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New multi-component reaction accessing 3-aminoimidazo[1,2-*a*]pyridines

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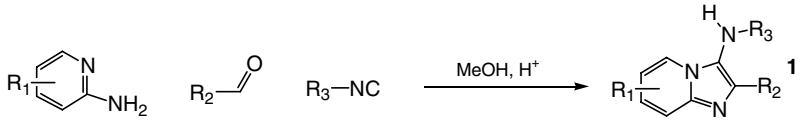
Abstract—The novel one step solution phase synthesis of an array of 3-aminoimidazo[1,2-*a*]pyridines is reported. Reactions were performed in methanol by mixing a α-amino-pyridine, aldehyde and trimethylsilylcyanide (TMSCN) to give the desired product. Mediated by microwave irradiation and catalyzed by scandium triflate, the methodology represents the first one pot preparation of 3-aminoimidazo[1,2-*a*]pyridines that avoids the use of an isonitrile and subsequent de-protection strategy. The reaction is an example of a formal three-centre-three-component multi-component reaction.

Today, with the emergence of high-speed parallel synthesis, the multi-component reaction (MCR) is widely employed for the rapid assembly of arrays with high molecular diversity.[1] Coupled with a post-condensation modification, the power of these reactions is increased even further, giving rise to a plethora of complex, pharmacologically relevant templates for screening purposes.[2] Several, novel intra-molecular variations of the Ugi reaction have been reported, producing constrained products that result from interception of the intermediate nitrilium ion.[3] The year 1998 witnessed virtually the simultaneous discovery of a three-component reaction by Blackburn et al.,[4] Bienayme et al.[5] and Groebke et al.,[6] producing imidazo[1,2-*a*]pyridines, **1**, via the acid catalyzed condensation of an aldehyde, an isonitrile and amino-pyridine, Scheme 1.

In fact, at an early stage the Bienayme group reported the preparation of in excess of 30,000 bi-cyclic heterocyclic structures via the solution phase protocol. Since that time, several groups have reported solid phase[7] and microwave[8] mediated versions of the reaction and multiple compound vendors have used this reaction for commercial gain. As such, imidazo[1,2-*a*]pyridines have emerged as versatile drug templates in areas of medicinal chemistry spanning applications in anti-inflammatory and antiulcer based therapies.[9] For example, Priaton has a selection of >30 million compounds available via this technology where knowledge management is key for compound selection.[10]

Consistent with the above theme, the following communication details the discovery of a unique application of TMSCN as a non-classical, yet functional, isonitrile equivalent, giving 3-aminoimidazo[1,2-*a*]pyridines, **5**, Scheme 2 that obviates the need for an acid mediated de-protection strategy involving the pungent 1,1,3,3-tetramethylbutylisonitrile, **2**.[11] Previously reported efforts at applying KCN only gave products in low yield and with moderate purity. Additional routes to this class



Scheme 1.

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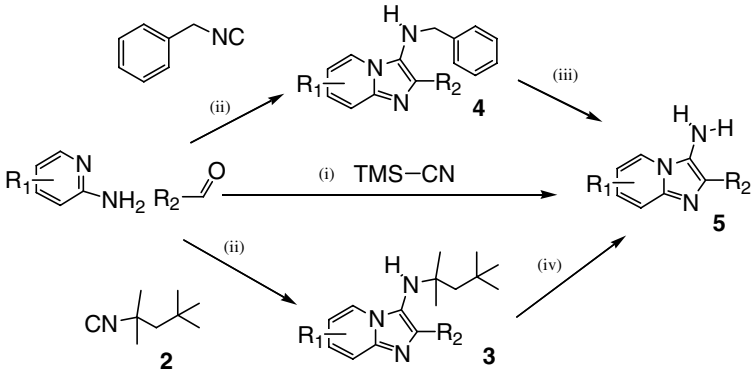


Scheme 2. Reagents and conditions: (i) Aminopyridine (1.2 equiv), R_2CHO (1 equiv), TMSCN (1 equiv), $Sc(OTf)_3$ (5 mol %), MeOH, microwave, 10 min, 140 °C. Followed by Si-trisamine (5 equiv); (ii) aminopyridine (1 equiv), R_2CHO (1 equiv), **2** (1 equiv) or benzylisonitrile (1 equiv), $Sc(OTf)_3$ (5 mol %), 16 h; (iii) H_2, EtOAc, 24 h; (iv) 10% TFA/CH_2Cl_2, 18 h.

of compound have also been reported, including hydrogenation of *N*-benzyl compounds **4**[5] and the condensation of α-halocarbonyls with 2-aminopyridines, followed by nitrosation and reduction.[12] Unfortunately, the latter routes have low compatability with library synthesis.

Thus, employing the catalyst originally used by Blackburn et al.[4] for conversion to **3** and **4**, the conditions in Scheme 2, (i), were followed. The catalytic amount of scandium triflate was then removed from the reaction mixture prior to purification by scavenging with Si-triamine, followed by simple filtration.[13] A representative procedure is given with analytical data confirming the structure of **13**.[14] Further confirmation of the structure was obtained by synthesizing **13** via intermediate **3**. Analytical data (^1H) obtained for final product was identical to that of the TMSCN procedure. Encouraged with the initial development work a 3 (aminopyridine) × 7 (aldehyde) array was produced and purified by supercritical fluid chromatography.[15] Crude purities ranged from 50% to 77% with isolated yields typically in the 30–70% range. Data for 12 representative examples, **6**–**17**, are reported in Table 1 and the procedure appears general for a range of diversity reagents. For

Table 1.

Compd #	CLND[a] (%)	UV[b] (%)	Yield[c] (%)	UV[d] (%)	MH^+ (%)
6	77	87	73	100	224
7	56	70	53	100	230
8	75	94	71	98	204
9	60	87	64	97	230
10	49	55	38	100	224
11	65	65	42	62	230
12	68	68	27	100	204
13	76	82	58	100	224
14	58	58	56	96	252
15	50	62	52	96	286
16	64	69	40	99	266
17	58	32	65	97	204

[a] CLND crude purity.
[b] Crude purity LC/MS at UV220.
[c] Isolated yield.
[d] Final purity, UV220.

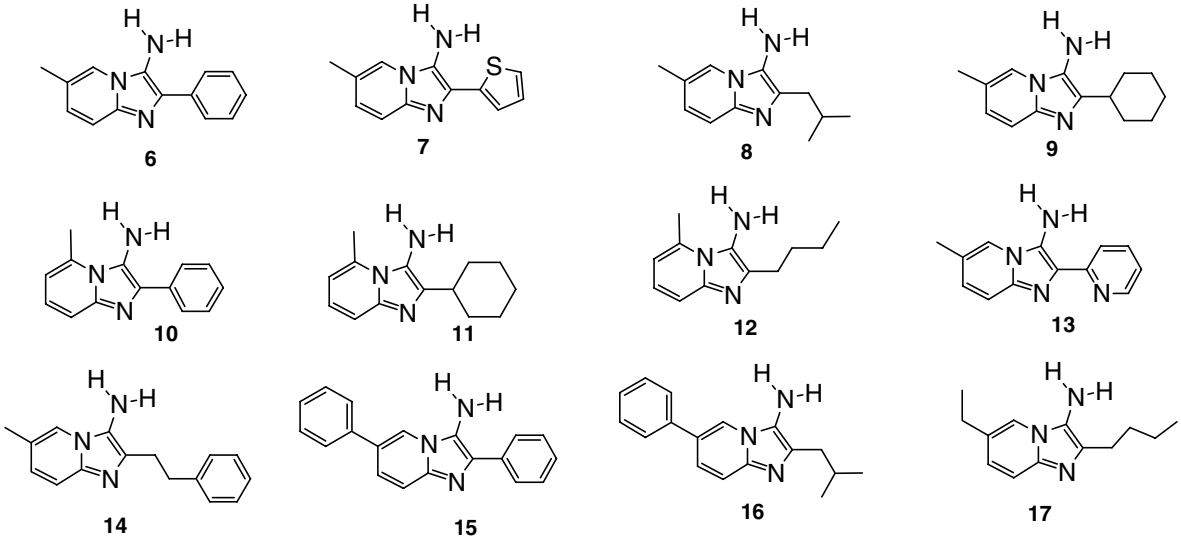
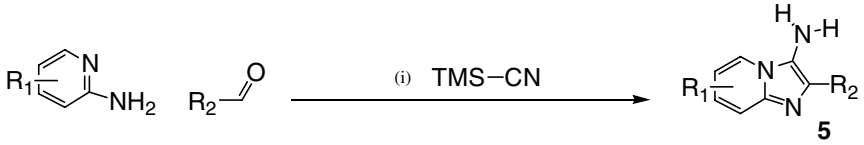


Figure 1.



Scheme 3.

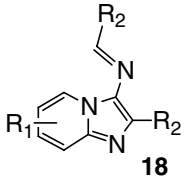


Figure 2.

instance, examples with $R_1 = H$ worked equally well, as those reported in Figure 1 and Scheme 3.

One side product observed in this transformation was further reaction of the product **5** with aldehyde to give what is possibly the corresponding Schiff base, **18**, Figure 2. This product was virtually eliminated from the crude reaction mixture by use of excess amine and is an example of a novel, formal three-component-four-centre MCR.

In summary, a novel one-step procedure for the solution phase synthesis of 3-aminoimidazo[1,2-*a*] pyridines has been reported, via the unique application of TMSCN as a functional, yet non-classical isonitrile. Current efforts are now focusing on development of the reactivity profile of TMSCN in other isonitrile based methodologies and on further studies of generic structure **18**. Results will be reported in the near future.

Acknowledgements

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13. Si-triamine was purchased from Silicycle™.
14. A mixture of aminopyridine (0.598 mmol), aldehyde (0.460 mmol) and scandium triflate (0.020 mmol) in MeOH (3 ml) in a microwave tube was stirred for few seconds. Trimethylcyanide (0.460 mmol) was added and the reaction was irradiated in a microwave apparatus at 140 °C for 10 min. After cooling to room temperature in the microwave cavity, the catalyst was filtered from the reaction mixture and solvent evaporated in vacuo. The reaction mixture was filtered and the solvent evaporated in vacuo. The crude materials were purified (SFC) to give the desired products in the 30–70% yield range. For example, imidazopyridine **13**: ^1H ($CDCl_3$, 400 MHz) 8.55 (m, 1H), 8.15 (m, 1H), 7.75 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.08 (m, 1H), 6.90 (m, 1H), 5.30 (br s, 2H), 2.30 (s, 3H). ^{13}C (DMSO, 125 MHz) 156.16, 148.86, 137.65, 137.05, 132.05, 125.58, 122.04, 120.48, 120.14, 120.10, 119.04, 116.90, 18.32.
15. Supercritical fluid chromatography (SFC) was explored as the technique for reaction purification. Reaction mixtures were screened using the below analytical method against four columns: diol, cyano, amino and 2-ethylpyridine to determine the optimal separation. Good chromatography was seen only using the Amino column and therefore was used for all subsequent analysis. Preparative experiments using preparative method below were performed to verify good recovery and purity. The success of mobile phase void of any additive was also confirmed and subsequently used. Samples for preparative work were dissolved in 1 ml 1/1 CH_2Cl_2/MeOH to assure solubility. Although the chromatography of the initial model reaction was excellent, there was a varying degree of success depending on the nature and arrangement of the substituents in the complete library. Sample recovery was calculated based on quantitative HPLC data using a Chemiluminescent Nitrogen Detector (CLND). Analytical method: 5–50% MeOH in CO_2 over 4.5 min at 3.3 ml/min using a 4.6×150 mm 5 mm particle column. Preparative method: 5–50% MeOH in CO_2 over 4.5 min at 70 ml/min using a 21.1×150 mm 5 mm particle amino column.