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Graphical Abstract

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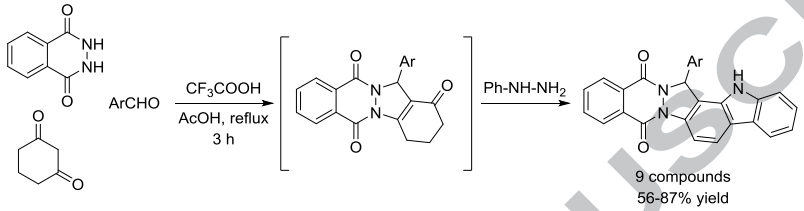

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Sequential MCR/Fisher indolization strategy for the construction of polycyclic carbazole derivatives

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ABSTRACT

A one-pot method for the synthesis of novel polycyclic carbazole derivatives from readily available starting materials using a sequential multicomponent reaction/Fisher indolization strategy is described.

The synthesis and application of carbazole derivatives have been a source of great interest due to their intriguing structural features and promising biological activities.[1] To improve the pharmacological profile of the carbazole moiety, numerous work in the literature has reported the synthesis of heterocyclic compounds condensed with the carbazole nucleus.[2] Many examples of compounds including cyclopentacarbazoles,[3] pyridocarbazoles,[4] pyrrolocarbazoles[5] and indolocarbazoles[6] have shown antitumor activities.

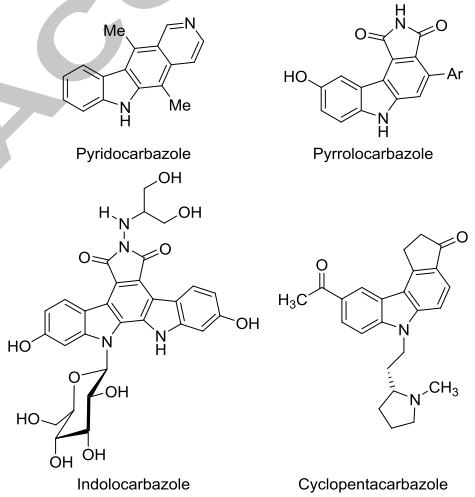

Figure 1. Selected heterocyclic compounds containing the carbazole motif

Condensed phthalazines, containing two bridgehead nitrogen atoms in a fused ring system, are of particular interest and significant work has been devoted to their synthesis. Numerous condensed phthalazine derivatives have been reported to show a broad range of biological activities; notably anticancer,[7] antimicrobial,[8] anti-inflammatory,[9] anticonvulsant,[10] antihypertensive[11] and antioxidant properties.[12]

The fusion of phthalazine to the carbazole heterocycle might result in novel biological activities. In this context, herein, we report the synthesis of new polycyclic carbazoles condensed to pyrazolophthalazine *via* a one-pot reaction.

Initially, the polycyclic carbazole formation reaction was tested on 13-phenyl-2,3,4,13-tetrahydro-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione **1a** under three sets of conditions: HCl in EtOH, H_2SO_4 in *i*-PrOH or CF_3COOH in AcOH. The desired carbazole **2a** was obtained in satisfying yield (70%) using CF_3COOH (1.7 eq.) in acetic acid in the presence of phenylhydrazine (Scheme 1). Conversely, neither of the first two conditions gave the desired cyclized product.

Since the synthetic utility of an acidic medium for the preparation of **1a** had already been reported,[13] we next explored the multicomponent reaction (MCR)/Fisher indolization cascade using the same conditions in order to extend this to a one-pot processes.

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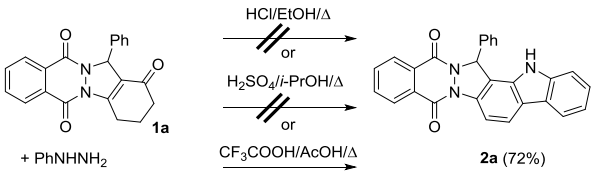
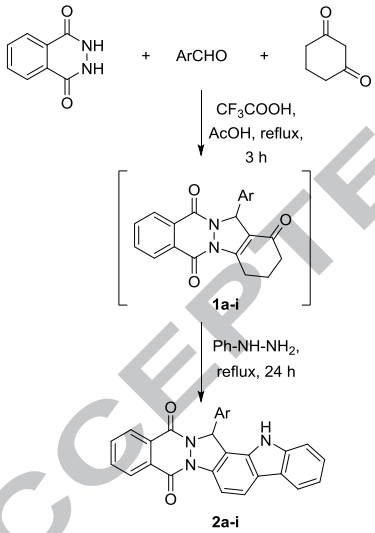


Scheme 1. Synthesis of polycyclic carbazole **2a**.

The model reaction of 2,3-phthalazine-1,4-dione (1 mmol), benzaldehyde (1.1 mmol) and cyclohexane-1,3-dione (1.2 mmol) at reflux in CF_3COOH/AcOH was performed in order to establish the effectiveness of this system for the synthesis of **1a**. Under these conditions, conversion to 13-phenyl-2,3,4,13-tetrahydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11-trione **1a** was complete after 4 h (TLC). Compound **1a** was used without isolation in the next step; under these conditions, **1a** is sufficiently pure to be used for further transformations. After the addition of phenylhydrazine (1.7 eq.), the reaction mixture was heated at reflux for 24 h to give **2a** in 77% yield.[14] A spontaneous oxidation occurs at the end of this sequence to give the carbazole ring instead of the dihydrocarbazole (Scheme 2).

To demonstrate the scope of the method, the reaction was performed using various substituted benzaldehydes. As shown in Table 1, substrates containing aromatic rings with electron-withdrawing groups (halide, nitro) or electron-donating groups (alkoxy, alkyl), gave the corresponding products **2** in good to high yield. Substituents on the aromatic ring had no obvious effect on the yield or reaction time.



Scheme 2. One-pot synthesis of polycyclic carbazoles **2a-i**.

The structures of compounds **2a-i** were confirmed by their spectral data. For example, the ^{1}H NMR spectrum of **2a** displayed a singlet at 11.04 ppm due to the N-H of the carbazole ring. Signals for the two aromatic protons 6 and 7 of the carbazole nucleus were observed as doublets at 8.35 and 8.30 ppm. The signals of the other aromatic protons appeared between 8.39 and 7.17 ppm as multiplets. The signal attributable to the proton of the pyrazole ring was found at 7.10 ppm as a singlet.

The ^{13}C NMR spectrum data of **2a** showed signals for the two C=O carbon at 154.2 and 154.3 ppm. The carbon of the pyrazolo ring resonated at 64.3 ppm, while the signals for the other aromatic carbons were between 140.9 and 106.9 ppm. Furthermore single crystal X-ray structural analysis was used to verify the proposed structure of **2a** (Fig. 2).

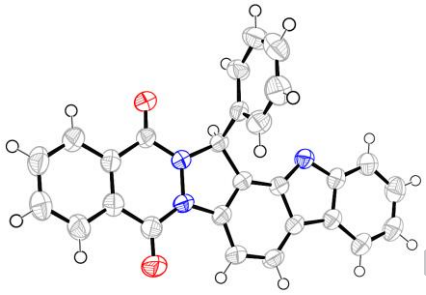
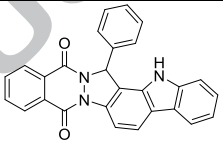
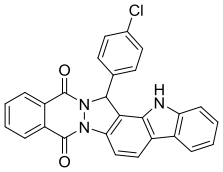
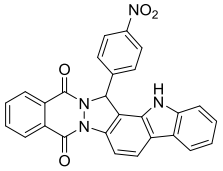
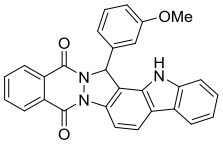
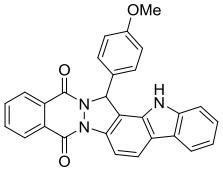
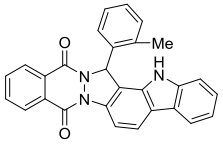
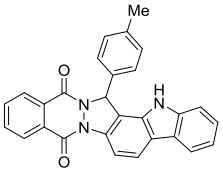
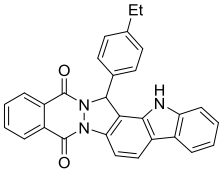
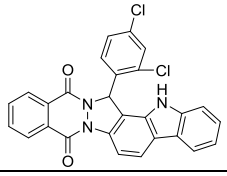


Figure 2. ORTEP plot of the X-ray crystal structure of **2a** with the DMF molecule omitted for clarity (thermal ellipsoids drawn at the 50% probability level).[15]

Bond lengths and angles were comparable to those reported previously for the starting material **1a**[16] and are in the expected range.

Table 1. Polycyclic carbazole derivatives prepared according to Scheme 2.[a]

	Product	Yield (%)[b]
2a		77
2b		87
2c		61
2d[c]		60
2e		62
2f[c]		75
2g		81
2h		56

2i		62

[a] Reagents and conditions: benzaldehyde (1.1 mmol), 1,3-cyclohexadione (1.2 mmol), phthalhydrazide (1 mmol), acetic acid (5 mL), trifluoroacetic acid (2 mL) then phenylhydrazine (1.7 eq.), trifluoroacetic acid (2 mL), reflux.
[b] Isolated yield from phthalhydrazide.
[c] Products precipitated during solvent evaporation and were isolated by filtration then washed with AcOH.

In conclusion, we have reported an efficient and convenient protocol for the one-potsynthesis of polycyclic carbazole derivatives from phthalhydrazide, benzaldehyde, cyclohexane-1,3-dione and phenylhydrazine using a sequential MCR/Fisher indolization strategy. This method is quite general and works with a broad range of substrates.

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14. Representative procedure for the synthesis of 16-phenyl-1,16-dihydrophthalazino[2',3':1,2]pyrazolo[4,3-*a*]carbazole-9,14-dione **2a**: To a mixture of acetic acid (5 mL) and trifluoroacetic acid (2 mL) in a 50 mL round-bottomed flask, benzaldehyde (1.1 mmol), 1,3-cyclohexadione (1.2 mmol) and phthalhydrazide (1 mmol) were added. The resulting mixture was magnetically stirred at reflux for 4 h. After completion (TLC), the reaction mixture was cooled and phenylhydrazine (1.7 eq.) and trifluoroacetic acid (2 mL) were added. The reaction mixture was heated at reflux for 24 h. Upon completion, the solvents were removed under reduced pressure and the product was isolated by chromatography. Compounds **2b-c, 2e, 2j-i** were obtained analogously to **2a**. Compounds **2d** and **2f** precipitated during solvent evaporation and were isolated by filtration then washed with AcOH.
15. Crystal structure analysis for **2a**: $C_{27}H_{17}N_3O_2$, Mr = 415.13 g/mol, Orthorhombic, space group P $2_12_12_1$, a=10.5723(6) Å; b=10.7384(6)Å ; c=21.6020(11)Å; α=β=γ=90°, Z=4, V= 2452.5(2)Å^3, Z=4, ρ_c=1.323, F(000)=1024, crystal size: 0.14×0.11×0.09 mm. Crystallographic data (excluding structure factors) for compound **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 978520. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Highlights

- A method for the synthesis of novel polycyclic carbazoles is described.
- A sequential MCR/Fisher indolization strategy was described.
- Phthalazine was used as a starting material for the construction of polycyclic compounds.