of 4,6-disubstituted dihydrodipyridopyrazines.

Therefore because of the incomplete conversion of starting material, we decided to proceed to the optimization of the reaction.

Replacement of *N*,*N*,*N*′-trimethylethylenediamine by *N*-methylpiperazine as amine component did not lead to the expected product; only unchanged starting material was recovered. Evaluation of the metalation conditions (temperature, time reaction, excess of base) were also carried out. The best conditions found for regioselective 6-substitution and a complete conversion utilized *N*,*N*,*N*′-trimethylethylenediamine as the amine component, 2.2 equiv of *n*-butyllithium as metalation agent at −50 °C, and 6 equiv of electrophile.

Under these conditions, after addition of methyl iodide and workup, 6-methyl-5,10-dimethyl-5,10-dihydrodipyridopyrazine-4-carbaldehyde **2** was isolated in 78% yield. We next turned our attention to the extension of this reaction to others electrophile agents, which allowed us easy access to interesting disubstituted dihydrodipyridopyrazines. The results obtained are gathered in Table 2.

The yields were rather good (55−79%), and only in the case of reaction with aldehydes (benzaldehyde, butyraldehyde, entries 8 and 9) or enolizable ketone (cyclohexanone, entry 10) as electrophile was degradation of the reaction mixture observed.

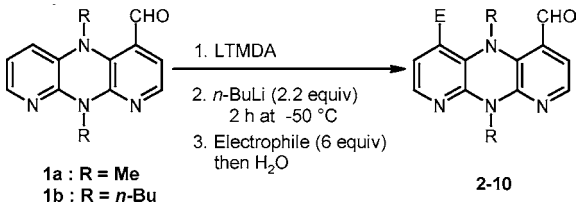
Replacement of the *N*-methyl group by *N*-butyl (entries 11 and 12) did not affect the regioselectivity of the lithiation and afforded similar compounds.

Compounds obtained in entries 3 and 4 are good starting materials for further functionalization such as palladium-catalyzed coupling reactions.

(6) (a) Blanchard, S.; Rodriguez, I.; Caubère, P.; Guillaumet, G. *Synlett* **2002**, 1356, (b) Grig-Alexa, I. C.; Finaru, A. L.; Ivan, L.; Caubère, P.; Guillaumet, G. *Tetrahedron Lett.* **2004**, *45*, 2343.

(7) (a) Caubère, P.; Guillaumet, G.; Rodriguez, I.; Vinter-Pasquier, K.; Kuehm-Caubère, C.; Blanchard, S.; Atassi, G.; Pierre, A.; Pfeiffer, B.; Renard, P. P. Eur. Pat. Appl. EP 96986, 1999; *Chem. Abstr.* **2000**, *132*, 22978. (b) Blanchard, S.; Rodriguez, I.; Tardy, C.; Baldeyrou, B.; Bailly, C.; Colson, P.; Houssier, C.; Léonce, S.; Kraus-Berthier, L.; Pfeiffer, B.; Renard, P.; Pierre, A.; Caubère, P.; Guillaumet, G. *J. Med. Chem.* **2004**, *47*, 978.

Table 2. Lithiation of Dihydrodipyridopyrazine-4-carbaldehydes **1a** and **1b**



entry	substrate	electrophile	E	product	yield (%)
1	**1a**	CH_3I	CH_3	**2**	78
2	**1a**	Me_3SiCl	Me_3Si	**3**	76
3	**1a**	Bu_3SnCl	Bu_3Sn	**4**	79
4	**1a**	I_2	I	**5**	55[a]
5	**1a**	DMF	CHO	**6**	73
6	**1a**	MeSSMe	MeS	**7**	72
7	**1a**	$C_6H_5COC_6H_5$	$Ph_2CH(OH)$	**8**	62
8	**1a**	C_6H_5CHO			
9	**1a**	$CH_3CH_2CH_2CHO$			
10	**1a**	cyclohexanone			
11	**1b**	DMF	CHO	**9**	63
12	**1b**	Me_3SiCl	Me_3Si	**10**	71

[a] Addition of electrophile at −78 °C.

The 6-iododihydrodipyridopyrazine-4-carbaldehyde **5** was used as starting material in palladium-catalyzed coupling reactions.[8] Under typical Suzuki, Sonogashira, and Stille conditions, expected coupling products are obtained in good yield (71−91%). The results of coupling reactions are presented in Table 3.

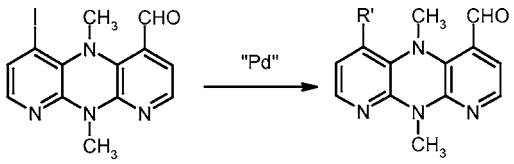
Heck cross-coupling reaction of **5** with methyl acrylate gave access to the corresponding methylpropenoate (stereoisomer *trans*, $J = 16.1$ Hz) in only 34% yield, while 53% of starting material was recovered (Table 3, entry 3).

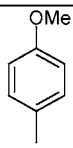
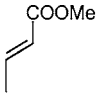
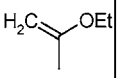
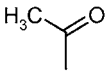
We report here an efficient synthesis of novel 4,6-substituted dihydrodipyridopyrazines via lithiation directed by α-amino alkoxides. This work significantly extends the scope of *ortho*-metalation.

The method is convenient and allows to obtain, in a one-pot reaction, interesting disubstituted products that are used for further transformations such as palladium-catalyzed coupling reactions.

Results described herein show that the dihydrodipyridopyrazines have interesting chemical properties and a good potential in the synthesis of biologically and pharmaceutically derivatives. Additional studies in this area are underway, and the results will be reported in due course.

Table 3. Palladium-Mediated Cross-Coupling Reactions of 6-Iodo-dihydrodipyridopyrazine-4-carbaldehyde **5**



Entry	Coupling conditions	R'	Product	Yield %
1	MeO-Ph-B(OH)$_2$ $Pd(PPh_3)_4$ aq. Na_2CO_3 DME, reflux, 1 h		**11**	91
2	Ph-C≡CH $Pd(PPh_3)_2Cl_2$, CuI Et_3N / DMF, TA, 1 h	Ph−C≡C−	**12**	89
3	H_2C=$CHCO_2CH_3$ $Pd(OAc)_2$, PPh_3, K_2CO_3, CuI DMF, 8 h		**13**	34[a]
4	H_2C=$C(OEt)SnBu_3$ $Pd(PPh_3)_4$ toluene, reflux, 3 h		**14**	79
5	H_2C=$C(OEt)SnBu_3$ $Pd(PPh_3)_4$ toluene, reflux, 3 h then hydrolysis HCl 10%		**15**	71

[a] 53% of starting material was recovered.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Organic Reactions*; Wiley: New York 1997; Vol. 50. (b) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (d) Arnautu, A.; Collot, V.; Ros, J. C.; Alayrac, C.; Witulski, B.; Rault, S. *Tetrahedron Lett.* **2002**, *43*, 2695. Collot, V.; Varlet, D.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 4363.