A Facile Synthesis of Telisatin A via Microwave-Promoted Annulation and Reformatsky Reaction

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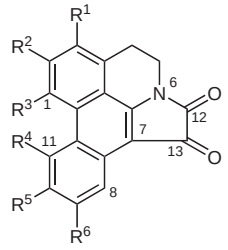
Abstract: A facile one-pot synthesis of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines is reported involving the ring formation of aryl pyruvate derivatives with 3,4-dihydroisoquinolines under basic conditions and utilizing the Reformatsky reaction. Using microwave irradiation, the required compounds were obtained in moderate to good yields.

Key words: microwave, annulation, Reformatsky reaction, dioxopyrrolo[2,1-*a*]isoquinoline, dioxoaporphine

12,13-Dioxoaporphine is a new subclass of aporphine alkaloids which possesses a 1,2-dione group linking N-6 and C-7 of aporphine and can be classified as an oxalyl-fused aporphine.[1] Up till now, five 12,13-dioxoaporphines have been found in nature (Figure 1). Telisatin A (**1a**) and telisatin B (**1b**), isolated from *Telitoxicum peruvianum*, were the first two representatives. The plant has been used as an ingredient of curare by the Huitoto Indians in Peru.[2] Laurodionine (**1c**) was isolated from the stems of *Phoebe formosana*, Hayata (Lauraceae) which is abundantly available in Taiwan.[3] The last two compounds, lettowianthine (**1d**) and 11-methoxylettowianthine (**1e**), were isolated from the root bark of *Lettowianthus stellatus*, a plant growing in coastal rain forests of Kenya and Tanzania. The root bark extracts of this plant have been shown to exhibit weak antimalarial activity.[4] Lettowianthine (**1d**) was also isolated from the fruits and stems of *Annona glabra*, a tropical plant in Taiwan, and was given another name, annobraine, by Wu.[5]

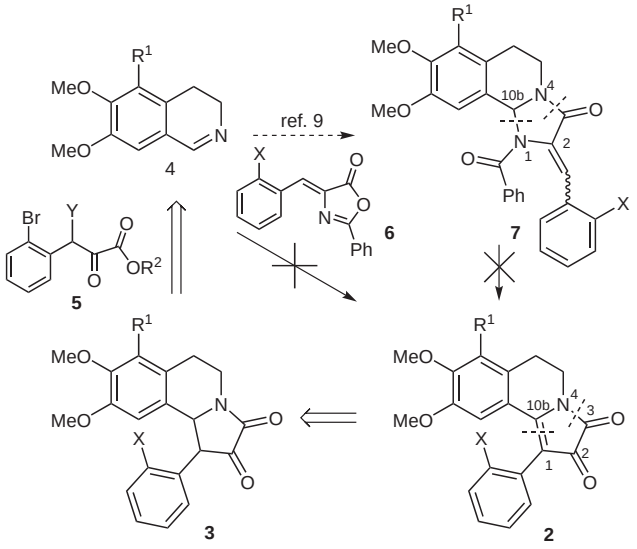
Telisatin A (**1a**) was previously synthesized by Cava[6] using dehydroaporphine with oxalyl chloride. It was also obtained as a [4+2]-cycloadduct in low yield as reported by Castedo.[7] Most isatins were prepared as the key intermediate for the synthesis of various alkaloids using oxalyl chloride as the source of the dioxo synthon.[8]

Recently, we reported the ring closure of dihydroisoquinoline **4** with azlactone **6** under neutral conditions to give the imidazoloisoquinolin-3-one **7** by simultaneous formation of two C–N bonds.[9] Herein, we report a facile synthesis of isatin skeleton **2**. Our new method is based on the



telisatin A (**1a**) $R^2 = R^3 = OMe$, $R^1 = R^4 = R^5 = R^6 = H$
telisatin B (**1b**) $R^1 = R^2 = R^3 = OMe$, $R^4 = R^5 = R^6 = H$
laurodionine (**1c**) $R^3 = R^5 = OMe$, $R^2 = R^6 = OH$, $R^1 = R^4 = H$
lettowianthine (**1d**) $R^2–R^3 = OCH_2O$, $R^1 = R^4 = R^5 = R^6 = H$
11-methoxylettowianthine (**1e**) $R^2–R^3 = OCH_2O$, $R^4 = OMe$, $R^1 = R^5 = R^6 = H$

Figure 1 Structure of natural 12,13-dioxoaporphine alkaloids



Scheme 1 Retrosynthetic analysis of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline **2**

construction of $C_1–C_{10b}$ and $N_4–C_3$ bonds by condensing 3,4-dihydroisoquinoline **4** with aryl pyruvate derivative **5** via dihydroisatin **3** which could be further oxidized to provide the desired 2,3-dioxopyrrolo[2,1-*a*]isoquinolines **2** as shown in Scheme 1.

It was originally anticipated that cleavage of the $C_{10b}–N_1$ bond of imidazoloisoquinolin-3-one **7** and subsequent hydrolysis of the corresponding enamide could furnish 2,3-

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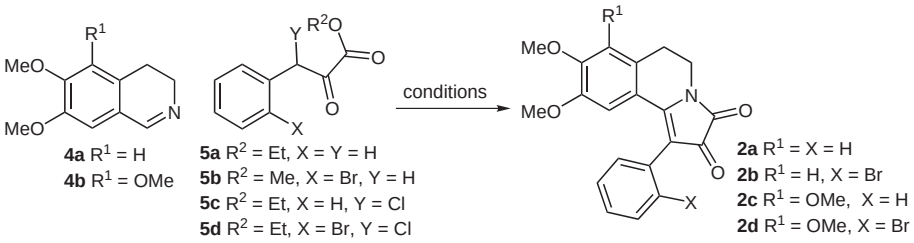
Table 1 Synthesis of 2,3-Dioxopyrrolo[2,1-*a*]isoquinolines **2**[14]



4a R^1 = H
4b R^1 = OMe

5a R^2 = Et, X = Y = H
5b R^2 = Me, X = Br, Y = H
5c R^2 = Et, X = H, Y = Cl
5d R^2 = Et, X = Br, Y = Cl

2a R^1 = X = H
2b R^1 = H, X = Br
2c R^1 = OMe, X = H
2d R^1 = OMe, X = Br

Entry	Imines	Phenyl pyruvates	Conditions[a]	Yield (%) **2**[b]
1	**4a**	**5a**	A	57
2	**4a**	**5a**	B	69
3	**4a**	**5b**	B	53
4	**4b**	**5a**	B	40
5	**4b**	**5b**	B	38
6	**4a**	**5a**	C	75
7	**4a**	**5b**	C	78
8	**4b**	**5a**	C	58[c]
9	**4b**	**5b**	C	54[c]
10	**4a**	**5c**	D	82[d]
11	**4a**	**5d**	D	77[d]
12	**4b**	**5c**	D	69
13	**4b**	**5d**	D	60

[a] Conditions A: NaOMe, MeOH, reflux, 12 h; B: NaOMe, DMF, reflux, 2 h; C: NaOMe, DMF, MW, 150 °C, 300 W, 100 psi, 10 min; D: Zn/Cu, benzene, MW, 150 °C, 300 W, 100 psi, 10 min.
[b] Isolated yields of pure product after column chromatography on silica.
[c] The C-2 demethylated by-product was observed in poor yields (5% and 8%, respectively).
[d] On using conventional heating for 14 h, yields of the desired products were 59% and 47%, respectively.

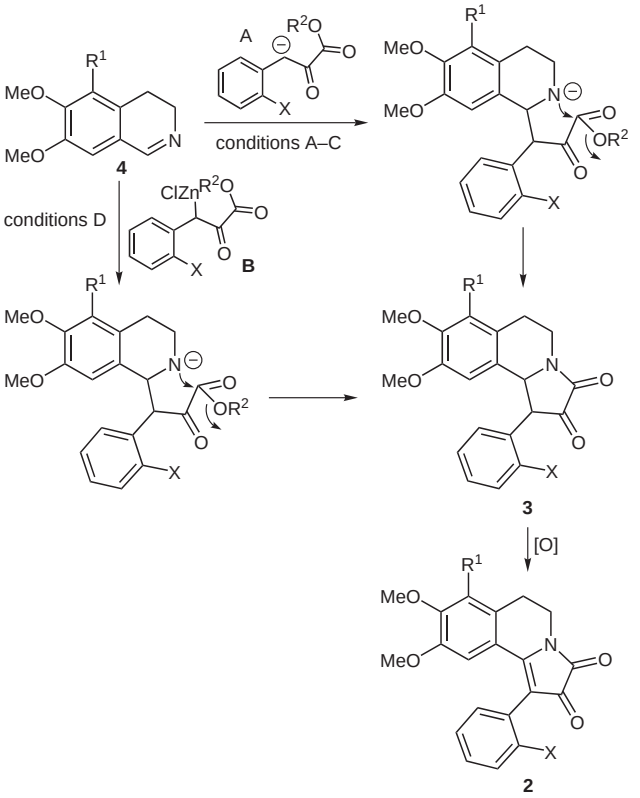
dioxopyrrolo[2,1-*a*]isoquinoline **2**. With this idea in mind, various hydrolysis conditions were studied. However, all conditions afforded mixtures of varying amount of the recovered compound **7** together with the target compound **2** in disappointing yields.

We then envisioned an alternative method for the synthesis of compound **2** using our developed methodology. The required 3,4-dihydroisoquinolines **4** were synthesized by the well-established Bischler–Napieralski reaction starting from the aryl ethylamine derivative which was converted into the corresponding formamide derivative and then cyclized to imine **4** using $POCl_3$.[10] The aryl pyruvate esters **5a** and **5b** were obtained by the Grignard reaction of different benzyl magnesium bromides with diethyl oxalate[11] as well as by the esterification of aryl pyruvic acid obtained from the hydrolysis of the azlactones **6**.[12] The α-chlorophenyl pyruvates **5c** and **5d** were obtained via the Darzens condensation.[13]

A model experiment for constructing the isatin framework was performed by reacting compound **4a** with **5a** in the presence of NaOMe in refluxing MeOH for four hours, furnishing the desired product **2a** in moderate yield and also the penultimate target compound **3a** albeit in poor yield. Better yield of the target compound could be obtained by increasing the reaction time to 12 hours. The yield was improved to a moderate 57% yield using conditions A (entry 1). Changing to a higher boiling-point solvent such as DMF under conditions B, the reaction was complete in only two hours and gave compounds **2a**–**d** in moderate 38–69% yields (entries 2–5).

Interestingly, by using microwave heating in conditions C,[15] the reaction time could be reduced from two hours to only a few minutes and compounds **2a**–**d** were obtained in moderate to good yields (entries 6–9). Under these conditions, however, the C-2 demethylation adducts were also observed in low yields (5–8%).

We have also investigated another procedure employing the Reformatsky reaction[16] to synthesize 2,3-dioxopyrrolo[2,1-*a*]isoquinoline **2**. Reaction of α-chloroaryl pyruvates **5c** and **5d** with Cu/Zn metals and dihydroisoquinoline **4a** in refluxing benzene for 14 hours gave compounds **2a** and **2b** in 59% and 47%, yields re-



Scheme 2 Proposed mechanism of the annulation of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline **2**

spectively. Using microwave irradiation (conditions D) instead of conventional heating led to a better yield of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines **2** (entries 10–13).

A proposed mechanism of the annulation of isatin **2** is shown in Scheme 2. The reaction possibly proceeded through a direct nucleophilic addition of either intermediate **A** or **B** to the dihydroisoquinoline **4** giving the dihydroisatin **3** which underwent further auto-oxidation to 2,3-dioxopyrrolo[2,1-*a*]isoquinoline **2** as shown in Scheme 2.

The photocyclization of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline **2b** in the presence of *tert*-butylamine by Hanovia 450 W high-pressure mercury lamp afforded the corresponding product, telisatin A (**1a**), in 27% yield.[8a]

In conclusion, we have devised a facile route for the synthesis of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines **2** in one step based on the ring formation of dihydroisoquinoline **4** with aryl pyruvate derivatives **5** under basic conditions and the Reformatsky reaction. Both conditions were examined using microwave irradiation which gave better yield than the conventional heating. The methodology should be applicable to the synthesis of dioxoaporphine and related alkaloids.

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(14) **Synthesis of 2,3-Dioxopyrrolo[2,1-*a*]isoquinoline 2; Typical Procedure (Conditions C)**: A mixture of imines **4** (0.1 mmol), aryl pyruvates **5** (0.1 mmol) and NaOMe (0.1 mmol) in DMF (1 mL) was irradiated using microwave. The microwave run time was set to 2 min, with power at 300 W, temperature at 150 °C, and pressure at 100 psi, and the conditions were maintained for 10 min. The reaction was quenched with H_2O and extracted with EtOAc, dried (Na_2SO_4) and evaporated in vacuo to yield a red residue. The residue was purified by column chromatography, affording crystals of **2** after recrystallization in moderate yields (54–78%).
Conditions D: A mixture of imines **4** (0.1 mmol), aryl pyruvates **5** (0.1 mmol), copper powder (0.1 mmol) and zinc powder (0.1 mmol) in DMF (1 mL) was irradiated using microwave. The microwave run time was set to 2 min, with power at 300 W, temperature at 150 °C, and pressure at 100 psi, and the conditions were maintained for 10 min. The reaction was quenched with H_2O and extracted with EtOAc, dried (Na_2SO_4) and evaporated in vacuo to yield a red residue. The residue was purified by column chromatog raphy, affording crystals of **2** after recrystallization in moderate to good yields (60–82%). Compound **2a**: deep-red solid; mp 178–179 °C (EtOAc–hexane). IR ($CHCl_3$): 3020, 1745, 1701, 1580, 1492, 1290 cm^{-1}. ^1H NMR (200 MHz,

$CDCl_3$): δ = 3.09 (t, *J* = 6.2 Hz, 2 H), 3.33 (s, 3 H), 3.85 (t, *J* = 6.2 Hz, 2 H), 3.96 (s, 3 H), 6.77 (s, 1 H), 6.95 (s, 1 H), 7.37 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.6, 36.6, 55.3, 56.2, 111.2, 112.2, 116.8, 127.9, 128.9, 130.2, 130.3, 132.8, 147.9, 153.5, 157.4, 158.3, 165.9, 183.1. MS (EI): *m*/*z* (%) = 263 (7), 306 (100), 307 (26), 335 (58) [M^+]. HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{20}H_{17}NO_4$: 336.1236; found: 336.1234.

Compound **2b**: wine-red solid; mp 198–199 °C (EtOAc–hexane; lit[8c] 176–178 °C). IR (KBr): 1746, 1692, 1575, 1514, 1396, 1290, 1223 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.11 (t, *J* = 6.2 Hz, 2 H), 3.30 (s, 3 H), 3.89 (t, *J* = 6.2 Hz, 2 H), 3.95 (s, 3 H), 6.65 (s, 1 H), 6.78 (s, 1 H), 7.31 (m, 3 H), 7.71 (d, *J* = 7.2 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4, 36.4, 55.2, 56.2, 107.9, 111.2, 111.5, 116.9, 125.9, 128.0, 129.9, 132.5, 132.8, 133.2, 148.3, 153.8, 158.1, 158.4, 181.6. MS (EI): *m*/*z* (%) = 306 (83), 334 (100), 384 (34), 386 (31), 413 (31) [M^+], 415 (31) [M^+ + 2]. HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{20}H_{16}BrNO_4$: 414.0341; found: 414.0343.

Compound **2c**: deep-red solid; mp 178–179 °C (EtOAc–hexane). IR ($CHCl_3$): 2941, 1742, 1692, 1573, 1472, 1403, 1343, 1299, 1111, 1029 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.10 (t, *J* = 6.2 Hz, 2 H), 3.30 (s, 3 H), 3.81 (t, *J* = 6.2 Hz, 2 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 6.82 (s, 1 H), 7.34 (m, 3 H), 7.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 36.1, 55.2, 61.0, 61.1, 109.1, 119.3, 125.6, 128.0, 128.9, 130.1, 130.2, 147.1, 147.7, 150.5, 151.9, 157.1, 157.9, 183.4. MS (EI): *m*/*z* (%) = 237 (37), 336 (100), 365 (60) [M^+]. HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{21}H_{19}NO_5$: 366.1341; found: 366.1338.

Compound **2d**: wine-red solid; mp 153–155 °C (EtOAc–hexane). IR (KBr): 1747, 1703, 1576, 1467, 1425, 1397, 1341, 1109, 1024 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.11 (t, *J* = 6.6 Hz, 2 H), 3.20 (s, 3 H), 3.75 (t, *J* = 6.2 Hz, 2 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 6.46 (s, 1 H), 7.20 (m, 2 H), 7.33 (t, *J* = 7.0 Hz, 1 H), 7.64 (d, *J* = 7.2 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 36.2, 55.2, 61.0, 61.1, 108.6, 119.4, 125.4, 125.8, 128.0, 129.9, 132.3, 132.7, 133.2, 147.0, 150.6, 152.3, 157.9, 158.0, 182.0. MS (EI): *m*/*z* (%) = 336 (54), 364 (100), 414 (34), 416 (36), 443 (93) [M^+], 445 (95) [M^+ + 2]. HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{21}H_{18}BrNO_5$: 444.0447; found: 444.0449.

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