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Synthesis of *N*-pyridyl azoles using a deprotometalation-iodolysis-*N*-arylation sequence and evaluation of their antiproliferative activity in melanoma cells

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ABSTRACT

N-Arylation of pyrrole with 3-iodo-4-methoxypyridine was investigated by copper catalysis under different conditions. The best conditions, that proved to be protocol A (CuI, DMEDA or TMEDA, K_3PO_4, DMF at 110 °C) and above all protocol B (Cu_2O, Cs_2CO_3, DMSO at 110 °C), were applied to the synthesis of various *N*-(methoxypyridyl) pyrroles, indoles and benzimidazoles. The behavior of the different iodinated methoxypyridines was rationalized by evaluating the partial positive charge on the carbon bearing iodine from the ^{1}H NMR chemical shift of the corresponding deiodinated substrates. The reaction was next connected with the deprotometalation-iodolysis step generating iodinated methoxypyridines: straight involvement of the crude iodo intermediates in pyrrole *N*-arylation afforded the expected *N*-(methoxypyridyl) pyrroles in good yields. Several synthesized *N*-(methoxypyridyl) azoles exerted low to moderate antiproliferative activity in A2058 melanoma cells.

1. Introduction

Aromatic heterocycles are present in numerous molecules of chemical or biological interest, as well as in organic materials for different applications. In particular, *N*-(pyridyl) azoles are key skeletons present in pharmaceuticals[1] and in functional materials.[1g,2]

The development of simple methods to build such scaffolds is thus of interest. Among them, deprotonative[3] and dehalogenative[4] metalations, using respectively polar organometallic bases and transition metal catalysts, are powerful tools.

Recently, metallic pairs with which deprotolithiation is followed by 'trans-metal trapping'[5] allowed sensitive substrates to be functionalized.[6] Within this context, we have developed the putative pair 1:1 $Zn(TMP)_2$-LiTMP·2LiCl±TMEDA[7] (TMP=2,2,6,6-tetramethylpiperidino; TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), generated from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio,[8] for the room temperature functionalization of numerous substrates including pyridines.[9] In addition, copper-catalyzed *N*-arylation of azoles has recently met a huge development.[4a,b,4d–f,10]

We here report our efforts to combine deprotometalation-iodolysis of methoxypyridines with *N*-arylation of azoles for the synthesis of pyridine-based C,N′-linked bis-heterocycles. The antiproliferative activation of the obtained scaffolds in melanoma cells has also been evaluated.

2. Results and discussion

We recently developed a deprotometalation-iodolysis-*N*-arylation sequence from benzothiophene, benzofuran, benzothiazole and benzoxazole to access various bis-heterocycles.[11] In this

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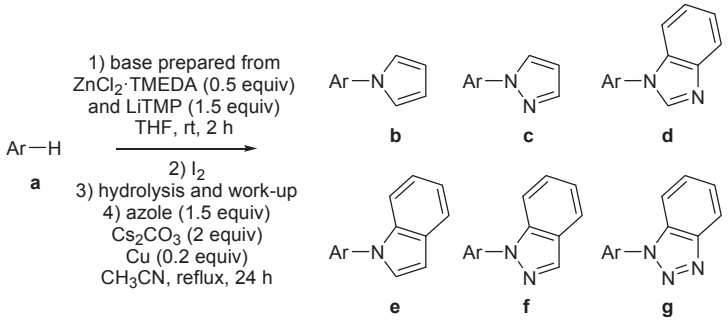
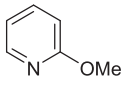
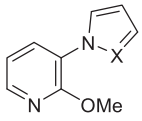
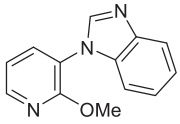
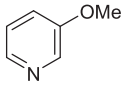
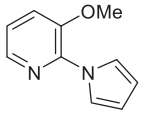
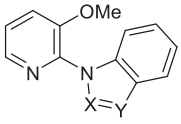
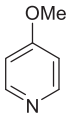
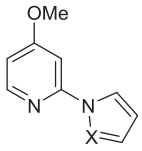
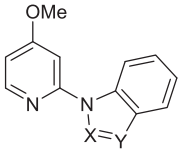
study, deprotolithiation followed by in situ *trans*-metal trapping of the five-membered aromatic heterocycles was carried out in THF (THF=tetrahydrofuran) before iodolysis by using a basic combination prepared from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio,[8,9,12] and supposed to afford 1:1 $Zn(TMP)_2$–LiTMP·2LiCl±TMEDA.[7,8] The crude iodides were directly involved in the *N*-arylation of different azoles (1.5 equiv) in the presence of metal copper (0.2 equiv), cesium carbonate (2 equiv) and acetonitrile, at the reflux temperature of the solvent for 24 h.[13]

In order to reach *N*-pyridyl azoles, we applied this procedure to the commercially available methoxypyridines **1a**, **2a** and **3a** (Table 1). From 2-methoxypyridine (**1a**), the expected *N*-(2-methoxy-3-pyridyl) azoles were isolated in the case of pyrrole (product **1b**, entry 1), pyrazole (**1c**, entry 2) and benzimidazole (**1d**, entry 3). The low yields are, at least to some extent, due to the insufficient amount of lithium-zinc base used; indeed, 2-methoxypyridine (**1a**) is much more completely deprotometalated by employing 1 equiv of $ZnCl_2$·TMEDA and 3 equiv of LiTMP.[9b] The *N*-arylation of benzimidazole (product **1d**) appears as less efficient, when compared with those of pyrrole and pyrazole.

We previously showed that 3-methoxypyridine (**2a**) can be deprotonated upon treatment by the lithium-zinc base, in situ prepared from 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP, in THF at 20 °C for 2 h. The regioselectivity of the reaction is however incomplete; indeed, subsequent quenching with iodine afforded the 4-iodo derivative **2a**–**I** in 85% yield together with 10% of the 2-

Table 1
Deprotometalation-iodolysis of the methoxypyridines **1a**, **2a** and **3a** followed by *N*-arylation of azoles with the crude iodides **1a**–**I**, **2a**–**I** and **3a**–**I**



Entry	Ar–H		Product, yield (%)[a]	
1		**1a**		**1b**, 36[b]
2				**1c**, 32[b]
3				**1d**, 12[b]
4		**2a**		**2b'**, 42[c]
5				**2e'**, 39[c]
6				**2d'**, 17[c]
7				**2f'**, 10[c]
8		**3a**		**3b'**, 14[d]
9				**3c'**, 10[d]
10				**3f'**, 9[d]
11				**3g'**, traces[d]

[a] After purification by column chromatography.
[b] 2-Methoxypyridine (**1a**, due to incomplete deprotometalation) and 3-iodo-2-methoxypyridine (**1a**–**I**) were also recovered.
[c] 4-Iodo-3-methoxypyridine (**2a**–**I**) and some 3-methoxypyridine (**2a**) were also recovered, and degradation was noticed.
[d] 3-Iodo-4-methoxypyridine (**3a**–**I**) and some 4-methoxypyridine (**3a**) were also recovered.