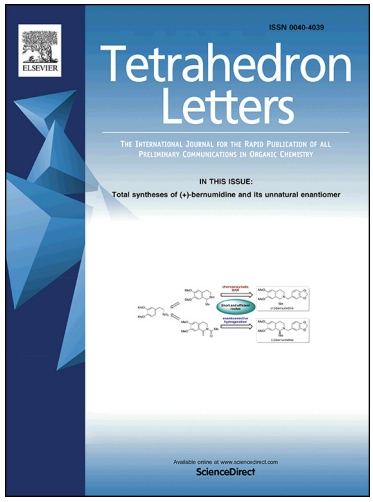

An efficient synthesis of indoles *via* a CuMgAl-LDH-catalyzed cyclization of 2-alkynylsulfonanilides

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PII: S0040-4039(18)31081-5
DOI: https://doi.org/10.1016/j.tetlet.2018.09.009
Reference: TETL 50248

To appear in: *Tetrahedron Letters*

Received Date: 28 July 2018
Revised Date: 31 August 2018
Accepted Date: 3 September 2018

Please cite this article as: Zhang, S-Y., Sun, S-G., Guo, Y-S., Lu, X-F., Guo, D-S., An efficient synthesis of indoles *via* a CuMgAl-LDH-catalyzed cyclization of 2-alkynylsulfonanilides, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.09.009

Graphical Abstract

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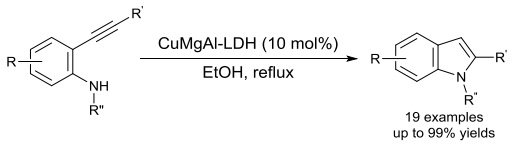
Sheng-Yan Zhang, Shan-Gang Sun, Yu-Shuang Guo, Xiao-Fan Lu and Dian-Shun Guo *



Tetrahedron Letters
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An efficient synthesis of indoles *via* a CuMgAl-LDH-catalyzed cyclization of 2-alkynylsulfonanilides

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ARTICLE INFO

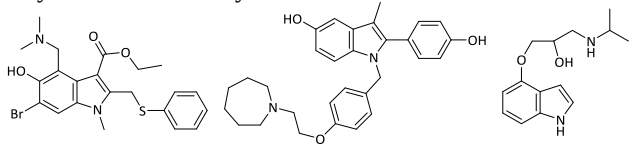
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Indole
2-Alkynylsulfonanilide
Cyclization reaction
CuMgAl-LDH catalyst
Hirshfeld surface analysis

ABSTRACT

A highly efficient method for the synthesis of indoles has been successfully developed *via* a CuMgAl-LDH-catalyzed intramolecular annulation reaction of 2-alkynylsulfonanilides. This CuMgAl-LDH catalyst features facile preparation, recovery, and reuse at least seven times without a marked loss in the catalytic activity, as well as the unique dual activation. Moreover, the crystal structures and Hirshfeld surface analysis of typical indole compounds were also presented.

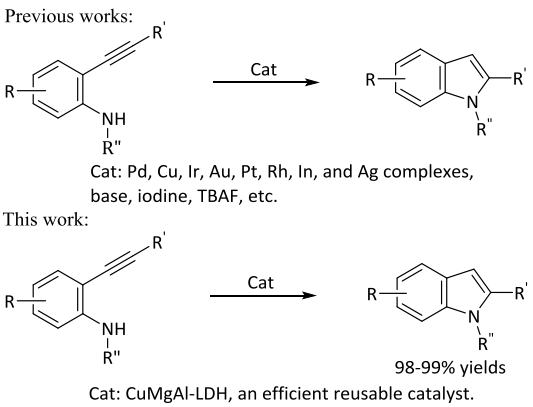
Indoles, one of the most prevalent nitrogen-containing fused heterocycles, are extensively found in natural products, bioactive molecules and new functional materials.[1] Especially, many indole derivatives are important pharmaceuticals,[2] involving arbidol,[2c] bazedoxifene,[2d] pindolol,[2e] etc. (Fig. 1). Thus the development of facile and practical strategies to construct indole scaffolds has been attracting great interest over a century. A large number of synthetic methods have been documented since the first practical preparation of indole compounds by Fischer et al. in 1883,[3] such as the classical strategies,[4] cyclization reactions,[5-10] and multi-component reactions.[11] Thereinto the most popular method is the intramolecular cyclization of 2-alkynylanilides under different metal-,[6] alkoxide-,[7] fluoride-,[8] TMG (tetramethylguanidine)-[9], or other reagents-[10] catalyzed conditions (Scheme 1); while several limitations involving harsh reaction conditions, recycle and residual of catalyst still restrict its wide applicability. Therefore, it is very significant to develop green, recyclable and efficient catalysts for the indole synthesis.



arbidol (viral fusion inhibitor) | bazedoxifene (selective estrogen receptor modulator) | pindolol (antihypertensive drug)

Figure 1. Typical bioactive indole derivatives.

Presently, layered double hydroxides (LDHs)[12] have attracted much attention largely because of their potential applications as ion exchangers, adsorbents, catalysts or supports owing to their high thermal stability, high dispersion and excellent catalytic performance.[13] To date, LDH-based heterogeneous catalysts have been applied to various kinds of reactions for their recyclability,[14] while there are no reports on the annulation of 2-alkynylanilides to indoles using such catalysts, for which to activate either the alkynyl function by some metals or the amino group by typical bases could efficiently accelerate the reaction. In fact, only single activation rather than dual activation was utilized to speed up the cyclization reaction in most cases.[6,7] Positively, the latter would give rise to a better result.



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Scheme 1. Strategies for synthesis of indoles *via* cyclization of 2-alkynylanilides.

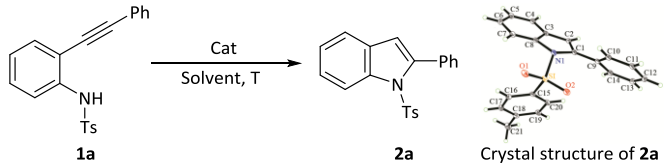
We envisioned that some metal species implanted in the layers of the LDHs could activate the alkynyl function to increase its electrophilicity, while the abundant alkalinity of LDHs could activate the amino group to improve its nucleophilicity, which might make the cyclization reaction to indoles more effectively. Herein, we smartly implanted Cu^{2+} species in the layers of the MgAl-LDH to create CuMgAl-LDH heterogeneous catalysts that can efficiently promote the cyclization of 2-alkynylanilides to yield indoles (Scheme 1) with a broad substrate scope. Moreover, the crystal structures and Hirshfeld surface analysis of the typical indole compounds were also reported.

To evaluate our hypothesis, three LDH-based catalysts MgAl-LDH (Cat-1), CuMgAl-LDH (Cat-2A, 5.0% Cu, w/w; Cat-2B, 2.0% Cu, w/w) were facilely prepared by co-precipitation with a double drop technique,[15] and fully confirmed by powder XRD, TEM and FT-IR techniques (Figs. S1-S3, ESI). Moreover, the SEM-mapping image of Cat-2A showed that the distribution of Cu^{2+} is uniformity (Fig. S4, ESI). The content of Cu in Cat-2A determined by ICP is 4.62%, similar to the theoretical content in the designed Cat-2A (Table S1, ESI). Their catalytic performance was assessed by a model reaction: the cyclization of 2-phenylethynylsulfonanilide **1a** in DCE. As shown in Table 1, when the cyclization reaction was carried out under the catalyst-free condition, no indole **2a** was monitored after a long reaction time (Table 1, entry 1). In a control experiment, indole **2a** was obtained in 11% yield in the presence of Cat-1 (Table 1, entry 2). This preliminarily proved that the catalytic performance resulted from the alkalinity of MgAl-LDH. Furthermore, Cat-2A showed the highest activity, giving the product **2a** in 50% yield within 5 h (Table 1, entry 3), which may be ascribed to a dual-activation effect of Cu^{2+} ions and bases in the CuMgAl-LDH. Note that the Cu^{2+} ions played a key catalytic effect. Differing loadings of Cu^{2+} ions in the CuMgAl-LDH were also tested. When Cat-2B was used, the reaction time was prolonged to 8 h (Table 1, entry 4). So Cat-2A was chosen to optimize the other reaction conditions.

To optimize the cyclization reaction conditions, a series of experiments were carried out. First, through extensive screening, we found that EtOH is the best solvent for the cyclization reaction among the solvents screened (Table 1, entries 3, 5-8 and 11). For example, the cyclization reaction can completed within 0.3 h under reflux conditions (Table 1, entry 11), giving indole **2a** in 99% yield. Interestingly, water is also an excellent solvent for this reaction when an appropriate PTC (TBAB) was utilized, although the reaction time is longer (Table 1, entry 8). Next, to elevate the temperature can markedly shorten the reaction time (Table 1, entries 9-11). Finally, the loading of catalyst on the cyclization reaction was also examined. To decrease the loading of Cat-2A catalyst to 10 mol% and 5 mol%, the reaction in EtOH needs 0.4 h and 0.8 h, respectively (Table 1, entries 12 and 13), still giving 99% yields. Moreover, when Cat-1 was used, the cyclization reaction is faster in EtOH than in DCE (Table 1, entries 1 and 13). In brief, the optimized cyclization parameters include: 10 mol% Cat-2A, EtOH solvent, and reflux conditions.

Table 1

Optimization of cyclization of 2-phenylethynylsulfonanilide **1a**[a]



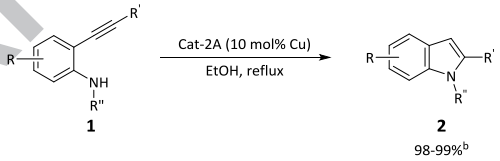
1a **2a** Crystal structure of **2a**

Entry	Cat	Cu/mol%	Solvent	T/°C	t/h	Yield/%[b]
1	Free		DCE	80	8	0
2	Cat-1	--[c]	DCE	80	8	11
3	Cat-2A	20	DCE	80	5	50
4	Cat-2B	20	DCE	80	8	49
5	Cat-2A	20	Dioxane	100	9	96
6	Cat-2A	20	Toluene	100	12	90
7	Cat-2A	20	NMP	100	1	98
8	Cat-2A	20	H_2O[d]	100	2	98
9	Cat-2A	20	EtOH	45	7	98
10	Cat-2A	20	EtOH	65	1.5	99
11	Cat-2A	20	EtOH	80	0.3	99
12	Cat-2A	10	EtOH	80	0.4	99
13	Cat-2A	5	EtOH	80	0.8	99
14	Cat-1[c]	--[c]	EtOH	80	0.4	20

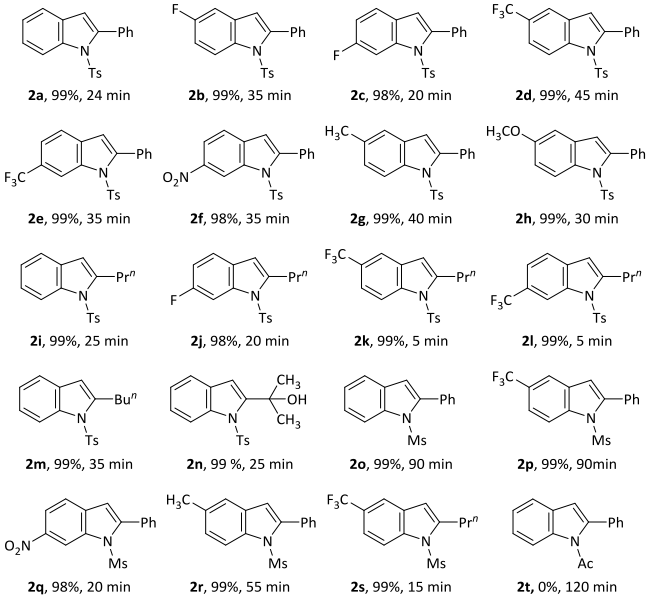
[a] Reaction conditions: **1a** (0.50 mmol), solvent (5 mL).
[b] Isolated yields.
[c] Amount of Cat-1 (Mg^{2+}/mmol) equals that of Cat-2A (Mg^{2+} and Cu^{2+}/mmol).
[d] TBAB (0.03 mmol) was needed.

Table 2

Scope of cyclization of 2-alkynylsulfonanilides[a]



1 **2** 98-99%[b]



[a] Reaction conditions: **1** (0.50 mmol), Cat-2A (0.05 mmol), EtOH (5 mL).
[b] Isolated yields.

With the optimized cyclization conditions in hand, the scope and generality of this methodology was evaluated by a majority of 2-alkynylsulfonanilides **1**. As demonstrated in Table 2, this cyclization reaction could tolerate a variety of functional groups, yielding the desired indole products **2a**-**2s** in near quantitative yields. The introduction of electron-withdrawing groups (**2b-2f**, **2j-2l**, **2p**, **2q** and **2s**) or electron-donating groups (**2g**, **2h** and **2r**) to the *N*-aryl ring hardly influences the cyclization reaction yields. Various substituents connected to the alkynyl function were also assessed. It was found that the cyclization of substrates with an aliphatic alkynyl group (**2i-2n** and **2s**) proceeds slightly faster

than those with a phenyl group (**2a-2h** and **2o-2r**). For instance, the annulation of **1k** and **1l** only needs 5 min, giving indoles **2k** and **2l** with 99% yields. Moreover, to replace the protecting group on nitrogen atom also altered the reaction speed. When the tosyl (Ts) group was changed into the methanesulfonyl (Ms) group, the reaction time was generally prolonged, but the yields keep well (e.g. **2a** and **2o**). Meanwhile, the cyclization of acetyl (Ac) protected substrate was tried under the standard reaction conditions, unfortunately, no desired indole product (**2t**) was formed after a long reaction time. All indoles prepared were fully confirmed through ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HR-MS analyses (ESI).

To evaluate the reusability of Cat-2A, the cyclization reaction of 2-alkynylsulfonanilide **1a** was repeated under the optimized conditions (ESI) and the results are shown in Fig. 2. It was found that the catalytic performance of Cat-2A still keeps high after seven cycles. All cyclization reactions proceeded smoothly and gave the desired product **2a** in almost the same yield as in the first run, needless to reactivate the catalyst.

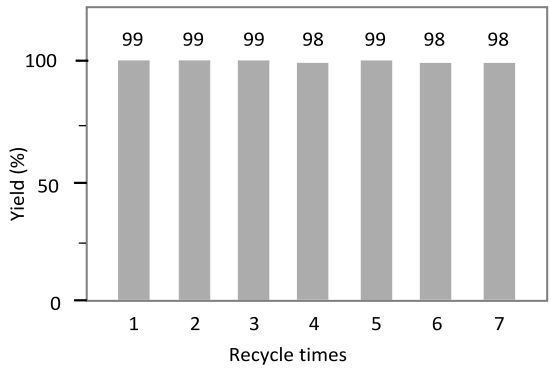


Figure 2. Recyclability of Cat-2A for cyclization reaction of **1a**.

Comprehensive analysis of the results shown in Table 1 and Table 2 revealed that the CuMgAl-LDH owns the dual-activation and high catalytic activity originated in its Cu^{2+} and alkalinity. Thus, based on such observations together with some suggestions documented in the literature,[6e,7a] a plausible mechanism for the CuMgAl-LDH-catalyzed cyclization of 2-alkynylsulfonanilides has been proposed (Fig. 3). First, the Cu(II) in the CuMgAl-LDH coordinates with the C≡C triple bond of **1** to form Cu(II) complex **I**, while the in-situ base in the CuMgAl-LDH abstracts an acidic N–H proton, yielding a sulfonanilide anion **II**. Next, the anion attacks the activated C≡C triple bond in a nucleophilic reaction, giving intermediate **III**. Finally, a proton transfer occurs between the LDH–H and **III**, creating the desired indole **2** and CuMgAl-LDH catalyst. Obviously, the coordination of Cu^{2+} with the C≡C triple bond can promote the electrophilicity of alkynyl function, and the formation of anion may increase the nucleophilicity of the sulfonamide. This dual-activation efficiently accelerates the cyclization reaction of 2-alkynylsulfonanilides, forming indoles with excellent yields.

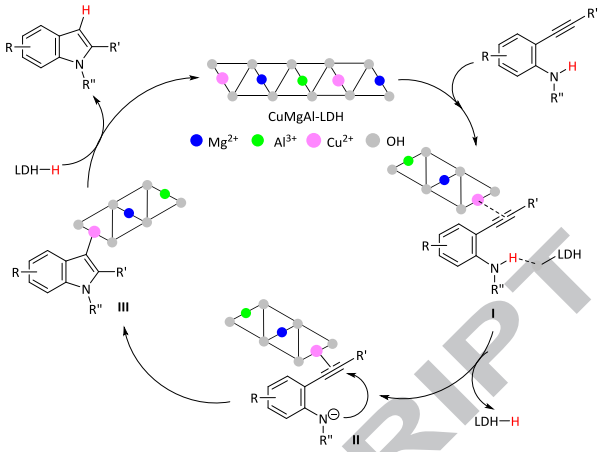


Figure 3. A plausible mechanism for CuMgAl-LDH-catalyzed cyclization of 2-alkynylsulfonanilides.

To understand the precise morphology of indole derivatives **2**, the crystal structures of **2a**, **2c**, and **2f** were assessed by single crystal X-ray diffraction analysis (Table 1, Table S2 and Fig. S5, ESI). In their crystal structures, the indolyl plane is not coplanar with the phenyl ring at its 2 position, creating dihedral angles of 43.5 and 43.9° for **2a** and **2f**, respectively. The benzene ring of the Ts leans toward the indolyl plane, yielding dihedral angles of 64.3 and 64.7° for **2a** and **2f**, respectively. However, for **2c**, the benzene ring of the Ts is almost perpendicular with the indolyl plane, giving a dihedral angle of 76.9°. This may be contributed to the influence of F atom at 6 position of the indole ring. In their packing, the key interactions are intermolecular C–H···O contacts (Table S6, ESI).

To wholly learn the crystal packing driving forces, the Hirshfeld surfaces and fingerprint plots were further analyzed with CrystalExplorer.[16] The surfaces mapped with close contacts between vicinal molecules for **2a**, **2c** and **2f** are shown in Fig. 4 and Figs. S6-S8 (ESI). The main C–H···O interactions of three indole compounds are all depicted as red spots, suggesting that they play a key role in their crystal packing. And the deep red spot in **2c** can be assigned to the C–H···F hydrogen bond due to the existence of the F group at 6 position of the indole ring. Moreover, various pale red spots were observed in other orientations, standing for the weaker C–H···π and π···π contacts (ESI).

The 2D fingerprint plots and decomposition for the primary intermolecular contacts (Figs. S9-S12, ESI) provide evidence of the crystal packing driving forces for **2a**, **2c** and **2f**. The relative contributions of the intermolecular contacts to the Hirshfeld surface areas are summarized in Fig. S13 (ESI). The main intermolecular contacts involve weak H···H, C···H/H···C and O···H/H···O interactions. They totally occupy 96.2, 79.3 and 85.2% in the packing of **2a**, **2c** and **2f**, respectively, in which the percentages of C···H/H···C contacts are 32.1, 19.7 and 23.1%, and those of O···H/H···O contacts are 14.1, 14.4 and 22.6%. In addition, the contribution of F···H/H···F contacts in **2c** is 9.3% for the existence of F atom, and results in the decrease of the percentage of C···H/H···C contacts. The decreased percentage of C···H/H···C contacts and the increased percentage of O···H/H···O contacts in **2f** can be ascribed to the existence of nitro group.

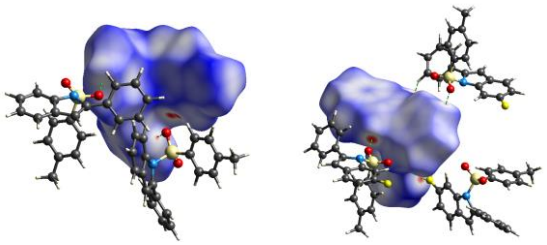


Figure 4. Hirshfeld surface for **2a** and **2c**. Vicinal molecules associated with close contacts are shown.

In conclusion, a green strategy has been developed for facile and efficient synthesis of indoles by the CuMgAl-LDH-mediated cyclization of 2-alkynylsulfonanilides in quantitative yields. The CuMgAl-LDH catalyst possesses dual-activation and recycling features. This work may contribute to easily building indole libraries.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21372147).

Supplementary data

Supplementary data (ESI) available: Experimental procedures, powder XRD, TEM, FT-IR, SEM, NMR spectra, HR-MS, X-ray crystallography, and Hirshfeld surface analysis can be found in ESI. Crystallographic data for the structures **2a**, **2c** and **2f** have been deposited with the Cambridge Crystallography Data Centre (CCDC No. 1849708, 1849710 and 1849709, respectively).

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Highlights:

1. A green synthesis of indoles *via* CuMgAl-LDH-catalyzed cyclization is reported

2. CuMgAl-LDH catalyst features facile preparation and unique dual activation

3. This method shows broad substrate scope, mild conditions and high efficiency