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One-pot multistep synthesis of 3,4-fused isoquinolin-1(*2H*)-one analogs

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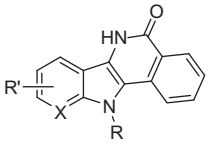
ABSTRACT

We have developed a robust approach for the synthesis of 3,4-fused isoquinolin-1(*2H*)-one analogs. A benzonitrile or a nicotinonitrile bearing an *ortho*-substituent, such as –OH, –SH, or –NHR (R = alkyl or aryl) can be deprotonated by KO*t*Bu and then reacted with methyl 2-(bromomethyl)benzoate (**8**) to form its corresponding O-, S-, or N-alkylation product. The product thus formed is then treated with KO*t*Bu again to initiate a cascade process that will lead to the formation of its corresponding 3,4-fused isoquinolin-1(*2H*)-one. This multistep synthesis as well as the final product purification is achieved in a one-pot manner.

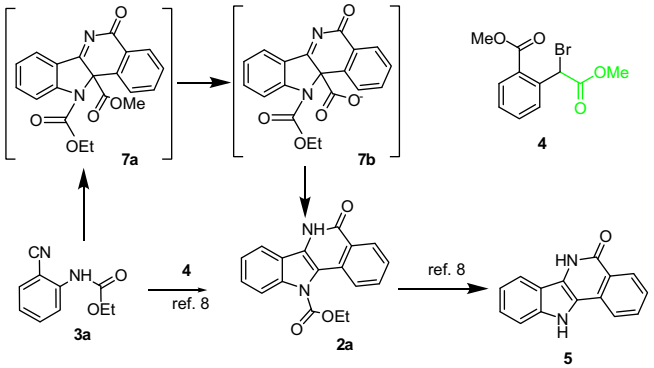
Improving efficiency is one of the main goals of modern organic synthesis.[1,2] This is further reinforced by our increasing awareness of various environmental concerns and the issue of sustainability in the past decades. To date, the design, development, and utilization of efficient and environmentally benign synthetic processes have become a conscientious choice of synthetic chemists.[3,4] One attractive strategy is to design and develop novel one-pot, multistep syntheses that will help simplify reaction handling and product purification, improve synthetic efficiency, and reduce solvent consumption and disposal. This, in turn, will reduce the consumption of natural resources, minimize the potential harmful impact of various chemicals on the environment, and ultimately, improve sustainability.[5]

In a recent medicinal chemistry program, we identified that substituted 11-alkyl-6,11-dihydro-*5H*-indolo[3,2-*c*]isoquinolin-5-one **1** (Fig. 1), after further transformations, served as a novel scaffold for the inhibition of an anti-viral target. To facilitate our SAR exploration, we needed an efficient and general approach to synthesize intermediate **1** where R and R' represent two key points for structural diversification. Indeed, compounds bearing a 6,11-dihydro-*5H*-indolo[3,2-*c*]isoquinolin-5-one core have previously been found to possess interesting biological activities[6,7] and their synthesis has been a subject of two prior publications.[8,9] After evaluating these two methods , the one in which compound **2a** was accessed via a simple and efficient one-pot process from **3a** and **4**, as outlined in Scheme 1, drew our attention.[8] Based on this report, we first explored the possibility of whether **3a** can be replaced by 2-methylaminobenzonitrile (**6a**) in the above-mentioned reaction. Unfortunately, we failed to obtain the desired product **1** (Scheme 2). This prompted us to test a few other substrates, such as **6b**, **3b**, and **3c** in the same reaction. Once again, in spite of the fact that the synthesis of compound **2a** from **3a** under the reported conditions proceeded similarly well in our hands, all three



1

Figure 1. Target structure.



Scheme 1.

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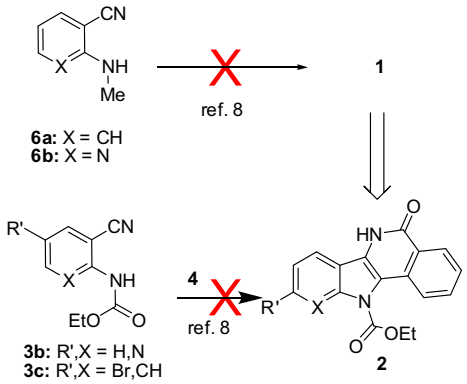
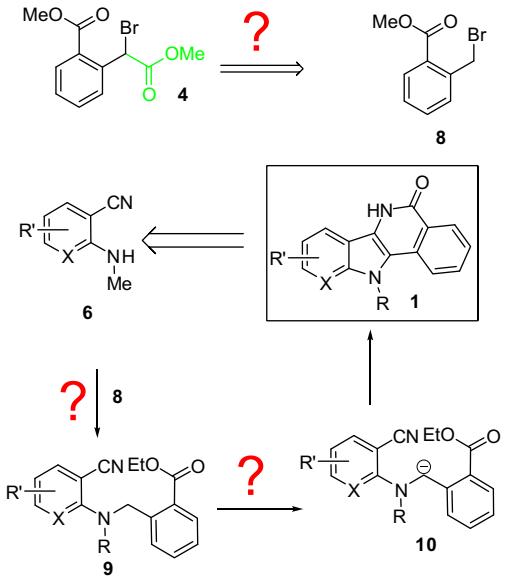


Scheme 2.

substrates failed to afford the desired product **1** (Scheme 2). These failures, especially with substrates **3b** and **3c**, suggested a narrow reactant scope of the original report and thus prevented us from developing an efficient, general synthesis of **1** from **2** (Scheme 2).

In order to determine what the root cause of this narrow reaction scope was, we analyzed the reaction mechanism postulated in the previous Letter[8] and hypothesized that the methoxycarbonyl group attached to the benzylic carbon in compound **4** was detrimental to the reaction. Firstly, the methyl ester activates its α-proton toward an initial, unproductive deprotonation versus the desired alkylation via bromide displacement. The carbanion thus formed is not stable and the reaction will then suffer from various decomposition pathways. Secondly, even for the material that underwent the desired S_N2 alkylation to furnish the cyclized intermediate **7a**, formation of **2** still required a subsequent decarboxylation step. Finally, the cumulative impact of the steric hindrance imparted by this ester group on all the reaction steps is negative. Consequently, we envisioned that if 1-[2-(bromomethyl)phenyl]-2-methoxyethanone (**8**) was used instead of compound **4**, the reported transformation should proceed much more readily (Scheme 3). This was supported by numerous literature examples where methyl 2-(bromomethyl)benzoate was used as an efficient alkylation reagent.[10–12]

For our initial proof-of-concept as well as subsequent reaction optimizations, we chose 2-hydroxybenzonitrile **11a** as our model



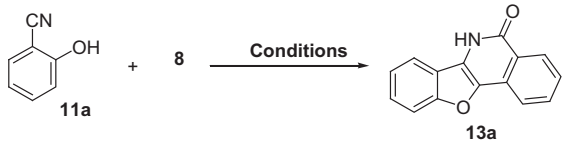
Scheme 3.

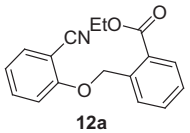
substrate. We found that by heating a mixture of **11a** (1.1 equiv) and compound **8** (1.0 equiv) with 4 equiv of K_2CO_3 in DMF at 80 °C for 3 h (Condition A, Table 1, entry 1), only the alkylation product **12a** was formed. No trace of the desired cyclization product **13a** was observed by LCMS. Apparently, the basicity of K_2CO_3 was not sufficient to affect a benzylic deprotonation of compound **12a** which was thought to be critical for the initiation of the following cascade process toward **13a**. However, the formation of **12a** in high yield was encouraging and all that remained was to find a base that can affect the requisite benzylic deprotonation. We found that compound **11a** (1.1 equiv), after being treated with 1.1 equiv of NaH in DMF at 0 °C (until the bubbling stopped), reacted smoothly with compound **8** (1.0 equiv) to furnish the desired alkylation product **12a** cleanly after 1.5 h at rt. At this point, we added another 1.1 equiv of NaH to the resulting reaction mixture and found that compound **12a** was completely consumed after 1 h at 80 °C to afford the desired product **13a**, based on LCMS analysis (Condition B, Table 1, entry 2). Following an acidic work-up, this was also confirmed by ^{1}H NMR analysis of the crude reaction mixture thus obtained (75% estimated yield). Unfortunately, various attempts to purify **13a** failed due to the presence of an inseparable by-product, the corresponding carboxylic acid of ester **12a**.[13] On the other hand, when the reaction was carried out with KO*t*Bu in THF and a slightly modified work-up (i.e., 4 equiv, of HCl was added dropwise to the reaction mixture at 80 °C and the desired product crystallized out of the reaction mixture upon cooling to room temperature), the desired cyclized product **13a** was obtained in 97% isolated yield (Condition C, Table 1, entry 3).[15]

With the newly optimized reaction conditions in hand, we then proceeded to explore its reactant scope. As shown in Table 2 and 2-hydroxybenzonitrile with a bromine substituent at various positions (i.e., **11b–d**), all furnished the desired cyclization product (i.e., **13b–d**) in good to excellent yield. As expected di-*ortho* substituted phenol **11b**, as a consequence of its greater steric demand, was found to be more recalcitrant toward cyclization. Interestingly, when simple 2-mercaptobenzonitrile **11e** was the substrate used, the desired product **13e** was obtained in a yield comparable to that of **13a**.

Unfortunately, when 2-alkylaminobenzonitrile **6a** was subjected to Condition C as described above, we only detected the partial formation of the desired N-alkylation product by LCMS. Besides, a coupling product between compound **8** and potassium *tert*-butoxide (i.e., methyl 2-(*tert*-butoxymethyl)benzoate) was

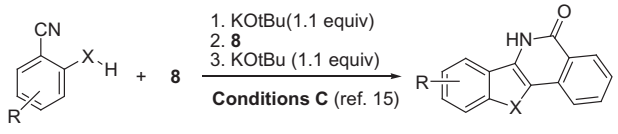
Table 1
Exploration of reaction conditions using 2-hydroxybenzonitrile as substrate

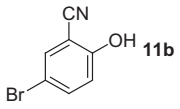
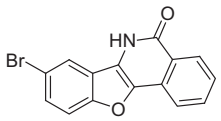
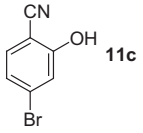
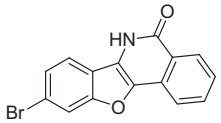
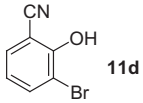
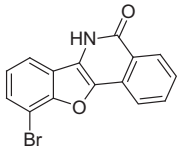
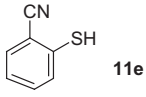
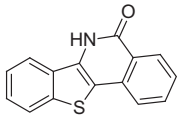


Entry	Conditions[d]	Product	Yield%
1	**A**	 **12a**	100[a]
2	**B**	**13a**	75[b]
3	**C** (Ref. 15)	**13a**	97[c]

[a] Based on LCMS.
[b] Based on ^{1}H NMR.
[c] Isolated yield.
[d] See text for detailed description.

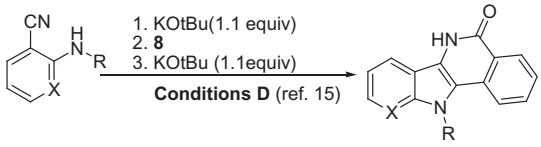
Table 2
Exploration of reaction scope



Entry	Benzonitrile	Product	Yield%[a]
1	 **11b**	 **13b**	88
2	 **11c**	 **13c**	80
3	 **11d**	 **13d**	73
4	 **11e**	 **13e**	95

[a] Isolated yield.

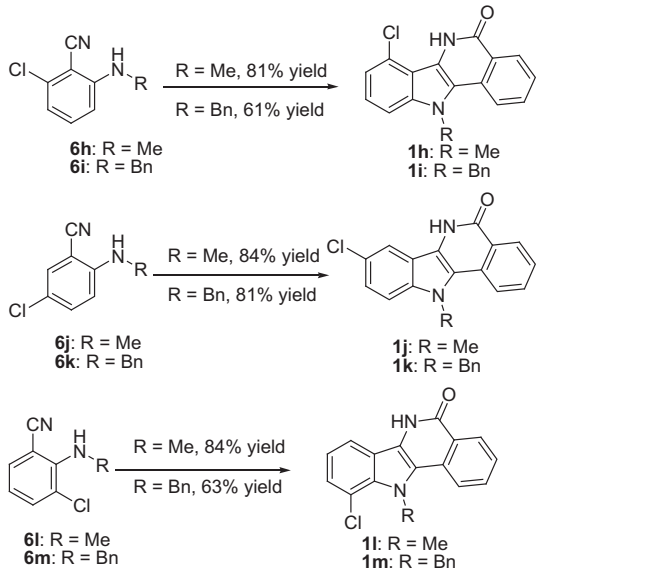
Table 3
Exploration of reaction scope with various X and R moieties

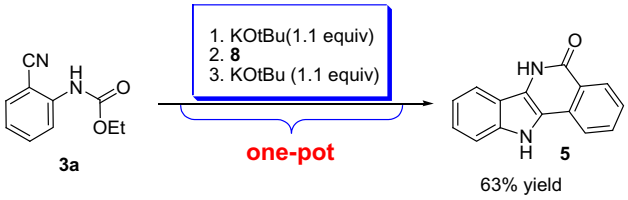


Entry	X, R	Nitrile	Product	Yield%
1	CH, Me	**6a**	**1a**	71
2	N, Me	**6b**	**1b**	84
3	CH, Bn	**6c**	**1c**	85
4	N, Bn	**6d**	**1d**	77
5	CH, isobutyl	**6e**	**1e**	70
6	CH, Ph	**6f**	**1f**	70
7	CH, *i*Pr	**6g**	**1g**	25

observed, suggesting that the initial reaction time between aniline **6a** and the base was not sufficient. On the other hand, by allowing the reaction between **6a** and KO*t*Bu to proceed for 1 h at 0 °C prior to the addition of compound **8**, the desired N-alkylation product was obtained without the formation of methyl 2-(*tert*-butoxymethyl)benzoate. After the addition of another 1.1 equiv of KO*t*Bu, the mixture was stirred for 1 h at 80 °C and the final cyclized product **1a** was detected by LCMS. After the in situ crystallization work-up conditions as described previously, spectroscopically pure compound **1a** was obtained in 71% yield. The pyridine-containing substrate **6b** afforded the cyclized product **1b** in 84% yield under these new conditions (assigned as Conditions D).[15] In order to evaluate how a substituent on the aniline nitrogen affected the reaction, substrates **6c–g** were subjected to the reaction sequence using Conditions D. To summarize, all these substrates, except **6g**, afforded the desired products in good yield. Substrate **6g**, which has an *N*-isopropyl moiety, gave product **1g** in 25% yield but in high purity. The low yield is likely due to the steric hindrance of the isopropyl group (Table 3).

Table 4
Exploration of reaction scope with various substituents on the phenyl ring





Scheme 4.

To evaluate the effect of substituents on the phenyl ring, substrates **6h–m** were then investigated. Gratifyingly, the transformation proceeded in good yield in all cases (Table 4). Finally, we decided to investigate if this transformation could be used to synthesize the biologically active compound **5**, an intermediate previously used for the synthesis of poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors.[14] Starting from substrate **3a** and using Conditions D, we were able to obtain compound **5** in one pot in 63% yield (Scheme 4).

In summary, we have developed a robust approach for the synthesis of several 3,4-fused isoquinolin-1(*2H*)-one derivatives. Both benzonitrile and nicotinonitrile bearing a substituent, such as –OH, –SH, or –NHR (R = alkyl or aryl) at the 2-position can be reacted with methyl 2-(bromomethyl)benzoate (**8**) in the presence of KO*t*-Bu to afford the corresponding 3,4-fused isoquinolin-1(*2H*)-one.[15] This multistep synthesis as well as the final product purification is achieved in an efficient one-pot manner.

References and notes

1. Trost, B. M. *Science* **1991**, *254*, 1471.
2. Trost, B. M. *Science* **1983**, *219*, 245.
3. Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Green Chem. Lett. Rev.* **2008**, *1*, 141.
4. Anastas, P. T.; Beach, E. S. *Green Chem. Lett. Rev.* **2007**, *1*, 9.
5. Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
6. Jagtap, P.; Roy, A.; Williams, W. U.S. Patent US 7393955, 2008.
7. Saundane, A. R.; Rudresh, K.; Satyanarayan, N. D.; Hiremath, S. P. *Indian J. Pharm. Sci.* **1998**, *60*, 379.

8. Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Salzman, A. L.; Szabo, C. *Org. Lett.* **2005**, *7*, 1753. The reaction was done by first reacting NaH with a 2-aminonitrile derivative (**3a–c** or **6a–b**) in toluene and then refluxing with compound **4** for certain period of time (4–10 h). An acidic work-up was then employed.
9. Hiremath, S. P.; Saundane, A. R.; Mruthyunjayaswamy, B. H. M. *J. Heterocycl. Chem.* **1993**, *30*, 603.
10. For an example of N-alkylation of a N-substituted aniline, see: Hanna, P. E.; Grund, V. R.; Anders, M. W. *J. Med. Chem.* **1974**, *17*, 1020.
11. For an example of S-alkylation of a thiophenol, see: Fink, B. E.; Gavai, A. V.; Tokarski, J. S.; Goyal, B.; Misra, R.; Xiao, H.-Y.; Kimball, S. D.; Han, W.-C.; Norris, D.; Spires, T. E.; You, D.; Gottardis, M. M.; Lorenzi, M. V.; Vite, G. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1532.
12. For an example of O-alkylation of a phenol, see: Dvornikovs, V.; Smithrud, D. B. *J. Org. Chem.* **2002**, *67*, 2160.
13. Our attempts to purify **13a** by trituration with various organic solvents such as ether or THF failed to remove the acid contaminant completely. The low solubility of **13a** in various organic solvents including DMSO prevented purification via silica gel flash chromatography.
14. Jagtap, P.; Roy, A.; Williams, W. US Patent, US 7393955, 2008.
15. *Method*: To a DMF (2 mL) solution of benzonitrile or nicotinonitrile (1.1 mmol) was added dropwise at 0 °C a THF solution of potassium *tert*-butoxide (1.1 mL, 1.1 mmol). Immediately following this addition (Conditions C) or after an additional hour at 0 °C (Conditions D), methyl 2-(bromomethyl)benzoate (8, 0.229 g, 1.0 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 1.5 h. To the mixture thus obtained was then added dropwise to a solution of potassium *tert*-butoxide in THF (1.1 mL, 1.1 mmol). The resulting mixture was heated at 80 °C for 1 h. The reaction was then quenched with the dropwise addition of 20 mL of HCl solution (0.2 M) at 80 °C. Upon cooling to room temperature, the desired product crystallized directly from the reaction media. The product was then collected via filtration and washed with distilled water and ether to afford a 3,4-fused isoquinolin-1(*2H*)-one in high purity.