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First Direct Lithiation of 2-Pyridylpiperazine on Solid Phase

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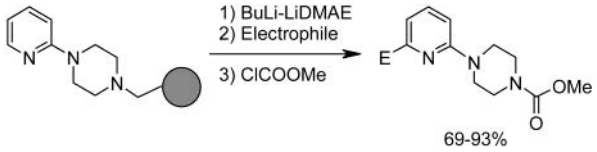
ABSTRACT



The first direct lithiation of a pyridine derivative on solid phase has been realized. Metalation of polymer-bound 2-pyridylpiperazine with the BuLi–LiDMAE reagent followed by electrophilic quenching and subsequent cleavage provided a range of new useful C-6 substituted 2-piperazinylpyridines.

Solid phase organic synthesis (SPOS) is a powerful tool for acceleration of drug discovery, allowing the preparation of highly diverse compound libraries.[1] In this context, the solid phase lithiation of heteroaromatic compounds is of high interest to introduce diversity and generate substance libraries. Unfortunately, possibly due to incompatibility of lithiating agents with the commonly used cross-linked polystyrene, only a few reports are found concerning such a promising reaction. For example, the direct α lithiation of furan and thiophene was nicely transposed onto polystyrene by Ganesan.[2] From our knowledge, a single example of ortholithiation of N-containing heterocycle has been reported by Bergtrup with polymer-bound oxyimidazoles.[3]

Our laboratory is working actively in the development of new reagents for lithiation of pyridine derivatives. Particularly, we have reported that the BuLi−$Me_2(CH_2)_2OLi$ (BuLi−LiDMAE) superbase promoted an exclusive α lithiation of heterosubstituted pyridines.[4] The selectivity was explained by formation of aggregates between BuLi−LiDMAE and substrates via lithium chelation by the pyridine nitrogen atom. We thought that such lithium aggregates could efficiently promote lithiation of polymer-bound pyridine nuclei without affecting benzylic positions of polystyrene. Thus, BuLi−LiDMAE could be a powerful tool for preparation of diversely substituted heterocyclic derivatives on solid phase.

Among the suitable substrates, 2-pyridylpiperazine was of interest for two main reasons. First, we have reported that our reagent efficiently metalated dialkylamino pyridines in the solution phase.[4a,i] Second, the 2-pyridylpiperazine moiety is found in numerous biologically active molecules,[5] making the preparation of libraries of such a compound family of broad interest for pharmaceutical chemistry.

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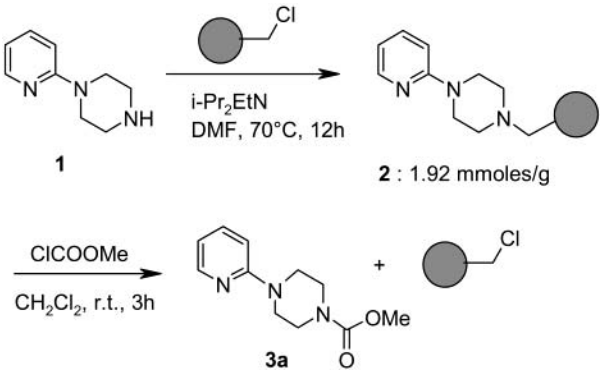
Herein, we report the first solid phase direct lithiation of a pyridine derivative with the BuLi−LiDMAE reagent and the preparation of useful 6-substituted-2-pyridylpiperazines after subsequent electrophilic quenching and cleavage.

The polymer-bound pyridylpiperazine **2** was prepared by reacting 2-pyridylpiperazine **1** with a 2% cross-linked chloromethyl polystyrene (ACROS, 200−400 mesh, 2.7 mmol Cl/g) in DMF in the presence of the Huenig's base (Scheme 1). Cleavage by methyl chloroformate[6] revealed a

Scheme 1

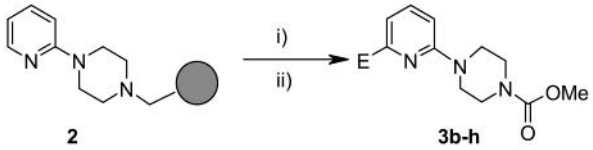


loading of 1.92 mmol/g corresponding to 70% of the initial chloromethyl content. This result was in full agreement with elemental analysis and the cleavage yield was considered as quantitative. Reaction with methyl chloroformate was particularly convenient since pyridylpiperazine was liberated as a carbamide with regeneration of starting chloromethyl polystyrene.

As no data were available for solid phase lithiation of pyridine, we first examined the reaction of **2** with some common lithiating agents such as LTMP and BuLi−TMEDA which are known to promote ortholithiation of substituted pyridines. With these bases, no metalation occurred in THF at −78 or 0 °C even with an excess of reagent (4−8 equiv) and under prolonged reaction times (3−6 h). We then turned to the metalation with BuLi−LiDMAE.

According to our previous work, the metalation had to be performed in a nonchelating solvent, with the best results obtained in hexane, unfortunately prohibiting the use of good swelling THF.[7] Obviously, hexane was also discarded for its bad swelling ability[7] and we chose toluene as polymer and base compatible[8] solvent. After preliminary experiments, we found that the metalation had to be performed with 8 equiv of basic reagent for 6 h at room temperature (or 12 h at 0 °C). The metalation procedure was also modified from those classically used in solution.[4] Here BuLi was added to a suspension of resin and dimethylaminoethanol in toluene. After condensation of a set of electrophiles, the substituted pyridylpiperazines were released by subsequent cleavage with methyl chloroformate (Table 1).[9]

Table 1. Solid Phase Functionalization of Pyridylpiperazine[a]



electrophile	E	product	yield, %[b]
MeOD	D	**3b**	85[c]
MeSSMe	SMe	**3c**	74
Me_3SiCl	Me_3Si	**3d**	74
C_2Cl_6	Cl	**3e**	73
CBr_4	Br	**3f**	93
I_2	I	**3g**	69
t-BuCHO	*t*-BuCH(OH)	**3h**	72
$PhCONMe_2$	PhCO	**3i**	86

[a] Reactions performed on 0.5 g of **2**. [b] Isolated yields calculated from **2** after column chromatography. [c] Determined by ^1H NMR.

The reaction was clean, and reaction mixtures were only contaminated by compound **3a** (5−10%), corresponding to unreacted pyridine. As shown, compounds **3b**−**i** were obtained in good to very good overall yields. Of particular interest was the efficient introduction of halogen, giving potential access to higher diversity by further functionalization of **3e**−**g**.

Finally, we verified that the released chloromethyl resin was reusable. **2** was thus prepared from the recovered resin and the metalation-condensation repeated. After cleavage, compound **3c** was isolated in 74% yield. Such yield was found to be constant even after five runs.

In conclusion, we have demonstrated that the BuLi−LiDMAE reagent performed the first direct solid -phase lithiation of a pyridine derivative. Moreover, this methodology overcomes the drawback of the slight solubility of pyridylpiperazines in usual organic solvents leading to poor metalation yields in solution. This new synthetic method

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(8) Under the optimized conditions (8 equiv of BuLi−LiDMAE, rt, 6 h), toluene was metalated in a trace amount (1−2%).

(9) **General procedure for C-6 functionalization of 2:** Resin **2** (0.5 g, 0.96 mmol) was first preswelled for 15 min in anhydrous toluene (10 mL). 2-Dimethylaminoethanol (0.8 mL, 8 mmol) was then added under a nitrogen stream. The suspension was cooled at −5 °C, and BuLi (10 mL of a 1.6 M solution in hexanes; 16 mmol) was added dropwise. After 15 min, the mixture was allowed to warm at room temperature and stirred for 6 h. The red suspension was then cooled at −5 °C, and a solution of appropriate electrophile (9 mmol) in THF (10 mL) was added dropwise. At the end of addition, stirring was continued for 1 h at 0 °C and overnight at room temperature. The reaction was then hydrolyzed at 0 °C with water (3 mL). The resin was then filtered and washed with water, THF, and ether. After drying, the resin was suspended in dichloromethane (10 mL and treated with methyl chlroformate (0.4 mL, 5.2 mmol) for 3 h at room temperature. The resin was filtered and washed with dichloromethane (20 mL). After evaporation of solvents under reduced pressure, the crude product was purified by column chromatography.

should be of interest to the pharmaceutical chemistry community for the preparation of new 6-substituted-2-piperazinylpyridines.

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Supporting Information Available: Text giving detailed experimental procedures and characterization data for compounds **3a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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