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Re-evaluation of the outcome of a multiple component reaction—2- and 3-amino-imidazo[1,2-*a*]pyrimidines?

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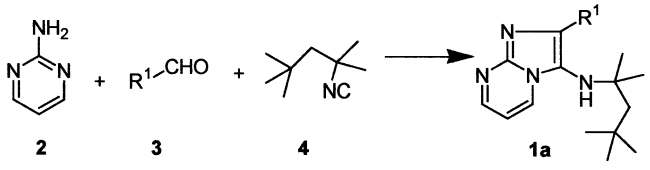
Abstract—Multi-component reactions between aldehydes, isonitriles and 2-aminoazines do not always give the expected products.

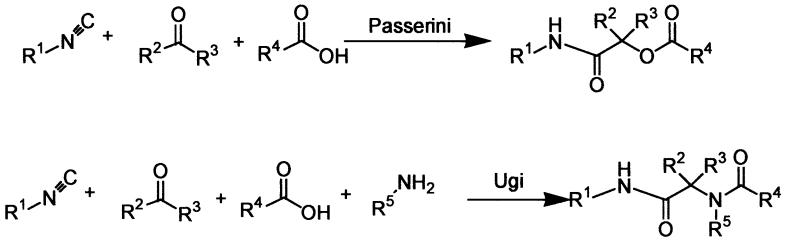
There are now large numbers of multi-component-reactions (MCRs) known in the literature. Passerini developed one of the first in 1921, with the treatment of an isonitrile with a carboxylic acid and an aldehyde or ketone to give α-acyloxy amides (Scheme 1a).[1] This reaction was later expanded by Ugi in 1961, to give bis-amides, by the introduction of ammonia (or an amine component) giving the four component MCR so well known today (Scheme 1b).[2]

Recently, a new variant of this reaction was described by Blackburn,[3] Bienaymé[4] and Groebke,[5] which enabled the ready synthesis of imidazo[1,2-*a*]azines by the acid-catalysed condensation of an aldehyde, an isonitrile and a 2-aminoazine to give 3-alkyl-amino-2-substituted-imidazo[1,2-*a*]azines **1a** (Scheme 2). Since imidazo[1,2-*a*]azines have emerged as versatile drug templates in broad areas of medicinal chemistry, ranging from cardiac stimulating, anti-inflammatory, anti-ulcer, and anti-viral based therapies[6], a parallel synthesis to these compounds is dramatically enhanced by a route comprising an efficient one-pot MCR. Subsequently, imidazo[1,2-*a*]azine libraries have been prepared both in solution and on the solid phase,[3,7] where one entity of the MCR is used to 'capture' the desired final product on the resin, with the Rink amine linker often proving to be the linker of choice for the provision of the amine component.

During the synthesis of a library of imidazo[1,2-*a*]-pyrimidines, while seeking to evaluate the performance of different catalysts ($Sc(OTf)_3$, AcOH, and $HClO_4$) in a model reaction using 2-aminopyrimidine as the amine component with five different aldehydes and



Scheme 2. Model multi-component imidazo[1,2-*a*]azine synthesis (from Ref. 3). All reagents 0.1 M, 48 h, catalysed with either (i) 0.05 equiv. $Sc(OTf)_3$, MeOH/DCM (1:4), (ii) 2.0 equiv. glacial AcOH, MeOH, or (iii) 1 M $HClO_4$, MeOH.



Scheme 1. (a) Passerini and (b) Ugi reactions.

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two different isonitrile components, it became clear that the products isolated were not only those which had been reported previously.[3,4]

The initial condensation reaction of 2-aminopyrimidine **2**, methyl-4-formyl-benzoate **3**, and 1,1,3,3-tetramethyl-butylisonitrile **4** (Scheme 2) was initially catalysed with 0.05 equiv. of $Sc(OTf)_3$ to give a yellow solid in 33% yield which on the basis of MS and NMR evidence we assumed was the expected 3CC product, namely the 3-alkylamino-2-substituted-imidazo[1,2-*a*]pyrimidine **1a**. According to several publications the low product yield could be attributed to the incomplete consumption of the amine component. However, closer scrutiny indicated that all the amine component had been consumed and a more polar second adduct had in fact been formed in 23% yield, which exhibited an R_f value very similar to the starting 2-aminopyrimidine **2**. Interestingly this compound had ^{1}H NMR and MS data that were essentially identical to those obtained for the suspected product **1a**. To allow the exact assignment of the two structures, the two samples were crystallised and subjected to X-ray analysis resulting in the two structures shown in Fig. 1.

The rationale for the formation of these two products is shown in Scheme 3. Thus the initial iminium species can be generated by addition of either the 2-amino group or the ring nitrogen to the aldehyde. The iminium species is then attacked by the isonitrile in the accepted manner followed by intramolecular cyclisation and aromatisation. In the latter case the expected 3-amino substituted product is formed, while in the former the mechanism proposed gives the 2-amino derivatised product. The question then arises as to which product is favoured in which case.

In the case of 2-aminopyrimidine, the symmetry of the starting material might be expected to enhance the yield of the 2-alkylamino product that might be obtained compared to other aminoazines. The relative nucleophilicity of the amines is another consideration. To the best of our knowledge, this is the first reported synthesis of 2-alkyl-amino-3-substituted-imidazo[1,2-*a*]pyrimidine derivatives **1b** using MCR protocols.

A series of reactions was carried out to look for trends in the formation of the two products **1a**,**b** varying the

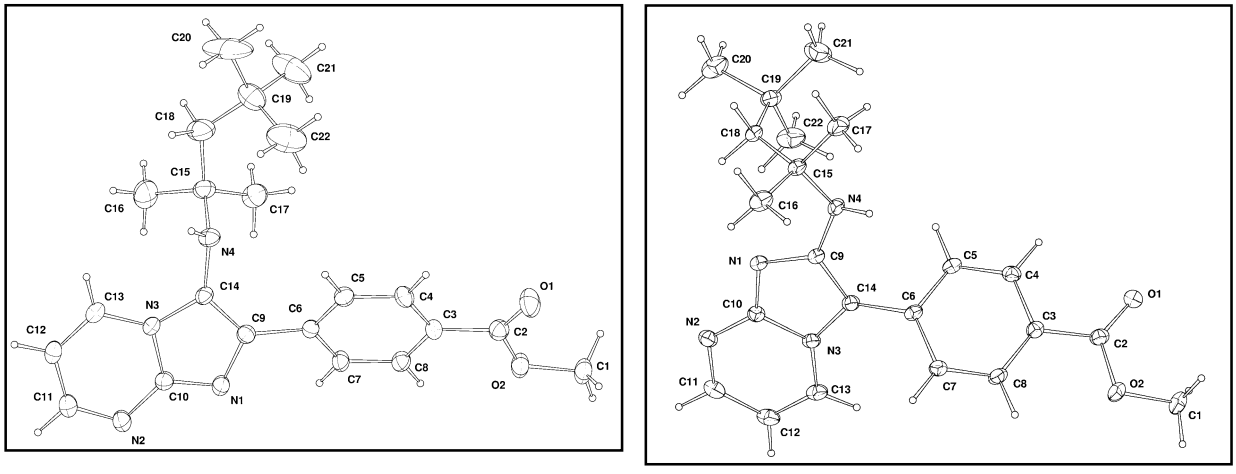
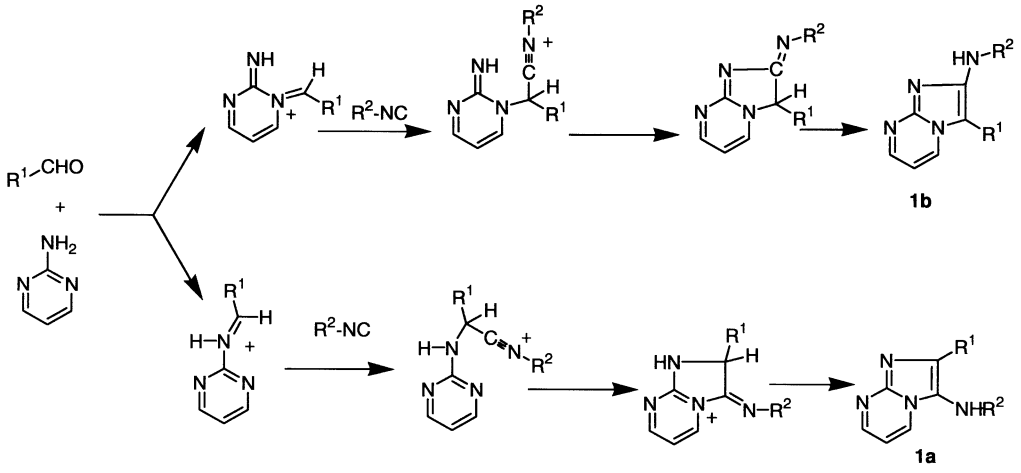


Figure 1. X-Ray structures of the two isolated substituted imidazo[1,2-*a*]pyrimidines **1a** (left) and **1b** (right).



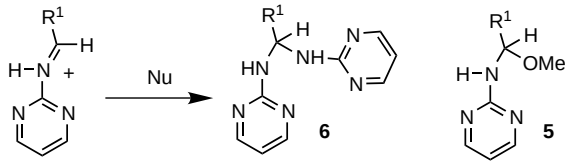
Scheme 3. Mechanistic rationale for the formation of the 2- and 3-amino-imidazo[1,2-*a*]pyrimidines.

Table 1. Substituted imidazo[1,2-*a*]pyrimidines prepared by multi-component condensation

Entry no.	Temp. (°C)	Catalyst	Aldehyde	Isonitrile	**1a** (Yield%)	**1b** (Yield%)
1	20	$Sc(OTf)_3$	ArCHO	$CNCMe_2CH_2Bu^t$	28	37
2	20	$Sc(OTf)_3$	*p*CHOArCO_2Me	$CNCMe_2CH_2Bu^t$	33	23
3	20	AcOH	*p*CHOArCO_2Me	$CNCMe_2CH_2Bu^t$	15	0
4	20	$HClO_4$	*p*CHOArCO_2Me	$CNCMe_2CH_2Bu^t$	11	11
5	20	$Sc(OTf)_3$	ArCH_2CH_2CHO	$CNCMe_2CH_2Bu^t$	34	33
6	50	$Sc(OTf)_3$	ArCHO	$CNCMe_2CH_2Bu^t$	40	35
7	50	$Sc(OTf)_3$	*p*CHOArCO_2Me	$CNCMe_2CH_2Bu^t$	36	32
8	50	$Sc(OTf)_3$	*p*CHOArOMe	$CNCMe_2CH_2Bu^t$	34	26
9	50	$Sc(OTf)_3$	2-C_4H_3S-CHO	$CNCMe_2CH_2Bu^t$	65	13
10	50	$Sc(OTf)_3$	ArCHO	$CNBu^t$	20	32

aldehyde and the isonitrile components. Overall there was little variation with the choice of the catalyst being the dominant feature. This side reaction might well explain the low yields reported by others[4] when using pyrimidines in these MCRs (Table 1).

Another novel product was also isolated. It is well known that the iminium cation shown in Scheme 4 can be trapped with methanol to give the by-product **5**. However, the bis(aminopyrimidine) derivative **6** was also observed here (although in low yield (5%)), generated by trapping of the iminium species by the azine. The structure of this derivative was also confirmed by ^1H and ^{13}C NMR, and X-ray crystallography.



Scheme 4. By-products isolated and characterised during aminoimidazo[1,2-*a*]pyrimidine synthesis.

In conclusion, these results suggest that a certain amount of reflection on the presumed structures from a MCR library is warranted. In this series of experiments a new series of MCR products have been identified which provide a novel scaffold for biological screening.

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