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A tandem aza-Friedel–Crafts reaction/Hantzsch cyclization: a simple procedure to access polysubstituted 2-amino-1,3-thiazoles

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ABSTRACT

A tandem aza-Friedel–Crafts reaction/Hantzsch cyclization is described to access various polysubstituted 2-amino-1,3-thiazoles from electron-rich (hetero)-aromatic rings, aldehydes, thiourea and α-chloroketones.

1. Introduction

The 2-amino-1,3-thiazoles are biologically important compounds with a broad range of activity like antiviral,[1] antifungal,[2] antiprion,[3] anti-inflammatory[4] and antibacterial activities.[5] Some 2-amino-1,3-thiazole derivatives have been reported as ligands of thrombopoietin,[6] neuropeptide Y5[7] and adenosine receptors[8] and as inhibitors of several physiological important enzymes like cyclin-dependant kinase,[9] tyrosine kinases (in the antitumoral agent dasatinib),[10] poly (ADP-Ribose) polymerase,[11] urokinase[12] etc. 2-amino-1,3-thiazole is also considered as a heterocyclic bioisostere of the phenol moiety in the widely used anti-parkinsonian agent pramipexol[13] and in morphinan derivatives.[14] Due to their broad utility in the pharmaceutical industry, the development of methods that give quick access to diverse 2-amino-1,3-thiazole libraries would provide additional lead molecules for drug discovery.

The Hantzsch reaction of α-halocarbonyl compounds with thioureas is the most commonly used method for the synthesis of 2-amino-1,3-thiazoles. However preparation of diverse monosubstituted thiourea libraries is time consuming and is often limited by the low solubility of compounds making them difficult to purify. In this report, we considered adapting aza-Friedel–Crafts reaction (AFCR) to access diverse methylene thiourea precursors, that could react to lead to substituted 2-amino-1,3-thiazoles in a one-pot process without any hazardous purification of the intermediates. In AFCR, three different molecules including a nitrogen source (amine, amide, urea), an aldehyde and an electron-rich aromatic ring (naphtol,[15] indole,[16] pyrrole[17] and furan,[18] etc…) are put together to yield one final product and water as the only byproduct. It is catalyzed by many Brønsted as well as Lewis acids.[15–18] More recently, it has been demonstrated that vitamin B1, also known as Thiamine hydrochloride, could catalyze the reaction.[19] To the best of our knowledge, although AFCRs are well described on amines, amides or urea only one example of AFCR with thiourea[15i] has been reported so far. In this case, solid silica sulfuric acid was used as catalyst to condense in a solvent-free procedure thiourea, liquid aldehydes, and β-naphthol. However, the reported condition is hardly compatible with our second objective, i.e., telescoping two reactions (AFCR and Hantzsch to heterocyclization) in a one-pot procedure.

This study is devoted to a tandem AFCR/Hantzsch reaction in a one-pot procedure to quickly access polysubstituted 2-amino-1,3-thiazoles (Scheme 1). In a first step, an electron-rich aromatic ring (ArH **1**) reacted with an aldehyde **2** and the thiourea **3** to afford a substituted methylene thiourea **4**. In a second step, the thiourea intermediate reacted in a one-pot procedure with an α-chloroketone **5** to lead to 2-amino-1,3-thiazole **6**. Three electron-rich aromatic rings, i.e., imidazo[1,2-*a*]pyridine (IP), β-naphthol and indole were considered as privileged structure because of their association with a variety of biological activities.[20] We were mainly interested by the IP derivatives since some 4-(2-methylimidazo[1,2-*a*]pyridin-3-yl) aminothiazoles have recently been reported as highly potent inhibitors of Hedgehog pathway-dependent cell proliferation.[20h,i]

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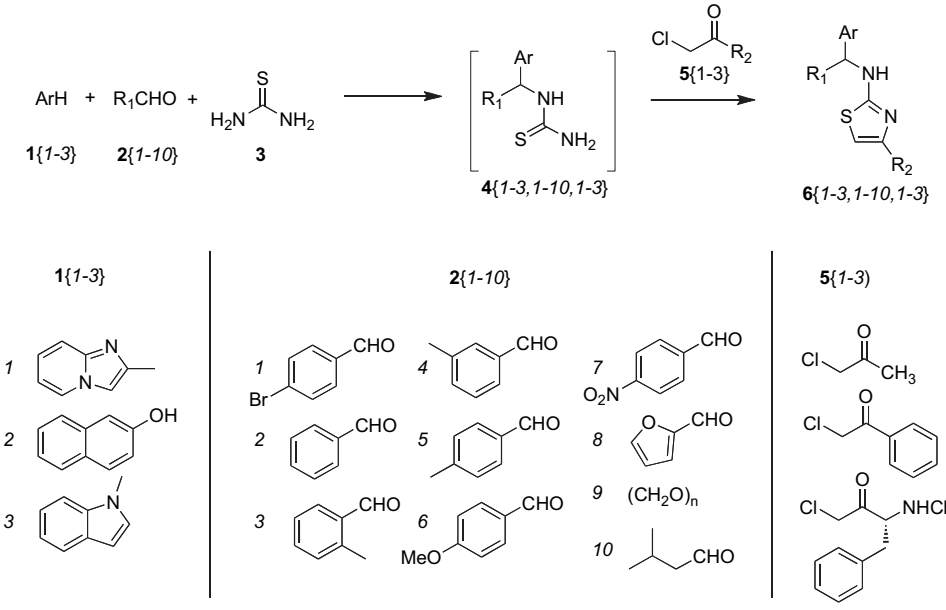
However, while IP is considered as an electron-rich aromatic ring,[21] no example of AFCR has been reported so far. Therefore, the first part of this paper is dedicated to the study of the aza-Friedel–Crafts reaction on the IP heterocycle to access imidazo[1,2-*a*]pyridin-3-yl methylene thioureas. The second part deals on the synthesis of polysubstituted 2-amino-1,3-thiazoles through a tandem AFCR/Hantzsch reaction without purification of the thiourea intermediates.

addition of 0.1 equiv $TiCl_4$ inhibited the reaction. We assumed that it results from a complexation of the titanium salts with the imidazo[1,2-*a*]pyridin-3-yl methylene thiourea.

Therefore we turned out our attention on the use of Thiamine, HCl as a promising alternative to $TiCl_4$ for a tandem AFCR/Hantzsch cyclization. We first controlled that Thiamine, HCl did not inhibit the Hantzsch reaction of thiourea **4**{1,1} and chloroacetone (data



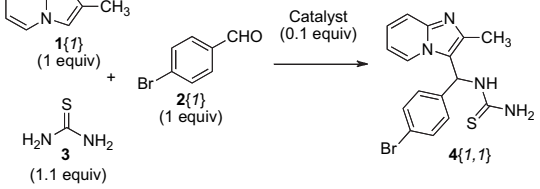
Scheme 1. Strategy for the synthesis of polysubstituted 2-amino-1,3-thiazoles. Chemset numbering of compounds **4**{*x*,*y*} and **6**{*x*,*y*,*z*} is standardized as follows: **4**{building block **1**, building block **2**} and **6**{building block **1**, building block **2**, building block **5**}.

2. Results and discussion

In order to access imidazo[1,2-*a*]pyridin-3-yl methylene thioureas by aza-Friedel–Crafts reaction, we initiated our study by subjecting 2-methylimidazo[1,2-*a*]pyridine **1**{1}, *p*-bromo-benzaldehyde **2**{1} and thiourea to various reaction conditions (Table 1). Several catalysts including Brønsted acids (Table 1, entries 2 and 4) and Lewis acids (Table 1, entries 5–12) were screened at 10 mol %. While all tested catalysts provided the desired thiourea **4**{1}, the best results were obtained using $TiCl_4$ (Table 1, entries 10–12). It appeared that the reaction was highly dependent on temperature limiting solvents to those having a boiling point higher than 100 °C, i.e., *n*-butanol or 1,4-dioxane (Table 1, entries 10–12). Since the reaction was not performed in anhydrous conditions, $TiCl_4$ could generate hydrochloride acid. However, when using 0.4 equiv HCl as catalyst the yield of the AFCR was decreased to 24% (data not shown) compared to 82% yield obtained with 0.1 equiv $TiCl_4$. This result suggested a catalytic effect of the titanium species.

We explored the scope of the AFCR on a set of various aromatic and aliphatic aldehydes, i.e., benzaldehyde **2**{2}, *o*-, *m*-, *p*-tolualdehyde **2**{3–5}, *p*-anisaldehyde **2**{6}, 4-nitrobenzaldehyde **2**{7} and isovaleraldehyde **2**{10} with $TiCl_4$ as catalyst. 1,4-Dioxane was preferred to *n*-butanol since in this solvent several compounds spontaneously precipitated at room temperature. Purities were higher than 85% determined by analytical HPLC for all thiourea derivatives. A fraction of each compound was purified by reverse phase preparative HPLC for characterization (Table 2). Encouraged by the results obtained from AFCRs, we turned our attention to the Hantzsch heterocyclization. The cyclization of thiourea **4**{1,1} and chloroacetone occurred at temperature higher than 70 °C in protic solvents, i.e., ethanol or *n*-butanol. We were surprised that the

Table 1
aza-Friedel–Crafts reaction on imidazo[1,2-*a*]pyridine **1**{1} using various reaction conditions



Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield[a] (%)
1	None	AcOH	80	24	0[b]
2	None	AcOH	117	24	22[b]
3	None	*n*-BuOH	117	24	22[b]
4	*p*-TSA	*n*-BuOH	117	24	43[b]
5	$BiCl_3$	*n*-BuOH	117	3	52[b]
6	$FeCl_3$	*n*-BuOH	117	3	53[b]
7	$Yb(OTf)_3$	*n*-BuOH	117	3	31[b]
8	$InCl_3$	*n*-BuOH	117	3	39[b]
9	$SnCl_2$	*n*-BuOH	117	3	35[b]
10	$TiCl_4$	EtOH	80	3	0[b]
11	$TiCl_4$	*n*-BuOH	117	3	80[b]
12	$TiCl_4$	1,4-Dioxane	105	3	82[b]
13	Thiamine, HCl	EtOH	80	24	0[b]
14	Thiamine, HCl	DMF	120	3	30[b]
15	Thiamine, HCl	*n*-BuOH	117	3	36[b]
16	Thiamine, HCl	*n*-BuOH	117	3	89[c]
17	Thiamine, HCl	1,4-Dioxane	105	3	80[c]

[a] Experimental conditions: see Experimental section 4.2.
[b] Volume of solvent 2 mL; concentration of **1**{1}: 0.2 M.
[c] Volume of solvent 0.5 mL; concentration of **1**{1}: 0.8 M.