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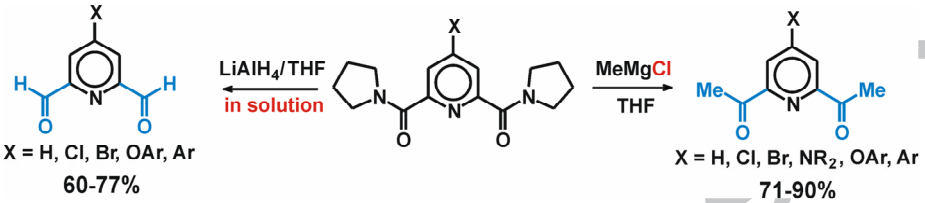

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A convenient approach for the synthesis of 2,6-diformyl- and 2,6-diacetylpyridines

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ABSTRACT

2,6-Diformyl- and 2,6-diacetylpyridines are readily accessed in good yields (60-90%) via the single-pot reaction of 2,6-pyridine dicarboxamides with $LiAlH_4$ or MeMgCl in THF at 0-20 °C . The high efficiency of the method illustrates the significance of solubility in the reduction and alkylation of difunctionalized substrates

2,6-Diformylpyridine, 2,6-diacetylpyridine and their 4-halo derivatives have often served as convenient starting materials for the synthesis of physiologically active compounds,[1] crown-ether-like macrocycles,[2] supramolecular coordination complexes,[3] metalloenzyme analogs,[4] and chemosensors.[5] Arguably the most important application of these compounds is in the preparation of bis(arylimino)pyridine ligands, $[2,6\text{-}(ArN{=}CR)_2C_5H_3N]$, which impart late transition metals (Fe, Co, Ni, V) with high catalytic activities for ethylene polymerization.[6] Bis(imino)pyridyl complexes also catalyse 1,3-butadiene polymerization (Fe, Co),[7] oxidation (Fe, Cu),[8] hydrogenation (Fe, Co, Ru, Rh),[9] hydrosilylation (Fe),[9h,i] hydrocarboxylation (Fe)[9j] and [2+2] cycloaddition (Fe).[10]

To date, pyridine-2,6-dicarbaldehydes have been synthesized by either the oxidation of 2,6-lutidine[11] or 2,6-bis(hydroxymethyl)pyridines,[3a,12] or by the reduction of 2,6-pyridinedicarboxylic acid chlorides[13] and esters[14] using relatively expensive composite reagents. In a recent publication, substituted 2,6-diformylpyridine (**1**) was prepared by the reduction of 2,6-pyridinedicarboxylic acid diamide with diisobutylaluminium hydride;[15] a high (75%) yield was achieved using a four-fold excess of the reducing agent and by temperature control (-70 ºC, 4 h). $LiAlH_4$, which can reduce aromatic acid amides to aldehydes,[16] has not previously been used to prepare compound **1**.[17]

The most convenient method for the synthesis of 2,6-diacetylpyridine (**2**)[18a] and its 4-substituted analogs[18b] entails the Claisen condensation of ethyl acetoacetate and dialkyl pyridine-2,6-dicarboxylates; alternative approaches to **2** use 2,6-pyridinedicarboxylic acid dichloride[19] or dinitrile.[12] 2,6-Diacetyl-4-chloropyridine was synthesized from the corresponding 4-chloro-substituted acid dichloride.[20] The reaction of amides with MeMgX, which has found use in the synthesis of methyl aryl ketones,[21] has not previously been used to prepare **2**.

Moreover, bis(arylimino)pyridines can be modified at position 4 by direct substitution using alkylmanganese(II) complexes,[22] but this method has limited synthetic scope.

We hypothesized that the reactions of 2,6-pyridinedicarboxamides with $LiAlH_4$ or Grignard reagents would be suitable for the preparation of pyridines **1**, **2** and their 4-substituted analogs. We chose the previously described bis-diethylamide **3** to identify and optimize the reaction conditions.[23]

Aldehyde **1** was prepared in 70-75% yield (Scheme 1) by reduction of **3** in THF[24] at 0-5 ºC for 30 min using $LiAlH_4$ pre-dissolved[25] in THF (**3**/$LiAlH_4$ ~ 1:0.7).[26] The use of a solution of $LiAlH_4$ was critically important: the addition of **3** to a suspension of $LiAlH_4$ in THF produced a reaction mixture with no more than 30% of **1**, even after 16 hours of stirring at 20 ºC followed by hydrolysis. In our opinion, the poor solubility of the product

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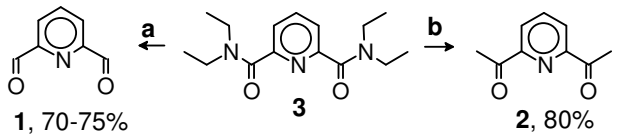
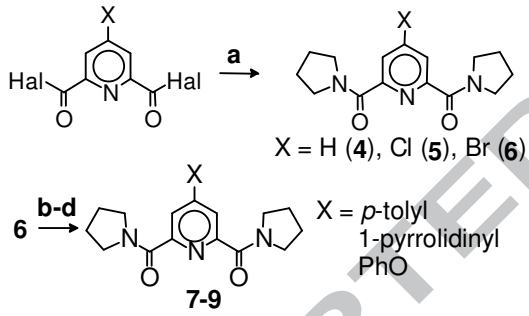
formed from **3** and $LiAlH_4$ on the surface of the latter hampers the transfer of $LiAlH_4$ to the solution and slows the entire reaction.

We established that commercially available MeMgCl in THF[27] reacts with **3** at 20 ºC over 1 hour to give **2** in ~80% yield (Scheme 1).[28] This reaction can also be performed with MeMgI provided that four equivalents of the Grignard reagent are used. The necessity of a twofold excess of MeMgI in the preparation of **2** can be attributed to the shift of the Schlenk equilibrium towards Me_2Mg observed for alkylmagnesium iodides in THF, which is driven by the formation of poorly soluble $MgI_2(THF)_x$.[29,30]



Scheme 1. Reaction of 2,6-pyridine dicarboxamide **3** with $LiAlH_4$ and MeMgCl in THF. **a**: (i) $LiAlH_4$ (dissolved in THF), 0 °C, 30 min; (ii) H^+/H_2O. **b**: (i) 2 eq. MeMgCl (THF), 0-20 °C, 1 h; (ii) H^+/H_2O.

Next, the synthesis of 4-substituted 2,6-diformyl- and 2,6-diacetylpyridines was investigated. The high solubility of amide **3** hampers its isolation and purification. The newly prepared pyrrolidine derivative **4** (Scheme 2) proved less soluble and more reactive towards $LiAlH_4$ and MeMgCl; therefore, we used pyrrolidinyl amides **5-9**, synthesized from previously described acid halides to ascertain the applicability of this method to the synthesis of 4-substituted 2,6-diformyl- and 2,6-diacetylpyridines[15b,31] (Scheme 2).

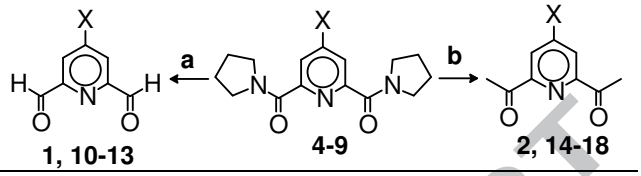


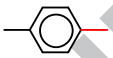
Scheme 2. Preparation of pyridine-2,6-dicarboxamides. **a**: pyrrolidine, CH_2Cl_2, 2 h (**4**, 86%; **5**, 71%; **6**, 78%). **b**: (*p*-tolyl)$B(OH)_2$, $Pd(OAc)_2$, PPh_3, DME/H_2O (**7**, 68%). **c**: pyrrolidine, DMSO, 150 °C, 3 h (**8**, 85%). **d**: PhONa, DMF, 150 °C, 3 h (**9**, 73%).

The reactions of diamides **4**-**7** and **9** with $LiAlH_4$ gave the corresponding 2,6-diformylpyridines (**1**, **10**-**13**) in satisfactory yields (Table 1). Amide **8** reacted with $LiAlH_4$ to give a complex mixture of the products of pyridine ring reduction.[32] The ease of reduction of **9** in the ring can be attributed to the donor properties of the pyrrolidine moiety, which increases the nucleophilicity of the pyridine nitrogen atom. The reactions of **4**-**9** with MeMgCl proceeded smoothly in all cases, resulting in 2,6-diacetylpyridines **2** and **14**-**18** in yields of at least 71% (Table 1).

In conclusion, we have developed a simple and convenient method for the preparation of 4-functionalized pyridine-2,6-dicarbaldehydes by the direct reduction of the corresponding pyrrolidyl amides with $LiAlH_4$ pre-dissolved in THF. The use of MeMgCl in the reactions with diamides provided 4-substituted 2,6-diacetylpyridines, which indicates that the enhancement of the reactivity of the customary reactants, achieved here by their dissolution, may be crucial in transforming an evident but unobserved reaction into an efficient synthetic procedure.

Table 1. Preparation of pyridine-2,6-dicarbaldehydes and 2,6-diacetylpyridines



X–	Diformylpyridine, Yield, %	Diacetylpyridine, Yield, %
H–	**1**, 76%	**2**, 88%
Cl–	**10**, 77%	**14**, 90%
Br–	**11**, 70%	**15**, 81%
	**12**, 60%	**16**, 72%
	–	**17**, 72%
	**13**, 66%	**18**, 71%

Reagents and conditions: **a**: (i) $LiAlH_4$ (dissolved in THF), 0 °C, 30 min; (ii) H^+/H_2O. **b**: (i) 2 eq. MeMgCl (THF), 0-20 °C, 1 h; (ii) H^+/H_2O.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http:// These data include experimental procedures and NMR spectra of new compounds.

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24. The choice of THF (*vs*. ether) was based on the greater stability of $LiAlH_4$ and the solubility of the substrates.
25. The solubility of $LiAlH_4$ in THF is good (~3 mol/L); however, the dissolution process is slow.
26. *Typical procedure:* $LiAlH_4$ (7 mmol) was stirred for 16 h in THF (30 ml) at 20 °C. After cooling to 0 °C, 2,6-pyridine dicarboxamide (10 mmol) in THF (20 ml) was added. After ~1 h of stirring (monitored by TLC) the mixture was hydrolyzed with 2 M aq. HCl and extracted with CH_2Cl_2 (5×10 ml). After evaporation of the solvent, the residue was purified by crystallization or flash chromatography (silica gel 40, $CHCl_3$).
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32. Based on analysis of the NMR spectra of the reaction mixture.