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Sequential Ugi/Strecker reactions via microwave assisted organic synthesis: novel 3-center-4-component and 3-center-5-component multi-component reactions

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Abstract—Two novel one-step microwave mediated syntheses of arrays of 3-iminoaryl-imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyridyn-3-ylamino-2-acetonitriles are reported. Reactions are performed under microwave condition in methanol by simply mixing α-amino-pyridines, aldehydes, and trimethylsilylcyanide (TMSCN) with distinct reagent stoichiometries, catalyzed by polymer-bound scandium triflate, to afford either product. Furthermore, functionally different aldehydes were shown to proceed to different end-points, adding an extra caveat to the studies. The new methodology represents examples of both formal 3-center-4-component and 3-center-5-component multi-component reactions.

The Strecker reaction was initially reported in 1850 and enables the oldest known synthesis of α-amino acids.[1] In its classical form the reaction consists of a condensation of an aldehyde, cyanide source, and ammonia. Hydrolysis of the newly formed α-amino nitrile then gives the desired α-amino acid.[2] As such, considerable effort has been applied into developing asymmetric processes for the production of both natural and unnatural amino acids for use as key building blocks in the pharmaceutical industry.[3] Today, 150 years after the discovery of this early multi-component reaction (MCR), interest in the field is high, having been re-invigorated with the emergence of high-speed parallel synthesis, high-throughput screening, and the need for novel highly tractable chemical starting points in drug discovery. In fact, a plethora of multi-component reactions (MCR) are now widely employed for the rapid assembly of arrays with high-molecular diversity.[4] Digging deeper into this field of study, IMCRs (I = isonitrile) are a powerful subset of these reactions. One example, reported by three independent groups, involves the production of widely available 3-imidazo[1,2-*a*]pyridines in an acid catalyzed condensation involving α-aminopyridines, **1**, aldehydes, and isonitriles.[5] Interestingly, this laboratory has recently reported that the isonitrile can be replaced by a traditional cyanide source, namely TMSCN, to afford 3-aminoimidazo[1,2-*a*]pyridines, **2**, in only one step.[6] The new procedure has the benefit of avoiding established protocols, where pungent isonitriles with removable side chains are required to access this chemotype in two steps.[7] The mechanism of the condensation is highly analogous to the classical Strecker and Ugi reactions and represents a novel 3-center 3-component MCR. Further studies with TMSCN as a classical isonitrile replacement gave rise to the results described herein. Thus, this letter reports two novel one-pot microwave mediated extensions of this reaction, enabling both the selective formation of 3-iminoaryl-imidazo[1,2-*a*]pyridines **3** and imidazo[1,2-*a*]pyridyn-3-ylamino-2-acetonitriles **4**, in good yield. Both conversions represent non-isocyanide based MCRs, mediated by careful adjustment of reagent stoichiometry. The reaction pathway detailing the formation of the three sequential products, **2**, **3**, **4**, is shown in Scheme 1 and

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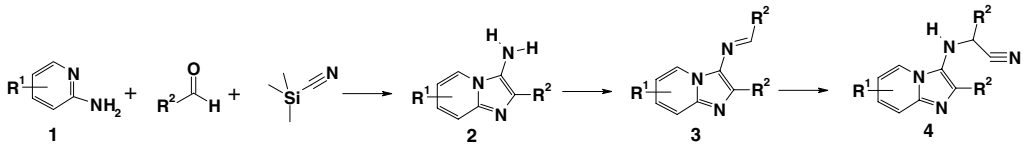

Scheme 1.

Table 1.

Conversion	Amine (equiv)	Aldehyde (R_2CHO) (equiv)	TMSCN (equiv)	PS-Sc(OTf)$_3$ (mol %)	Reaction time (min)	Temp (°C)
1 to **2**	1	0.9	1	5	5	140
1 to **3**	1	2.2	1	5	5	140
1 to **4**	1	4.0	3	5	20	140

Note: Irradiated with the Biotage Initiator™ 60.

reaction conditions and reagent stoichiometries are described in Table 1.

We begin with the formation of 3-iminoaryl-imidazo[1,2-*a*]pyridines, **3**, which initially were observed as a minor side product (0–10%) during the pseudo-Ugi reaction affording 3-aminoimidazo[1,2-*a*]pyridines, **2**.[7] The reaction was optimized by simply increasing the aldehyde input to 2.2 equiv allowing access to products **3** in good yield. However, the reaction only proceeded well with aromatic aldehydes, producing the corresponding highly conjugated and stable Schiff bases. Presumably, products derived from non-aromatic aldehydes equilibrated back to the starting aldehyde and amine, **2**, under reaction or work-up conditions. The products were then purified by reverse-phase chromatography.[8] Crude purities, as judged by area% under the curve of the desired product at UV214, ranged from 50% to 77% with isolated yields typically in the 30–70% range. Example structures with isolated yields and UV area% of crude reaction in brackets are presented in Figure 1.[9]

Fortunately, many of the products crystallized out of the solution affording an array of differently colored 3-iminoaryl-imidazo[1,2-*a*]pyridines. With crystals in hand, two structures were confirmed by X-ray crystallography. [Note: these structures, coupled with NMR studies, ruled out the possibility of 6Π-electrocyclization[10] product formation] (Fig. 2).

The formation of stable 3-iminoaryl-imidazo[1,2-*a*]pyridines, although confined to those derived from aromatic aldehydes, was found to represent a new formal 3-center-4-component multi-component reaction. Interestingly, on completion of this MCR, another side product (<5%–A% UV214 nM) was observed. This new byproduct was initially assigned structure **4** based on the observed molecular ion, excitingly a possible product of a sequential Strecker reaction. However, attempted further conversion of the crude reaction mixture of benzaldehyde derived **3** to its Strecker product, via exposure to TMSCN (3 equiv) in methanol under microwave irradiation at 140 °C for 20 min, proved to have little effect. Undeterred and enticed with the possibility

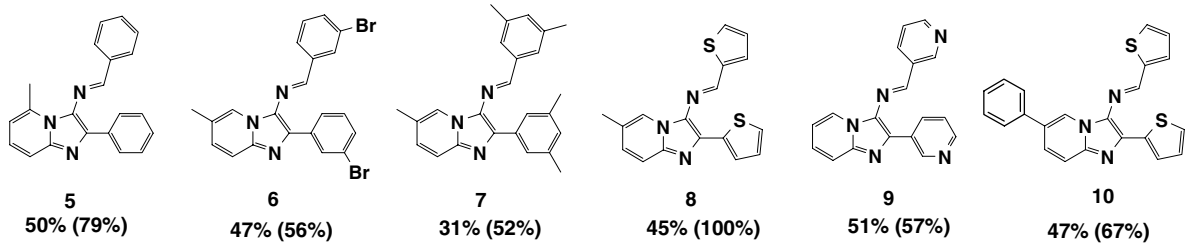

Figure 1.

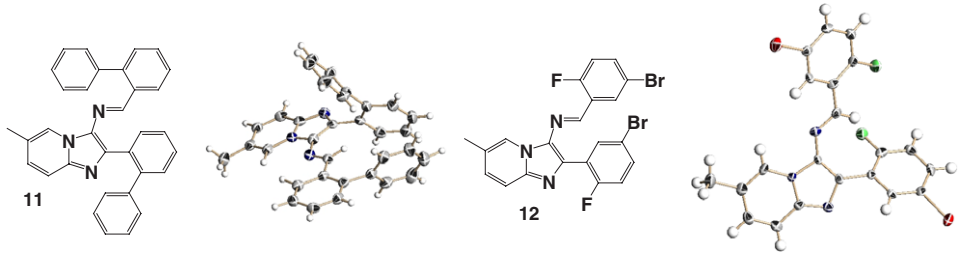

Figure 2.

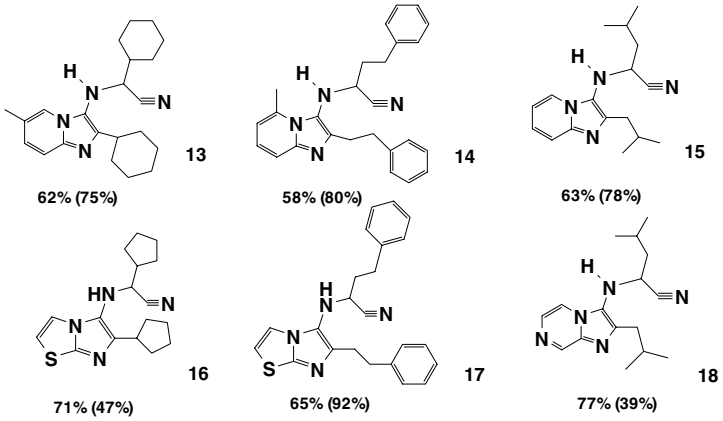

Figure 3.

of optimizing a powerful tandem Ugi/Strecker reaction, a series of reactions were thus performed in the Biotage Initiator™, using a variety of diversity reagents and an excess of TMSCN (3 equiv) and aldehyde (4.0 equiv). As previously observed, only low yields of **4** were detected with aromatic aldehydes, whereas non-aromatic aldehydes proceeded in excellent fashion giving products of the second Strecker reaction in one step and high isolated yield. Clearly the relative reactivity of the imines derived from alkyl appended aldehydes enabled the observed second Strecker transformation. Representative examples 13–18 with isolated yields and initial crude purities in brackets are shown in Figure 3.[11]

In summary, novel one-step procedures for the synthesis of 3-iminoaryl-imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyridyn-3-ylamino-2-acetonitriles have been reported, using TMSCN as a functional isonitrile. Both conversions represent novel MCRs and further studies are ongoing to explore additional transformations, feasible with these chemotypes. In addition, efforts are also focusing on the reactivity profile of TMSCN in other isonitrile based methodologies. Results will be reported in the near future.

Acknowledgments

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8. Method used: 12% isocratic @ 80 ml/min for 8 min on a 30 × 75 mm, 5 mm, C18 ODB MS Xterra column. Solvent A—H_2O w 0.01 M NH_4HCO_3, Solvent B—acetonitrile.
9. To a stirring mixture of an amino pyridine (0.598 mmol), an aldehyde (1.32 mmol) and PS-scandium triflate (0.020 mmol) in MeOH (3 ml) was added trimethylcyanide (0.460 mmol). The reaction was then irradiated at 140 °C for 5 min. After cooling to room temperature in the microwave cavity, the catalyst was filtered from the reaction mixture and solvent evaporated in vacuo. The crude materials were purified by reverse-phase chromatography to give the desired products. For example, iminoaryl-imidazopyridine, **5**: ^{1}H ($CDCl_3$, 400 MHz) 8.50 (s, 1H), 7.65–7.78 (m, 4H), 7.25–7.50 (4× m, 6H), 7.07–7.13 (m, 2H), 6.52–6.57 (m, 1H), 3.00 (s, 3H). ^{13}C ($CDCl_3$, 125 MHz) 158.96, 144.32, 137.24, 136.40, 131.08, 128.83, 128.78, 128.28, 128.18, 127.62, 125.11, 115.54, 113.97, 21.53.
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11. To a stirring mixture of an amino pyridine (0.50 mmol), an aldehyde (2 mmol), and PS-scandium triflate (0.025 mmol) in MeOH (3 ml) was added trimethylsilylcyanide (1.5 mmol). The reaction was then irradiated in a Biotage Initiator™ 60 at 140 °C for 20 min. After cooling to room temperature in the microwave cavity, the catalyst was filtered from the reaction mixture and solvent evaporated in vacuo. The crude material was purified by preparative hplc to give imidazo[1,2-*a*]pyridyn-3-ylamino-2-acetonitrile, **13**, (108 mg, 62%) as a pale yellow solid: ^{1}H (DMSO, 400 MHz) 7.80 (s, 1H), 7.25–7.35 (m, 1H), 6.95–7.00 (m, 1H), 5.35–5.40 (m, 1H), 3.80–3.90 (m, 1H), 2.75–2.90 (m, 1H), 2.25 (s, 3H), 1.95–2.15 (m, 2H), 1.45–1.90 (m, 10H), 1.05–1.40 (m, 8H). ^{13}C (DMSO, 125 MHz) 148.2, 144.4, 140.3, 126.8, 120.1, 116.4, 112.2, 58.3, 40.5, 36.0, 34.5, 30.1, 28.7, 26.2, 19.5.