A multi-component domino reaction for the direct access to polyfunctionalized indoles *via* intermolecular allylic esterification and indolation†

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Abstract

A novel multi-component reaction for the synthesis of polyfunctionalized indoles and bis-indoles has been established. The reaction pathways were controlled by varying enamines with different substitution patterns to give polyfunctionalized indoles and bis-indoles selectively. The reaction proceeds at a fast speed within 15–30 min with water as the major byproduct, which makes work-up convenient.

Indoles are probably the most ubiquitous heterocycles in nature and have been referred to as "privileged structures" in drug discovery because of their capacity to bind many receptors with high affinity.[1] Accordingly, many powerful methodologies for the synthesis of these heterocycles have been developed,[2] the majority of these methods involve Fischer-type indole synthesis,[3] reductive cyclization,[4] metal-catalyzed coupling/condensation cascades[5] and electrophilic activation of *N*-aryl amides.[6] Recently, the utility of enamines in metal catalysis for the formation of valuable indoles has also been reported.[7,8] The development of concise approaches to multi-functionalized indoles from readily available and inexpensive starting material is of great importance and challenging.

Meanwhile, the direct and selective functionalization of allylic C–H bonds into C–C and/or C–X bonds (X = O, N, halogen, *etc.*) has become an important topic because it provides a powerful tool for the synthesis of numerous complex molecules.[9] In this regard, there has been enormous interest in developing sp^3-C–H bond functionalization,[10] especially those of metal-free couplings.[11] Among the various known synthetic methodologies, the direct formations of C–C and/or C–X bonds from allylic C–H bonds have attracted great attention.[12] These methodologies can provide a series of intrinsic advantages, such as higher atom economy, shorter synthetic routes, and less energy and manpower usage, which leads to "benign by design".[13] Therefore, the design of efficient allylic functionalization without the use of metal catalysts is a continuing challenge at the forefront of organic chemistry.

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Over the past several years, our group has developed various multicomponent domino reactions (MDRs) that can offer easy access to useful multiple functionalized ring structures of chemical and pharmaceutical interest.[14] During our continuous efforts on the development of useful multi-component domino reactions,[15,16] herein, we report the challenging annulation of enamines with arylglyoxal monohydrate and the subsequent allylic activation with aliphatic carboxylic acids as nucleophilic reagents yielding multifunctionalized indoles (Scheme 1). The great aspect of the present domino reaction is shown by the fact that the formation of indole skeleton and its functionalization were readily achieved *via* metal-free allylic activation in an intermolecular manner and in a one-pot operation.

To begin this study, we chose 3-(*p*-tolylamino)-5,5-dimethyl-cyclohex-2-enone (**1a**), phenylglyoxal monohydrate (**2a**), and acetic acid (**3a**) as the standard substrates to search for suitable reaction conditions under microwave (MW) irradiation. Various solvents including DMF, benzene, $CHCl_3$, EtOH, and HOAc were optimized. Non-protonic solvents, such as DMF, benzene, $CHCl_3$, resulted in poor to moderate yields under MW irradiation for 10 min at 100 °C. In another case, when EtOH was selected as the solvent, the reaction occurred and product **4a** was obtained in 54% isolated yield after purification is performed.[‡] After systematic screening was made, we found that, in the presence of acetic acid, **1a** was transformed into the desired product **4a** in an excellent yield (84%). It is anticipated that acetic acid serves as nucleophile, reaction media and Bronsted acid promoter for the allylic functionalization simultaneously.

With these optimized conditions in hand, we examined the scope of this new multicomponent domino process by using various easily available starting materials. As revealed in Table 1, a range of invaluable polysubstituted indole derivatives can be synthesized in good to excellent yields. The reaction is easy to perform simply by subjecting a mixture of enamine **1** and arylglyoxal monohydrate **2** in various carboxylic acids to microwave heating. Subsequently, the enamine scope of this interesting transformation was investigated (Table 1). Several different N-substituents were compared and substituents bearing electron-withdrawing or electron-donating groups were found to be suitable for this domino reaction. Furthermore, using various carboxylic acids, such as propionic acid (**3b**), butyric acid (**3c**), and isobutyric acid (**3d**), together with different N-substituted enamines **1a–f** resulted in the cyclization to corresponding substituted indoles **4e–4s** smoothly. The benzo[*d*][1,3]dioxol-6-ylglyoxal monohydrate **2b** was subjected to the reaction with various carboxylic acids, providing the corresponding benzo[*d*][1,3]dioxol-6-yl substituted indoles **4t–4v**. The results exhibit the scope and generality of the novel allylic activation-based multicomponent domino reaction with respect to a range of enamine and carboxylic acid substrates. Indeed, the protocol provides a straightforward pathway to construct highly substituted indoles, which are generally prepared *via* metal-catalyzed coupling reactions.[10]

In view of these results, we turned our attention to investigate several differently substituted enamines. The reactions of arylglyoxal monohydrate (**2a–2h**) with N-substituted 3-amino-cyclohex-2-enones (**1g–1j**) in acetic acid were performed under the conditions described above for a short period (26–30 min). Interestingly, acetic acid was found to be the only efficient solvent and Bronsted acid catalyst, not as a nucleophile. Two molecules of arylglyoxal monohydrate and N-substituted 3-aminocyclohex-2-enones were introduced into

the final poly-substituted bis-indoles (Scheme 2). The results are summarized in Table 2. Both electron-deficient and electron-rich aromatic groups on the N-substituted 3-aminocyclohex-2-enones gave very good chemical yields (**5a–5l**). Furthermore, functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.

In all cases, the complexity of resulting products from this new reaction illustrates the remarkable chemo-, and regioselectivity of the sequence starting from very common and easily accessible inexpensive starting materials. The structural elucidation and the attribution of regioselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystals that were obtained by slow evaporation of the solvent, as in the case of bis-indoles **5a** (Fig. 1). During these domino processes, up to two indole rings and five sigma-bonds were formed accompanied by cleavage of two C=O and four C–O bonds of the aryl glyoxal, and direct indolation of hydroindoles **B** was simultaneously achieved *via* intermolecular coupling between sp^2-C–H and sp^3-C–H bonds (Scheme 3). This observation is truly rare, very interesting and important in organic chemistry. Only microwave irradiation can make the present multi-component domino reaction to occur rapidly and efficiently, while normal heating diminished both yield and speed.

Complete regioselectivity and excellent yields (particularly for multicomponent reactions) were achieved for all cases that were examined. Furthermore, the reaction occurred at a very fast speed; in fact, all cases can be finished within 15–30 minutes. Water is nearly a sole by-product, which makes work-up convenient. In most cases, the products can precipitate out after cold water was poured into the reaction mixture. The continuing work on this reaction will be focused on the development of its asymmetric version in our lab.

The mechanism of this domino reaction is proposed in Scheme 3. An initial condensation generated imine-isomeric enamines **A**, which successively underwent intramolecular cyclization to give hydroindoles **B**. The key step of a divergence in reaction paths depends on the aromatization of hydroindoles **B**. With two methyl groups on the 5-position of cyclohex-2-enones, the 6-position of the hydroindoles **B** was activated to an electrophilic center and coupled with carboxylic acid, leading to multifunctionalized indoles **4**. The hydroindoles **B** without methyl groups (R_1 = H) were easily converted into the aromatic indoles **D** with a nucleophilic center at the 3-position, which through intermolecular coupling reaction with activated hydroindoles **B** resulted in the final polysubstituted bis-indoles.

In conclusion, a novel multicomponent domino reaction for the divergent synthesis of polyfunctionalized indoles and bis-indoles has been discovered. The reaction is easy to perform simply by mixing common reactants under microwave irradiation. The reaction is very fast and can be finished within 15–30 min with water as the major byproduct, making workup convenient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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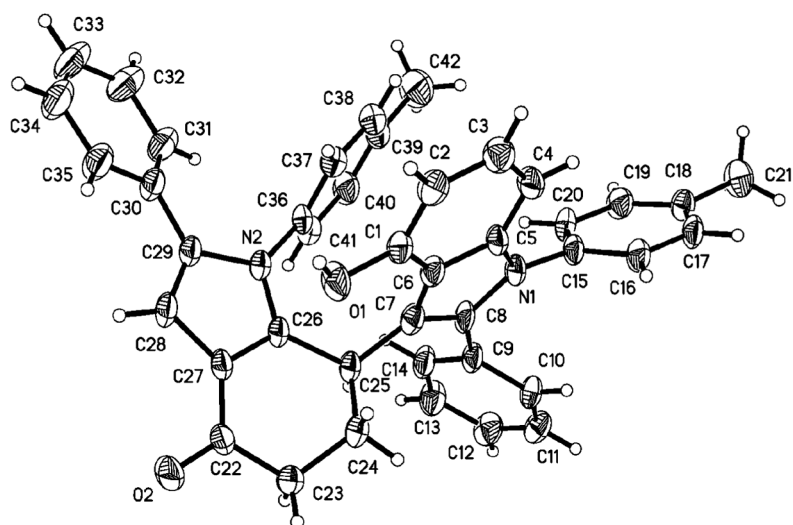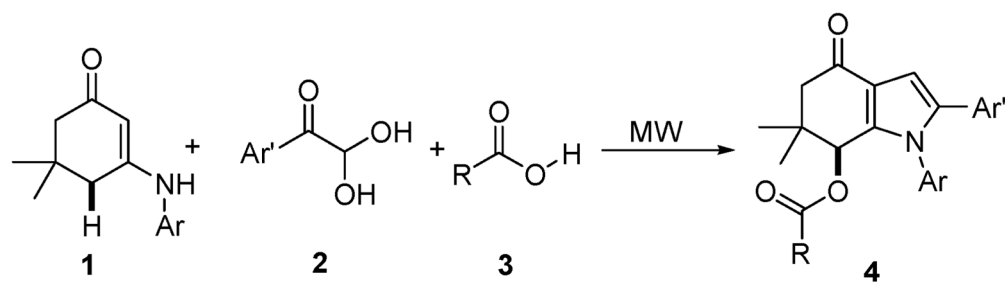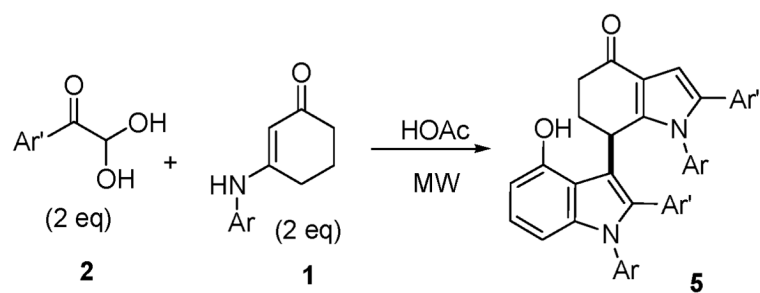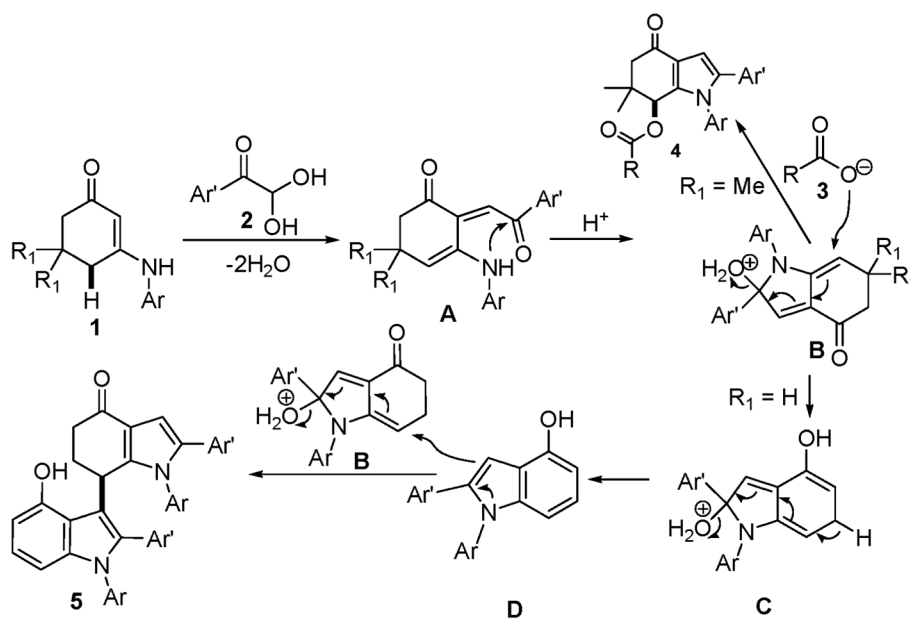
Fig. 1.
X-Ray structure of **5a**.

Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Domino synthesis of indoles **4** under MW[a]

Entry	Product	R or R′	Time/min	Yield[b]/%
1		**4a**, H (**1a**)	18	85
2		**4b**, 4-Fluoro (**1b**)	20	81
3		**4c**, 4-Bromo (**1d**)	22	82
4		**4d**, 4-Methyl (**1e**)	16	88
	4a–4d			
5		**4e**, H (**1a**)	18	86
6		**4f**, 4-Fluoro (**1b**)	24	82
7		**4g**, 4-Chloro (**1c**)	20	84
8		**4h**, 4-Bromo (**1d**)	18	85
9		**4i**, 4-Methyl (**1e**)	16	87
	4c–4j			
10		**4j**, 4-Methoxy (**1f**)	15	89
11		**4k**, 4-Chloro (**1b**)	22	79
12		**4l**, 4-Bromo (**1d**)	20	75
13		**4m**, 4-Methyl (**1e**)	18	81
14	**4k–4n**	**4n**, 4-Ethoxy (**1f**)	18	84
15		**4o**, 4-Fluoro (**1b**)	26	82
16		**4p**, 4-Chloro (**1c**)	22	77
17		**4q**, 4-Bromo (**1d**)	22	79
18		**4r**, 4-Methyl (**1e**)	18	84
19	**4o–4s**	**4s**, 4-Methoxy (**1f**)	18	85
20		**4t**, Methyl (**3a**)	20	79
21		**4u**, Ethyl (**3b**)	22	76
22		**4w**, Propyl (**3c**)	22	78
23		**4v**, Isopropyl (**3d**)	20	80
	4t–4v			

[a] Reagents and conditions: 120 °C, microwave heating.

[b] Isolated yield.

Table 2

Domino synthesis of bis-indoles **5** under MW[a]

Entry	5	Ar	Ar′	Time/ min	Yield[b]/ %
1	**5a**	4-Tolyl (**1g**)	Phenyl (**2a**)	30	51
2	**5b**	4-Tolyl (**1g**)	4-Fluorophenyl (**2c**)	28	54
3	**5c**	4-Tolyl (**1g**)	4-Chlorophenyl (**2d**)	26	50
4	**5d**	4-Tolyl (**1g**)	4-Bromophenyl (**2e**)	26	52
5	**5e**	4-Tolyl (**1g**)	4-Methoxyphenyl (**2f**)	30	48
6	**5f**	4-Tolyl (**1g**)	3-Methoxyphenyl (**2g**)	30	45
7	**5g**	4-Chlorophenyl (**1h**)	4-Fluorophenyl (**2c**)	28	43
8	**5h**	4-Chlorophenyl (**1h**)	4-Tolyl (**2h**)	30	40
9	**5i**	4-Chlorophenyl (**1h**)	Benzo[*d*][1,3]dioxol-6-yl (**2b**)	30	52
10	**5j**	4-Fluorophenyl (**1i**)	Phenyl (**2a**)	28	49
11	**5k**	4-Fluorophenyl (**1i**)	Benzo[*d*][1,3]dioxol-6-yl (**2b**)	30	47
12	**5l**	4-Methoxyphenyl (**1j**)	Phenyl (**2a**)	30	53

[a]Reagents and conditions: HOAc (2.0 mL), 100 °C, microwave heating.

[b]Isolated yield.