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ONE-POT SYNTHESIS OF BENZ[*f*]INDOLO[3,2-*c*]ISOCHROMENO-5,7,13-TRIONE DERIVATIVES FROM 2-AMINO-1,4-NAPHTHOQUINONES AND NINHYDRIN

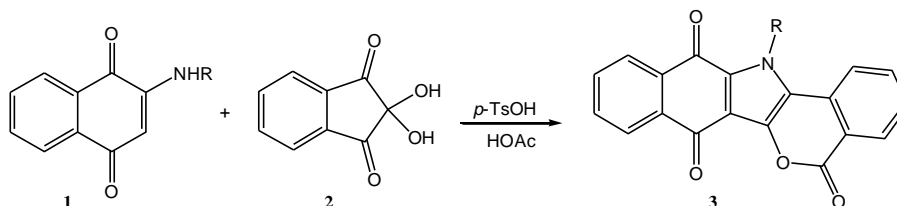
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Abstract – An efficient method for the preparation of novel benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-triones **3** was described. The construction of this new pentacyclic system was achieved undergo a domino reaction of 2-amino-1,4-naphthoquinones **1** with ninhydrin **2** in one-pot with good yields.

Functional heterocycles of chemical and biomedical importance, particularly those containing the isocoumarin ring, have played a pivotal role in organic and medicinal research for several decades.¹ They exhibit significant biological activities such as anti-inflammatory,² antimalarial,³ cytotoxicity,⁴ and anti-HIV.⁵ So development of a new and efficient methodology for the synthesis of biologically potent isocoumarins and their hetero-annulated analogues has drawn great attention of synthetic as well as medicinal chemists.⁶

Domino reactions have emerged as an effective tool for the assembly of complex cyclic structures by the combination of two or more distinct reactions into a one-pot transformation.⁷ Recently, we have developed several domino reactions toward the construction of diverse heterocyclic structures.⁸ In continuation of this project, we now report the novel benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-triones **3** preparation *via* domino reaction from 2-amino-1,4-naphthoquinones⁹ **1** with ninhydrin **2**, providing indole-fused isocoumarins in the presence *p*-toluenesulfonic acid (*p*-TsOH) (Scheme 1).



Scheme 1. Synthesis of benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-triones

In our initial study, various reaction conditions including solvents and temperatures were tested in the synthesis of the 12-methyl-12*H*-benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-trione **3a** from 2-methylamino-1,4-naphthoquinone (**1a**) and ninhydrin (**2**) using 1.0 equiv of *p*-TsOH as a promoter. Among different polar solvents, such as EtOH, MeCN, HOAc, DMF, and 3-butyl-1-methylimidazolium bromide ([bmim]Br), the best result was obtained when the reaction was carried out in HOAc at 100 °C in 72% yield. When using 0.5 equiv of *p*-TsOH as a promoter, this reaction worked affording **3a** in 51% yield. Increasing the amount of *p*-TsOH to 1.5 equiv has no effect on the product yield and reaction time.

In addition, other organic acids such as sulfamic acid, trifluoroacetic acid, and trifluoromethanesulfonic acid were also tested under similar reactions and 38%, 56% and 60% yields were obtained, respectively. The results indicated that *p*-TsOH was still the best choice.

Under these optimized reaction conditions, a series of benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-triones **3** were synthesized. As shown in Table 1, the reaction was successful for 2-amino-1,4-naphthoquinones **1** incorporating alkyl (entries 1-4), and aromatic (entries 5-8) R groups carrying either electron-donating or electron- withdrawing substituents reacted efficiently giving good yields (70-83%).

Table 1. Synthesis of benz[*f*]indolo[3,2-*c*]isochromeno-5,7,13-triones **3**¹⁰

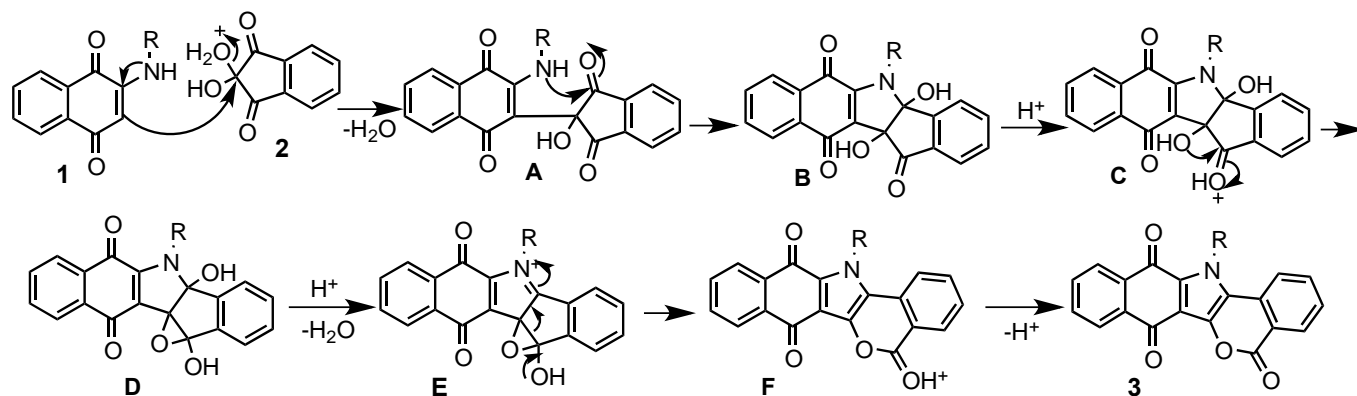
Entry	1 / R	Time (h)	Product	Yield (%)
1	1a Me	5	3a	72
2	1b Et	6	3b	70
3	1c <i>n</i> -Bu	5	3c	80
4	1d C ₆ H ₅ CH ₂ CH ₂	6	3d	83
5	1e C ₆ H ₅	8	3e	76
6	1f 4-MeOC ₆ H ₄	6	3f	78
7	1g 4-FC ₆ H ₄	7	3g	75
8	1h 4-ClC ₆ H ₄	8	3h	74

In most cases, the products can precipitate out after diluted basic solution was poured into the reaction mixture. The structural elucidation was unequivocally determined by IR, NMR spectroscopic analysis and elemental analysis.

The present work represents the special example for construction of these types of pentacyclic system heterocycles containing isocoumarin and indole unit with high regioselectivity.

On the basis of literature reports¹¹ and observations of the above results, the proposed mechanism of the process is summarized in Scheme 2. Firstly, amine **1** reacts with protonated **2** to generate intermediate B.

The intermediate B undergoes two subsequent intramolecular cyclizations to give three-membered-ring intermediate D; ring-opening and deprotonation follow, to yield the final indolo-fused isocoumarins **3**.



Scheme 2. Proposed mechanism for the synthesis of compounds **3**

In summary, we have developed a general and efficient strategy for the synthesis of benz[*f*]indolo[3,2-*c*]-isochromeno-5,7,13-triones through a novel domino reaction from 2-amino-1,4-naphthoquinones with ninhydrin in a one-pot manner. Features of this strategy include the relatively mild conditions, convenient one-pot operation, easy work-up, inexpensive reagents and good yields.

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10. The general procedure is represented as follow: To a solution of 2-amino-1,4-naphthoquinones **1** (1.0 mmol) and ninhydrin **2** (1.0 mmol) in HOAc (20.0 mL) *p*-TsOH (172 mg, 1.0 mmol) was added, and the reaction was heated at 100 °C. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature, and then water (20 mL) was added to the mixture. The solid was filtered and recrystallized from HOAc to give crystalline powder **3** (yield of the products is summarized in Table 1). Selected data of compound. **3a**: mp > 300 °C; IR (KBr): ν 1712, 1669, 1652 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO- d_6): δ 4.59 (3H, s, CH₃), 7.64-7.67 (3H, m), 7.95-8.05 (3H, m), 8.17 (1H, d, J = 8.0 Hz), 8.35 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO- d_6): δ 35.2, 112.3, 118.6, 121.2, 121.9, 126.8, 127.1, 128.4, 128.7, 129.5, 131.9, 132.2, 133.0, 134.4, 134.7, 136.5, 137.6, 163.4, 177.5, 180.8. *Anal.* Calcd for C₂₀H₁₁NO₄: C 72.95, H 3.37, N 4.25. Found: C 73.08, H 3.48, N 4.38. **3c**: mp > 300 °C; IR (KBr): ν 1708, 1663, 1655 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO- d_6): δ 0.97 (3H, t, J = 7.2 Hz), 1.51-1.57 (2H, m), 1.95-1.99 (2H, m), 5.01-5.04 (2H, m), 7.65-7.72 (3H, m), 7.93-8.10 (4H, m), 8.42 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO- d_6): δ 12.5, 19.3, 31.6, 47.9, 112.7, 119.1, 120.9, 121.1, 127.2, 127.3, 128.7, 128.8, 129.5, 132.4, 132.7, 133.4, 134.6, 134.8, 136.7, 138.3, 163.7, 177.7, 181.4. *Anal.* Calcd for C₂₃H₁₇NO₄: C 74.38, H 4.61, N 3.77. Found: C 74.46, H 4.69, N 3.89. **3e**: mp > 300 °C; IR (KBr): ν 1706, 1678, 1650 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO- d_6): δ 6.65-6.66 (1H, m), 7.54-7.61 (4H, m), 7.70-7.79 (5H, m), 8.01-8.02 (1H, m), 8.16-8.18 (1H, m), 8.35 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO- d_6): δ 113.4, 118.9, 120.9, 122.6, 126.6, 127.2, 127.3, 128.3, 129.5, 129.6, 130.4, 130.8, 131.9, 132.4, 133.0, 134.6, 134.8, 136.1, 136.6, 137.7, 164.1, 176.7, 181.7. *Anal.* Calcd for C₂₅H₁₃NO₄: C 76.72, H 3.35, N 3.58. Found: C 76.84, H 3.46, N 3.67.
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