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Parallel Synthesis of 3-Aminoimidazo[1,2-a]pyridines and pyrazines by a New Three-Component Condensation

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Abstract: A three-component condensation reaction between 2-aminopyridine, an aldehyde and an isonitrile catalyzed by scandium triflate affords derivatives of 3-aminoimidazo[1,2-a]pyridine; aminopyrazine reacts similarly. A library of heterocycles, prepared in high yield by parallel synthesis and purification on an ion-exchange resin, was subjected to further reactions at the amino group. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Developments in high-throughput screening have placed more exacting time constraints on the synthesis of potential therapeutic agents. To meet this challenge, combinatorial methods of synthesis[1] have been developed among which parallel synthesis of single compounds now plays a prominent role. Multiple component condensations (MCCs)[2] are particularly attractive for parallel synthesis because large arrays of compounds with diverse substitution patterns can be prepared in one step, often in high yields under mild reaction conditions. There has thus been renewed interest in the Ugi[2-4], Passerini[2b], Biginelli[5], and other MCCs implemented by both solution and solid-phase techniques.

It is of value if the MCC reaction provides compounds with established drug-like structures. In this respect, imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrazines are of interest, there being reports of cytoprotective,[6] cardiac stimulating,[7] anti-bacterial,[8] and anti-fungal[9] properties as well as examples of benzodiazepine receptor antagonists.[10] The most common synthetic route to these compounds, which involves the synthesis of α-halocarbonyl compounds followed by reaction with the appropriate 2-aminoazine,[7-10] is not readily adapted to parallel synthesis methods and cannot be used to prepare the synthetically valuable 3-amino derivatives directly. An alternative synthesis of this class of compounds with a primary amino group at the 3-position involves a presumed Strecker-type reaction between a 2-aminoazine, cyanide ion and a limited number of aldehydes.[11] It occurred to us that a new three-component condensation (3CC) reaction might result from the use of an isonitrile in place of cyanide ion affording previously unreported 3-alkylamino- and 3-arylamino- derivatives of the title compounds. We report herein that 2-aminopyridine and aminopyrazine undergo a Lewis-acid catalysed 3CC with an aldehyde and an isonitrile. The reaction is readily adapted to the parallel synthesis and purification of arrays of compounds some of which can be further functionalized by acylation or by urea formation at the 3-amino group.

Reaction of 2-aminopyridine with benzaldehyde and benzylisonitrile in MeOH at ambient temperature gave 3-benzylamino-2-phenylimidazo[1,2-a]pyridine[12a] denoted as compound **1.1.1** (the amine, isonitrile and aldehyde inputs, respectively, listed in Figure 1). Interestingly, when the reaction was conducted in the

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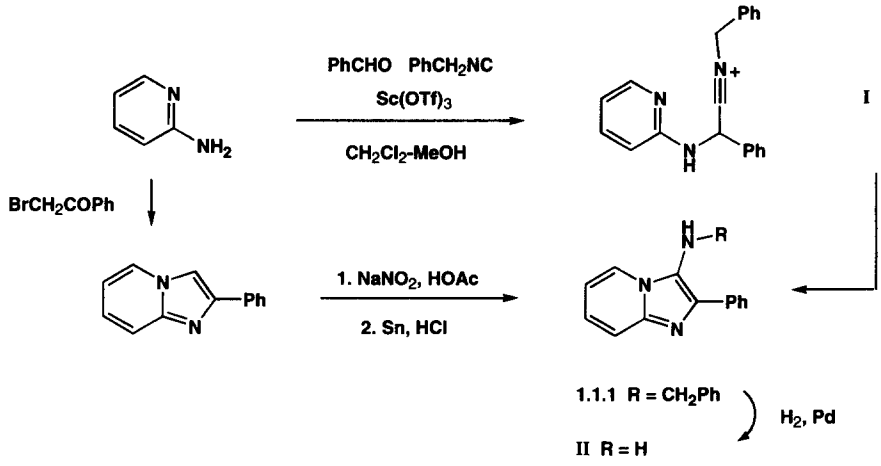
presence of a carboxylic acid, compound **1.1.1** was again isolated in somewhat higher yield and no 4CC Ugi condensation product was detected.[12b] This 3CC reaction presumably follows the same initial course as the Ugi reaction[2-4] with an intermediate imine being attacked by the isonitrile to give nitrilium ion **I** (Scheme 1) which then undergoes intramolecular cyclization in preference to nucleophilic attack by a carboxylic acid. The orientation of **1.1.1** was established by debenzylation (Scheme 1) which gave the same primary amine **II** as that obtained by the reported method[13] commencing with the condensation of 2-aminopyridine with α-bromoacetophenone. The mechanism of this latter reaction[14] and of related[10] condensations has been shown to involve initial displacement of bromine by the pyridine ring nitrogen followed by dehydrative ring closure. That the products obtained by the two routes are identical establishes the orientation of the 3CC products and supports the proposed mechanism involving intermediate **I.**

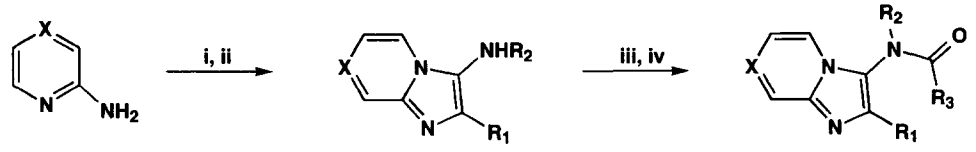
Scheme 1



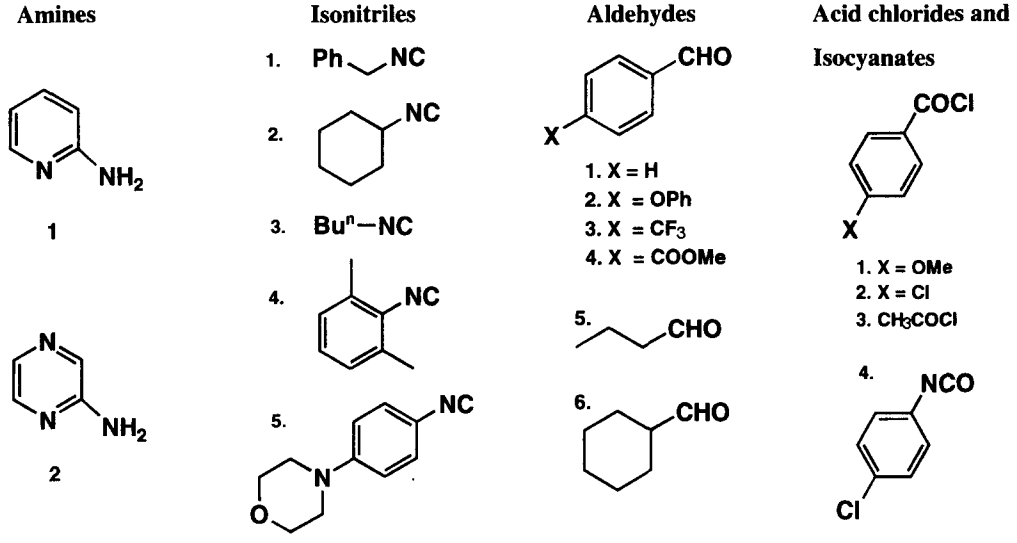
The most efficient reaction conditions[15] found to date for the 3CC involved treatment of a 0.5 M solution of 2-aminopyridine in CH_2Cl_2-MeOH (3:1) with 1.2 eq each of aldehyde and isonitrile in the presence of 0.05 mol eq of $Sc(OTf)_3$ catalyst[16] at ambient temperature for 72 h. Isolation of pure product from the reaction mixture was achieved by capture[17] on a solid support. Thus, the basic product was adsorbed on a cation-exchange resin[18] and excess aldehyde, isonitrile and neutral impurities were removed by a solvent wash. Treatment of the resin with 2M methanolic ammonia eluted compound **1.1.1** in 90% yield. Using the same reaction and purification conditions two 6 x 5 arrays were prepared by reaction of 2-aminopyridine or aminopyrazine with the aldehyde and isonitrile reactants listed in Figure 1. The reactions and purifications proved to be highly efficient for most of the inputs listed in Figure 1; isolated yields of 3CC products were typically in the 75-95% range and purities exceeded 85% in all cases.[15] Lower yields (35-66%) obtained for

compounds derived from amine **2** and aldehyde **4** were due, at least in part, to losses incurred during isolation because of low solubilities.

Figure 1: Reaction Conditions and Reactants for the Three-Component Condensation



Reagents and conditions: i. R_1CHO, R_2NC, $Sc(OTf)_3$, CH_2Cl_2-MeOH; ii. Cation exchange resin; iii. R_3COCl, polymer-supported morpholine, CH_2Cl_2 or RNCO, CH_2Cl_2. iv. Polymer-supported tris(2-aminoethyl)amine.



3-Aminoimidazo[1,2-a]pyridines and pyrazines derived from isonitriles 1 and 3 could be further functionalized by reaction with 1.3 eq of an acid chloride[19] (Figure 1) in the presence of polymer-supported morpholine resin as catalyst followed by removal of excess acid chloride by reaction with polymer-supported tris(2-aminoethyl)amine.[20b] The same compounds reacted cleanly when treated with excess of isocyanate **4** to give ureas; excess isocyanate was again removed by polymer-supported quench.[20] 3-Aminoimidazo[1,2-a]pyridines derived from hindered or aryl isonitriles were recovered unchanged after treatment with acid chlorides or isocyanates under the same conditions.

In conclusion, a new 3CC leading to pharmacologically relevant heterocycles has been developed that is amenable to high throughput synthesis and purification. Large arrays of compounds with diverse substitution patterns will be accessible given the availability of aldehydes and the ease of synthesis of isonitriles and substituted 2-aminoazines. Further application of this condensation reaction to aminopyrimidines and related heterocycles and to resin-bound reactants is in progress and will be reported in due course.

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12. (a) Compound **1.1.1** was isolated in 35% yield by chromatogaphy on alumina eluting with hexane-ethyl acetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.12 (1H, d, J= 7Hz), 7.96 (2H, d, J= 9 Hz), 7.5-7.3 (3H, m), 7.2-7.15 (m, 6H), 6.78, (1H, t, J= 7 Hz). ESI-TOF HRMS m/z 300.1556 ($C_{20}H_{17}N_3$ + H^+ requires 300.1501). (b) After conducting the reaction in the presence of either cyclopentanecarboxylic acid or anisic acid, 1.1.1 was isolated in yields of 44% and 55%, respectively, with starting materials accounting for most of the remaining mass.
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15. 0.5 M solutions of amine (1.5 ml) in MeOH-CH_2Cl_2 (1:3) were treated with 1.2 eq of aldehyde and 0.05 eq of scandium triflate. After 30 min 1.2 eq of isonitrile was added and the solutions were agitated for 72 h at ambient temperature. Reaction mixtures were allowed slowly to adsorb onto 5 g of Dowex 50WX 2-200 strongly acidic cation exchange resin that had previously been equilibrated with MeOH-5N HCl. The resin bed was washed with MeOH, CH_2Cl_2 and MeOH. The 3CC product was eluted from the resin using 2M NH_3 in MeOH (10 ml) and the solvent evaporated. All products were analysed by LC-MS recorded on a Micromass Platform LC in positive ion ESI mode; "purities" were assessed from peak areas recorded with the uv detector set at 280 nm. LC conditions: C-18 column, linear gradient from 90% A, 10% B to 100% B over 10 min. Solvent A-5mM NH_4OAc in H_2O, B-5mM NH_4OAc in MeCN. Selected compounds were characterized fully by ^{1}H nmr and high resolution ESI-TOF mass spectrometry. Selected data: **1.4.6:** *m/z 320.2068 ($C_{21}H_{25}N_3$ + H^+ requires 320.2127);* **1.1.5:** m/z 266.1612 ($C_{17}H_{19}N_3$ + H^+ requires 266.1657); **2.1.5:** *m/z* 267.1704 ($C_{16}H_{18}N_4$ + H^+ requires 267.1610); **2.1.1:** m/z 301.1479 ($C_{19}H_{16}N_4$ + H^+ requires 301.1453).
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19. **1.1.1.2** (70% yield) m/z 438.1383 ($C_{27}H_{20}ClN_3O$ + H^+ requires 438.1373); **1.1.1.4** (80% yield) m/z 453.1451 ($C_{27}H_{21}ClN_4$ + H^+ requires 453.1482)
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