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

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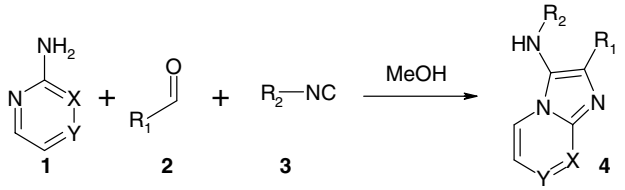
Abstract—A new and versatile synthesis of imidazo[1,2-*c*]pyrimidines via a [4+1]-cycloaddition is described. The reported novel synthetic approach leads to pharmacologically interesting scaffolds containing three points of potential diversity, which previously were not accessible under conventional 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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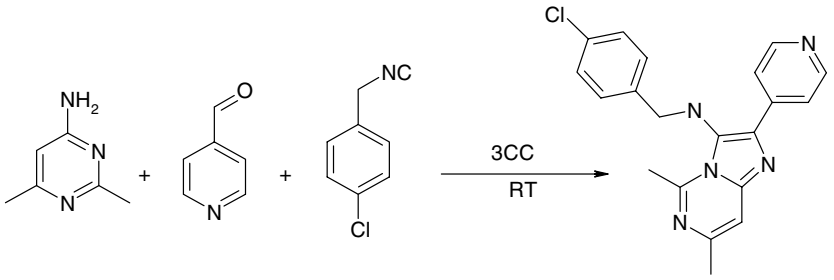
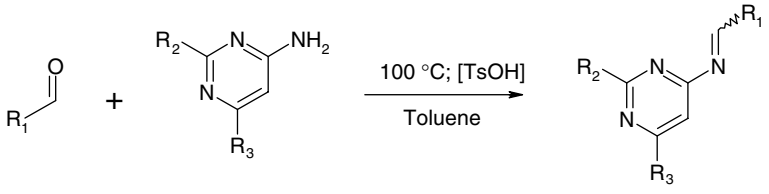
Table 1. Reaction-screen under classical 3CC conditions



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

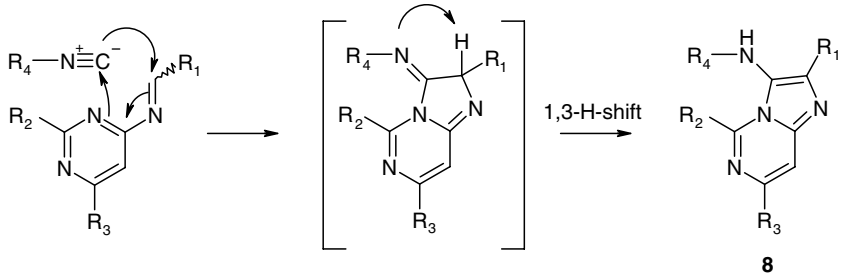
TFE: trifluorethanol; TMOF: trimethylorthoformate; rt: room temperature.

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.