Efficient synthesis of polyfunctionalized carbazoles and pyrrolo[3,4-c]carbazoles via domino Diels–Alder reaction

Ren-Jie Fang, Chen Yan, Jing Sun*, Ying Han and Chao-Guo Yan*

Abstract
The p-TsOH-catalyzed Diels–Alder reaction of 3-(indol-3-yl)maleimides with chalcone in toluene at 60 °C afforded two diastereoisomers of tetrahydropyrrolo[3,4-c]carbazoles, which can be dehydrogenated by DDQ oxidation in acetonitrile at room temperature to give the aromatized pyrrolo[3,4-c]carbazoles in high yields. On the other hand, the one-pot reaction of 3-(indol-3-yl)-1,3-diphenylpropan-1-ones with chalcones or benzylideneacetone in acetonitrile in the presence of p-TsOH and DDQ resulted in polyfunctionalized carbazoles in satisfactory yields. The reaction mechanism included the DDQ oxidative dehydrogenation of 3-(indol-3-yl)-1,3-diphenylpropan-1-ones to the corresponding 3-vinylindoles, their acid-catalyzed Diels–Alder reaction and sequential aromatization process.

Introduction
Carbazole is one of the most well-known privileged nitrogen-containing heterocycles. The carbazole skeleton is widely occurring in natural alkaloids and pharmacologically active compounds representing a broad spectrum of important bioactivities such as anticancer, antituberculosis, anti-protein kinase C, antipsychotic, and antioxidative activities [1-5]. For some examples, carprofen is a nonsteroidal anti-inflammatory pharmaceutical used to treat joint pain and postoperative pain [6] (Figure 1). Ellipticine was considered to be based mainly on DNA intercalation and topoisomerase II inhibition [7]. Midostaurin and carvediol have been approved by the FDA for tumor therapy and treatment of congestive heart failure [8]. On the other hand, carbazole derivatives also have potential applications in optoelectronic materials, conducting polymers, and synthetic dyes [9-11]. Over the past decades, many efficient synthetic methodologies for functionalized carbazole derivatives have been successfully developed [12-18]. Because indoles are readily available materials, the direct extension of indoles to carbazole skeletons has a great advantage [19-27]. Therefore, the Diels–Alder reaction of activated 2-vinylindolines or 3-vinylindolines with diverse dienophiles has become the most attractive strategy for the synthesis of carbazole deriv-
atives [28-40]. In recent years, by using the one-pot domino synthetic strategy of in situ-generated 2-vinyl- or 3-vinylindo-
lines and sequential Diels–Alder reaction with activated dienophiles, we have successfully developed several efficient synthetic protocols for diversely functionalized tetrahydropyrrolo[3,4-
c]carbazoles and the corresponding carbazole derivatives [41-47]. To further demonstrate the synthetic application of domino Diels–Alder reactions and in continuation of our aim to providing efficient domino reactions for the synthesis of biologically important carbazole derivatives [48-53], herein we wish to report the DDQ-mediated dehydrogenative Diels–Alder reaction of 3-(indol-3-yl)maleimides and benzoyl-substituted 3-ethylin-
doles with readily available chalcones for the convenient synthesis of polyfunctionalized carbazole derivatives.

Results and Discussion
According to our previously established reaction conditions for the preparation of spiro[indoline-3,5'-pyrrolo[3,4-c]carbazoles] [48], an equivalent amount of 3-(indol-3-yl)maleimide with chalcone was stirred in toluene at 60 °C for two hours in the presence of p-toluene sulfonic acid. After workup, two diaste-
eroisomers 3a and 3b of tetrahydropyrrolo[3,4-c]carbazoles were successfully isolated in 18% and 71% yields, respectively (Scheme 1). It should be pointed out that nearly no reaction was detected in the absence of p-toluene sulfonic acid. The structures of both products were fully characterized by various spectroscopy methods and confirmed by determination of their single crystal structures (Figure 2 and Figure 3).

From Figure 2, it can be seen that the phenyl group and the adjacent p-chlorobenzoyl group are trans-oriented. Additionally, the phenyl group is cis-oriented to the 1-benzylpyrrolidine-2,5-dione ring in compound 3a. On the other hand, for compound 3b (Figure 3), it can be seen that the phenyl group is trans-oriented to both, the p-chlorobenzoyl group and the 1-benzylpyrrolidine-2,5-dione ring in this compound. Thus, the isomers 3a and 3b are diastereoisomers. It is known that the starting chalcones usually have E-configuration. The phenyl group and p-chlorobenzoyl group still exist in the trans-position in both diastereoisomers 3a and 3b as in the starting chalcone. This result clearly showed that this acid-catalyzed cyclo-
addition reaction proceeded through a concerted Diels–Alder reaction mechanism.

The acid-catalyzed Diels–Alder reaction afforded a mixture of two diastereoisomers, which decreased the synthetic value of the reaction. Thus, after the first step reaction, a DDQ dehydro-
genation reaction was carried out in acetonitrile at room temper-

Figure 1: Representative bioactive carbazole derivatives.

Scheme 1: Synthesis of tetrahydropyrrolo[3,4-c]carbazoles 3a and 3b.
A series of aromatized pyrrolo[3,4-c]carbazoles 4a–l were successfully synthesized by the one-pot two-step reaction and the results are summarized in Table 1. All reactions proceeded smoothly to give the corresponding pyrrolo[3,4-c]carbazoles 4a–l in satisfactory yields. Indole itself and N-methylindole could also be successfully employed in the reaction. The N–Me, N–Ph, and N–Bn substitution in the maleimide moiety showed only a marginal effect on the reaction outcome. Various chalcones with electron-donating methyl and methoxy groups and electron-withdrawing m-chloro and p-chloro substituents gave the products in good yields. However, the nitro-substituted chalcone gave the product 4h in a slightly lower yield. The structures of the pyrrolo[3,4-c]carbazoles 4a–l were established by various spectroscopy methods. Further, the single crystal structure of compound 4g was determined by X-ray diffraction (Figure 4). It can be seen that the ring of pyrrolo[3,4-c]carbazole exists in a slightly twisted plane. The dihedral angles of the phenyl and the benzoyl group to the central benzene ring are 72.018° and 88.402°.

To further expand the scope of this domino Diels–Alder reaction, another kind of 3-vinylindoles was employed in the one-pot reaction. First, the 3-(indol-3-yl)-1,3-diphenylpropan-1-ones prepared through Friedel–Crafts alkylation of indole with chalcones, were oxidized by DDQ in acetonitrile to generate in situ the expected active diene, indole-substituted chalcones. Then, the p-TsOH-catalyzed Diels–Alder reaction of indole-chalcones with second chalcones and sequential aromatization through DDQ dehydrogenation resulted in the polyfunctionalized carbazoles 6a–l in good yields (Table 2). Additionally, the similar reaction with benzylideneacetone gave the desired carbazoles 6m and 6n albeit in significantly lower yields. Thus, this one-pot domino reaction successfully constructed carbazoles with four substituents on the benzene ring from the corresponding indole derivatives with two molecules of chalcones. It should be pointed out that the Diels–Alder reaction resulted in a complex mixture comprising four diastereoisomers of the tetrahydrocarbazoles, which was very difficult to
Table 1: Synthesis of pyrrolo[3,4-c]carbazoles 4a–l.

| entry | compound | R₁ | R₂ | Ar¹ | Ar² | yield (%)₁ |
|-------|----------|----|----|-----|-----|------------|
| 1     | 4a       | H  | Ph | p-CH₃C₆H₄ | C₆H₅ | 87         |
| 2     | 4b       | CH₃| CH₃| p-ClC₆H₄ | C₆H₅ | 89         |
| 3     | 4c       | CH₃| CH₃| C₆H₅ | p-CH₃C₆H₅ | 92         |
| 4     | 4d       | CH₃| CH₃| p-CH₃C₆H₄ | p-CH₃C₆H₄ | 91         |
| 5     | 4e       | CH₃| Ph | C₆H₅ | CH₃ | 85         |
| 6     | 4f       | CH₃| Ph | C₆H₅ | C₆H₅ | 84         |
| 7     | 4g       | CH₃| Ph | p-CH₃C₆H₄ | C₆H₅ | 93         |
| 8     | 4h       | CH₃| Ph | m-NO₂C₆H₄ | p-CH₃C₆H₄ | 76         |
| 9     | 4i       | CH₃| Ph | p-CH₃C₆H₄ | p-CH₃OC₆H₄ | 86         |
| 10    | 4j       | CH₃| Ph | p-CH₃C₆H₄ | m-ClC₆H₄ | 84         |
| 11    | 4k       | CH₃| Bn | p-CH₃C₆H₄ | C₆H₅ | 93         |
| 12    | 4l       | CH₃| Bn | C₆H₅ | p-ClC₆H₄ | 87         |

₁Reaction conditions: 1) 3-(indol-3-yl)maleimide (1.0 mmol), chalcone (1.0 mmol), toluene (10.0 mL), p-TsOH (0.2 mmol), 80 °C, 2 h; 2) DDQ (1.2 mmol), CH₃CN (10.0 mL), rt, 2 h. Isolated yields.

To explain the formation of the products, a plausible reaction mechanism was proposed in Scheme 2 on the basis of the previously reported reaction [48,53]. Firstly, the DDQ oxidative dehydrogenation of 3-(indol-3-yl)-1,3-diphenylpropan-1-one gave the expected indole-substituted chalcone A, which comprises the desired 3-vinylindole scaffold as the reactive diene. In the meantime, the carbonyl group of the chalcone is protonated to give the activated dienophile in the presence of p-toluene-sulfonic acid. Secondly, the Diels–Alder reaction of indolechalcone A with the dienophile results in the tetrahydrocarbazole B having an exocyclic C=C bond. Thirdly, a new tetrahydrocarbazole intermediate C is formed by a 1,3-H shifting process. The resulting tetrahydrocarbazole intermediate (C) might be a mixture of several possible diastereoisomers because it has four substituents on the cyclohexenyl ring. After a further DDQ oxidation, the aromatized carbazole 6 is successfully produced as the final product.

Conclusion

In summary, we have investigated the domino Diels–Alder reaction of 3-(indol-3-yl)maleimides and in situ-generated indole-chalcones with dienophilic chalcones. This one-pot two-step reaction successfully provided the polyfunctionalized carbazole derivatives in an extremely simple and highly effi-
Table 2: Synthesis of the polysubstituted carbazoles 6a–n.a

| entry | compound | Ar¹ | Ar² | Ar³ | Ar⁴ (R) | yield (%)b |
|-------|----------|-----|-----|-----|---------|------------|
| 1     | 6a       | C₆H₅ | C₆H₅ | C₆H₅ | C₆H₅    | 61         |
| 2     | 6b       | p-CH₃C₆H₄ | p-CH₃C₆H₄ | p-CH₃C₆H₄ | p-CH₃C₆H₄ | 63         |
| 3     | 6c       | p-CH₃C₆H₄ | p-CH₃C₆H₄ | p-CIC₆H₄ | p-CH₃C₆H₄ | 68         |
| 4     | 6d       | p-CH₃C₆H₄ | p-CH₃C₆H₄ | o-CH₃C₆H₄ | p-CH₃C₆H₄ | 64         |
| 5     | 6e       | p-CH₃OC₆H₄ | p-CH₃C₆H₄ | o-CH₃C₆H₄ | p-CH₃C₆H₄ | 62         |
| 6     | 6f       | p-ClC₆H₄ | p-CH₃C₆H₄ | p-CH₃OC₆H₄ | p-ClC₆H₄ | 66         |
| 7     | 6g       | p-ClC₆H₄ | p-CH₃C₆H₄ | C₆H₅    | C₆H₅    | 59         |
| 8     | 6h       | p-ClC₆H₄ | p-CH₃C₆H₄ | p-ClC₆H₄ | p-CH₃C₆H₄ | 60         |
| 9     | 6i       | p-ClC₆H₄ | p-CH₃C₆H₄ | p-NO₂C₆H₄ | p-CH₃C₆H₄ | 69         |
| 10    | 6j       | o-ClC₆H₄ | p-CH₃C₆H₄ | p-CH₃OC₆H₄ | p-ClC₆H₄ | 63         |
| 11    | 6k       | p-CH₃C₆H₄ | p-ClC₆H₄ | m-ClC₆H₄ | p-CH₃C₆H₄ | 61         |
| 12    | 6l       | p-CH₃C₆H₄ | p-ClC₆H₄ | p-CH₃OC₆H₄ | p-ClC₆H₄ | 62         |
| 13    | 6m       | C₆H₅   | C₆H₅   | C₆H₅   | CH₃     | 31         |
| 14    | 6n       | p-ClC₆H₄ | p-CH₃C₆H₄ | C₆H₅   | CH₃     | 32         |

aReaction conditions: 1) 3-(indol-3-yl)-1,3-diphenylpropan-1-one (0.6 mmol), chalcone (0.5 mmol), DDQ (0.72 mmol), MeCN (15.0 mL), rt, 0.5 h; 2) p-TsOH (0.06 mmol), reflux, 4 h; 3) DDQ (0.6 mmol), rt, 1 h. bIsolated yields.

Scheme 2: Proposed domino reaction mechanism for the formation of carbazoles 6.

cient fashion. This protocol has the advantages of using readily available starting reagents, simple manufacture, high efficiency and atomic economy. The unusual feature of this reaction is the normal electron-demand Diels–Alder reaction between electron-deficient dienes such as (3-(indol-3-yl))maleimides and indole-chalcone to electron-deficient dienophilic chalcones. The potential applications of this reaction in organic and medicinal chemistry might be significant.
Experimental

1. General procedure for the preparation of the carbazoles 4a–l: To a round-bottomed flask were added 3-(indol-3-yl)maleimide (1.0 mmol), chalcone (1.0 mmol), p-toluene sulfonic acid (0.2 mmol), and toluene (10.0 mL). The solution was heated to 60 °C for two hours. After removing the solvent by rotary evaporation, DDQ (1.2 mmol) and acetonitrile (10.0 mL) were added and the mixture was stirred at room temperature for two hours. After removing the solvent, the residue was subjected to column chromatography with petroleum ether and ethyl acetate 8:1 (v/v) as eluent to give the pure products for analysis.

5-Benzoyl-2-phenyl-4-(p-tolyl)pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione (4a): green solid, 440 mg, 87%; mp 234–236 °C; 1H NMR (400 MHz, CDCl3) δ 9.24 (s, 1H, ArH), 9.15 (d, J = 8.0 Hz, 1H, ArH), 7.60–7.56 (m, 1H, ArH), 7.53–7.44 (m, 7H, ArH), 7.42–7.31 (m, 3H, ArH), 7.21–7.14 (m, 4H, ArH), 6.92 (d, J = 7.6 Hz, 2H, ArH), 2.18 (s, 3H, CH3); 13C 1H NMR (100 MHz, CDCl3) δ 172.0, 167.3, 142.9, 141.7, 138.2, 137.6, 137.2, 132.9, 131.9, 131.7, 130.7, 129.1, 129.0, 128.8, 128.2, 127.9, 127.8, 127.7, 126.7, 126.1, 125.6, 121.7, 120.7, 120.3, 119.2, 111.3, 21.1; IR (KBr): ν 3075, 2970, 2907, 2360, 2339, 1720, 1605, 1482, 1320, 1267, 1172, 1099, 936, 805, 743, 612, 447 cm−1; HRMS–ESI (m/z): [M + Na]+ calcd for C39H27NO2, 564.1932; found, 564.1926.

The crystallographic data of the compounds 3a (CCDC 2099074), 3b (CCDC 2099075), and 4g (CCDC 2099076) have been deposited at the Cambridge Crystallographic Database Centre (http://www.ccdc.cam.ac.uk).

Supporting Information
Supporting Information File 1
Characterization data and 1H NMR, 13C NMR, and HRMS spectra of the synthesized compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-159-S1.pdf]

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ORCID® iDs
Chao-Guo Yan - https://orcid.org/0000-0002-2777-9582

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