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Three-component synthesis of new unsymmetrical oxindoles via Friedel–Crafts type reaction

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Abstract

The synthesis of 2-(3-(4-(dimethylamino)phenyl)-2-oxoindolin-3-yl)-1H-indene-1,3(2H)-diones as new unsymmetrical oxindoles via a Friedel–Crafts type three-component reaction of 1,3-indandion, N,N-diethylaniline and isatins in ethanol in the presence of LiClO4 is reported.

Keywords: Isatin Indandion Friedel–craft reaction Oxindole

1. Introduction

Multi-component reactions (MCRs) have offered many fascinating and challenging transformations in organic synthesis.1 The atom-economy, convergent character, operational simplicity, structural diversity, and complexity of the molecules are the major advantages associated with multi-component reactions. Besides this multi-component reactions are emerging as a powerful tool in the synthesis of biologically important compounds.2 Friedel–Crafts reaction3 is one of the oldest carbon–carbon bond forming processes, and is still an attractive method to introduce substituents on aromatic rings. Initial works concerned Friedel–Crafts acylation from acyl chlorides or alkylation from alkyl halides. To perform acylations, Lewis acids are needed. More than stoichiometric amounts of AlCl3 or BF3 are required, whereas catalytic amounts of rare-earth triflates,4 more specially scandium triflate,5 perﬂuorinated rare-earth metals,6 gallium triflate7 or bismuth triflate,8 allow the formation of the expected products.

Isatin is a privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad spectrum of bioactivity as many of which were assessed anti-HIV,9 antiviral,10 anti-tumor,11 antifungal,12 anti-angiogenic,13 anticonvulsants,14 anti-Parkinson’s disease therapeutic,15 and effective SARS coronavirus 3C1 protease inhibitor.16 These interesting properties prompted many efforts toward the synthesis and pharmacological screening of isatin derivatives. During these investigations, the indol-2-one (oxindole) moiety has been recognized as a biologically active framework.17 Oxindole is an integral constituent of many natural products.18 Thus, it is not surprising that access to several members of this class may be the goal of many research laboratories.

Recently, LiClO4 has emerged as a powerful promoter in many chemical processes and in different organic media.19 The development of method, which allows the reaction under essentially mild and neutral conditions should heighten the synthetic potential of the reaction. The LiClO4 medium provides a convenient procedure to carry out reactions under simple and neutral conditions.

Although several isatin-based reactions have been reported by our20 or other research groups21 for the synthesis of new oxindoles, the synthesis of 2-(3-(4-(dimethylamino)phenyl)-2-oxoindolin-3-yl)-1H-indene-diones 4 has not been reported yet. In this paper, for the first time we report an efficient synthesis of new unsymmetrical oxindoles 4 based on a Friedel–Crafts type three-component reaction of 1,3-indandione 1, isatins 2 and N,N-diethylaniline 3 in the presence of LiClO4 as an inexpensive and available catalyst (Scheme 1).

![Scheme 1. Synthesis of unsymmetrical oxindoles 4.](attachment:image)
2. Results and discussion

Our initial experiments were focused on the three-component reaction of 1,3-indandione 1 (1 mmol), isatin 2a (1 mmol), and N,N-dimethylaniline 3 (1 mmol) as a simple model substrate using different catalysts in refluxing EtOH, and the results are listed in Table 1.

It was observed that when HOAc, p-TSA, ZnCl2, CAN, and InCl3 were used, it led to the formation of 5 as major product and desired product 4a as a minor product in a low yield (Table 1). AlCl3 showed better selectivity for 4a in comparison to 5. LiClO4 was found to be the best catalyst for the synthesis of unsymmetrical oxindole 4a. As can be seen from Table 1, when the amount of the LiClO4 increased from 5 to 10, and 15 mol %, the yields increased from 80 to 95 and 96%, respectively. It was found that 10 mol % LiClO4 in EtOH is sufficient to push this reaction forward (Table 1, entry 2). More amounts of the LiClO4 (15 mol %) did not improve the yields and decreasing the amount of LiClO4 (5 mol %) resulted in a decrease in the yield of 4a and increase in the yield of 5. When this reaction was carried out without LiClO4 the yield of the product was Trace even after 7 h (entry 10).

Then, we examined the solvent effect on the LiClO4-catalyzed model reaction. The results of Table 2 demonstrate that solvent affected the efficiency of the reaction and EtOH was the best choice of solvent (Table 2). In other solvents, such as CH3CN, CH2Cl2, THF, H2O, and CHCl3, low yield of 4a was obtained with significant formation of 5. Therefore, the use of the commercially available, inexpensive, and easily handled LiClO4 in EtOH provides a convenient procedure for the synthesis of unsymmetrical oxindole 4a under neutral and simple conditions.

To study the generality of this protocol, a library of nine substituted 2-(3-(4-(dimethylamino)phenyl)-2-oxoindolin-3-yl)-1H-indene-1,3(2H)-diones 4a–i were built using 1,3-indandione 1, isatins 2a–i, and N,N-dimethylaniline 3 (Table 3). All compounds are stable solids whose structures were established by IR, 1H and 13C NMR spectroscopy, and elemental analysis.

The plausible mechanism of this Friedel–Crafts type reaction is given in Scheme 2. Aromatic amine 3 reacts with isatin 2 to generate an intermediate 6, followed by a nucleophilic addition with 1,3-indandione 1 to afford unsymmetrical oxindole 4. Compound 5 was also formed by the attack of another molecule of 3 on intermediate 6.

To further explore the potential of the reaction, we investigated the reaction of acenaphthylene-1,2-dione 7 and ninhydrin 8 instead of isatin 2 and obtained 2-(1-(4-(dimethylamino)phenyl)-2-oxo-1,2-dihydroacenaphthylene-1-yl)-1H-indene-1,3(2H)-dione 9 and 2-(4-(dimethylamino)phenyl)-1H,1′H-2,2′-biindene-1,1′,3,3′(2H,2′H)-tetraone 10 in 73% and 60% yield, respectively (Scheme 3).

It is notable, when we carried out the reaction with another cyclic 1,3-dicarbonyl compounds 11, the TLC and 1H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; low yields of desired products 12 were obtained and compound 5 was produced as a major product (Scheme 4).

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### Table 1
Screening of catalysts

| Entry | Catalyst (mol %) | Time (h) | Yields 4a (%) | Yields 5 (%) |
|-------|-----------------|----------|---------------|--------------|
| 1     | LiClO4 (5)      | 3        | 80            | <10          |
| 2     | LiClO4 (10)     | 3        | 95            | Trace        |
| 3     | LiClO4 (15)     | 3        | 96            | Trace        |
| 4     | p-TSA (10)      | 3        | 30            | 35           |
| 5     | HOAc (10)       | 3        | 25            | 43           |
| 6     | AlCl3 (10)      | 3        | 55            | 27           |
| 7     | ZnCl2 (10)      | 3        | 37            | 46           |
| 8     | CAN (10)        | 3        | 32            | 37           |
| 9     | InCl3           | 3        | 35            | 49           |
| 10    | None            | 7        | Trace         | Trace        |

*a Isolated yield based on precipitation.

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### Table 2
Solvent effect on the reaction

| Entry | Solvent (Reflux) | Yield 4a (%) | Yield 5 (%) |
|-------|-----------------|--------------|-------------|
| 1     | CH3CN           | 33           | 52          |
| 2     | CH2Cl2          | Trace        | 37          |
| 3     | THF             | <20          | 63          |
| 4     | H2O             | Trace        | 52          |
| 5     | EtOH            | 95           | Trace       |
| 6     | CHCl3           | <20          | 49          |

*a Reaction time—3 h, LiClO4 (10 mol %).

*b Isolated yield.

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### Table 3
Synthesis of unsymmetrical oxindoles 4

| Product 4 | R   | X   | Yields (%) | Time* (h) |
|-----------|-----|-----|------------|-----------|
| a         | H   | H   | 95         | 3         |
| b         | Me  | H   | 90         | 4.5       |
| c         | Et  | H   | 87         | 6         |
| d         | H   | Br  | 90         | 4         |
| e         | H   | NO2| 91         | 3.5       |
| f         | H   | Me  | 94         | 4         |
| g         | H   | F   | 98         | 4         |
| h         | Me  | Br  | 90         | 6         |
| i         | Et  | NO2| 85         | 7         |

*a Isolated yield.
and 75.47 MHz, respectively. $^1$H and $^{13}$C NMR spectra were obtained on solutions in DMSO-$d_6$. IR spectra were recorded using an FTIR apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

4.1. 2-(3-(4-(Dimethylamino)phenyl)-2-oxindolin-3-yl)-1H-indene-1,3(2H)-dione (4a). A mixture of 1,3-indandione (1 mmol), isatin (1 mmol), $N,N$-dimethylaniline (1 mmol), and LiClO$_4$ (10 mol%) in refluxing ethanol (5 mL) was stirred for 3 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with diethyl ether (10 ml) to afford the pure product 4a as greenish powder (0.396 g, 90%); mp $240^\circ$C; IR (KBr) ($\nu_{max, cm^{-1}}$): 3425, 3043, 1742, 1706. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_{H}$ = 2.86 (6H, s, 2CH$_3$), 4.71 (1H, s, CH), 6.64–7.89 (12H, m, H–Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_{C}$ = 26.8, 40.5, 54.8, 57.5, 109.4, 112.4, 122.3, 123.1, 124.5, 128.2, 128.6, 129.1, 129.5, 136.5, 143.2, 144.2, 149.2, 178.0, 179.4, 197.7, 198.0. MS (EI, 70 eV) m/z: 396 (M$^+$). Anal. Calcd for C$_{25}$H$_{20}$N$_2$O$_3$: C, 75.74; H, 5.08; N, 6.74%.

4.1.2. 2-(3-(4-(Dimethylamino)phenyl)-1-methyl-2-oxindolin-3-yl)-1H-indene-1,3(2H)-dione (4b). Yellow powder (0.41 g, 90%); mp 230 $^\circ$C; dec; IR (KBr) ($\nu_{max, cm^{-1}}$): 3425, 3043, 1742, 1706. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_{H}$ = 3.00 (6H, s, CH$_3$), 3.13 (3H, s, CH$_3$), 4.78 (1H, s), 6.66–7.89 (12H, m, H–Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_{C}$ = 26.8, 40.5, 54.8, 57.5, 109.4, 112.4, 122.3, 123.1, 124.5, 128.2, 128.6, 129.3, 136.4, 136.6, 141.7, 142.4, 149.2, 178.0, 179.4, 197.5, 197.6, 197.8. MS (EI, 70 eV) m/z: 410 (M$^+$). Anal. Calcd for C$_{26}$H$_{22}$N$_2$O$_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 75.97; H, 5.47; N, 6.74%.

4.1.3. 2-(3-(4-(Dimethylamino)phenyl)-1-ethyl-2-oxindolin-3-yl)-1H-indene-1,3(2H)-dione (4c). Yellow powder (0.42 g, 87%); mp 243 $^\circ$C; dec; IR (KBr) ($\nu_{max, cm^{-1}}$): 3415, 3045, 1718, 1605. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_{H}$ = 1.17 (3H, t, J = 5.7 Hz, CH$_3$), 2.86 (6H, s, CH$_3$), 3.58–3.76 (2H, m, CH$_2$), 4.80 (1H, s, CH), 6.46–7.91 (12H, m, H–Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_{C}$ = 12.4, 34.7, 40.5, 54.8, 57.5, 109.4, 112.4, 122.1, 123.0, 123.1, 124.7, 125.0, 128.1, 129.0, 129.3, 136.4, 136.6, 141.7, 143.0, 143.8, 149.9, 176.1, 197.5, 197.8. MS (EI, 70 eV) m/z: 424 (M$^+$). Anal. Calcd for C$_{27}$H$_{24}$N$_2$O$_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 75.97; H, 5.47; N, 6.69%.

4.1.4. 2-(5-Bromo-3-(4-(Dimethylamino)phenyl)-2-oxindolin-3-yl)-1H-indene-1,3(2H)-dione (4d). Cream powder (0.474 g, 90%); mp 250 $^\circ$C; dec; IR (KBr) ($\nu_{max, cm^{-1}}$): 3190, 3111, 1711, 1617. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_{H}$ = 2.87 (6H, s, 2CH$_3$), 4.83 (1H, s, CH), 7.91 (12H, m, H–Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_{C}$ = 26.8, 40.5, 54.8, 57.5, 109.4, 112.4, 122.1, 123.0, 123.1, 124.7, 125.0, 128.1, 129.0, 129.3, 136.4, 136.6, 141.7, 143.0, 143.8, 149.9, 176.1, 197.5, 197.8. MS (EI, 70 eV) m/z: 442 (M$^+$). Anal. Calcd for C$_{28}$H$_{24}$BrN$_2$O$_3$: C, 74.39; H, 5.70; N, 6.60. Found: C, 74.45; H, 5.86; N, 6.69%.

3. Conclusion

In conclusion, we have developed an efficient three-component reaction of 1,3-indandione, isatins, and $N,N$-dimethylaniline using LiClO$_4$ as a catalyst. The reaction is operationally simple and offers high yields of the new unsymmetrical oxindole derivatives. Prominent among the advantages of this new method are novelty, operational simplicity and easy work-up procedures employed.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 MHz.
10.1.11. 2-(4-(Dimethylamino)phenyl)-1H,1'H-2,2'-bindene-1,1',3',3'(2H,2'H)-tetrone (10). Yellow powder (0.41 g, 60%); mp 291 °C dec; IR (KBr) (νmax, cm⁻¹): 3243, 3078, 1716, 102. 13C NMR (300 MHz, DMSO-d₆): δc=4.04, 57.7, 109.7, 112.0, 120.0, 123.3, 123.8, 126.6, 127.9, 130.6, 135.8, 136.8, 141.4, 142.2, 149.7, 150.1, 197.0, 197.4, 198.3, 199.9. MS (EI, 70 eV) m/z: 409 (M⁺). Anal. Calcld for C₂₅H₂₀N₂O₂: C, 76.72; H, 4.68; N, 3.42. Found: C, 76.16; H, 4.60; N, 3.51.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supplementary data

Supplementary data related to this article can be found in online version at doi:10.1016/j.tet.2011.02.054

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