Me₃Al-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

Krishna M. S. Adusumalli¹,², Lakshmi N. S. Konidena¹, Hima B. Gandham², Krishnaiah Kumari¹, Krishna R. Valluru¹, Satya K. R. Nidasanametla¹, Venkateswara R. Battula² and Hari K. Namballa¹,³

Abstract
A simple and efficient protocol for the construction of 1-aminoisoquinolines was achieved by treating 2-(2-oxo-2-phenylethyl)benzonitriles with amines in the presence of Me₃Al. The reaction proceeds via a domino nucleophilic addition with subsequent intramolecular cyclisation. This method provides a 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 the anti-tumor 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 [1-4]. The isoquinoline template represents a huge family of aza-heterocycles with unparalleled structural diversity, and is considered to be associated with a huge range of applications in medicinal and materials sciences [5-12]. 1-Amino...
substituted isoquinoline derivatives are extensively studied owing to their therapeutic applications in medicinal chemistry such as antimalarial, anti-Parkinson and antitumor activity (Figure 1) [13-17]. They also display remarkable enzymatic inhibitory activities on topoisomerase I, [18] mutant B-Raf [19] and exhibit antagonistic activities towards adenosine A3 [20] and PDE4B [21] receptors. They are useful in the synthesis of phosphorescent materials [22-24], fluorosensors [25], and also found as chiral ligands in a variety of transition metal catalysts [26-30].

Given the pharmacological promiscuity of this scaffold, extensive efforts from different groups led to the development of several approaches for the efficient construction of these heterocyclic frameworks (Scheme 1). Traditional preparations for 1-aminoisoquinolines include nucleophilic substitution of 1-haloisoquinolines with amines either employing a base [31-35] or a transition metal catalyst [36-40]. However, pre-functionalization of isoquinolines to the 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 isoquinoline N-oxides [41,42], condensation of lithiated o-tolualdehyde tert-butylinines with nitriles [43], electrophilic cyclization of 2-alkynylbenzamides [44,45] or 2-alkynylbenzal-
Table 1: Optimization of the reaction conditions for the synthesis of 1-aminoisoquinolines.

| Entry | Lewis acid (equiv) | Solvent | Temperature (°C) | Time (h) | Yield (%)
|-------|-------------------|---------|------------------|----------|---------|
| 1     | BF₃·OEt₂ (2)      | toluene | 110              | 8        | –       |
| 2     | TiCl₄ (2)         | toluene | 110              | 8        | 18      |
| 3     | AlCl₃ (2)         | toluene | 110              | 8        | 16      |
| 4     | Me₃Al (2)         | toluene | 110              | 8        | 85      |
| 5     | TMS-OTf (2)       | toluene | 110              | 8        | 45      |
| 6     | Me₃Al (2)         | DCM     | 40               | 8        | 34      |
| 7     | Me₃Al (2)         | dioxane | 100              | 8        | 50      |
| 8     | Me₃Al (2)         | DCE     | 80               | 8        | 48      |
| 9     | Me₃Al (2)         | THF     | 60               | 8        | 27      |
| 10    | Me₃Al (2)         | toluene | 90               | 8        | 63      |
| 11    | Me₃Al (2)         | toluene | 130              | 8        | 82      |
| 12    | Me₃Al (2)         | rt      | –                | –        | –       |

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

**Results and Discussion**

Initially we targeted the synthesis of 2-(2-oxo-2-phenylethyl)benzonitrile (3a) by reacting 2-methylbenzonitrile with the appropriate ester of benzoic acid in the presence of a base. 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 (4a) 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 BF₃·OEt₂ in toluene under reflux conditions (Table 1, entry 1). To our delight, the ex-
pected product 5a was formed in 18% yield in the presence of TiCl₄ (Table 1, entry 2). AlCl₃ 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 Me₃Al in toluene at 110 °C, 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 MeAl₃ leading to generation of the desired product in comparably lesser yields than Me₃Al (Table 1, entry 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 toluene was the solvent of choice, better than DCM, DCE, THF and dioxane (Table 1, entries 5–9). The temperature of the reaction also has notifiable impact on the yields, where increasing the reaction temperature beyond 110 °C or decreasing the reflux temperature led to a slight decrease in the yields of the product (Table 1, entries 10 and 11). No desired product was observed when the reaction was performed at room temperature (Table 1, entry 12).

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

![Scheme 2](image-url)
the substituents have influenced the yields of the reaction substantially. Comparably better yields were observed with electron donating substituents than the electron withdrawing halo groups on the aniline ring (Scheme 2, 5b–m). 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 the corresponding products in comparable yields (Scheme 2). While least yields were observed with ortho-substituted anilines (Scheme 2, 5b and 5k), which can be rationalized by the steric hindrance created by the ortho-substituents. It is also worth mentioning that secondary anilines also reacted with 2-(2-oxo-2-phenylethyl)benzonitrile (3a) and delivered the corresponding product 5m, albeit in lesser yields.

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–e) 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–m) 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 the corresponding products in almost similar yields (3b–e, Scheme 3).

Interestingly, different alkylamines such as methylamine, ethylamine and piperazines were also found to be compatible with the present protocol delivering the corresponding 1-aminoisouquinolines (5v–x) in good yields (Scheme 4). The synthetic utility of this method was further extended towards the gram-scale synthesis of the antitumor agent CWJ-a-5. Accordingly, 2-(2-oxo-2-phenyl-ethyl)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% yield (Scheme 4).

The mechanism for the formation of 1-aminoisouquinolines was depicted in Scheme 5. Initially, 2-(2-oxo-2-phenylethyl)benzonitrile (3) condenses with amine/aniline in the presence of Me₃Al to afford imine intermediate A.

Scheme 3: Substrate scope of 2-(2-oxo-2-phenylethyl)benzonitrile (3b–e) for the synthesis of 1-aminoisouquinolines (5n–u). Reaction conditions: 3 (1 equiv), 4 (1.5 equiv), Me₃Al (2 equiv) in toluene at 110 °C for 8 h. Isolated yields are shown.
Intermediate A then undergoes an intramolecular cyclisation to afford intermediate B. This intermediate B then undergoes an $N$-[1,3]-shift leading to the generation of intermediate C, which subsequently abstracts a proton to yield the product 5.

**Conclusion**

In summary, an efficient Me$_3$Al-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 demonstrated in the successful synthesis of the antitumor agent CWJ-a-5 in gram scale. Good to higher yields and a wide substrate scope are the key advantages associated with the current protocol. Further biological investigations of the synthesized compounds are currently underway.

**Supporting Information**

**Supporting Information File 1**

Experimental and analytical data.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-186-S1.pdf]
39. Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. Chem. – Asian J. 2007, 2, 306–313. doi:10.1002/asia.200600322
40. Shen, Q.; Ogata, T.; Harwig, J. F. J. Am. Chem. Soc. 2008, 130, 6586–6596. doi:10.1021/ja077074w
41. Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. J. Org. Chem. 2007, 72, 4554–4557. doi:10.1021/jo070189y
42. He, L.; Nie, H.; Ou, G.; Gao, Y.; Wu, J. Org. Biomol. Chem. 2014, 12, 9045–9053. doi:10.1039/c4ob01618a
43. Si, C.; Myers, A. G. Angew. Chem., Int. Ed. 2011, 50, 10409–10413. doi:10.1002/anie.201104769
44. Tovar, J. D.; Swager, T. M. J. Org. Chem. 1999, 64, 6499–6504. doi:10.1021/jo990810x
45. Long, Y.; She, Z.; Liu, X.; Chen, Y. J. Org. Chem. 2013, 78, 2579–2588. doi:10.1021/jo300794z
46. Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. Adv. Synth. Catal. 2009, 351, 2702–2708. doi:10.1002/adsc.200900442
47. Ye, S.; Wang, H.; Wu, J. Eur. J. Org. Chem. 2010, 6436–6439. doi:10.1002/ejoc.20100140
48. Ye, S.; Wang, H.; Wu, J. ACS Comb. Sci. 2011, 13, 120–125. doi:10.1021/co100266y
49. Zheng, D.; Chen, Z.; Liu, J.; Wu, J. Org. Biomol. Chem. 2011, 9, 4763–4765. doi:10.1039/c1ob05582h
50. Ye, C.; Chen, Z.; Wang, H.; Wu, J. Tetrahedron 2012, 68, 5197–5202. doi:10.1016/j.tet.2012.03.081
51. Li, W.; Wang, Y.; Lu, T. Tetrahedron 2012, 68, 6843–6848. doi:10.1016/j.tet.2012.06.030
52. Wang, T.; Li, R.; Yu, D.; Gu, C.; Xiong, F.; Chen, Z. Synthesis 2014, 46, 3213–3220. doi:10.1055/s-0034-1378654
53. Li, Y.; Gao, L.; Zhu, H.; Li, G.; Chen, Z. Org. Biomol. Chem. 2014, 12, 6982–6985. doi:10.1039/c4ob01301h
54. Song, J.; Fan, C.; Liu, G.; Ou, G. Org. Chem. Front. 2014, 1, 1045–1049. doi:10.1039/c4qo00209a
55. Wei, X.; Zhao, M.; Du, Z.; Li, X. Org. Lett. 2011, 13, 4636–4639. doi:10.1021/ol1018505
56. Jayakumar, J.; Parthasarathy, K.; Chen, Y.-H.; Lee, T.-H.; Chuang, S.-C.; Cheng, C.-H. Angew. Chem., Int. Ed. 2014, 53, 9889–9892. doi:10.1002/anie.201405183
Angew. Chem. 2014, 126, 10047–10050. doi:10.1002/ange.201405183
57. Li, J.; John, M.; Ackermann, L. Chem. – Eur. J. 2014, 20, 5403–5408. doi:10.1002/chem.201304944
58. Reddy, V.; Jadhav, A. S.; Anand, R. V. Eur. J. Org. Chem. 2016, 453–458. doi:10.1002/ejoc.201501390

License and Terms
This is an Open Access article under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0). Please note that the reuse, redistribution and reproduction in particular requires that the author(s) and source are credited and that individual graphics may be subject to special legal provisions.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (https://www.beilstein-journals.org/bjoc/terms)

The definitive version of this article is the electronic one which can be found at: https://doi.org/10.3762/bjoc.17.186