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# Efficient Domino Approaches to Multifunctionalized Fused Pyrroles and Dibenzo[*b*,*e*][1,4]diazepin-1-ones

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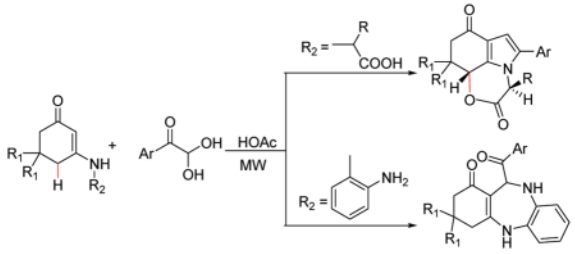
## Abstract




Efficient domino approaches for the synthesis of multifunctionalized tricyclic fused pyrroles and dibenzo[*b*,*e*][1,4]diazepin-1-ones have been established. The reaction pathways were controlled by varying enaminones with different substituted patterns to give a series of new fused pyrroles and dibenzo[*b*,*e*][1,4]diazepin-1-ones selectively. The complete *anti* diastereoselectivity was achieved for the first reaction.

Polycyclic fused pyrroles are among the most ubiquitous heterocycles in nature and often referred to as “privileged structures” in drug discovery because of their biological activities such as antibacterial, antiviral, anti-inflammatory, antitumoral and antioxidant activities.[1] In the past several decades, many methodologies for the synthesis of polycyclic fused pyrroles have been developed; most of them involved metal-catalyzed cascade cyclization of alkynes,[2] rearrangement–cyclization of alkynol[3a] and alkynyl ketones,[3b] cycloketone annulations,[4] and 1,3-dipolar cycloaddition reactions of much none derivatives.[5] The development of new convenient and step-economical approaches to this family of heterocyclic compounds, producing less waste and by product, continues to be of considerable interest and important for modern organic and medicinal chemistry, particularly, for drug discovery and development. However, to the best of our knowledge, a



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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

one-pot synthesis of lactonized fused pyrroles via domino reaction involving intramolecular allylic activation has not been well documented yet.

In the meantime, there has been enormous interest in developing the direct and selective functionalization on allylic C–H bonds[6,7] including the direct formations of C–O bonds.[8] These methodologies would provide the intrinsic advantages, such as step-economy, high chemoselectivity and easy operation leading to “benign by design” of green synthesis.[9] The design of efficient allylic lactonization without the use of metal catalysts has remained as a challenge at the forefront of organic chemistry.

In the past several years, we and others have developed a series of domino reactions that provided easy access to multiple functionalized ring structures of chemical and pharmaceutical interest.[10–12] We also established a new three-component domino reaction for the synthesis of multifunctionalized indole derivatives.[10f] The reaction is easy to perform simply by mixing readily available carboxylic acids, *N*-aryl enaminones, and arylglyoxal monohydrate under microwave (MW) irradiation. During the continuation of this project, we found that when *N*-aryl enaminones were replaced by *N*-amino acid counterparts, the reaction can be directed toward lactonization to form tricyclic fused pyrrole derivatives that can directly serve for pharmaceutical research (Scheme 1). In this paper, we disclose novel domino reactions for the synthesis of polyfunctionalized and tricyclic fused pyrroles and dibenzo[*b*,*e*][1,4]diazepin-1-ones. The attractive aspect of the present domino reaction is shown by the fact that the novel construction of two new rings including pyrrole and oxazinone skeletons and the direct C–O bond formation can be easily achieved via metal-free allylic lactonization in a one-pot operation.

In the initial experiment, the enaminone **1a** which was derived from glycine and 5,5-dimethylcyclohexane-1, 3-dione was subjected to the reaction with phenylglyoxal monohydrate (**2a**) under microwave (MW) irradiation. Various solvents, such as DMF, benzene, HOAc, EtOH, HCOOH, and $CF_3COOH$, were employed as reaction media. Among these solvents, the first two aprotic ones (DMF and benzene) led to poor yields (<10%) even at an enhanced temperature of 80 °C under MW irradiation. The weak protic solvent, EtOH, resulted in product **3a** in 38% isolated yield. We found that in acetic acid, **1a** was converted into the product **3a** in a good yield (81%). It turned out that acetic acid can serve not only as a suitable medium but also as an adequate Bronsted acid promoter for the present reaction, while the stronger acids, HCOOH and $CF_3COOH$, led to much lower chemical yields (<15%).

With these optimized conditions in hand, we next examined the scope of the reaction by using readily available and common starting materials. As revealed in Table 1, a range of tricyclic fused indole derivatives can be formed under the optimized condition in good to excellent yields (65–89%). Enaminones derived from three different amino acids (R = H, Me and Et, **1a**–**c**) were proven to be suitable for this reaction. Meanwhile, a variety of aryl-glyoxal monohydrates **2** bearing either electron-withdrawing or electron-donating groups can react with above enaminones **1a**–**c** to give corresponding tricyclic fused pyrrole products **3a**–**x** (67%–89%). The performed enaminone substrate **1d** can also participate in the reaction yielding products **3y**–**z** in good yields of 65–73%. Interestingly, the complete *anti* diatereoselectivity products **3f**–**z** was achieved as determined by $^1$HNMR and X-ray diffractional analyses. Furthermore, pyrrolo[3,2,1-*kl*]phenoxazin-3(4*H*)-one **3aa** can be readily generated by reacting 2-aminophenol-derived enaminone **1e** with arylglyoxal monohydrate under these conditions.

As usual, this reaction is easy to perform simply by mixing enaminones **1** and arylglyoxal monohydrates **2** in HOAc under microwave irradiation and exhibits the great substrate scope

with respect to a range of enaminones and arylglyoxal monohydrates. In all cases, the complexity of resulting products from this new domino synthesis illustrates the remarkable chemo- and regioselectivity of the cyclic sequence originated from very simple and easily accessible starting materials. The resulting functionalities of these tricyclic fused pyrroles offer a great flexibility for further structural modifications. These amino lactone analogs are directly useful for drug design, discovery, and development and for peptide/protein mimetic research. For example, after the ester group is carefully hydrolyzed, a series of special *N*-protected α-amino acids can be obtained; concurrently, a hydroxyl group is attached onto the six-membered enaminone rings.[13]

The structural elucidation with stereo- and regiochemistry was unambiguously determined by NMR analysis and X-ray diffraction analysis of single crystals that were obtained by slow evaporation of the solvent, as represented by the case of [1,4]oxazino[2,3,4-*hi*]pyrroles **3p** (Figure 1).

After the synthesis of tricyclic fused pyrroles was achieved, we turned our attention to the formation of dibenzo[*b,e*][1,4]diazepin-1-ones that are another family of building blocks of pharmaceutical importance by using benzene-1,2-diamine-derived enaminones to replace their amino acid counterparts. Pleasantly, we found that the reactions of arylglyoxal monohydrates (**2a**, **2c**, **2f**, and **2g**) with 3-(2-aminophenylamino)-5,5-dimethylcyclohex-2-enones (**1e**–**g**) can smoothly occur in acetic acid under the above condition to give multifunctionalized dibenzo[*b,e*]-[1,4]diazepin-1-ones **4**. The reactions can proceed to completion within shorter periods of 12–18 min at 60 °C (Scheme 2). As summarized in Table 2 the reaction also showed a great substrate, scope in which a series of electron-deficient or electron-withdrawing groups can be attached aromatic rings of 3-(2-aminophenylamino)-5,5-dimethylcyclohex-2-enones. The same situation existed for arylglyoxal monohydrates substrates to give good to excellent yields of 76–88% (**4a**–**i**). For vicinal diamino moieties, both bromide and chloride were proven to tolerate the microwave irradiation at 60 °C. These functional groups provide many opportunities for further manipulations via cross-couplings.

Similar to our previous domino processes,[10a–c] the present two new reactions showed the following attractive characteristics: (1) the reaction can be performed at fast reaction rates and be finished within 12–36 min; (2) energy and manpower are saved for potential industrial production; (3) water is formed as the major byproduct, which belongs to environmentally friendly chemistry; (4) the convenient workup is needed via simple filtration since the products directly precipitate out of solution after the reaction mixtures are diluted with cold water, which belongs to GAP chemistry;[14] (5) readily available starting materials of enaminones[15] and arylglyoxal monohydrates[16] can be employed. Besides the fact that up to two new rings including pyrrole and oxazinone skeletons were formed in a one-pot operation without using any metal catalysts or promoters, *this rapid and efficient synthesis is truly rare, interesting and useful in organic chemistry, which was made possible by microwave irradiation while normal heating led to very limited success.*

The mechanisms of these chemoselective domino reactions are proposed and shown in Scheme 3. An initial nucleophilic reaction of enaminones with protonated arylglyoxal monohydrates affords intermediate **A**. The key divergent steps in the present domino pathways depend on the nucleophilicity of amino group on the phenyl ring and carboxylic acid functionality. With the stronger nucleophilicity, $NH_2$ group prefers to undergo second nucleophilic substitution of protonated arylglyoxal monohydrate and results in polysubstituted dibenzo[*b,e*][1,4]diazepin-1-ones **4**. The weak nucleophilicity of hydroxy moiety from carboxylic acid can direct the intermediate **A** toward dehydration to yield imine-isomeric enaminones **B**, which subsequently undergo intramolecular cyclization

leading to hydroindoles **C**. The 7-position of hydroindoles **C** can be activated to form an electrophilic center for coupling with carboxylic acid to give the final products, tricyclic fused pyrroles **3**.

In conclusion, novel domino reactions have been established for the synthesis of poly functionalized and tricyclic fused dibenzo[*b*,*e*][1,4]diazepin-1-one and pyrrole derivatives that are important building blocks for organic synthesis and medicinal chemistry. The reaction is easy to perform simply by mixing common reactants under microwave irradiation. The reaction can be performed to completion within 12–36 min with water as the major byproduct. The complete *anti* diastereoselectivity was achieved for the formation of tricyclic fused pyrrole derivatives. The workup and purification are convenient without the need of using traditional purifications of chromatography and recrystallization.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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[PubMed: 15382913] Li Z, Cao L, Li CJ. Angew Chem, Int Ed. 2007; 46:6505–6507.Zhang Y, Li CJ. Angew Chem, Int Ed. 2006; 45:1949–1952.Li Z, Li CJ. J Am Chem Soc. 2005; 127:6968–6969. [PubMed: 15884937] Li Z, Li CJ. J Am Chem Soc. 2005; 127:3672–3673. [PubMed: 15771482] Zhang Y, Li CJ. J Am Chem Soc. 2006; 128:4242–4243. [PubMed: 16568995] Stuart DR, Fagnou K. Science. 2007; 316:1172–1175. [PubMed: 17525334] Dwight TA, Rue NR, Charyk D, Josselyn R, DeBoef B. Org Lett. 2007; 9:3137–3139. [PubMed: 17616203]

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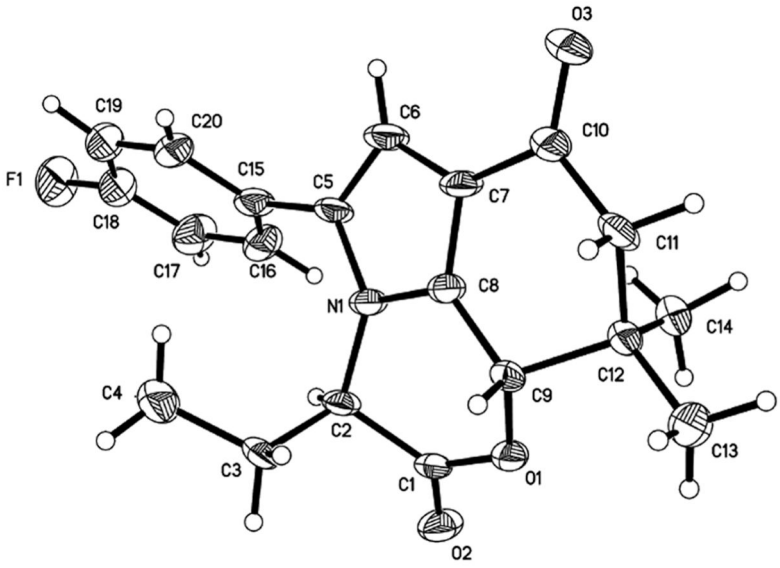
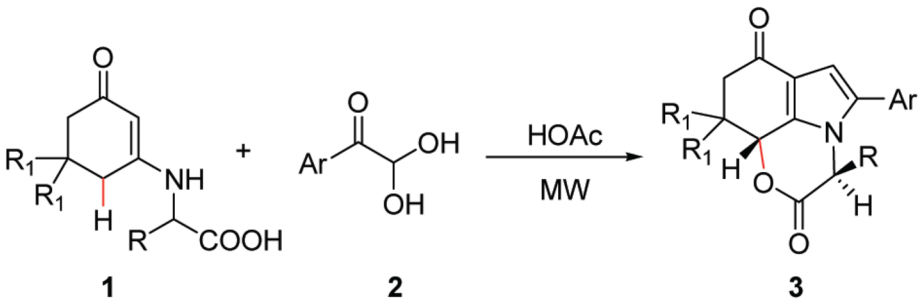
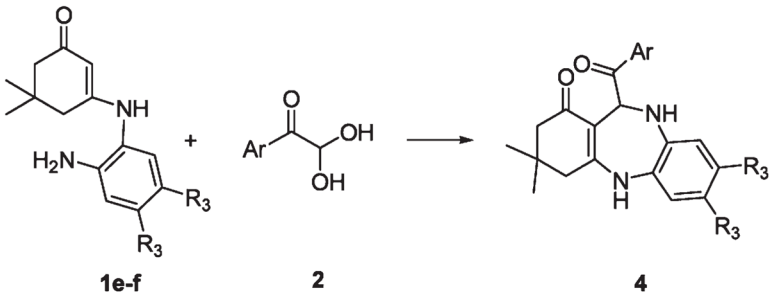


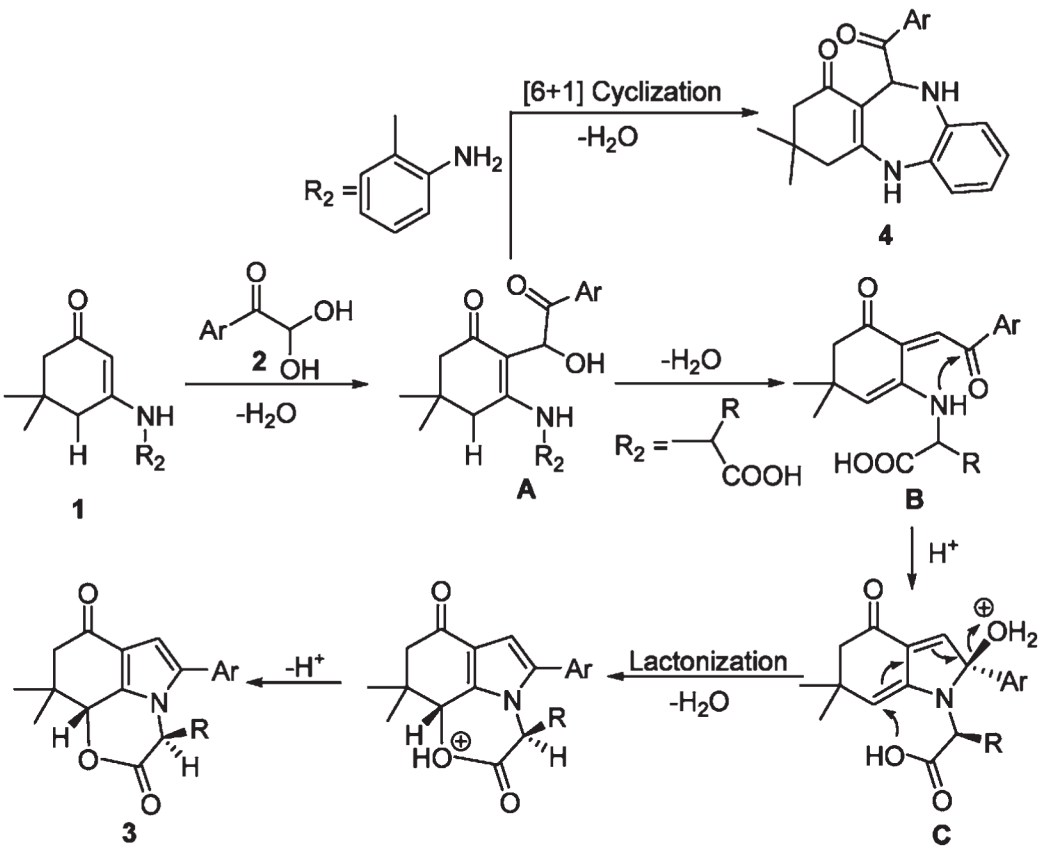

**Figure 1.**
X-ray structure of **3p**.




**Scheme 1.**



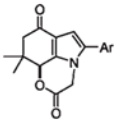
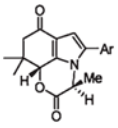
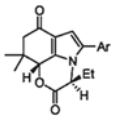
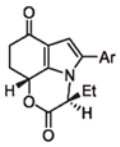
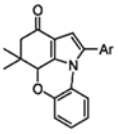

**Scheme 2.**




**Scheme 3.**

## Table 1

Domino Synthesis of Polycyclic Fused Pyrroles **3** under MW[a]

| Entry | Product | Ar | Time[b] | Yield[c]/% |
|---|---|---|---|---|
| 1 |  | **3a,** Phenyl (**2a**) | 20 | 81 |
| 2 | | **3b**, 4-Fluorophenyl (**2b**) | 18 | 78 |
| 3 | | **3c**, 4-Chlorophenyl (**2c**) | 18 | 80 |
| 4 | | **3d**, 3,4-Dichlorophenyl (**2d**) | 16 | 83 |
| 5 | **3a–3e** | **3e,** Benzo[*d*][1,3]dioxol-6-yl (**2e**) | 22 | 67 |
| 6 |  | **3f,** Phenyl (**2a**) | 22 | 86 |
| 7 | | **3g**, 4-Chlorophenyl (**2c**) | 20 | 79 |
| 8 | | **3h**, 3,4-Dichlorophenyl (**2d**) | 24 | 89 |
| 9 | | **3i**, 4-Bromophenyl (**2f**) | 20 | 81 |
| 10 | **3f–3n** | **3j**,4-Tolyl(**2g**) | 30 | 84 |
| 11 | | **3k**, 4-Methoxyphenyl (**2h**) | 30 | 80 |
| 12 |  | **31**, 3-Methoxyphenyl (**2i**) | 30 | 83 |
| 13 | | **3m**, Benzo[*d*][1,3]dioxol-6-yl (**2e**) | 28 | 78 |
| 14 | | **3n,** 3,4-Dimethoxyphenyl (**2j**) | 32 | 71 |
| 15 | **3o–3x** | **3o,** Phenyl (**2a**) | 30 | 76 |
| 16 |  | **3p**, 4-Fluorophenyl (**2b**) | 30 | 84 |
| 17 | | **3q**, 4-Chlorophenyl (**2c**) | 28 | 85 |
| 18 | | **3r**, 3,4-Dichlorophenyl (**2d**) | 26 | 83 |
| 19 | | **3s**, 4-Bromophenyl (**2f**) | 30 | 81 |
| 20 | **3y–3z** | **3t**, 4-Tolyl (**2g**) | 36 | 83 |
| 21 | | **3u**, 4-Methoxyphenyl (**2h**) | 34 | 76 |
| 22 |  | **3w**, 3-Methoxyphenyl (**2i**) | 34 | 72 |
| 23 | | **3v**, Benzo[*d*][1,3]dioxol-6-yl (**2e**) | 30 | 70 |
| 24 | | **3x,** 3,4-Dimethoxyphenyl (**2j**) | 36 | 74 |
| 25 | | **3y,** 4-Fluorophenyl (**2b**) | 30 | 65 |
| 26 | **3aa** | **3z**,4-Chlorophenyl (**2c**) | 32 | 73 |
| 27 | | **3aa,** Phenyl (**2a**) | 30 | 70 |

[a]Reagents and conditions: HOAc (1.5 mL), 80 °C, microwave heating.

[b]Time (min).

[c]Isolated yields.

**Table 2**

Domino Synthesis of Dibenzo[*b,e*][1,4]diazepin-1-ones **4** under MW[a]

| entry | 4 | $R^3$ | Ar | time, min | yield[b]/% |
|---|---|---|---|---|---|
| 1 | **4a**, | H**(1e)** | phenyl (**2a**) | 12 | 85 |
| 2 | **4b** | H **(1e)** | 4-chlorophenyl (**2c**) | 14 | 84 |
| 3 | **4c** | H **(1e)** | 4-tolyl (**2g**) | 18 | 80 |
| 4 | **4d** | Cl **(1f)** | phenyl (**2a**) | 14 | 84 |
| 5 | **4e** | Cl **(1f)** | 4-bromophenyl (**2f**) | 14 | 81 |
| 6 | **4f** | Cl **(1f)** | 4-tolyl (**2g**) | 18 | 76 |
| 7 | **4g** | Me **(1 g)** | phenyl (**2a**) | 16 | 87 |
| 8 | **4h** | Me **(1 g)** | 4-chlorophenyl (**2c**) | 17 | 82 |
| 9 | **4i** | Me **(1 g)** | 4-tolyl (**2g**) | 14 | 88 |

[a]Reagents and conditions: HOAc (1.5 mL), 60 °C, microwave heating.

[b]Isolated yield.