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Parallel synthesis of 4-amino-2,6-dialkylamino-pyridines

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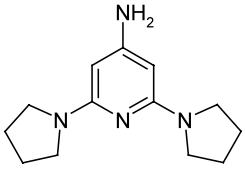
Abstract—In this letter a fast and useful parallel synthesis approach to 4-amino-2,6-dialkylamino-pyridines is described starting from commercially available 2,6-difluoro-3,5-dichloro-pyridine. Both symmetrical and unsymmetrical derivatives have been synthesized respectively in two or three steps in good yields. The method described is mild, adaptable to combinatorial purposes and applicable to a variety of amines.

During the course of our work we became interested in the synthesis of 4-aminopyridines bearing alkylamino substituents onto positions 2 and 6, at least one of the two being a pyrrolidinyl ring. One of the most representative examples of these compounds is 4-amino-2,6-dipyrrolidinyl-pyridine **1** (Fig. 1).

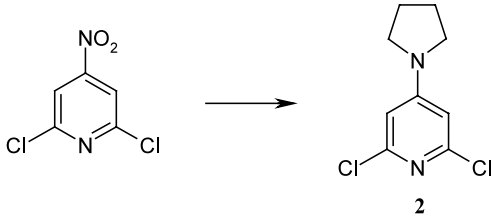


1

Figure 1.

A first attempt to synthesize compound **1** is reported in Scheme 1 where 4-nitro-2,6-dichloro-pyridine, prepared according to known procedure,[1] has been subjected to nucleophilic substitution in the presence of neat pyrrolidine at reflux temperature. Under these reaction conditions we have only observed formation of product **2** confirming the good leaving group nature of the nitro group.

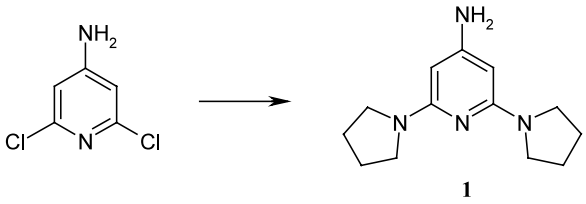
On the other hand we could synthesize compound **1** only under harsh conditions and in low yield by heating at 200°C the commercially available 4-amino-2,6-dichloro-pyridine in a sealed tube[2,3] (Scheme 2). This behavior was in agreement with that of 2,6-dichloro-pyridine in nucleophilic aromatic substitution reactions.



2

Scheme 1. *Reagents and conditions*: neat pyrrolidine, reflux, 2 h, 70%.

These unsatisfactory results, due to the poor leaving group properties of the chlorine atoms of the starting material, prompted us to study a milder and more efficient method suitable for the parallel synthesis of both symmetrical and unsymmetrical 4-amino-2,6-dialkylamino-pyridines. This effort allowed us to develop a convenient two-step process comprising first the nucleophilic substitution of the fluorine atoms of the commercially available pyridine **3**, and second the hydrogenolytic removal of the chlorine atoms of the



1

Scheme 2. *Reagents and conditions*: neat pyrrolidine, sealed tube, 200°C, 4 h, 20%.

Keywords: parallel synthesis; 4-amino-2,6-dialkylamino-pyridines; aromatic substitution.

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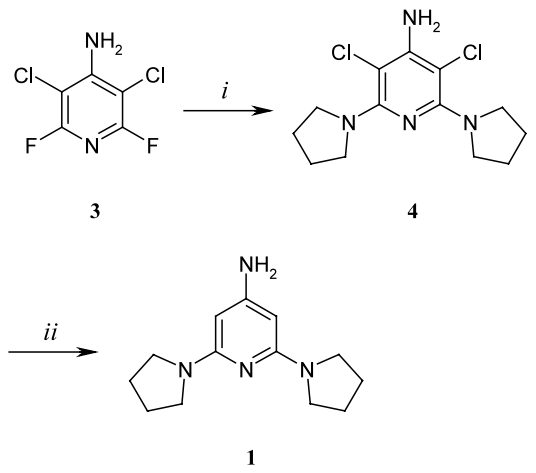
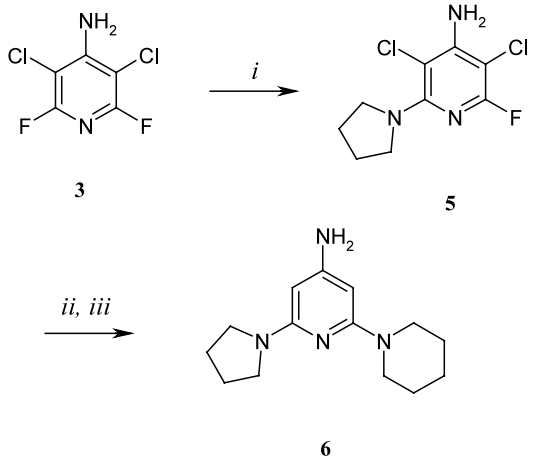
corresponding intermediate. By applying this method compound **1** was obtained in 80% overall yield through the double fluorine replacement with pyrrolidine at 90°C and subsequent hydrogenolysis of the dichloro intermediate **4** (Scheme 3).[4]



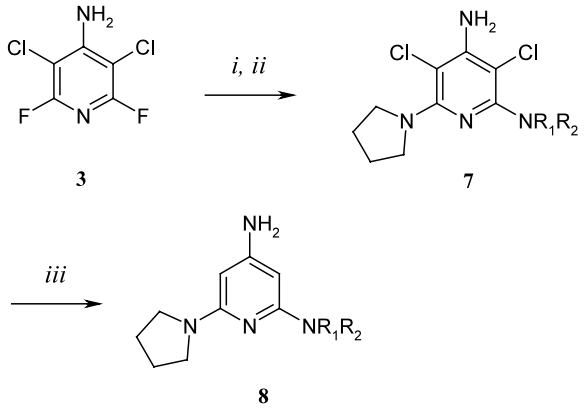
Scheme 3. *Reagents and conditions*: (i) neat pyrrolidine, reflux, 1 h, 80%; (ii) H_2, Pd–C 10%, 30 psi, EtOH, 0.5 h, 80%.

When nucleophilic replacement reaction with pyrrolidine was carried out in toluene at room temperature, the only isolated product was the monofluoro derivative **5**, an intermediate useful for the synthesis of unsymmetrical products. In fact when compound **5** was reacted with piperidine and then hydrogenolyzed, the unsymmetrically substituted compound **6** was achieved in good yield (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) pyrrolidine 1 equiv., toluene, rt, 18 h, 80%; (ii) piperidine, AcOEt, reflux, 8 h, 55%; (iii) H_2, Pd–C 10%, 30 psi, EtOH, 0.5 h, 80%.

The possibility to sequentially introduce different amines onto position 2 and 6 proved to be crucial for the preparation by parallel synthesis of a small library of unsymmetrical compounds. In the final optimized conditions, *N*-methyl-pyrrolidinone at 90°C turned out to be the solvent of choice for the nucleophilic aromatic substitution. Furthermore as compound **3** was more reactive than the mono-substituted intermediate **5**, we considered the use of selected amines of unknown reactivity in the first step followed by an excess of the highly reactive pyrrolidine in the second step (Scheme 5).



Scheme 5. *General reagents and conditions*: (i) 1.3 equiv. R_1R_2NH, NMP, 90°C, DIPEA, 18 h; (ii) 2.3 equiv. pyrrolidine, 90°C, NMP, DIPEA, 18 h; (iii) $HCOONH_4$, Pd–C 10%, MeOH, 2 h.

The dichloro intermediates **7** were purified over silica gel by flash chromatography.[5] At last parallel hydrogenation of the intermediates **7** with NH_4HCOO/Pd in MeOH gave the final products of general formula **8** (Scheme 5).[6,7] Unexpectedly we observed hydrogenolysis of final compounds just for entry 4 and 15. The investigated amines (R_1R_2NH) and the overall yields of products **8** are reported in Table 1. Derivatives **8** were analyzed by HPLC-MS and ^1H NMR. Anilines and carboline gave complex product mixtures; sterically hindered as well as poorly reactive amines, like 1-adamantyl amine and glycine derivatives, did not react at all as inferred by the presence of only symmetrically substituted compound **1** at the end of the synthetic sequence. In conclusion our new method represents an easy way for the preparation in solution phase of 4-amino-2,4-dialkylamino-pyridines both symmetrical and unsymmetrical and it is applicable to combinatorial synthetic purposes.

References

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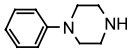
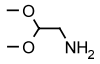
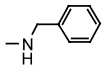
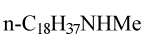
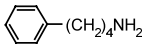
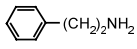
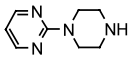
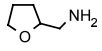
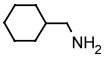
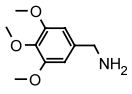
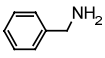
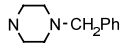
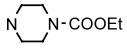
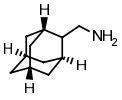
2. (a) Jameson, D. L.; Goldsby, K. A. *J. Org. Chem.* **1990**, *55*, 4992–4994; (b) McCall, J. M.; Jacobsen, E. J.; Van Doorick, F. J. European Patent 0263213 B1, 1986.
3. Jünemann, W.; Opgenorth, H. J.; Scheuermann, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 388–389.
4. Chambers, R. D.; Hall, C. W.; Hutchinson, J.; Millar, R. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1705–1713.
5. *General procedure for preparation of intermediate* **7***:* To a solution of 2,6-difluoro-3,5-dichloro-4-amino-pyridine in

Table 1. Investigated amines and overall yields

Entry	*Amine R_1R_2NH*	*Yield product **8** (%)* [a]
1		64
2		61
3		55
4		83[b]
5		70
6		70
7		65
8		63
9		68
10		70
11		76
12		50
13		62
14		69
15		45[c]
16		64
17		37
18		60

[a] *All the products were characterized by NMR and MS spectroscopy; unoptimized yields.* [b, c] *The final products were isolated as debenzylated compounds.*

N-methyl-pyrrolidinone (0.2 M) were added 3 equiv. of the proper amine, 3 equiv. of *N*,*N*-diisopropylethylamine and the mixture was heated to 90°C for 18 h. Then 6 equiv. of pyrrolidine were added and the mixture was heated for 18 h. The solvent was evaporated to dryness and the residue was purified by flash column chromatography (eluant: *n*-hexane/ethyl acetate from 5/1 to 1/1). Representative ^{1}H NMR and MS data for Table 1, entry 1: ^{1}H NMR (400 MHz, DMSO-d_6), ppm: 1.80 (m, 4H), 3.20 (m, 4H), 3.34 (m, 4H), 3.54 (m, 4H), 5.87 (sb, 2H), 6.77 (t, 1H), 6.96 (d, 2H), 7.21 (t, 2H); MS *m*/*z*: 392 (MH^+); entry 2: ^{1}H NMR (400 MHz, DMSO-d_6), ppm: 1.78 (m, 4H), 3.22 (s, 3H), 3.30 (s, 3H), 3.38 (t, 2H), 3.42 (m, 4H), 4.56 (t, 1H), 5.62 (m, 3H); MS *m*/*z*: 335 (MH^+).

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7. *General procedure for preparation of compound **8**:* Derivative of general formula **7** was dissolved in 2 ml of methanol and 10 mg of Pd–C 10% catalyst and 150 mg of ammonium formate were added. The mixture was then stirred for 3 h at rt and solution was filtered over Celite and the solvent evaporated. The residue was dissolved in DCM, washed with aqueous satured $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness. No further purification was made. Representative ^{1}H NMR and MS data for Table 1, entry 6: ^{1}H NMR (400 MHz, $CDCl_3$), ppm: 0.83 (s, 3H), 1.22 (s, 32H), 1.92 (m, 4H), 2.96 (s, 3H), 3.38–3.44 (m, 6H), 3.66 (sb, 2H), 5.04 (s, 1H), 5.17 (s, 1H); MS *m*/*z*: 445 (MH^+); entry 17: ^{1}H NMR (400 MHz, $CDCl_3$), ppm: 1.86 (m, 4H), 3.25–3.77 (m, 12H), 4.76 (sb, 2H), 5.15 (s, 1H), 5.30 (s, 1H); MS *m*/*z*: 249 (MH^+).