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$AlCl_3$-promoted three-component cascade reaction for rapid access to [1,2,3]triazolo[5,1-*a*]isoquinolines

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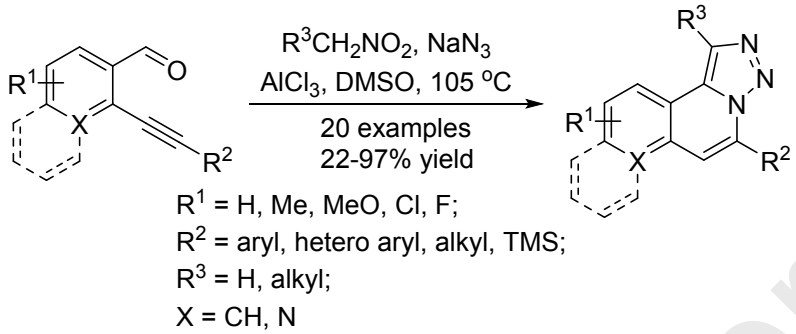
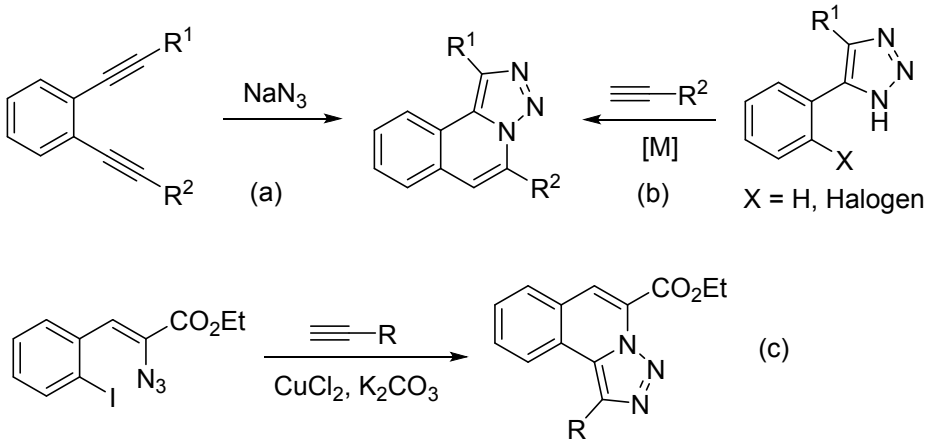
Abstract: Novel $AlCl_3$-promoted, three component cascade Henry reaction–triazole formation–intramolecular 6-*endo*-dig cyclization reactions between 2-alkynylaryl aldehydes, nitroalkanes, and sodium azide for the assembly of [1,2,3]triazolo[5,1-*a*]isoquinolines have been developed. Further transformations of representative [1,2,3]triazolo[5,1-*a*]isoquinolines are also described.



Keywords: [1,2,3]triazolo[5,1-*a*]isoquinoline; cascade reaction; Henry reaction; triazole; 6-*endo*-dig cyclization

Introduction

The [1,2,3]triazolo[5,1-*a*]isoquinolines are an important class of heterocyclic compounds possessing a wide spectrum of biological activities[1] and are also important building blocks in organic synthesis.[2] Like many other fused polyheterocyclic molecules, their assembly from simple starting materials in a rapid and efficient manner remains a challenge.[3-9] The traditional syntheses involve hydrazone formation *via* the condensation of 2-acylpyridines with hydrazine, followed by oxidative cyclization.[3] Overall, this process requires harsh conditions and the desired products are usually obtained in low yields. In recent years, a number of alternative approaches have been developed, based on cascade reactions. For example, the cyclization of 1,2-diacetylenic benzenes with NaN_3 (Scheme 1a) gives the corresponding [1,2,3]triazolo[5,1-*a*]isoquinolines, but with low regioselectivity for substrates bearing two different alkyne substituents ($R^1 \neq R^2$).[4] Alternatively, the target compounds could be obtained *via* the transition-metal catalyzed annulation of acetylenes with (2-halo)phenyl-1,2,3-triazoles[5] (Scheme 1b) or 2-azido-3-(2-iodophenyl)acrylates[6] (Scheme 1c). However, multiple steps were needed to access the required substrates. In 2013, Kundu and co-workers reported a [3 + 2] cycloaddition/6-*endo* cyclization sequence of (*E*)-1-(2-nitrovinyl)-2-(alkynyl)benzene species for the synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines.[7] Unfortunately, the requirement for the isolation of the former was troublesome and the reactions could not be used to form 1-substituted products. In recent years, we have become interested in the development of strategies toward the synthesis of biologically active nitrogen-containing heterocyclic compounds.[10] Herein, we report a novel one-pot $AlCl_3$–catalyzed, three-component Henry reaction–triazole formation–intramolecular 6-*endo*-dig cyclization cascade for the rapid access to such [1,2,3]triazolo[5,1-*a*]isoquinolines.

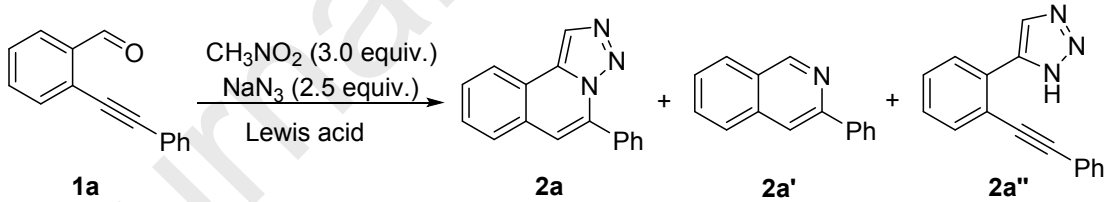


Scheme 1. Recent approaches for the synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines.

Results and Discussion

Our investigation started with the model reaction of 2-(phenylethynyl)benzaldehyde **1a**, nitromethane, and sodium azide. Initially, the reaction was carried out in the presence of 10 mol% of a Lewis acid in DMF at 100 °C, which resulted in the formation of a mixture of [1,2,3]triazolo[5,1-*a*]isoquinoline **2a** and isoquinoline **2a′** (Table 1, entries 1–5). Among those investigated, $Sc(CF_3SO_3)_3$ and $AlCl_3$ were superior to other Lewis acids tested to promote the formation of **2a**. $AlCl_3$ was selected for further optimization since it is cheaper and gave higher **2a**/**2a′** ratios as determined by ^{1}H NMR integration of the crude reaction mixtures. Our studies indicated that the amount of $AlCl_3$ applied was crucial to the products formed. To a certain extent, the formation of **2a** was favored with higher catalyst loading (Entries 5–9). An 18:1 ratio of **2a**:**2a′** was observed in the presence of 60 mol% $AlCl_3$, in which case **2a** could be isolated in 85% yield (Entry 9). However, triazole **2a″** predominated if the amount of $AlCl_3$ was further increased (Entries 10, 11). Next, the solvents and reaction temperatures were screened. While the desired product **2a** was isolated in 90% yield in DMSO (Entry 12), no reaction occurred in other solvents including toluene, 1,4-dioxane and ethylene glycol (Entries 13–15). With DMSO as solvent, the yield of **2a** could be improved to 97% at 105 °C (Entry 17). However, further raising (Entry 18) or lowering (Entry 16) the reaction temperature provided **2a** in reduced yield.

Table 1. Optimization of reaction conditions for the synthesis of [1,2,3]triazolo[5,1-*a*]isoquinoline **2a**.



1a **2a** **2a'** **2a"**

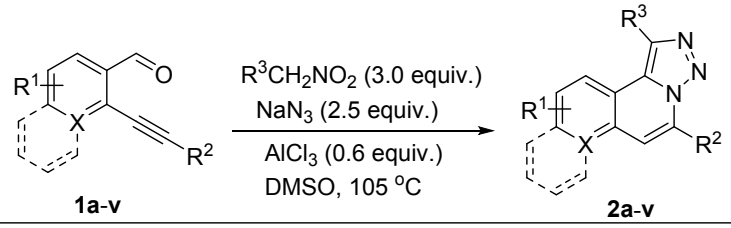
Entry	Lewis acid (equiv.)	Solvent	Temp (°C)	**2a** (% yield)	**2a′** (% yield)	**2a″** (% yield)
1	$FeCl_3$ (0.1)	DMF	100	87[a]	13[a]	0[a]
2	$Sc(CF_3SO_3)_3$ (0.1)	DMF	100	90[a]	10[a]	0[a]
3	$ZnCl_2$ (0.1)	DMF	100	83[a]	17[a]	0[a]
4	$Cu(OAc)_2$ (0.1)	DMF	100	87[a]	13[a]	0[a]
5	$AlCl_3$ (0.1)	DMF	100	91[a,b]	9[a]	0[a]
6	$AlCl_3$ (0.05)	DMF	100	87[a]	13[a]	0[a]
7	$AlCl_3$ (0.2)	DMF	100	92[a,c]	8[a]	0[a]
8	$AlCl_3$ (0.5)	DMF	100	94[a,d]	6[a]	0[a]
9	$AlCl_3$ (0.6)	DMF	100	95[a,e]	5[a]	0[a]
10	$AlCl_3$ (0.8)	DMF	100	42[a]	5[a]	53[a]
11	$AlCl_3$ (1.0)	DMF	100	3[a]	6[a]	91[a]
12	$AlCl_3$ (0.6)	DMSO	100	90[f]	-[g]	-[g]
13[h]	$AlCl_3$ (0.6)	toluene	100	0	0	0
14[h]	$AlCl_3$ (0.6)	1,4-dioxane	100	0	0	0
15[h]	$AlCl_3$ (0.6)	ethylene glycol	100	0	0	0

16	$AlCl_3$ (0.6)	DMSO	90	87[f]	-[g]	-[g]
17	$AlCl_3$ (0.6)	DMSO	105	97[f]	-[g]	-[g]
18	$AlCl_3$ (0.6)	DMSO	110	86[f]	-[g]	-[g]

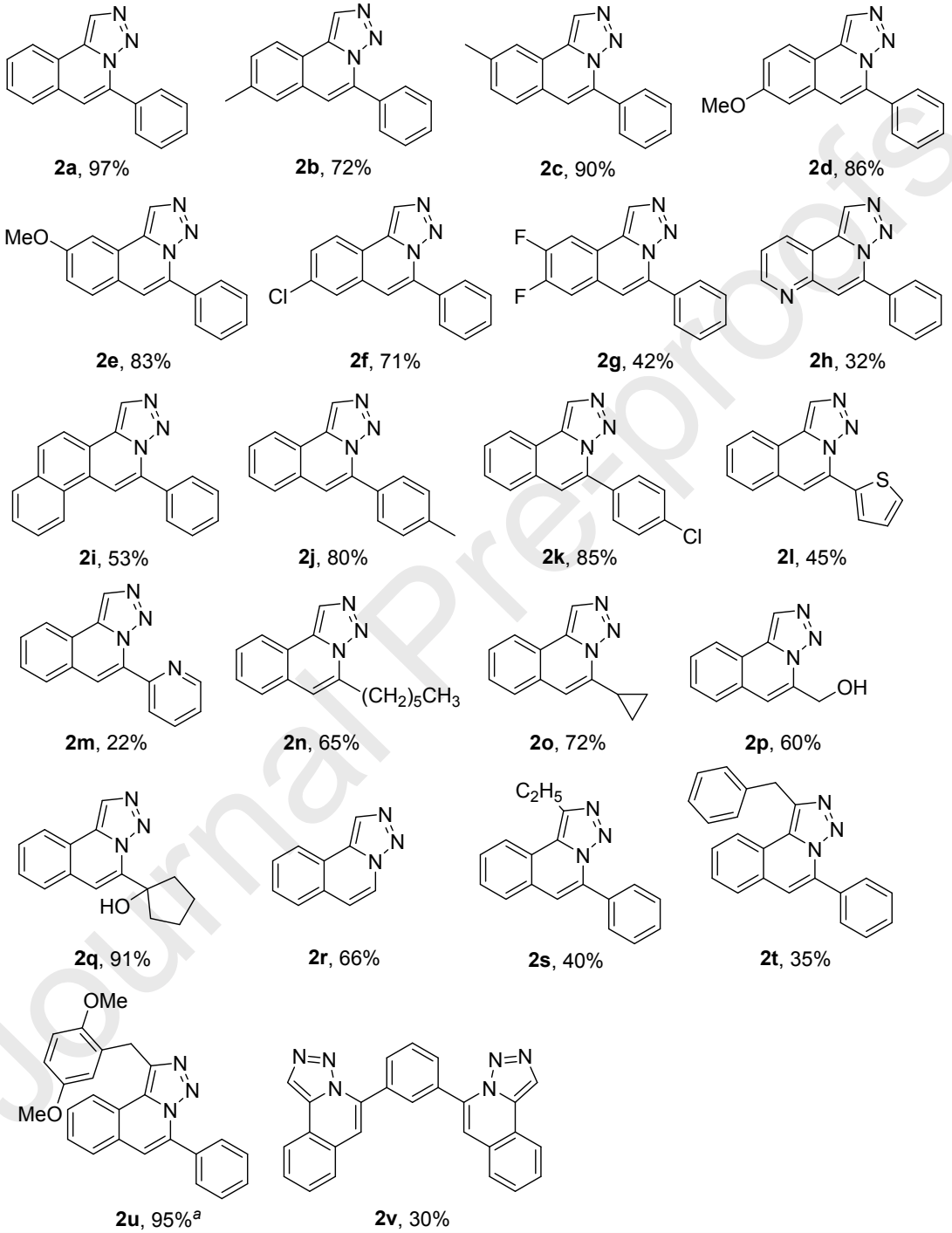
[a] Yield determined based on ^{1}H NMR integration of the crude reaction mixture; [b] 64% isolated yield of **2a**; [c] 67% isolated yield of **2a**; [d] 76% isolated yield of **2a**; [e] 85% isolated yield of **2a**; [f] isolated yield; [g] not determined; [h] No reaction, **1a** was recovered.

With the optimized reaction conditions in hand, we embarked on examining the scope of this $AlCl_3$-promoted three-component synthesis of various [1,2,3]triazolo[5,1-*a*]isoquinolines and analogues. As shown in Table 2, [1,2,3]triazolo[5,1-*a*]isoquinolines **2b**–**g** with different substituents (R^1) on the phenyl ring could be obtained. In general, **2b**–**e** with electron-donating groups were isolated in higher yields than **2f**, **g** with electron-withdrawing groups. Under the reaction conditions, **2h** with an electron-deficient pyridine, as well as **2i** with a more π-electron delocalized naphthalene in place of the phenyl ring, could also be synthesized, albeit in moderate isolated yields. Replacing R^2 on the alkyne with a substituted phenyl ring, heterocycle, or alkyl group afforded **2j**–**q** as expected. The yields were generally good to excellent except in the cases of **2l** and **2m** with a tethered heterocyclic ring. Concomitant desilylation occurred during the reaction of **1r** (R^2 = TMS), which resulted in the formation of **2r** in 66% isolated yield. Finally, the developed method could also be applied to the synthesis of 1-substituted [1,2,3]triazolo[5,1-*a*]isoquinolines **2s**–**u** and bis-[1,2,3]triazolo[5,1-*a*]isoquinoline **2v**.

Table 2. Substrate scope.

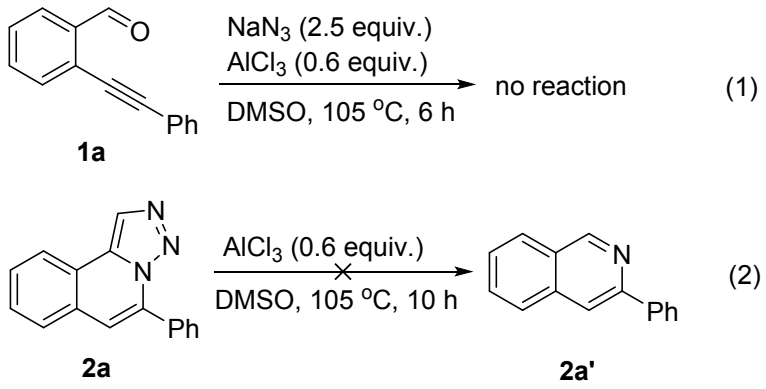


1a-v **2a-v**



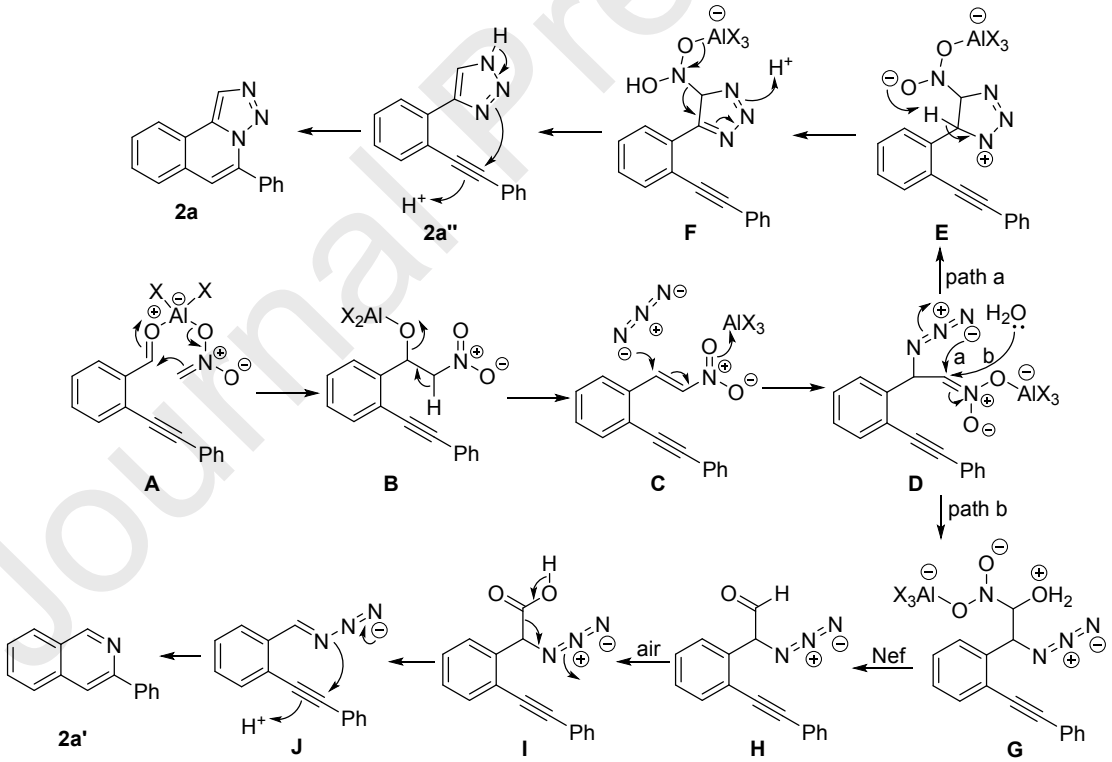
[a] DMF as solvent.

To determine the reaction mechanism, we carried out some control experiments (Scheme 2). First, no reaction occurred in the absence of nitromethane, indicating that **2a′** was not formed from the direct reaction of **1a** with sodium azide. Second, no trace of **2a′** was detected when the isolated **2a** was re-subjected to the standard reaction conditions.



Scheme 2. Control experiments.

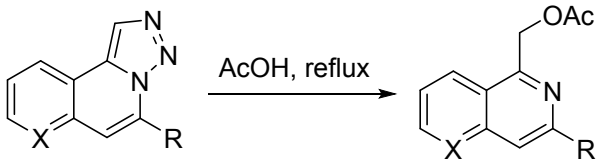
Based on the results of these experiments and literature reports,[11] a plausible mechanism is depicted in Scheme 3. The coordination of 2-(phenylethynyl)benzaldehyde and nitromethane to aluminium **A** could trigger a Henry reaction to provide 1-(2-nitrovinyl)-2-(alkynyl)benzene **C**. Subsequent attack of intermediate **C** by azide would then provide intermediate **D**, the cyclization of which gives intermediate **E** (path a). Proton transfer of **E** gives **F**, which undergoes aromatization upon releasing a molecule of nitrous acid and re-generating the aluminium catalyst to give (phenylethynyl)phenyltriazole **2a″**. The 6-*endo*-dig cyclization of **2a″** then gives [1,2,3]triazolo[5,1-*a*]isoquinoline **2a**. On the other hand, nucleophilic attack of **D** with water gives **G** (path b). The Nef reaction of **G** gives aldehyde **H**, which can then be oxidized to acid **I** under the reaction conditions. Finally, the decarboxylation of **I** gives **J**, which leads to the formation of **2a′** *via* denitrogenative ring closure.



Scheme 3. Proposed mechanism.

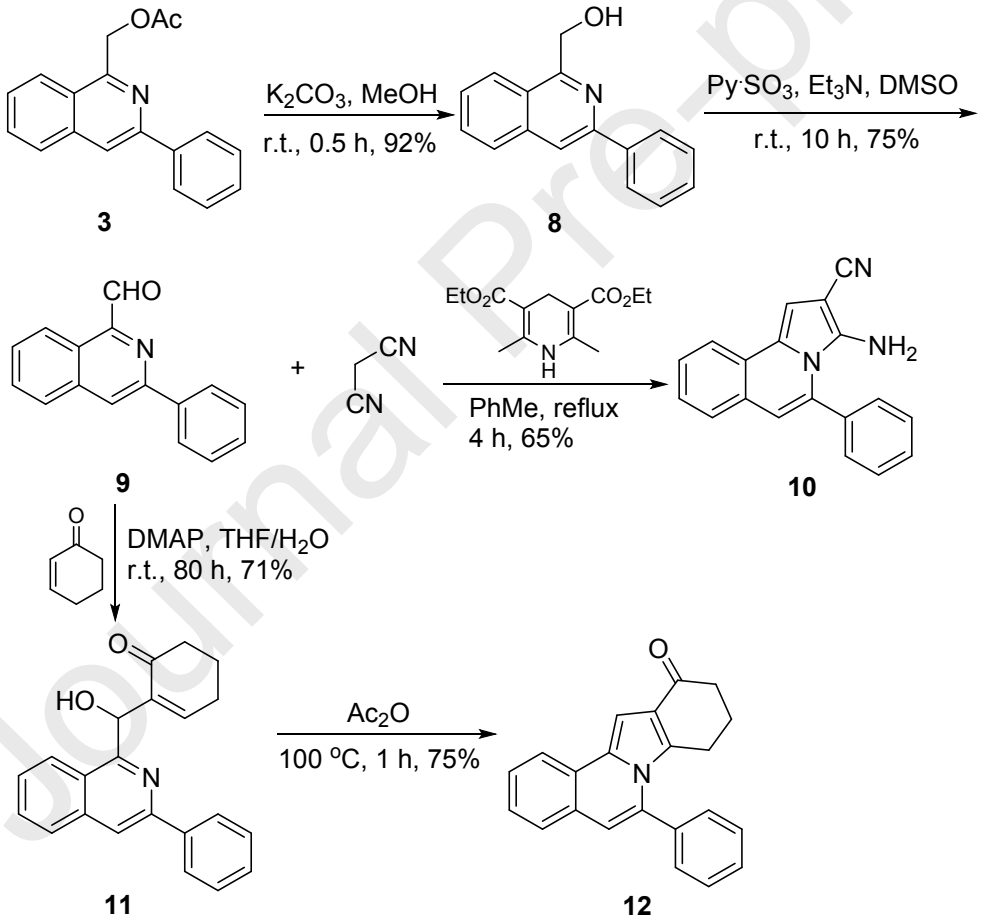
Having established this new method for the synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines, we then explored the feasibility of transforming these fused heterocycles into other useful molecules. Thus, treatment of **2a**, **2h**, **2l**, **2m** and **2p** with AcOH at reflux[5b] gave the corresponding denitrogenative ring-opened products **3**–**7**, respectively, in good to excellent isolated yields (Scheme 4). Compounds containing such structural motifs are ideal metal ligands.[12] Some of them have also shown important

biological activities.[13] However, the reported methods for their synthesis are tedious. Our approach represents a novel and facile strategy towards these valuable molecules. As shown in Scheme 5, hydrolysis of **3** provided alcohol **8**, Parikh-Doering oxidation of which gave aldehyde **9** in excellent combined yield over the two steps. Following a modified literature procedure,[14] compound **9** could be converted into pyrrolo[2,1-*a*]isoquinoline derivative **10** in 65% isolated yield upon treatment with malononitrile in the presence of Hantzsch ester. On the other hand, Baylis-Hillman reaction between **9** and 2-cyclohexenone promoted by DMAP yielded **11**, which could be transformed into dihydroindolo[2,1-*a*]isoquinolinone **12** in good isolated yield upon treatment with acetic anhydride.



2a, X = CH, R = Ph — **3**, 91%
2h, X = N, R = Ph — **4**, 95%
2l, X = CH, R = 2-thiophenyl — **5**, 93%
2m, X = CH, R = 2-pyridinyl — **6**, 92%
2p, X = CH, R = CH_2OH — **7**, 62%

Scheme 4. Denitrogenative ring-opening for the synthesis of **3**–**7**.



3 **8** **9** **10** **11** **12**

Scheme 5. Synthesis of pyrrolo[2,1-*a*]isoquinoline **10** and dihydroindolo[2,1-*a*]isoquinolinone **12**.

Conclusion

In summary, we have developed a novel $AlCl_3$-promoted, three-component cascade consisting of a sequential Henry reaction–triazole formation–intramolecular 6-*endo*-dig cyclization combination for the rapid, single-pot access to diversely substituted [1,2,3]triazolo[5,1-*a*]isoquinolines from simple and readily available precursors. Cleavage of the triazole ring by loss of nitrogen gave the highly valuable

but difficult to prepare ring-opened products **3**–**7**. Compounds **3** could be further transformed into pyrrolo[2,1-*a*]isoquinoline derivative **10** and dihydroindolo[2,1-*a*]isoquinolinone **12**. Studies on the biological properties of these molecules are underway in our laboratory.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

- [1,2,3]triazolo[5,1-*a*]isoquinolines have been synthesized;
- A three-component cascade reaction has been developed;
- [1,2,3]triazolo[5,1-*a*]isoquinolines have been converted to other molecules.