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Three-component synthesis of poly-substituted tetrahydroindoles through p-TsOH promoted alkoxylation

Qing-Qing Shi †, Li-Ping Fu †, Yu Shi †, Hua-Qin Ding †, Jing-Hua Luo †, Bo Jiang *, Shu-Jiang Tu *

School of Chemistry and Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, PR China

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ABSTRACT

Concise and efficient three-component domino reactions to highly substituted tetrahydroindole derivatives promoted by *p*-TsOH have been developed under microwave irradiation condition. The direct C3-alkoxylation of indole framework was achieved in a one-pot operation. The reaction proceeds at fast rates and can be finished within 30 min, which makes workup convenient to give good chemical yields.

The functional indoles oxygenated in the 3-position skeletons serve as 'privileged structures' in many biologically active molecules and pharmaceutical substances;[1] they have also been found in natural alkaloids, such as Indican[2] and koniamborine[3] (Fig. 1). In addition, a variety of synthetic 3-alkoxyindoles exhibited various biological activities, including reversible inhibitors of aminopeptidase N/CD13,[4] tubulin polymerization inhibitors,[5] selective serotonin 5-HT2 receptor ligands,[6] and 5-HT6 receptor ligand mimics.[7] Moreover, they have been used in the development of COX-2 inhibitors[8] as well as applied as Mcl-1 inhibitors in the design of novel antitumor agents.[9] Because of their unique chemical and biological characteristics, many methodologies for the synthesis of 3-alkoxyindoles have been developed. Most of them involved Pd-catalyzed alkoxylation of 3-bromoindoles,[9] Baeyer–Villiger oxidation sequence of 3-formylindoles,[10] Ti- and Zn-mediated hydroamination of silyl-protected propargylic alcohol with arylhydrazine,[11] palladium-catalyzed domino cyclizations,[12] rhodium-catalyzed insertion of 3-diazoindole,[13] and benzoylperoxide oxidation of *N*-alkylindoles,[14] and so on.[15] Despite these limited 3-oxyindole syntheses, an exploration of a facile protocol for the direct construction of indole skeleton and its C3-alkoxylation would be highly favorable.

In organic synthesis, the high-efficient synthetic strategies reflect the sum of enormous efforts aimed at atom-economic and environmental aspects, and remarkable selective control of constructing natural products or natural-like structures.[16] Multi-component domino reactions (MDRs) have been successfully applied to total synthesis of natural and natural-like products,[17] becoming one of the key tools that allows the creation of several bonds in a one-pot manner and offer remarkable advantages like convergence, operational simplicity, and facile automation.[18] These reactions not only can enable constructing complex structures in a single operation but also avoid tedious isolation and purification work-up. Among these methodologies, MDRs toward the formation of various heterocycles have been extensively studied.[19] However, more efficient methodologies for the synthesis of azaheterocyclic products from readily available reactants remain to be extremely challenging in the fields of organic and medicinal chemistry.

Recently, we have developed a series of unique MDRs for the construction of multiple functional ring structures of chemical and pharmaceutical importance.[20] As a result of our continuous effort on these domino processes, herein, we would like to disclose another new *p*-TsOH promoted MDRs of enaminones **2** with arylglyoxal monohydrate **1** in the presence of alcohols **3** yielding poly-substituted tetrahydroindoles (Scheme 1). The unique characteristic of the present domino reaction demonstrates that the

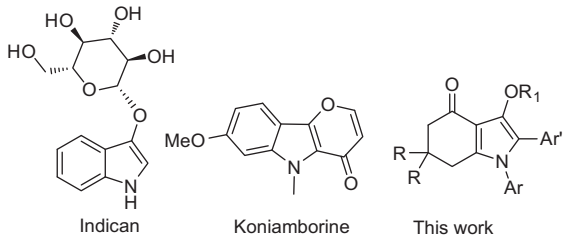

Figure 1. several representative natural products.

* Corresponding authors. Tel./fax: +86 516 83500065.
E-mail addresses: jiangchem@jsnu.edu.cn (B. Jiang), laotu@jsnu.edu.cn (S.-J. Tu).
† These authors contributed equally to this work.

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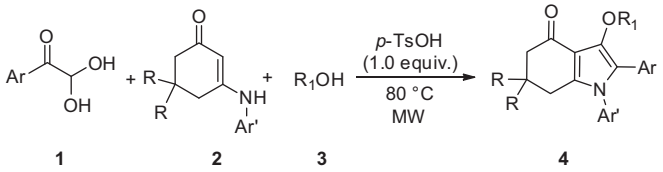
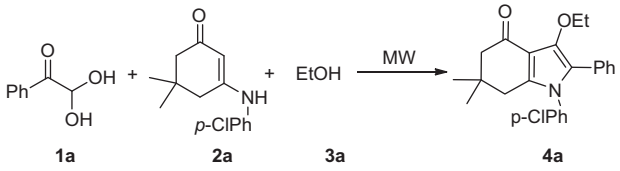


Scheme 1. The MDRs of enaminones **2** with **1** and **3**.

formation of *indole skeleton* and *its C3-alkoxylation* were readily achieved via metal-free [3+2] heterocyclization in a one-pot operation. To the best of our knowledge, the utilization of alkoxylation strategy combined with multi-component domino reactions for the preparation of polysubstituted tetrahydroindoles has not been documented so far.

Our investigation was initiated by evaluating the domino reaction of 2,2-dihydroxy-1-phenylethanone **1a** with 3-(4-chlorophenyl amino)-5,5-dimethylcyclohex-2-enone **2a,** and ethanol **3a**. The reaction was tested under a variety of different conditions. The representative data are summarized in Table 1. It was found that the reaction could not proceed at 80 °C under microwave (MW) heating using HOAc or CF_3COOH as a Brønsted acid promoter (Table 1, entries 1–2). 1.0 equiv of H_2SO_4 gave the expected product **4a** in 70% yield (Table 1, entry 3). The identical reaction promoted by 1.0 equiv of *p*-TsOH generated slightly higher yield of product **4a** (78%) than that promoted by H_2SO_4. Subsequently, the same reaction promoted by *p*-TsOH was performed and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 20–30 min. The yield of product **4a** was increased from 52% to 78% as the temperature varied from 60–80 °C. Further increase of reaction temperature failed to improve the yield of desired product **4a** (entry 6). Next, we investigated the amount of *p*-TsOH required for this domino reaction. The results indicated that increasing the amount of *p*-TsOH from 0.5 to 1.0 equiv led to an increase in the yield from 49% to 78%

Table 1
Optimization of reaction conditions

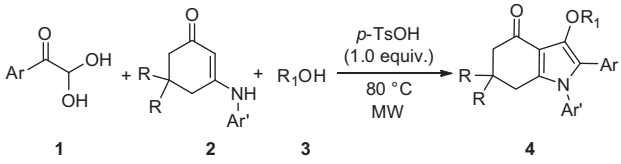


Entry	Promoter (equiv)	*T* (°C)	Time (min)	Yield (%)
1	HOAc (1.0)	80	30	no
2	CF_3COOH (1.0)	80	30	trace
3	H_2SO_4 (1.0)	80	20	70
4	*p*-TsOH (1.0)	80	20	78
5	*p*-TsOH (1.0)	60	30	52
6	*p*-TsOH (1.0)	100	20	73
7	*p*-TsOH (0.5)	80	20	49
8	*p*-TsOH (1.5)	80	20	76

(Table 1, entries 4 and 7). The addition of larger amounts of *p*-TsOH did not improve the yield of **4a** (Table 1, entry 8). It was anticipated that ethanol serves as an etherification reagent and reaction media for the MDRs simultaneously.

With the above optimized conditions, we then proceeded to probe the substrate diversity of this *p*-TsOH promoted three-component domino reaction by using readily available starting materials. The reactions presented in Table 2 preceded efficiently and afforded the desired products in moderate to good yields. The substituents on the aromatic ring of arylglyoxal monohydrate **1** did not hamper the reaction process. Reactions of methyl-, chloro-, bromo-, or fluoro-substituted phenylglyoxal monohydrate **1** with **2** all worked well to provide the desired products in moderate to good yields. The variation of Ar' groups of β-enaminones including electron-withdrawing groups or with electron-donating groups all furnished the desired alkoxy-substituted indoles **4a**–**4f** in good

Table 2
Domino synthesis of tetrahydroindoles **4** under MW[21]



Entry	4	Ar	Ar'	R	R_1	Time (min)	Yield[a] (%)
1	**4a**	Ph (**1a**)	4-ClPh (**2a**)	Me	Et	20	78
2	**4b**	4-BrPh (**1b**)	4-ClPh (**2a**)	Me	Et	25	81
3	**4c**	4-ClPh (**1c**)	4-BrPh (**2b**)	Me	Et	25	84
4	**4d**	4-MePh (**1d**)	4-BrPh (**2b**)	Me	Et	22	79
5	**4e**	4-MeOPh (**1e**)	4-MePh (**2c**)	Me	Et	26	74
6	**4f**	4-FPh (**1f**)	Ph (**2d**)	Me	Et	24	80
7	**4g**	4-FPh (**1f**)	Ph (**2d**)	Me	Me	24	86
8	**4h**	Ph (**1a**)	4-ClPh (**2a**)	Me	Me	22	83
9	**4i**	4-BrPh (**1b**)	4-ClPh(**2a**)	Me	Me	30	87
10	**4j**	4-ClPh (**1c**)	4-ClPh(**2a**)	Me	Me	25	85
11	**4k**	4-MePh (**1d**)	4-ClPh(**2a**)	Me	Me	28	76
12	**4l**	Ph (**1a**)	4-BrPh (**2b**)	Me	Me	25	83
13	**4m**	4-BrPh (**1b**)	4-BrPh(**2b**)	Me	Me	22	81
14	**4n**	4-MePh (**1d**)	4-BrPh(**2b**)	Me	Me	22	78
15	**4o**	4-FPh (**1f**)	4-MePh(**2c**)	Me	Me	21	85
16	**4p**	Ph (**1a**)	4-ClPh (**2e**)	H	Et	25	75
17	**4q**	4-BrPh (**1b**)	4-ClPh (**2e**)	H	Et	24	70
18	**4r**	4-BrPh (**1b**)	4-ClPh (**2e**)	H	Me	20	76
19	**4s**	4-MeOPh (**1e**)	4-ClPh(**2e**)	H	Me	30	65
20	**4t**	4-MeOPh (**1e**)	4-MePh (**2f**)	H	Et	25	69

[a] Isolated yield.

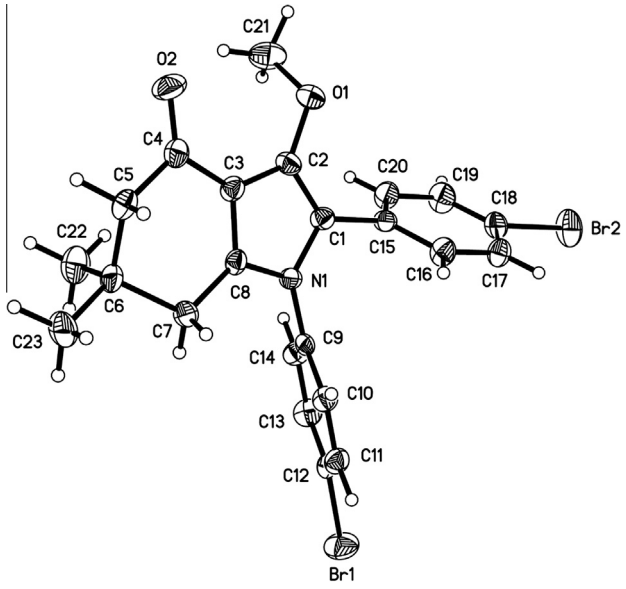
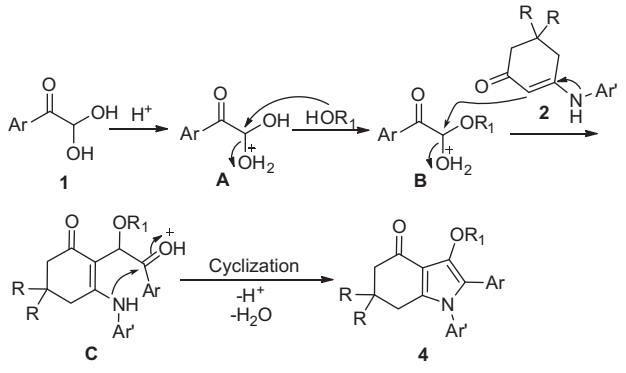


Figure 2. X-ray structure of **4m**.

yields within a short period of time (Table 2, entries 1–6). Next, we replaced ethanol **3a** with methanol **3b** and subjected to reaction with enaminones and arylglyoxal monohydrates to investigate the possibility of this transformation. Substituents on the phenyl ring of **1** regardless of its electronic property were all successfully engaged in this reaction, which can be readily transformed into the corresponding methoxyl-substituted tetrahydroindoles **4g**–**4o** with 76%–87% yields. 5,5-Unsubstituted 3-aminocyclohex-2-enones bearing both electron-deficient and electron-rich aromatic groups **2e** and **2f** were converted into the corresponding alkoxy-substituted tetrahydroindoles **4p**–**4t** in 65%–76% yields, respectively. The tolerance of functionalities, such as chloro, bromo in this protocol provides the opportunity of their various further chemical manipulations in products. It is worth mentioning that the protocol provides a straightforward pathway to synthesize alkoxy-substituted indoles, which are generally prepared via metal-catalyzed alkoxylation.[11–13]

In general, the reaction occurred at a very fast speed; in fact, all cases can be finished within 20–30 min. Water is nearly a sole by-product, which makes the work-up convenient. In most cases, the products can precipitate out after the reaction mixture was poured into cold water and was neutralized by diluted basic solution. The structural elucidation of the products was determined from its IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. The structure of compound **4m** was unequivocally confirmed by X-ray analysis (Fig. 2).[22]



Scheme 2. The possible mechanism for tetrahydroindoles **4**.

On the basis of experimental results, a reaction mechanism for this domino reaction is postulated in Scheme 2. Firstly, arylglyoxal monohydrate protonated by *p*-TsOH undergoes etherification of **3** to convert into intermediate **B**, followed S_N2 type reaction of enaminones **2** to yield **C**. Then, intramolecular cyclization of **C** promoted by *p*-TsOH occurs, affording final tetrahydroindoles **4**.

In conclusion, we have described a new *p*-TsOH promoted three-component domino reaction involving alkoxylation process which provides a general and efficient strategy for the synthesis of tetrahydroindole derivatives with good yields in a one-pot manner. The reaction process employs readily available enaminones and arylglyoxal monohydrate as starting materials and involves tandem protonation of hydroxyl group/etherification/second S_N2/intramolecular cyclization sequences. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates, and to synthesize closely related natural-like products and test their biological activity.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and spectroscopic characterization of all compounds along with ^{1}H, IR and mass spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.029.

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21. General procedure for the synthesis of tetrahydroindoles **4b**: 1-(4-bromophenyl)-2,2-dihydroxyethanone (**1b**, 1.0 mmol, 0.231 g.) was introduced in a 10 mL initiator reaction vial, and 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-enone (**2a**, 1.0 mmol, 0.25 g), *p*-TsOH (1.0 mmol, 0.17 g), and EtOH (**3a**, 1.5 mL, excess) were then successively added into the reaction system. Subsequently, the reaction vial was capped and then pre-stirred for 20 sec. The mixture was irradiated (time: 25 min, temperature: 80 °C; Absorption level: high; fixed hold time) until TLC (petroleum ether/acetone 3:1) revealed that conversion of the starting material **2a** was complete. The reaction mixture was cooled to room temperature and was then neutralized by 10% NaOH solution. Next, the system was diluted with cold water (10 mL). The solid was collected by Büchner filtration and was purified by recrystallization from 50% EtOH to afford the desired pure tetrahydroindoles **4b** as a pale white solid (Mp: 211–212 °C). **2-(4-bromophenyl)-1-(4-chlorophenyl)-3-ethoxy-6,7-dihydro-6,6-dimethyl-1H-indol-4(5H)-one (4b)** IR (KBr, ν cm^{-1}): 3465, 1657, 1497, 1422, 1366, 1133, 1075, 1009, 831, 735, 696, 655, 514; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J = 6.4 Hz, 3H, Ar–H), 7.29 (s, H, Ar–H), 7.10 (d, J = 8.0 Hz, 2H, Ar–H), 6.99 (d, J = 8.4 Hz, 2H, Ar–H), 4.10 (m, 2H, CH_2), 2.49 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 1.23 (t, J = 6.8 Hz, 3H, CH_3), 1.07 (s,6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.5, 142.9, 140.6, 138.3, 136.5, 133.7, 132.4, 129.3, 129.1, 128.7, 122.6, 121.1, 112.8, 70.1, 52.7, 37.2, 35.3, 28.5, 15.4. HRMS (ESI): m/z calcd for $[M+H]^+$ $C_{24}H_{24}BrClNO_2$, 472.0679; found: 472.0635.
22. The single-crystal growth was carried out in co-solvent of EtOH and DMF at room temperature. Crystal data for **4m** (CCDC-921884): $C_{23}H_{21}Br_2NO_2$, crystal dimension 0.45 × 0.40 × 0.21 mm, Triclinic, space group P-1, a = 8.8419(9) Å, b = 9.6936(11) Å, c = 13.4897(13) Å, α = 97.4180(10) Å, β = 91.3370(10) Å, γ = 110.504(2) Å, V = 1070.96(19) Å^3, Mr = 503.23, Z = 2, λ = 0.71073 Å, μ (Mo K_α) = 3.803 mm^{-1}, F(000) = 504, R_1 = 0.0584, wR_2 = 0.1078.