Recyclable Indium(III) Chloride Catalyzed Site-Selective Double Substitution in One Pot for the Synthesis of Isatin *N*-Ribonucleosides under Microwave Irradiation

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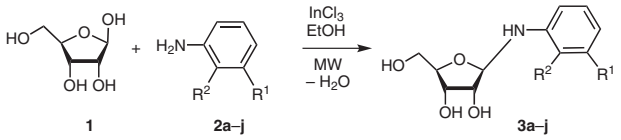
Abstract: A novel one-pot synthesis of isatin *N*-ribonucleosides from *N*-phenylribosylamines and diethyl oxalate in ethanol catalyzed by recyclable indium(III) chloride under microwave irradiation has been developed. The transformation consists of indium(III) chloride catalyzed nucleophilic substitution by *N*-phenylribosylamines on diethyl oxalate followed by rapid intramolecular electrophilic substitution, which results in annulation of a five-membered nitrogen heterocycle on to the benzene ring yielding isatin *N*-ribonucleosides. The reaction proceeded smoothly in quantitative yields at ambient temperatures. The starting materials, *N*-phenylribosylamines, were prepared by indium(III) chloride catalyzed nucleophilic substitution of the anomeric hydroxy group of β-D-ribofuranose by an arylamine under microwave irradiation.

Key words: isatin *N*-ribonucleoside, indium(III) chloride, one-pot reaction, microwave, double substitution

The development of *N*-methylisatin β-thiosemicarbazone (methisazone) and *N*-ethylisatin β-thiosemicarbazone (N-Et-ISTCH) for the inhibition of Moloney leukemia virus,[1] as an antiviral for pox virus, and in HIV-1 therapy for clinical use[2] has renewed the interest in the development of efficient, inexpensive, and green process for the synthesis and synthetic manipulation of isatin and its nucleoside analogues. Glycosylated isatin derivatives are also of considerable pharmacological relevance. Notably, most available drugs approved by the FDA to treat AIDS and other viral diseases are nucleoside analogues. However, negligible effort has so far been made to synthesize nucleoside analogues incorporating an isatin unit as a nucleobase and, therefore, they appear to be an attractive scaffold to provide a chemical diverse drug-like library. The development and applications of catalytic reactions is a fundamental issue for the organic synthesis.[3] Recent years have witnessed a phenomenal growth in the application of catalysts in organic transformations especially those of Lewis acid character associated with normal/transition metal halides. Indium(III) chloride has attracted attention because it has a non-toxic nature and it is recyclability, readily availability, high selectivity,[4] and moisture compatibility.[5] Indium(III) chloride has been reported as an efficient catalyst in many organic transformations.[6–9]

Recent years have witnessed a phenomenal growth in the application of microwave irradiation[10–12] and the use of recyclable, less expensive metal halide catalysts in organic transformations. The application of microwave irradiation in conjugation with metal halide catalysts provides an environmentally benign process with additional advantages, such as enhanced reaction rates, higher yield of products, easier workup, and considerable reduction in reaction times, all of which are ecofriendly attributes in the context of green chemistry.[13–15]

As part of our programme to develop new, simple, selective, ecofriendly methodologies for the synthesis of biodynamic heterocyclic compounds and their nucleoside analogues,[16–19] we devised an original indium(III) chloride catalyzed microwave-activated synthesis of some novel isatin *N*-ribonucleosides via site-selective nucleophilic and electrophilic substitution reactions between *N*-phenylribosylamines **3** and diethyl oxalate (**4**) in ethanol in one-pot.



Scheme 1 Indium(III) chloride catalyzed microwave-activated synthesis of *N*-phenylribosylamines

The strategy of the synthesis is outlined in Table 1. Mixture of *N*-phenylribosylamine **3**, diethyl oxalate (**4**), and indium(III) chloride in ethanol at 50 °C was subjected to intermittent microwave irradiation for two minutes in a microwave oven at 600 W, followed by thorough mixing for two minutes outside the oven. This intermittent irradiation/mixing cycle was repeated for a total irradiation time specified in Table 2 to afford isatin *N*-ribonucleosides **5a–j** in 75–85% yield. The starting compounds, *N*-phenylribosylamines **3a–j**, were prepared by irradiating a mixture of β-D-ribofuranose, aniline, and an alcoholic so-

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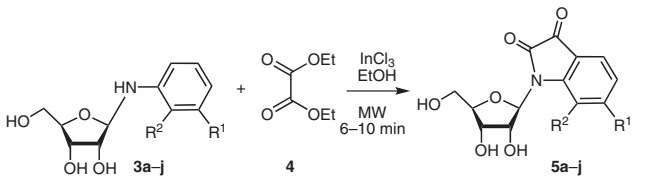
lution of indium(III) chloride in the manner as described in Scheme 1.

Table 1 Indium(III) Chloride Catalyzed Microwave-Activated Synthesis of Isatin *N*-Ribonucleosides



Compounds **3**, **5**	R^1	R^2
a	H	H
b	H	Cl
c	Cl	H
d	H	OMe
e	OMe	H
f	H	F
g	F	H
h	H	NO_2
i	NO_2	H
j	OMe	OMe

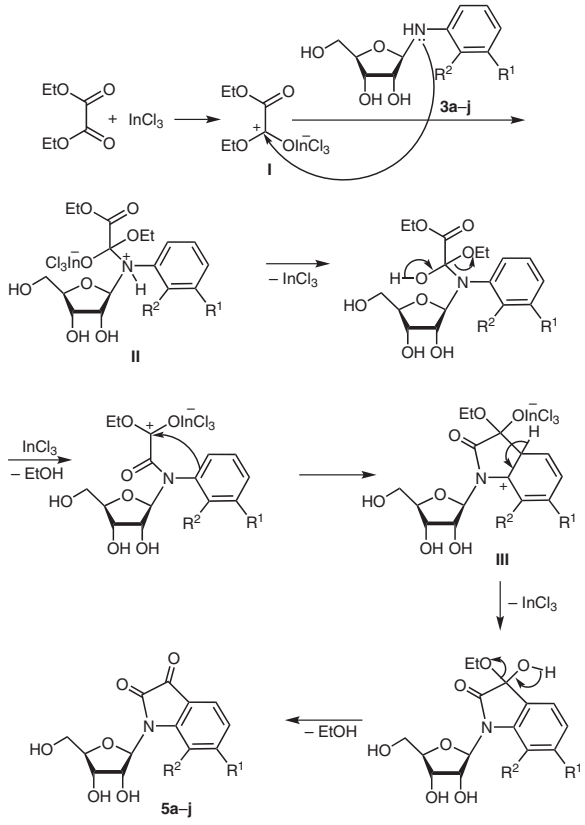
The reactions to give isatin *N*-ribonucleosides **5** did not take place if they were performed using microwave irradiation without indium(III) chloride, either neat or in organic solvents. However under the conditions described above, the desired products **5a–j** were isolated in high yield. After subsequent workup, the catalyst indium(III) chloride was recycled and reused for three or four runs without loss in activity. The results are shown in Table 2.

All products **5a–j** were characterized by spectral analysis. All data were fully consistent with the assigned molecular structure.

For comparison purpose the reactions were also carried using a thermostated oil-bath at the same temperature (50 °C) as for the microwave-activated and indium(III) chloride catalyzed method for a longer (optimized) period of time (Table 2), to ascertain whether the indium(III) chloride catalyzed and microwave activated method improved the yield or simply increased the conversion rate. It was found that significantly lower yields (30–40%) were obtained and much higher reaction times were needed than for the indium(III) chloride catalyzed and microwave-activated method (Table 2). This observation can be rationalized due to the increased electrophilicity of the carbonyl group of diethyl oxalate (**4**) because of complexation with indium(III) chloride and formation of dipolar activated complexes **I**, **II**, and **III** from uncharged reagents. In the reaction (Scheme 2) resulting in a greater stabilization

Table 2 Indium(III) Chloride Catalyzed Microwave-Irradiated Synthesis of Isatin *N*-Ribonucleosides

Product	Time		Yield (%)		Mp (°C)
	$MW/InCl_3$ (min)	Thermal (h)	$MW/InCl_3$	Thermal	
5a	7	8	80	37	130–131
5b	9	9	78	36	137–138
5c	8	9	77	35	137–138
5d	5	7	82	38	134–135
5e	6	8	83	39	134–135
5f	8	9	77	34	131–132
5g	9	9	78	33	131–132
5h	10	10	75	30	140–141
5i	10	10	76	32	140–141
5j	5	7	85	40	133–134



Scheme 2 Proposed mechanism for indium(III) chloride catalyzed and microwave activated synthesis of isatin *N*-ribonucleoside

of the more dipolar activated complex by dipole–dipole interactions with the electromagnetic field of the microwave, which may reduce the activation energy ($\Delta G^{\#}$), resulting in rate enhancement. Both of these factors may, therefore, cause the considerable reduction in reaction time.

In conclusion, a novel and efficient, environmentally benign, straightforward, and important cyclization procedure for the synthesis of isatin *N*-ribonucleosides from simple, readily available starting materials, using the recyclable indium(III) chloride catalyst, under microwave irradiation conditions has been achieved. This procedure provides an important route for the synthesis of *N*-ribonucleosides without protecting functionalities of β-D-ribofuranose and may find application in the library synthesis of such and other related aglycone modified *N*-ribonucleosides.

All chemicals used were reagent grade and were used as received without further purification. NMR spectra were recorded on a Bruker Avance DPX-400 FT spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) using $CDCl_3$ as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV.

Isatin *N*-Ribonucleosides 5a–j; General Procedure

Diethyl oxalate (**4**, 2.5 mmol), *N*-phenylribosylamine **3a–j** (2.5 mmol) and $InCl_3$ (3 mol%) in EtOH (20 mL) was taken in a flame-dried 50-mL round-bottom flask. The mixture was stirred and the solvent was evaporated. The content was subjected to microwave irradiation for 2 min at 600 W. The reaction mixture was thoroughly mixed outside the microwave oven for 1–2 min and again irradiated for another 2 min. This irradiation mixture cycle was repeated for the total irradiation time (Table 2). After completion of the reaction as indicated by TLC (*n*-hexane–EtOAc, 7:3) the product was extracted with Et_2O and purified by flash column chromatography to give analytically pure **5a–j**. The catalyst $InCl_3$ was eluted with EtOH and reused.

1-(β-D-Ribofuranosyl)-1*H*-indole-2,3-dione (5a)

Orange-red solid; yield: 80% (MW), 37% (thermal); mp 130–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.19–7.79 (m, 4 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.5, 120.9, 124.6, 128.6, 129.9, 134.5, 139.4, 155.7, 187.0.

MS (EI): *m*/*z* = 279.

7-Chloro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5b)

Orange-red; yield: 78% (MW), 36% (thermal); mp 137–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.13–7.67 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.0, 126.0, 126.2, 128.0, 30.0, 134.9, 139.8, 155.7, 187.0.

MS (EI): *m*/*z* = 313.

6-Chloro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5c)

Orange-red; yield: 77% (MW), 35% (thermal); mp 137–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.20–7.84 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.5, 121.3, 125.0, 126.7, 131.3, 139.8, 140.8, 155.7, 187.0.

MS (EI): *m*/*z* = 313.

7-Methoxy-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5d)

Orange-red; yield: 82% (MW), 38% (thermal); mp 134–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.73 (s, 3 H, OCH_3), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.19–7.79 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.9, 70.0, 75.4, 75.7, 82.8, 120.1, 122.2, 125.0, 125.6, 154.4, 155.7, 187.0.

MS (EI): *m*/*z* = 309.

6-Methoxy-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5e)

Orange-red; yield: 83% (MW), 39% (thermal); mp 134–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.73 (s, 3 H, OCH_3), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 6.70–7.68 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 61.9, 70.0, 75.4, 75.7, 82.5, 106.5, 110.2, 120.9, 140.4, 155.7, 168.0, 187.0.

MS (EI): *m*/*z* = 309.

7-Fluoro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5f)

Orange-red; yield: 77% (MW), 34% (thermal); mp 131–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.17–7.56 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.5, 121.5, 125.5, 126.2, 126.4, 130.2, 154.5, 155.7, 187.0.

MS (EI): *m*/*z* = 297.

6-Fluoro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5g)

Orange-red; yield: 78% (MW), 33% (thermal); mp 131–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 6.90–7.77 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.5, 107.9, 111.6, 124.2, 131.5, 141.0, 155.7, 168.1, 187.0.

MS (EI): *m*/*z* = 297.

7-Nitro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5h)

Orange-red; yield: 75% (MW), 30% (thermal); mp 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 7.45–8.18 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 81.5, 125.5, 129.5, 129.6, 134.5, 136.0, 140.8, 155.7, 187.0.

MS (EI): *m*/*z* = 324.

6-Nitro-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5i)

Orange-red; yield: 76% (MW), 32% (thermal); mp 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 8.05–8.76 (m, 3 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9, 70.0, 75.4, 75.7, 82.5, 116.0, 119.7, 130.8, 134.7, 140.3, 154.4, 155.7, 187.0.

MS (EI): *m*/*z* = 324.

6,7-Dimethoxy-1-(β-D-ribofuranosyl)-1*H*-indole-2,3-dione (5j)

Orange-red; yield: 85% (MW), 40% (thermal); mp 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.5 (br s, 3 H, 3 OH, exch. D_2O), 3.65–3.66 (m, 3 H, H3′, 5′-CH_2), 3.91 (m, 1 H, H4′), 3.73 (s,

6 H, OCH_3), 4.28 (m, 1 H, H2′), 5.93 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, H1′), 6.59–7.24 (m, 2 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3, 61.9, 70.0, 75.4, 75.7, 82.8, 111.2, 121.9, 123.2, 126.0, 140.0, 153.6, 155.7, 187.0.

MS (EI): *m*/*z* = 339.

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