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Expeditious synthesis of imidazo[1,2-*c*]pyrimidines via a [4+1]-cycloaddition

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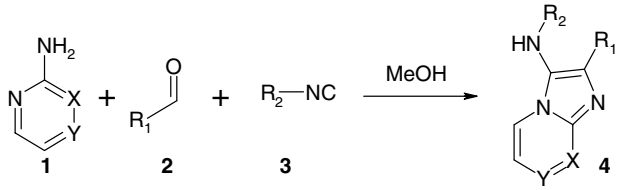
Abstract—A new and versatile synthesis of imidazo[1,2-*c*]pyrimidines via a [4+1]-cycloaddition is described. The reported novel synthetic approach leads to pharmacologically interesting scaffolds containing three points of potential diversity, which previously were not accessible under conventional conditions. In addition, this novel synthetic procedure is amenable to the assembly of libraries with this interesting core structure.

In 1998 a number of independent research groups described a new three component condensation (3CC) of heterocyclic amidine-systems (1), aldehydes (2) and isocyanides (3) producing highly diverse 3-amino-substituted imidazo[1,2-*a*]heterocycles (4)[1–4] (Scheme 1). These structural moieties can be found in pharmacological compounds such as benzodiazepine receptor agonists,[5] anti-inflammatory agents,[6] inhibitors of gastric acid secretion,[7] calcium channel blockers[8] and anti-bacterials.[9]

Since that time, additional groups have published their studies on this pivotal reaction in the Lead Discovery setting, which include a microwave facilitated process



Scheme 1. Imidazo[1,2-*a*]heterocycles via 3CC.

and a Design of Experiment (DOE) study.[10–14] Despite this work, to the best of our knowledge the successful use of very electron deficient 4-amino-pyrimdines, yielding imidazo[1,2-*c*]pyrimidines, has never been reported.

In fact using the initially reported classical one-pot room temperature conditions with 4-amino-pyrimidines in the 3CC, gives only nominal amounts of the product (typically <1%; see Table 1). Considering the therapeutic importance of the chemo-type potentially derived from 4-amino-pyrimidines in the 3CC, investigations in this laboratory were directed at developing a new methodology to gain access to this biologically relevant chemical space.

Thus, an alternative synthetic approach was sought and the results are described in the following text. Initial efforts focused on pre-formation of the Schiff base involved in the reaction pathway to these products. Thus several imines derived from 4-amino-pyrimidines were synthesized and isolated for further functionalization (Table 2, **7a**–**d**).[15] These imines were then subjected to an equi-molar amount of isocyanide in dry toluene and stirred for 16 h under nitrogen at 100 °C.[16] Under these conditions, the desired bi-cyclic products were formed via thermal [4+1]-cycloaddition with a high consumption of starting materials (Scheme 2). The expected compounds were purified and isolated in moderate yields (Table 4, **8a**–**n**). Data obtained from ^{1}H NMR, ^{13}C NMR, DEPT and HPLC–MS experiments was

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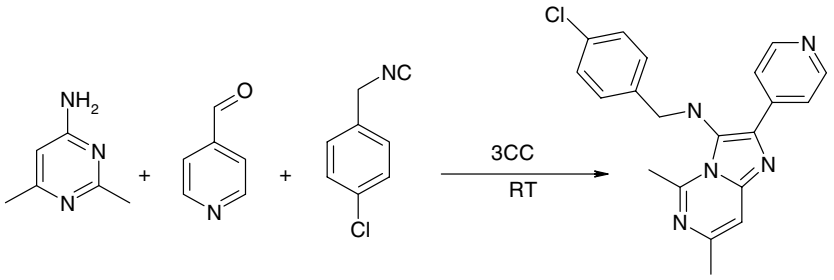
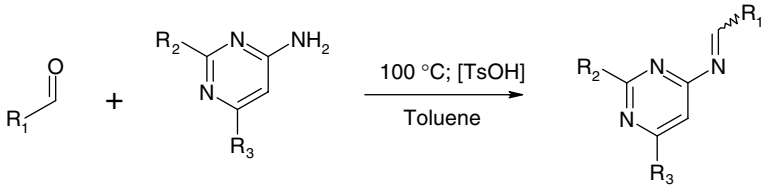
Table 1. Reaction-screen under classical 3CC conditions



Catalyst	Solvent	
	TFE	MeOH/TMOF/$CHCl_3$ = 1/1/1
TsOH	Amount of product <1%	Amount of product ≪1%
CH_3COOH	Passerini-product	Passerini-product
$HClO_4$	No product	No product
$Yb(OTf)_3$	No product	Passerini-product
$Sc(OTf)_3$	No product	Passerini-product
$InCl_3$	No product	No product

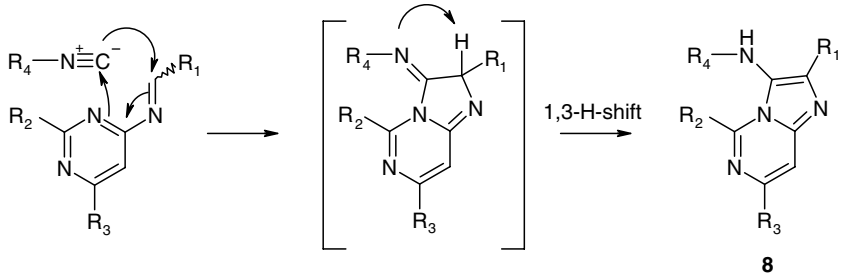
TFE: trifluorethanol; TMOF: trimethylorthoformate; rt: room temperature.

Table 2. Performed imine condensations



5 **6** **7**

ID	R_1	R_2	R_3	Product
1	3-C_5H_4N	CH_3	CH_3	**7a**
2	3-C_5H_4N	H	CH_3O	**7b**
3	4-C_5H_4N	H	CH_3O	**7c**
4	3-C_5H_4N	H	H	**7d**
5	C_6H_5	CH_3	CH_3	**7e**
6	F–C_6H_4	CH_3	CH_3	**7f**
7	CH_3O–C_6H_4	CH_3	CH_3	**7g**
8	NO_2–C_6H_4	CH_3	CH_3	**7h**
9	3,4-Cl_2–C_6H_3	CH_3	CH_3	**7i**



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Scheme 2. Imidazo[1,2-*c*]pyrimidines via [4+1]-cycloaddition.

consistent with that of the expected imidazo[1,2-*c*]-pyrimidine chemo-types, with all isolated compounds having purities of >90%.

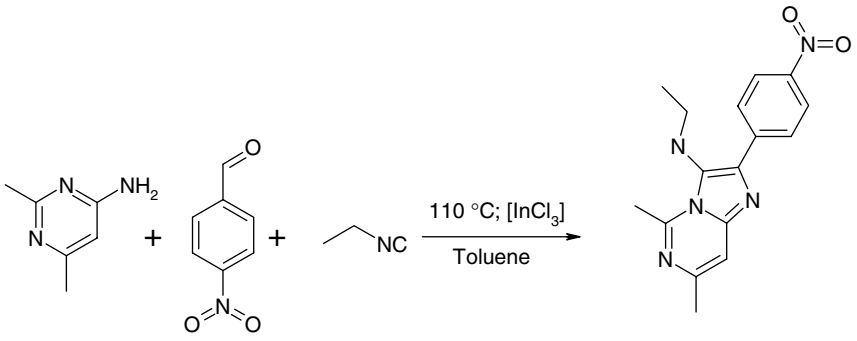
Unfortunately this novel two-step approach was only successful for very electron deficient pyridine carbaldehydes.

Attempts at imine formation and isolation with benzaldehydes were unsuccessful (Table 2, **7e–i**). In these cases, it was suspected that the electrophilicity of the aldehydes was too low to enable sufficient condensation with electron deficient amidine-systems. However, by application of Lewis acid catalysis, it was anticipated that the likelihood of sufficient in situ imine-formation would be far higher with this class of aldehyde. Furthermore the use of $InCl_3$ as Lewis acid catalyst in imino Diels–Alder reactions is described.[17] Therefore we expect that $InCl_3$ could also accelerate a thermal [4+1]-cycloaddition with isocyanide. Side reactions like isocyanide decomposition and hydrolysis could be suppressed by the use of aprotic solvents, hence the decision to employ toluene. To prove this theory, equimolar amounts of starting materials were mixed in dry toluene.[18] The reaction mixture was then stirred in a pressure tube with a catalytic amount of $InCl_3$ for 24–72 h at 110 °C. The clean conversion of starting material was monitored by HPLC–MS, but unfortunately it was not possible to raise the conversion above 50%, even under microwave irradiation. Therefore the desired products could only be isolated with moderate yields. The expected compounds were characterized by HPLC–MS and NMR experiments (Table 4, **8o–s**).

The influence of different concentrations of $InCl_3$ was also investigated (see Table 3), and as expected best results were observed with a catalytic amount of $InCl_3$. Consequently, the reactions (**8o–s**) were performed with a catalytic amount of $InCl_3$. The overall yields (Table 4) and purities via this one pot procedure were comparable to those of products (**8a–n**) attempted via two-step methodology except that reaction times were considerably longer. For proving the advantage of the two-step procedure, a selected synthesis, as exemplified by compound **8a** was repeated under one-pot conditions, whereby a lower conversion of starting material and the formation of several byproducts was observed. Thus the two-step procedure is preferable for entry 1–14 (Table 4).

In summary, this article describes an efficient synthesis of a variety of poly-substituted imidazo[1,2-*c*]pyrimidines (Table 3). Of additional note, the reactivity range

Table 3. Variation of catalyst concentration



$InCl_3$	Reaction time	Conversion
No catalyst	72 h/110 °C	Traces
5 mol %	72 h/110 °C	37%
1 equiv	72 h/110 °C	Diverse side reactions

Table 4. Synthesized 4-amino-imidazo[1,2-*c*]pyrimidines

Entry	R_1	R_2	R_3	R_4	Yield (%)	Product
1	3-C_5H_4N	CH_3	CH_3	C_2H_5	42	**8a**
2	3-C_5H_4N	CH_3	CH_3	C_6H_5–$(CH_2)_2$	33	**8b**
3	3-C_5H_4N	CH_3	CH_3	3-F–C_6H_4	27	**8c**
4	3-C_5H_4N	H	CH_3O	C_6H_4–CH_2	31	**8d**
5	3-C_5H_4N	H	CH_3O	4-Cl–C_6H_4–CH_2	29	**8e**
6	3-C_5H_4N	H	CH_3O	4-CH_3O–C_6H_4–CH_2	30	**8f**
7	4-C_5H_4N	H	CH_3O	4-CH_3O–C_6H_4	26	**8g**
8	4-C_5H_4N	H	CH_3O	C_6H_5	32	**8h**
9	4-C_5H_4N	H	CH_3O	C_5H_{11}	39	**8i**
10	3-C_5H_4N	H	CH_3O	3-F–C_6H_4	28	**8j**
11	3-C_5H_4N	H	H	4-CH_3O–C_6H_4–CH_2	27	**8k**
12	3-C_5H_4N	H	H	3-CH_3–OC_6H_4	26	**8l**
13	4-C_5H_4N	H	H	C_6H_5	21	**8m**
14	4-C_5H_4N	H	H	C_5H_9	29	**8n**
15	C_5H_5	CH_3	CH_3	C_2H_5	34	**8o**
16	F–C_6H_4	CH_3	CH_3	C_2H_5	32	**8p**
17	CH_3O–C_6H_4	CH_3	CH_3	C_2H_5	30	**8q**
18	NO_2–C_6H_4	CH_3	CH_3	C_2H_5	37	**8r**
19	3,4-Cl_2–C_6H_3	CH_3	CH_3	C_2H_5	33	**8s**

of the isocyanides was broad, opening avenues to the possibility of preparing cassettes of such chemotypes via combinatorial processes. With final products containing three points of potential diversity and a facile and rapid production protocol, access to large sized compound libraries with the aforementioned core structure is now feasible.

Acknowledgements

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15. *Typical procedure*:
The aldehyde (5 mmol) and the amidine (5 mmol) were refluxed with a catalytic amount of *p*-toluenesulfonic acid in 5 mL dry toluene for 2 h. Afterwards the reaction mixture was cooled down and the desired imines precipitated. The solid imines were collected and used in the next reaction step without further purification.
16. *Typical procedure*:
The imine (0.5 mmol) and isocyanide (0.5 mmol) were suspended in 3 mL dry toluene. The reaction mixture was stirred under nitrogen for 16 h at 100 °C. When the reaction was completed, the solvent was evaporated and the resulting residue was dissolved in ethyl acetate and filtered through a pad of silica. After evaporation of the solvent, the crude product was purified by preparative HPLC.
Compound **8a** was isolated in a 42% yield as a yellow-brown oil.
^{1}H NMR (DMSO, 250.13 MHz): 1.09 (t, $^3J = 7.1$ Hz, 3H, CH_3); 2.36 (s; 3H, CH_3); 2.88–2.99 (m, 2H, CH_2); 3.02 (s; 3H, CH_3); 4.68 (t, $^3J = 5.7$ Hz, 1H, NH); 7.16 (s, 1H, C$_4H$N$_2$); 7.47 (dd, $^3J_a = 4.36$ Hz; $^3J_b = 7.90$ Hz, 1H, C$_5H_4$N); 8.41–8.45 (m, 1H, C$_5H_4$N); 8.51 (d, $^3J =$ 7.90 Hz, 1H, C$_5H_4$N); 9.30 (s, 1H, C$_5H_4$N).
^{13}C NMR (DMSO, 62.90 MHz): 14.8 (*C*H$_3$); 21.2 (*C*H$_3$); 22.7 (*C*H$_3$); 44.5 (*C*H$_2$); 107.3; 123.5; 127.3 (Cq); 133.8; 134.1 (Cq); 143.1 (Cq); 147.6 (Cq); 147.8; 148.1; 148.2 (Cq). MS (ESI): $m/z = 268.5$ [M+H]$^+$.
Compound **8j** was isolated in a 28% yield as a yellow-brown oil. ^{1}H NMR (CD$_3$CN, 250.13 MHz): 3.93 (s, 3H, CH_3O); 6.38–6.56 (m, 3H, C$_6H_4$); 6.76 (d, $^5J = 1.10$ Hz, 1H, C$_4H$N$_2$); 7.11–7.20 (m, 1H, C$_6H_4$); 7.36 (dd, $^3J_a = 4.90$ Hz; $^3J_b = 8.05$ Hz, 1H, C$_5H_4$N); 7.97 (s, 1H, NH); 8.28–8.33 (m, 1H, C$_5H_4$N); 8.47–8.66 (m, 1H, C$_5H_4$N); 8.65 (d, $^5J = 1.10$ Hz, 1H, C$_4H$N$_2$); 9.16 (s, 1H, C$_5H_4$N). MS (ESI): $m/z = 336.0$ [M+H]$^+$. Note several examples exist of toluene being used as the reaction medium of the Ugi reaction. See: (a) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.*, **2001**, *3*, 4079–4082; (b) Janvier, P.; Xiaowen, S.; Bienayme, H.; Vors, J.-P.; Zhu, J. *J. Am. Chem. Soc.*, **2002**, *124*, 2560–2567.
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18. *Typical one-pot procedure*:
The aldehyde (0.5 mmol), amidine (0.5 mmol) isocyanide (0.5 mmol) and 5 mol % of InCl$_3$ were suspended in 3 mL dry toluene. The reaction mixture was stirred for 24–72 h at 110 °C in pressure tubes. When the reaction was completed, the solvent was evaporated and the resulting residue was dissolved in ethyl acetate and filtered through a pad of silica. After evaporation of the solvent the crude product was purified by preparative HPLC.
Compound **8o** was isolated in a 34% yield as a yellow-brown oil. ^{1}H NMR (CDCl$_3$, 250.13 MHz): 1.18 (t, $^3J = 6.89$ Hz, 3H, CH_3CH$_2$); 2.45 (s, 3H, CH_3); 3.00–3.06 (m, 3H, CH_2, NH); 3.10 (s, 3H, CH_3); 7.09 (s, 1H, CH=C); 7.32–7.49 (m, 3H, C$_6H_5$); 7.90–7.94 (m, 2H, C$_6H_5$). MS (ESI): $m/z = 266.9$ [M+H]$^+$.
Compound **8r** was isolated in a 37% yield as a yellow-brown oil. ^{1}H NMR (CD$_3$CN, 250.13 MHz): 1.17 (t, $^3J = 7.11$ Hz, 3H, CH_3CH$_2$); 2.38 (s, 3H, CH_3); 2.99–3.04 (m, 2H, CH_2); 3.01 (s, 3H, CH_3); 4.08 (t, $^3J = 5.68$ Hz, 1H, NH); 7.05 (s, 1H, CH=C); 8.26 (d, $^3J = 9.17$ Hz, 2H, C$_6H_4$); 8.37 (d, $^3J = 9.17$ Hz, 2H, C$_6H_4$). MS (ESI): $m/z = 312.3$ [M+H]$^+$.
Compound **8s** was isolated in a 33% yield as a yellow-brown oil. ^{1}H NMR (CDCl$_3$, 250.13 MHz): 1.21 (t, $^3J = 6.90$ Hz 3H, CH_3CH$_2$); 2.45 (s, 3H, CH_3); 2.90–2.92 (m, 1H, NH); 2.99–3.05 (m, 2H, CH_2); 3.07 (s, 3H, CH_3); 7.06 (s, 1H, CH=C); 7.49 (d, $^3J = 8.54$ Hz, 1H, C$_6H_3Cl_2$); 7.84 (d, $^3J_a = 8.54$ Hz, $^3J_b = 1.91$ Hz, 1H, C$_6H_3Cl_2$); 8.14 (d, $^3J = 1.91$ Hz, 1H, C$_6H_3Cl_2$). MS (ESI): $m/z = 335.0$; 337.0 [M+H]$^+$.