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Me_3Al mediated domino nucleophilic addition/intramolecular cyclisation of 2-(2-oxo-2-phenylethyl)benzonitriles with amines; A convenient approach for the synthesis of substituted 1-aminoisoquinolines

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Abstract:

A simple and efficient protocol for the construction of 1-aminoisoquinolines was achieved by treating 2-(2-oxo-2-phenylethyl)benzonitrileswith amines in the presence of Me_3Al. The reaction proceeds via a domino nucleophilic addition with subsequent intramolecular cyclisation. This method provides wide variety of substituted 1-aminoisoquinolines with good functional group tolerance. Furthermore, the synthetic utility of this protocol was demonstrated in the successful synthesis of antitumor agent CWJ-a-5 in gram scale.

Introduction:

Heterocyclic compounds have always been recognized as the frameworks of interest in organic and medicinal fields. Particularly, aza-heteroarenes have attracted burgeoning interest in the research community owing to their structural and biological significance. The isoquinoline template represents a huge family of azaheterocyclics with unparalleled structural diversity, and is considered to be associated with a huge range of applications in medicinal and material sciences.[2] 1-Amino substituted isoquinoline derivatives are extensively studied owing to their therapeutic applications in the medicinal chemistry such as antimalarial, anti-Parkinson's and antitumor activity (Figure 1)[3].They also display remarkable enzymatic inhibitory activities on topoisomerase I,[4a]mutant B-Raf[4b] and exhibit antagonistic activities towards adenosine A3[4c]and PDE4B[4d] receptors. They are useful in the synthesis of phosphorescent materials,[5] fluorosensors,[6] and also found as chiral ligands in a variety of transition metal catalysts.[7]

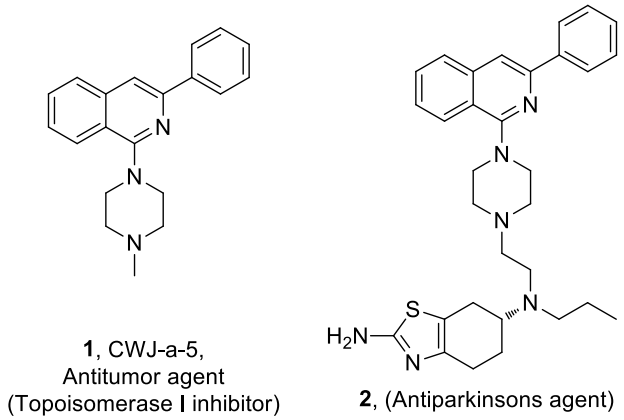
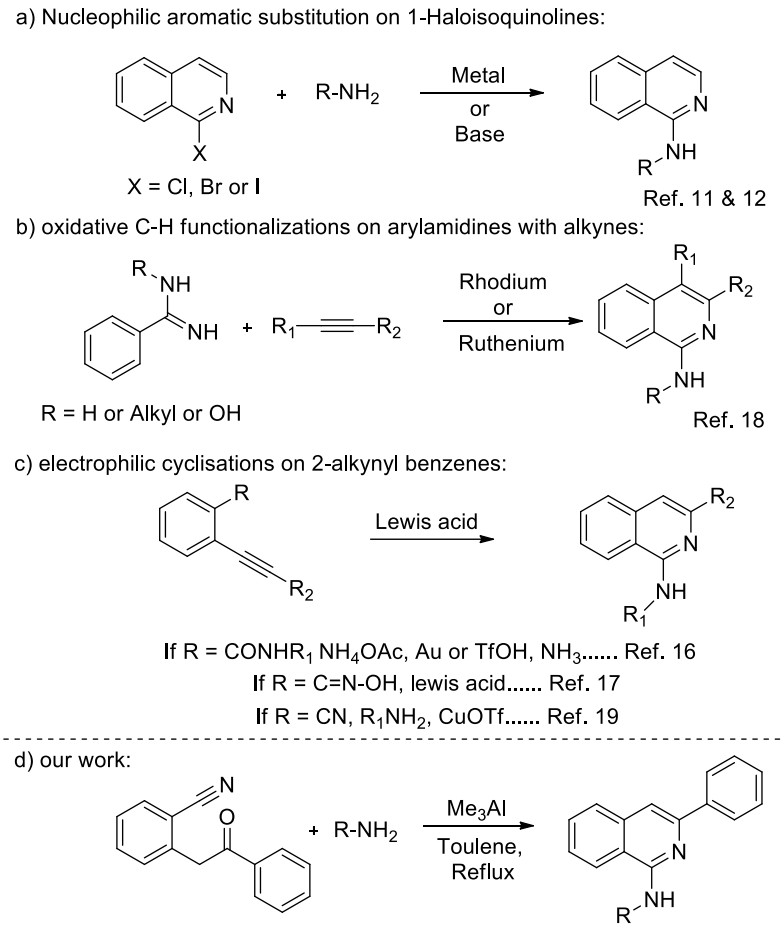


Figure 1: Biologically active 1-aminoisoquinolines

Given the pharmacological promiscuity of this scaffold, extensive efforts from different groups led to development of several approaches for the efficient construction of these heterocyclic frameworks. Traditional preparations for the 1-aminoisoquinolines include nucleophilic substitution of the 1-halo isoquinolines with amines either employing a base[8] or a transition metal catalyst.[9] However, pre-functionalization of isoquinolines to corresponding halogenated isoquinolines is the main limitation associated with these protocols as they require noxious halogenated acids for their starting materials preparation. Alternative strategies include, amination of isoquinolines *N*-oxides,[10] condensation of lithiated *o*-tolualdehyde *tert*-butylimines with nitriles,[11] electrophilic cyclization of 2-alkynylbenzamides[12] or 2-alkynylbenzaldoximes,[13] oxidative C-H functionalizations (coupling) on aryl and heteroaryl amidines with alkynes catalyzed by either rhodium or ruthenium,[14] or a metal catalyzed aminative cyclization of 2-alkynylbenzonitriles with secondary amines.[15] Despite the advantages associated with the aforementioned protocols such as the functional group tolerance and huge substrate scope, they are associated with few limitations including: utilization of metals, harsher reaction conditions, and difficulties in accessing the starting materials, which provoke the attention of synthetic community for the development of simple and efficient methodologies towards the construction of these heterocyclic frameworks.



Scheme 1: Comparison of our work with the previous approaches for the synthesis of 1-aminoisoquinolines

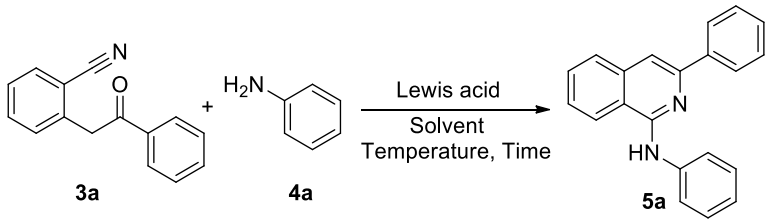
On the other hand organonitrile, the most accessible polar unsaturated carbon−nitrogen multiple bond, recognized as the most versatile chemo type in both the laboratory and industry because of their vital role displayed in various transformations.[1] They foray a major area in the synthesis of wide array of heterocyclic compounds by creating C-C, C-N, C-O and C-S bonds. The cyano group is considered as a versatile functional group in various organic syntheses because of its participation in various electrophilic, necleophilic and bipolar cycloaddition reactions and also serves as a precursor for the generation of important functional groups like amines, aldehydes, ketones and carboxylic acids. Even though the nitrile functional group is prevalent in the transformation into different functional groups, the synthetic approaches that incorporate the nitrogen atom of the cyano group into heterocyclic products is still challenging for the synthetic community. In an effort to develop a synthetic strategy for 1-aminoisoquinolines with increased selectivity and step economy by minimizing the generation of by-products, we hypothesized that if suitably tailored benzonitriles (**3**) were cyclized in an intramolecular fashion by installing nuclophilic nitrogen on to the nitrile functionality would generate 1-aminoisoquinolines. Herein we describe our efforts on Me_3Al mediated nucleophilic addition followed by an intramolecular

cyclisation of 2-(2-oxo-2-phenylethyl)benzonitrileswith amines to deliver 1-aminoisoquinolines and its successful application in the synthesis of antitumor agent CWJ-a-5.

Results and discussion:

Initially we targeted the synthesis of 2-(2-oxo-2-phenylethyl)benzonitrile (**3a**) by reacting 2-methylbenzonitrile with appropriate ester of benzoic acid. After having the starting material in hand, we commenced our investigations for the synthesis of 1-aminoisoquinolines by treating 2-(2-oxo-2-phenylethyl)benzonitrile (**3a**) with aniline in the presence of different Lewis acids under varying reaction parameters. Formation of no desired product was observed when the reaction was carried out in BF_3OEt_2 in toluene under reflux conditions (**Table 1**, entry 1). To our delight, the expected product **5a** was formed in trace amounts in the presence of $TiCl_4$ (**Table 1**, entry 2). $AlCl_3$ was also found to be inefficient for this transformation under similar reaction conditions yielding the desired product only in 16% yield (**Table 1**, entry 3). Interestingly, a substantial improvement in the yield of the reaction was observed by switching to Me_3Al in toluene at 110 ^oC, delivering 85% of the desired product in 8 h (**Table 1**, entry 4). Moreover, TMS-OTf was also found to be not much effective as $MeAl_3$ leading to generation of desired product in comparably lesser yields than Me_3Al (**Table 1**, entries 5). After identifying the suitable Lewis acid for this transformation, we next moved to optimize other reaction parameters such as solvent and temperature. From the list of solvents tested, it is clear that the toluene was the best solvent of choice over DCM, DCE, THF and dioxane (**Table 1**, entries 5 to 9). The temperature of the reaction also has notifiable impact on the yields, where increasing the reaction temperature beyond 110 ^oC or decreasing the reflux temperature led to slight decrease in the yields of the product (**Table 1**, entries 10 & 11). No desired product was observed if the reaction was performed at room temperature (**Table 1**, entry 12).

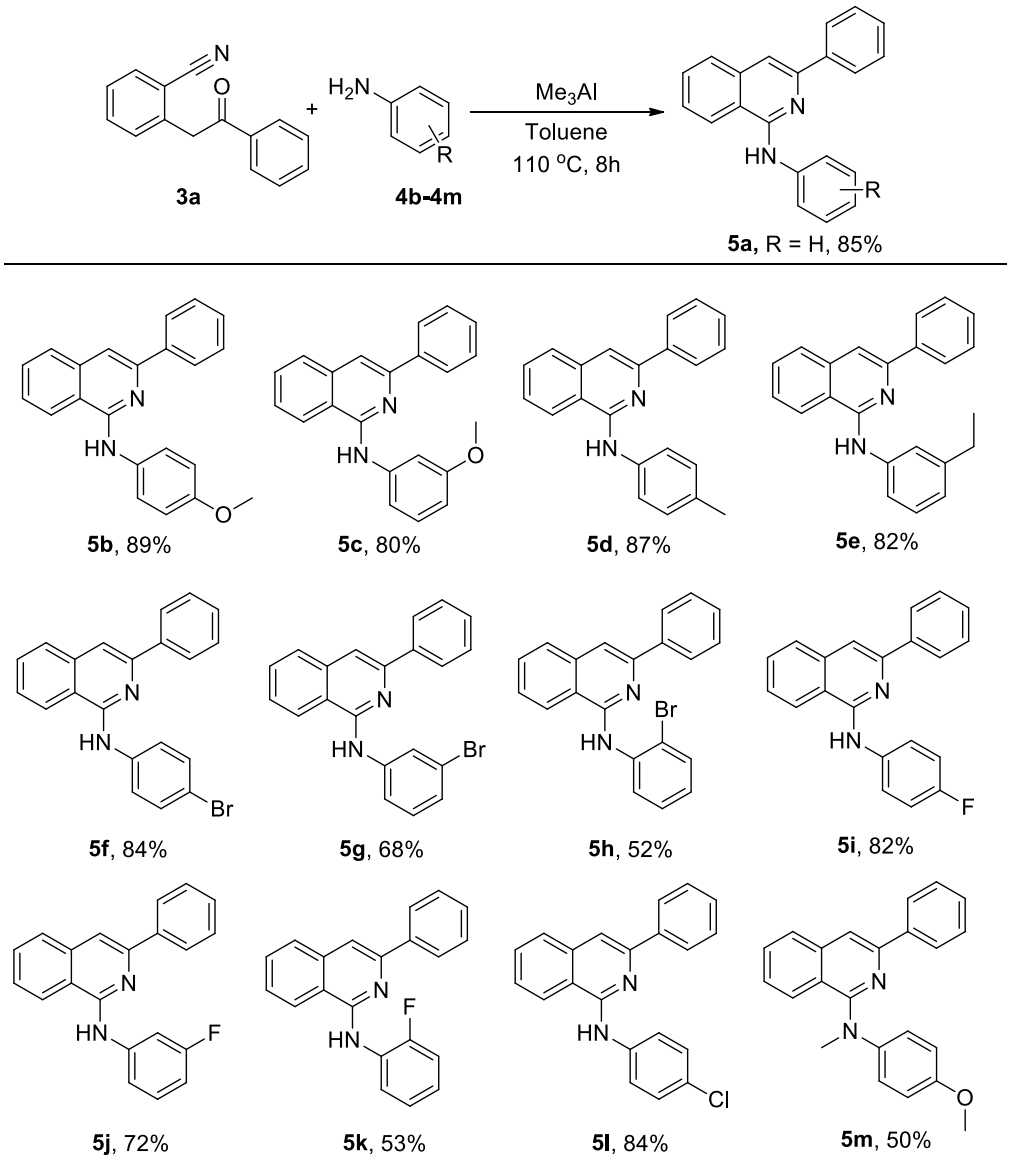
Table 1: Optimization of the reaction conditions for the synthesis of 1-aminoisoquinolines[a,b]



Entry	Lewis acid (equiv)	Solvent	Temperature (^oC)	Time (h)	Yeild (%)
1	BF_3OEt_2(2)	Toluene	110	8	-
2	$TiCl_4$(2)	Toluene	110	8	18
3	$AlCl_3$(2)	Toluene	110	8	16
4	**Me_3Al (2)**	**Toluene**	**110**	**8**	**85**
5	TMS-OTf(2)	Toluene	110	8	45
6	Me_3Al (2)	DCM	40	8	34
7	Me_3Al (2)	Dioxane	100	8	50
8	Me_3Al (2)	DCE	80	8	48
9	Me_3Al (2)	THF	60	8	27
10	Me_3Al (2)	Toluene	90	8	63
11	Me_3Al (2)	Toluene	130	8	82
12	Me_3Al (2)	Toluene	rt	12	-

[a]Reaction conditions: **3a**(1 equiv.), **4a**(1.5 equiv.) in the presence of Lewis acid(2 equiv.). [b]Isolated yield.

Scheme 2: Substrate scope of anilines for the synthesis of 1-aminoisoquinolines (**5a**-**5m**)[a,b]

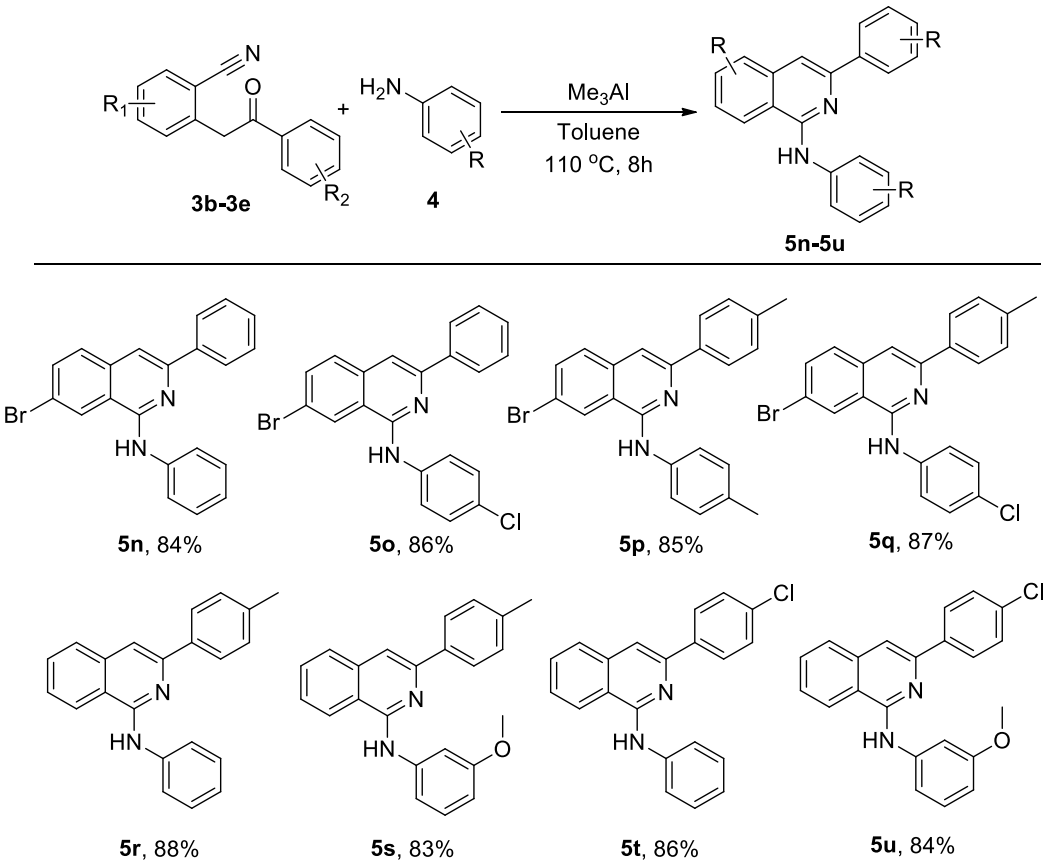


[a]Reaction conditions: **3**(1 equiv.), **4**(1.5 equiv.), Me_3Al (2 equiv.) in toluene at 110 °C for 8 h. [b]Isolated yield.

With the optimal reaction conditions in hand, we next explored the substrate scope of this protocol. Initially, 2-(2-oxo-2-phenylethyl)benzonitrile (**3a**) was treated with various anilines under the optimized reaction conditions (**scheme 2**). The yields of the reactions were not influenced significantly by the electronic effects of the substituents. However, the steric effects of the substituents have influenced the yields of the reaction substantially. Comparably better yields were observed with electron donating substituents than the electron with-drawing halo

groups on the aniline ring (**scheme 2**, **5b**-**5m**). Importantly, the steric effects on the aniline ring have huge impact on the reaction efficiency and efficacy, where para- and meta-substituents have minimal impact on the yields of the reaction delivering corresponding products in comparable yields (**scheme 2**).While least yields were observed with ortho-substituted anilines (**scheme 2**, **5h** & **5k**), which can be rationalized by the steric hindrance created by the ortho-substituents. It is also worth mention that secondary anilines also reacted with 2-(2-oxo-2-phenylethyl)benzonitrile and delivered corresponding product **5m**, albeit in lesser yields.

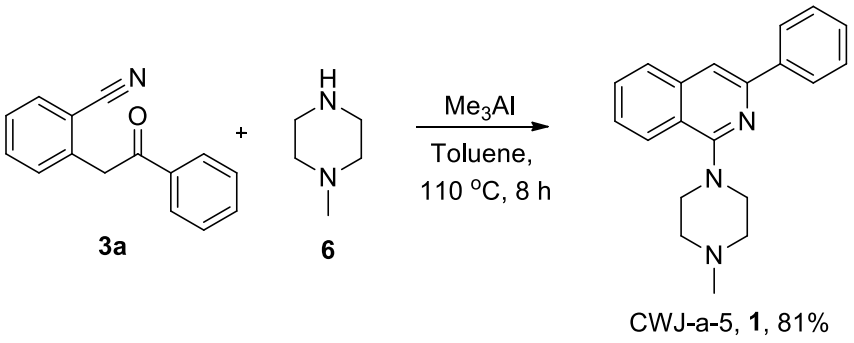
Scheme 3: Substrate scope of 2-(2-oxo-2-phenylethyl)benzonitrile (**3b**-**3e**) for the synthesis of 1-aminoisoquinolines (**5n**-**5u**)



[a]Reaction conditions: **3** (1 equiv.), **4** (1.5 equiv.), Me_3Al (2 equiv.) in toluene at 110 °C for 8 h. [b]Isolated yield.

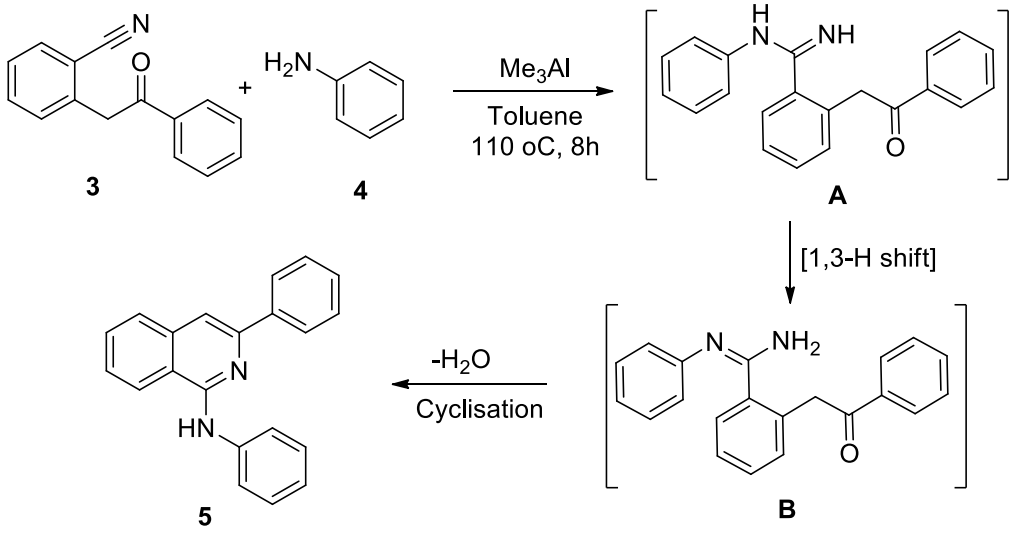
Later, the substrate scope of 2-(2-oxo-2-phenylethyl)benzonitriles was also examined. Scheme 3 summarizes the scope of 2-(2-oxo-2-phenylethyl)benzonitriles (**3b**-**3e**) towards the domino nucleophilic addition followed by an intramolecular cyclisation of 2-(2-oxo-2-phenylethyl)benzonitriles with amines under optimal reaction conditions. Accordingly, 2-(2-oxo-2-phenylethyl)benzonitriles substituted with various groups (Br, Cl and Methyl) on both the benzene rings were treated with different anilines to yield respective products (**5a**-**5m**) in good

yields (**scheme 3**). Examination of the effect of the substituents on the reaction revealed that the substituents on both the benzene rings of 2-(2-oxo-2-phenylethyl)benzonitriles have no significant impact on the yields of the reaction delivering corresponding products in almost similar yields (**3b**-**3e, scheme 3**).



Scheme 4: Gram scale synthesis of antitumor agent CWJ-a-5 (**1**)

The synthetic utility of this method was further extended towards the gram scale synthesis of antitumor agent CWJ-a-5. Accordingly, 2-(2-oxo-2-phenylethyl)benzonitrile (**3a**) was treated with 1-methylpiperazine (**6**) under the optimized reaction conditions for 8 h, which delivered antitumor agent CWJ-a-5 (**1**) in 81% (**scheme 4**).



Scheme 5: Proposed mechanism for the synthesis of 1-aminoisoquinolines

The mechanism for the formation of 1-aminoisoquinolines was depicted in scheme **5**. Initially it is believed that intermediate **A** would be generated *via* nucleophilic addition of amine on to the cyano group of 2-(2-oxo-2-phenylethyl)benzonitrile **3** in the presence of Me_3Al.This intermediate **A** undergoes [1,3-H shift] leading to the generation of *N*-Arylamidines intermediate **B**, which then undergoes intramolecular dehydrative condensation to yield the cyclic product **5**.

Conclusion:

In summary, an efficient Me_3Al mediated domino nucleophilic addition with a subsequent intramolecular cyclisation on 2-(2-oxo-2-phenylethyl)benzonitriles with amines was developed allowing access to widely substituted 1-aminoisoquinolines. Furthermore, the synthetic utility of this protocol was extended in the successful synthesis of antitumor agent CWJ-a-5 in gram scale. Good to higher yields, wide substrate scope are the key advantages associated with the current protocol. Further biological investigation on the synthesized compounds is currently underway.

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