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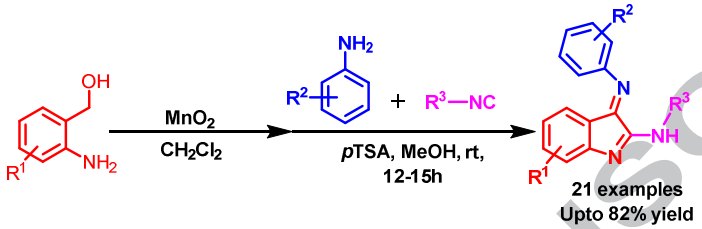

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Ugi three-component reaction of alcohols, amines and isocyanides: A new approach to the synthesis of cyclic amidines

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ABSTRACT

We have developed a novel, simple, efficient and one pot synthetic protocol for the synthesis of cyclic amidines via Ugi three-component reaction of alcohols, amines, and isocyanides.

[#] Authors contributed equally

1. Introduction

Multicomponent reactions (MCRs) are one pot process during which three or more substrates react in a single chemical step to yield a product that incorporates all of the substrates. Since MCRs represent one of the most powerful approaches for combinatorial chemistry and diversity-oriented synthesis due to the generation of an adduct in a single operation from three or more reactants with high atom economy and bond-forming efficacy.[1] Among many variants of multi-component transformations, Ugi reactions are the most powerful tool in the creation of molecular diversity.[2] In Ugi reaction, Mumm rearrangement is the key step for the synthesis of amide prototype compounds whereas several reactions of isocyanides with amines and aldehydes/ketones have been reported which do not involve Mumm rearrangement and lead to the biologically active molecules.[3]

Indole is a ubiquitous scaffold frequently found in numerous natural products and pharmaceutical agents.[4] Among widely existing indole derivatives 3-iminoindole, 2-aminoindole and 2,3-diaminoindoles are much more attractive due to their interesting biological activities like anti-Alzheimer, antibacterial, anti-inflammatory, antifungal and anticancer activities.[5-6] These prototypes are also important core structure of several natural products and some clinical candidates such as psychotrimine I (**1**)[7], kapakahine E (**2**)[8], kapakahine F (**3**)[8], chetomine (**4**)[9], chaetocochin I (**5**)[10] (Figure 1). 2,3-Diimino indoles exhibited antioxidant properties for lubricating oils.[11]

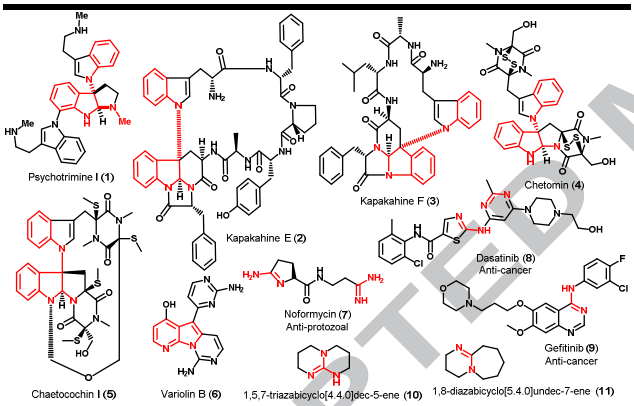


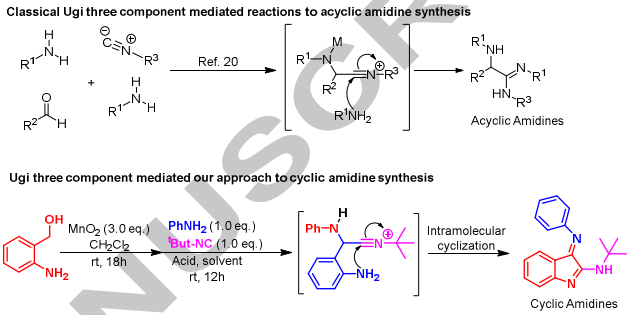
Figure 1: Representative examples of 2,3-diaminoindoles and amidines containing natural products, clinical candidates, and common bases.

Due to the easy conversion from imino to amino group and backward, it plays an interesting role in electrochemical reactions.[12] Similarly, azaindole another privileged structure and bioisostere of indole have attracted chemists, due to its interesting physiochemical[13] and pharmacological properties.[14] In recent years, several bioactive azaindoles have been reported, including the synthetic analogues of the natural variolin B (**6**),[15] for their CDK (cyclin dependent kinase) inhibitory activity.[16]

Amidines are valuable building blocks of various bioactive molecules[17] and have versatile application in organic reactions as superbases[18] (Figure 1). They have been utilized in the synthesis of heteroaromatic compounds such as benzimidazoles and quinazolines and acyl group transfer reactions for the synthesis of antimuscarinic compounds with improved pharmacokinetic and pharmacodynamic profile.[19] As per wide application of amidines in synthetic organic chemistry and medicinal chemistry, different methodologies have been developed for their synthesis, by employing various reagents such as *p*-toluenesulphinic acid, metal triflates, $BF_3.OEt_2$, ZnO nanoparticles, bromodimethylsulphonium bromide, molecular iodine and silica gel catalyzed reactions.[20] Besides, these successful methods, some other routes like Pinner reaction[21] and thioimidate[22] are also used for the synthesis of simple amidines from their corresponding nitriles. However, all these reported methods are only capable in the synthesis of acyclic amidines by utilization of expensive and unstable aldehydes and also 2.0 equiv. of amine is needed for the synthesis of α-amino amidines (Scheme 1).

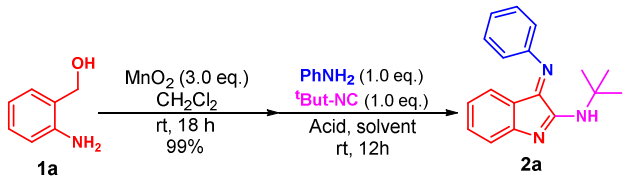
Therefore, we were interested in developing a novel protocol for the synthesis of cyclic amidines by the utilization of economical 2-aminobenzyl alcohols via Ugi three component reactions.

Scheme 1: Comparison of classical Ugi and our approach to the synthesis of amidines



For the synthesis of cyclic amidines, analogous to 2,3-diaminated indoles, we started from commercially available 2-aminobenzyl alcohol. Initially, 2-aminobenzyl alcohol was treated with MnO_2 (3.0 equiv.) in dichloromethane for 18 hrs to oxidize alcohol into their corresponding 2-aminobenzaldehyde based on earlier work.[23] This was further (without purification) treated with aryl amines and isocyanides in methanol for 12-15 hrs to get desired compound α-imino cyclic amidines. We began our scouting experiments to optimize the reaction conditions for the second step, with one pot synthesized starting material 2-aminobenzaldehyde. This was treated with aniline (1.0 equiv.), *tert*-butyl isocyanide (1.0 equiv.) and *p*-toluene sulphonic acid (*p*TSA, 100 mol%) as reaction promoter in dichloromethane (50 mL) solvent for 12h at room temperature, failed to deliver the desired product (**2a**) (Table 1, entry 1). In spite of the desired compound, it was yielded oligomeric mixture of side products. This was not surprising because the tendency of 2-aminobenzaldehyde to form polymers is well documented.[24] To prevent the formation of oligomers of 2-aminobenzaldehyde, we took *N*-Boc-2-aminobenzyl alcohol, but the reaction failed to produce the desired product (Table 1, entry 2). Our observations and possible mechanism of the formation of desired product **2a** revealed that the unprotected amine group is necessary for the substrate **1a**. Presumably, it may be happened due to the weak nucleophilicity of protected substrate and lesser extent of rearrangement at final step. With this analysis, again we started the reaction with same substrate **1a** and decreased the amount of *p*TSA to 50 mol%, and delighted with 10% yield of the desired product **2a** (Table 1, entry 3). The product **2a** was purified by column chromatography and characterized with the help of 1D, 2D-NMR, and mass spectrometric analysis. Now, the literature survey of multi-component reactions helped to choose methanol as a choice of solvent. Further optimizations were carried out by varying amount of *p*TSA and solvent.[25] Again, the use of *p*TSA (20 mol%) and methanol as solvent, afforded increased yield of the desired product **2a** (Table 1, entry 4).

Table 1: Optimization of reaction conditions[a]



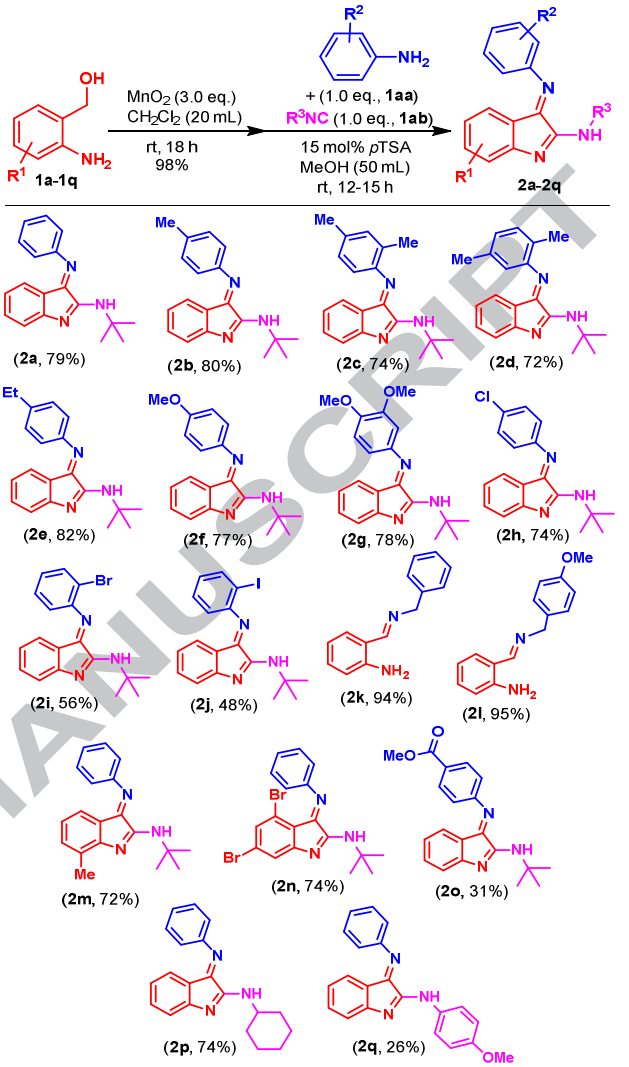
Entry	Acid	equiv. (mol%)	Solvent	Yield (%)[b]
1	*p*TSA	100	DCM	0[c]
2[d]	*p*TSA	100	DCM	0[c,e]
3	*p*TSA	50	DCM	10[c]
4	*p*TSA	20	MeOH	40[c]
5	***p*TSA**	**15**	**MeOH**	**79**
6	*p*TSA	10	MeOH	55
7	*p*TSA	15	MeCN	63
8[f]	*p*TSA	10	MeOH	56
9	*p*TSA	15	THF	40
10	*p*TSA	15	PhMe	45
11	*p*TSA	15	DMF	30
12	$BF_3.OEt_2$	15	MeOH	0[c]
13	$TiCl_4$	15	MeOH	52
14	$SnCl_4$	15	MeOH	48
15	$AlCl_3$	15	MeOH	35
16	$Ti(O^iPr)_4$	15	MeOH	Trace

[a]Reaction conditions: **1a** (1.0 mmol), Solvent (50 mL), [b]Isolated yields, [c]Oligomeric mixture, [d]2-*N*-Boc-aminobenzyl alcohol (1.0 mmol), [e]Undesired side products, [f]4.0 eq. MnO_2 was used.

Further, decreasing the amount of *p*TSA (15 mol%) in methanol, provided improved yield (79%) of the desired product **2a** (Table 1, entry 5). Though, there was no further improvement in yield of **2a** observed, on decreasing the amount of *p*TSA (10 mol%) and changing the choice of solvent (Table 1, entries 6-11). Besides, *p*TSA as an acid component, other Lewis acids were also screened and none of them were suitable for this multi-component reaction (Table 1, entries 12-16).

With a set of suitable reaction conditions developed, next, we investigated the scope of substrates and the generality of the methodology (Schemes 2 & 3). The optimized reaction conditions successfully applied to synthesize compounds **2b** and **2c** in very good yields, by using 4-methyl aniline and 2,4-dimethyl aniline respectively. One pot reaction of 2-aminobenzaldehyde generated from 2-aminobenzyl alcohol, 2,5-dimethyl aniline (**1ad**) and *tert*-butyl isocyanide (**1ab**) yielded compound **2d** in 72% yield. Fortunately, we got the crystals of the compound **2d**, and further X-ray analysis confirmed the structure and the *trans*-geometry of 3-imino group in the molecule (Figure 2). Again, the reaction of 2-aminobenzyldehydes with aryl amines having weak electron-withdrawing substituents like 4-chloroaniline (**1ah**) and *tert*-butyl isocyanide (**1ab**) provided better yield of product **2h** (74%) whereas other halogen containing substrates 2-bromoaniline (**1ai**) and 2-iodoaniline (**1aj**) provided moderate yields 56% and 48% of the products **2i** and **2j**, respectively. Presumably, this decrease in yield of the products **2i** and **2j** due to steric hindrance at reaction centre.

Scheme 2: Substrate scope of the reaction for the synthesis of α-imino cyclic amidines[a,b]



[a]Reaction conditions: (1). **1a** (1.0 mmol), MnO_2 (3.0 eq.), CH_2Cl_2 (20 mL), 18h. (2). $ArNH_2$ (1.0 eq.), R^3NC (1.0 eq.), *p*TSA (15 mol%), MeOH (50 ml), rt, 12-15h, [b]Isolated yields.

The formation of Schiff bases **2k** and **2l** instead of desired products from aliphatic amines *i.e. N*-benzylamine (**1ak**) and 4-methoxy *N*-benzylamine (**1al**), restricted us to choose only aryl amines. Again, this strategy was successfully applied for substituted 2-aminobenzyl alcohols like 3-methyl (**1m**) and 4,6-dibromo (**1n**), provided their corresponding products **2m** (72%) and **2n** (74%) in good yields. The substrate methyl 4-aminobenzoate (**1ao**) having strong electron-withdrawing group *i.e p*-COOMe (**1ao**) provided the product **2o** in poor yield. Similarly, the other isocyanides like cyclohexyl isocyanide (**1ap**) and *p*-methoxyphenyl isocyanide (**1aq**), also showed better compatibility and yielded their respective product **2p** and **2q** in moderate to good yield (Scheme 2).

For more generalization of the protocol and the interest to the synthesis of α-imino cyclic amidines more similar to azaindoles, we again investigated the methodology by taking (2-aminopyridin-3-yl)-methanol as a substrate (Scheme 3). The one pot reaction of the substrate **1r** with MnO_2 (3.0 equiv.) in DCM (20 mL) as solvent to produce corresponding *o*-aminoaldehyde followed by the evaporation of dichloromethane and then treated with aryl anilines (1.0 equiv.), alkyl isocyanides (1.0 equiv.) and

*p*TSA (15 mol%) in methanol (50 mL) for 12-15h to yield the corresponding desired products **2r-2t** at room temperature in good yields.

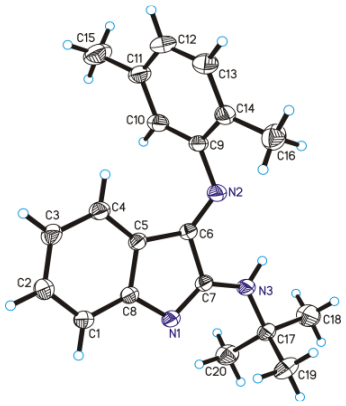
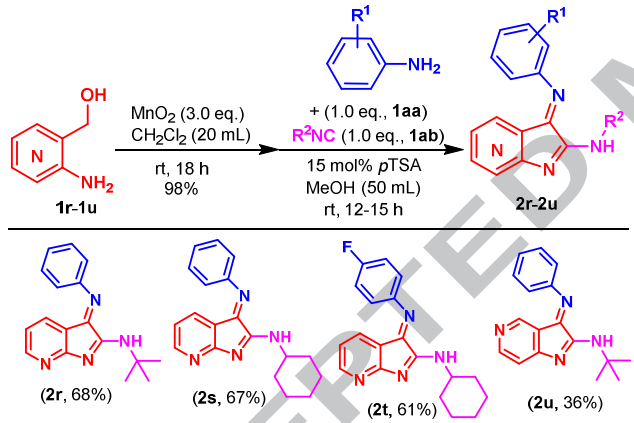


Figure 2: ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of the crystal structure of compound 2d determined at 293 K.

Similarly, the compound **2u** was prepared in moderate yield from its corresponding commercially available (4-aminopyridin-3-yl)-methanol (**1u**) at optimized reaction conditions.

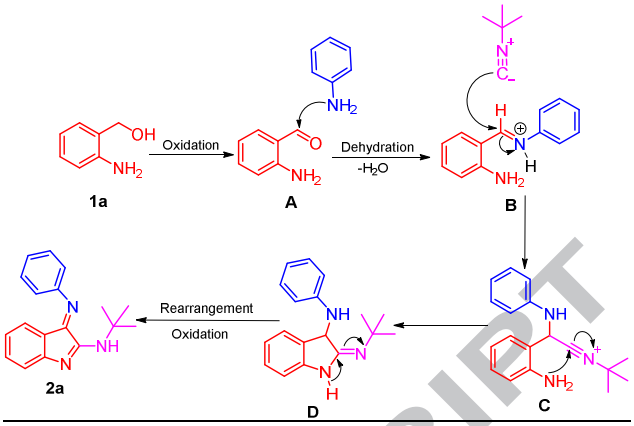
Scheme 3: Substrate scope of the methodology and the synthesis of α-imino cyclic amidines[a,b]



[a]Reaction conditions: (1). **1r** (1.0 mmol), MnO_2 (3.0 eq.), CH_2Cl_2 (20 mL), 18h. (2). $ArNH_2$ (1.0 eq.), R^2NC (1.0 eq.), *p*TSA (15 mol%), MeOH (50 ml), rt, 12-15h, [b]Isolated yields.

The mechanism for this three component Ugi reaction can be depicted as shown in Scheme 4. Initially, MnO_2 reacted with the substrate 2-aminobenzyl alcohol **1a** to give 2-aminobenzaldehyde **A** which reacted with aryl amine to provide Schiff base **B**. The Schiff base **B** undergoes acid promoted electrophilic reaction with isocyanide component and generated an electron deficient species **C**. The species **C** undergo intramolecular electrophilic reaction to yield intermediate **D**. The species **D** undergoes intramolecular rearrangement followed by oxidation[26] to yield the final product **2a**.

Scheme 4: Proposed mechanism of the reaction



In summary, we have developed one pot novel, simple, and efficient protocol for the synthesis of α-imino cyclic amidines. Likewise, we have developed a novel methodology for the synthesis of aminoindoles. In addition, we discussed the utilization of economical and readily available *o*-aminobenzyl alcohols instead of *o*-amino benzaldehydes which is quite expensive and have the stability problem. The operational simplicity, easy availability of starting materials and mild reaction conditions of this novel method, could be useful applications in organic chemistry and medicinal chemistry for the synthesis of substituted indoles.

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Supplementary data

Supplementary data is associated with this manuscript. It contains general experimental procedures, compounds characterization data, X-ray Crystallographic information for compound **2d** and copies of ^1H and ^{13}C-NMR spectra of all synthesized compounds.

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Highlights

- One pot synthesis of cyclic amidines
- Application of alcohols in multi-component reactions.
- Structural determination and conformational analysis by X-ray.
- Wide range of functional group tolerability.
- Good yield of the products.