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Regioselective two step synthesis of 3-substituted 2-aminoimidazo[1,2-*a*]pyrimidines

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Abstract—A two step procedure for the regioselective synthesis of 3-substituted-2-aminoimidazo[1,2-*a*]pyrimidines is described. The key step is a Dimroth rearrangement of a mixture of 2 and 3-substituted aminoimidazo[1,2-*a*]pyrimidines that yields quantitatively one regioisomer. Reaction screening for the rearrangement step is reported. A multicomponent isocyanide based reaction is chosen as the preferred way for the synthesis of the precursors. Elucidation of regiochemistry has been done by X-ray determination of some representative compounds.

During the recent years an increasing number of papers have been published for the synthesis or further transformations of fused [5,6] ring systems. Among them, great interest has been focused on imidazo[1,2-*a*]pyridines and pyrimidines (Fig. 1). They represent a class of molecules capable of binding to multiple receptors with a high affinity giving useful biological activities (e.g., antifungal, antibacterial, local anesthetic activity, etc.).[1]

There are several methods reported in the literature to prepare 2-substituted or 3-substituted imidazo[1,2-*a*]-pyridines, the majority relying on the condensation of 2-aminopyridine or 2-aminopyrimidine with α-bromoketones to form the five member cyclic system.[2] Particularly interesting are those structures that contain amino groups at C-2 or C-3. While there are well established methods for the preparation of 3-amino substituted products; by nitration at C-3 of the already formed heterocycle and subsequent reduction,[3] multicomponent reaction between 2-aminopyridines, aldehydes and isonitriles[4] or preparation from pyridiniumfluorides,[5] Strecker-type reaction between a 2-aminoazine, cyanide ion and a limited number of aldehydes,[6] or by use of benzotriazoles as auxiliary groups,[7] the introduction of an alkyl/aryl amino side chain at C-2 has remained more challenging. The most common synthetic route for the preparation of these compounds involves the condensation of 2-aminoazine or *N*-tosyl 2-aminoazines with α-amino carboxamides.[8] These methods involve three or more sequential synthetic steps, use harsh reaction conditions that give a low yield and frequently obtain mixtures of regioisomers when 2-aminopyrimidine is used.[9]

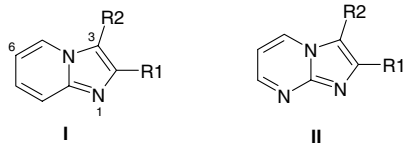

Figure 1.

As part of our continuing interest in the chemistry of fused [5,6] ring systems, we were aware of the formation of 2-aminoimidazopyrimidines as a by product from an isocyanide based multicomponent reaction.[10] Given the ease of synthesis of these heterocycles in a combinatorial way, we envisioned the possibility of getting selectivity in the synthesis of these 2-amino imidazopyrimidines by changing the reaction medium. Unfortunately the driving force of this condensation reaction makes the formation of 3-amino derivatives easier, as demonstrated by Krasavin and co-workers.[11] We turned our attention to obtaining regioselectivity by Dimroth rearrangement of the system. While the Dimroth rearrangement is typically a reversible process,[12] in some systems substitution at the 2-position with an aryl group is thermodynamically favoured to substitution at the

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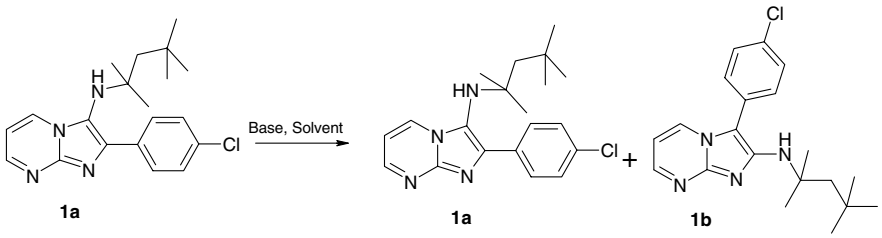
Table 1.



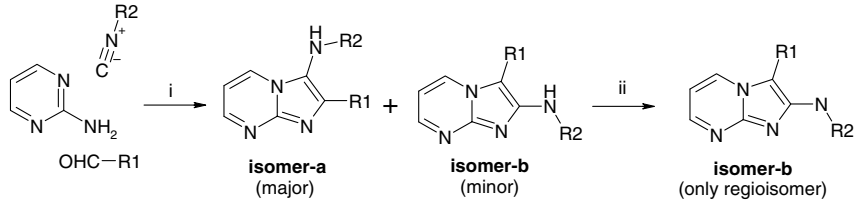
Entry	Base	Solvent	*T*	**1a/1b** (1 h)	**1a/1b** (3 h)	**1a/1b** (24 h)
1	1% NaOH	H_2O	100	—	—	95:5
2	5% NaOH	H_2O	100	—	—	95:5
4	2.5% NaOH	H_2O/MeOH 1:4	80	1:1	5:95	0:100
5	KOH/MeOH 1M	—	80	97:2	—	7:3[a]
6	5% LiOH	H_2O/MeOH 1:4	80	66:33		
7	5% KOH	H_2O/MeOH 1:4	80	25:75		
8	1% NaOH	H_2O/MeOH 1:4	80	40:60	1:1	—
9	*5% NaOH*	*H_2O/MeOH 1:4*	*80*	*5:95*	*0:100*	—
10	10% NaOH	H_2O/MeOH 1:4	80	0:100	—	—

Ratio **a/b** determined by the integration of peaks at HPLC 300 nm. No other peaks detected.
[a] For entry 5 by products can be detected in LCMS in a high quantity.

3-position. There is, however, no literature references for the successful rearrangement of disubstituted systems containing an amino side chain at C-2 or C-3.

The Dimroth rearrangement is usually performed under acidic or basic conditions, and usually yields a mixture of the two possible regioisomers, depending mainly upon the pattern of substitution. In a first attempt, compound **1a**[13] was treated in NaOH/H_2O 100 °C for 24 h yielding a mixture 95/5 of both regioisomers. The reaction was very clean and by products were not detected by LCMS and ^{1}H NMR; but the insolubility of the

Table 2.



i: MeOH/DCM 1:4 (0.3M); $Sc(OTf)_3$ 0.05 eq., 65ºC; ii: NaOH 5% H_2O/MeOH 1:4, 80ºC

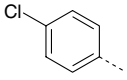
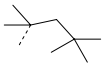
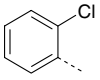
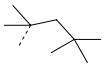
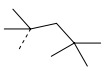
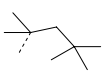
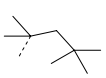
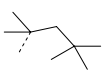
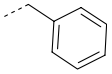
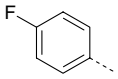
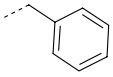
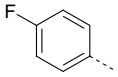
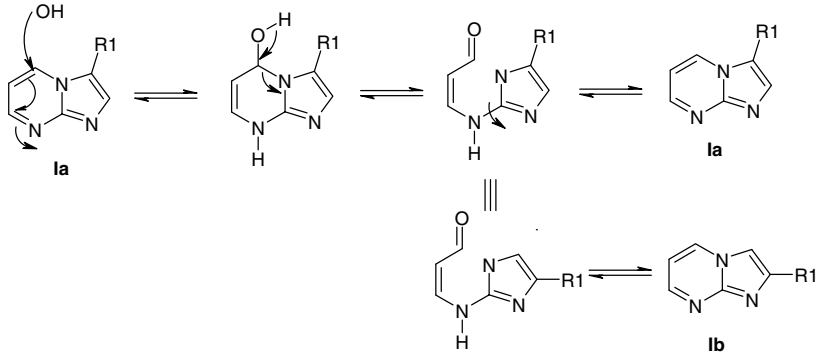
Entry	R1	R2	Ratio **a/b** (first step)	Starting material used for second step	*T* (°C)/time (h)	Ratio **a/b** (second step)	Yield of isomer **b** (%)
1			3:2	**1a** **1b**	80 (3) 80 (3)	0:100 0:100	94 95
2			9:1	**2a**	80 (3)	0:100	92
3			1:1	**3a/3b** (1:1)	80 (4)	0:100	95
4			95:5	**4a/4b** (95:5)	80 (3)	0:100	91
5			1:4	**5a**	80 (3)	0:100	99
6			1:1	**6a**	80 (3)	5:95	94

Table 2 (*continued*)

Entry	R1	R2	Ratio **a/b** (first step)	Starting material used for second step	*T* (°C)/time (h)	Ratio **a/b** (second step)	Yield of isomer **b** (%)
7			4:1	**7a/7b** (4:1)	80 (3)	0:100	92
8			3:1	**8a**	80 (3)	1:99	98
9			1:1	**9a/9b** (1:1)	80 (3)	0:100	62
10			3:1	**10a/10b** (3:1)	100 (4)	21:79	73

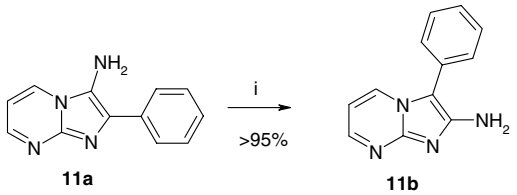
Yield based in isolated compound for the rearrangement step. For entries 9 and 10 the yield was calculated by integration of the peaks by HPLC.
For entries 1, 3 and 4, the first step was also performed with NH_4Cl, Toluene, 120 °C, 48 h, yielding only isomer **a**.
Yield for first step is generally above 70% except for entries 5, 6, 9, 10 (25–50%).
For entry 6, the experiment was done with NaOH 10% in MeOH/H_2O 3:1, heating overnight.



Scheme 1. Proposed mechanism for Dimroth rearrangement of imidazopyrimidines.

products in the reaction medium could be masking the results. We decided to explore broadly the reaction conditions by changing the bases, mixtures of solvents, temperature and reaction times. The use of a mixture H_2O/MeOH prompts an increase of the ratio **b/a**, while changes in the base did not afford any better result. The reaction is very clean and no purification was needed. If the concentration of base is increased, the reaction time can be reduced up to 1 h; however, we wanted to use mild conditions in order to avoid possible decomposition of intermediates when the reaction is applied to other substrates.[12b]

The experimental conditions listed in Table 1 were applied to a variety of products to study the influence of several groups at C-2 and C-3. We used the known Groebke multicomponent reaction to synthesize a mixture of the two regioisomers, since the method is straightforward and the variety of the products formed can be almost unlimited. The ratio **a/b** obtained in the first step is quite dependent on the substituents, when protic condition are used, and in general a mixture of both regioisomers is obtained. The reaction works cleanly and fast with MeOH/DCM and $Sc(OTf)_3$, heating for 3 h



Scheme 2. Reagents and conditions: (i): NaOH 5% H_2O/MeOH 1:4, 80 °C, 1 h.

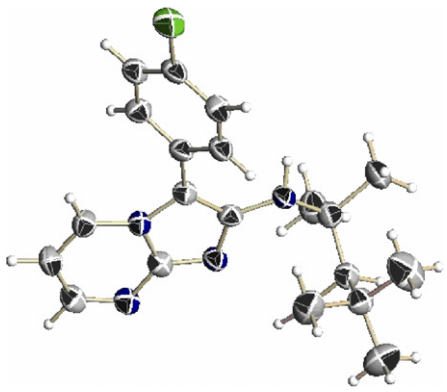
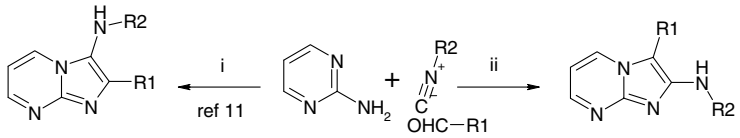


Figure 2. X-ray crystallographic structure of compound **1b**.



Scheme 3. Reagents and conditions: (i) toluene, NH_4Cl, 120 °C, 24–48 h; (ii) (a) MeOH/DCM 1:4 (0.3 M), $Sc(OTf)_3$ 0.05 equiv, 65 °C; (b) NaOH 5% H_2O/MeOH 1:4, 80 °C.

at 65 °C.[14] A crude mixture is treated with NaOH/MeOH/H_2O at 80 °C for 3 h to yield, in most cases, only regioisomer **b** in yields higher than 90% usually without requiring purification.[15] In some cases, pure starting materials were used for the rearrangement step (Table 2).

Interestingly, the reaction can be expanded to compounds bearing a free $-NH_2$ group. When the commercially available compound **11a** is treated under the same conditions, **11b** is formed as the only regioisomer quantitatively. It seems that the selectivity in the cyclization step (see Scheme 1) is not only driven by the steric effects, but also by the different electronic pattern of the imidazole intermediate due the presence of an amino group at C-3 (Scheme 2). The correct identity of compound as 2-amino imidazo[1,2-*a*]pyrimidines was confirmed by LCMS analysis, ^1H NMR, by comparison with those compounds already characterized by Krasavin and co-workers[11] and finally, by the X-ray structure of some representative products (**1b**, Fig. 2).

In summary, we have developed a new way to prepare 2-aminoimidazopyrimidines by a selective rearrangement. The process has been tested in a great variety of products including free amino groups, which indicates the broad scope of the reaction. The process can be coupled to an isocyanide MCR affording a very versatile process for the rapid synthesis of 2-aminoimidazopyrimidines (Scheme 3).

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15. *Experimental procedure*: To a solution of 300 mg of 2-aminopyrimidine (3.15 mmol, 1 equiv) dissolved in 5 ml of DCM/MeOH (3:1) placed in a screw capped glass tube was added $Sc(OTf)_3$ (0.13 mmol, 0.05 equiv), benzaldehyde (4.1 mmol, l.3 equiv) and benzylisocyanide (4.1 mmol, 1.3 equiv). The reaction mixture was heated overnight at 65 °C. Isolation of pure product from the reaction mixture was achieved by capture on a solid support. Thus, the basic product was adsorbed on cation exchange resin and excess of aldehyde, isonitrile and neutral impurities were removed by a solvent wash. Treatment of the resin (SCX) with 2 N methanolic ammonia eluted a mixture of **7a/7b** (8:2) very clean. The mixture of regioisomers can be either isolated previously to Dimroth rearrangement (purification in normal phase with DCM/MeOH) or treated directly with NaOH/MeOH 5% and later on purified if needed. Compound **7a** placed in a screw capped glass tube under nitrogen was dissolved in deoxygenated NaOH 5% MeOH/H_2O (4:1) (0.1 M) and heated 3 h at 80 °C affording **7b** (92%). The reaction mixture was diluted with DCM and extracted with water, and the organic solvent was evaporated under vacuum. ^1H NMR (**7b**) (DMSO-d_6, 300 MHz) δ 8.65 (dd, $J = 2.0$, 7.0 Hz, 1H), 8.19 (dd, $J = 1.8$, 4.3 Hz, 1H), 7.62–7.18 (m, 10H), 6.88 (dd, $J = 4.4$, 11.1 Hz, 1H), 6.57 (t, $J = 6.41$ Hz, 1H), 4.57 (d, $J = 4.5$ Hz, 2H) ppm.