Synthesis of 2,3-Dihydroimidazo[1,2-b]isoquinoline-5(1H)-one and Derivatives

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Abstract: A novel and efficient synthesis of 2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one by microwave irradiation is reported. Several new derivatives of 2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one have been synthesized by acylation using DMAP as catalyst. A kinetic study employing HPLC allowed the determination of the N- and C-acylated isomers formed.

Key words: acylation, DMAP, isomerizations, heterocycles, microwave synthesis

There are several human protozoal parasites that cause devastating diseases (malaria, sleeping sickness, Chagas’ disease and leishmaniasis) in the underdeveloped regions of the world. So far, there is no effective treatment and the intensive use of commercial drugs has led to the development of resistant parasites.1 There is an urgent need for new rather than economic drugs for the treatment of these diseases.

Isoquinolines generally constitute an important branch of heterocyclic compounds and are used nowadays against parasitic infections. Imidazoisoquinolinones are valuable substrates for the synthesis of potential biologically active compounds with structural features different from that of existing drugs. We required a synthesis of 2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one (1) and chemical exploration of this heterocycle, in order to determine what kind of derivatives can be achieved and find a ‘prototype’ molecule.

In 1976, Grinberg et al.2 reported the synthesis of this heterocycle by condensation of homophthalic anhydride with ethylenediamine, and isolating the intermediate amide, which upon heating to its melting point, loses two water molecules to give 1 in poor yield. Other authors3,4 published the condensation of homophthalic acid with two mol equivalents of ethylenediamine in o-dichlorobenzene under reflux for six hours to give 1 in 91% yield. However, these classical methods required high temperatures, prolonged reaction times and drastic reaction conditions and in the method reported by Grinberg, the yields are far from satisfactory due to the occurrence of several side reactions.

In recent years, microwave-assisted reactions5,6 are of great interest because of their simplicity in operation, enhanced reaction rates and greater selectivity. Particularly, solvent-free reactions have gained popularity as they provide an opportunity to work with open vessels. This avoids the risk of the development of high pressure and provides the possibility of scaling-up the reaction.

A novel and efficient approach for the synthesis of 1 in solvent-free conditions is of much interest. Such a synthesis has been achieved now by us by treating homophthalic acid with ethylenediamine under microwave irradiation over six minutes to afford compound 1 in 96% yield. The microwave irradiation was carried out using a domestic microwave oven at constant power with a reflux condenser (Scheme 1).

Scheme 1

In order to obtain new compounds related to the isoquinoline 1 in a large scale and low cost, we developed an exploration of the chemical reactions of heterocycle 1. In the first attempt we explored the acylation reaction by two regular methods: Schotten–Baumann reaction and using 4-(dimethylamino)pyridine (DMAP) as catalyst.7,8 In the acylation of the heterocycle 1 by acid chlorides using Schotten–Baumann method, N-1 selective acylation is favored, however we found the C-10 isomer as a side-product of the reaction. This mixture can be resolved by chromatography although the subsequent separation constituted a problem and it reduced yields. In general, the tested acid chlorides gave N-1 acylation products with an amount of C-10 isomer. The corresponding C-10 isomers were detectable by TLC.

DMAP is well-established in synthetic chemistry as an extremely useful ‘hypernucleophilic’ acylation catalyst, and thus is routinely employed to accelerate the acylation of nucleophilic nitrogen atom.9–11 Inclusion of DMAP in acylation reaction mixture leads directly to carbon acylation, as it seems to be a regioselective reaction. This reaction was kinetically studied by HPLC at different temperatures. During the first minutes of reaction, 80% of
the product was C-10 acylated and 20% N-1 acylated. As the reaction proceeded, an increase of C-10 isomer fraction was evidenced. A complete conversion to C-10 acyl isomer was observed after 90 minutes reaction time. This suggested a migratory process of N-1 acylation to C-10 acylation product. We verified that the migratory process was viable for all substrates and we could determine that the migration was a general phenomenon.

A mixture of N- and C- isomers obtained from Schotten–Baumann reaction in dichloromethane solution was treated with DMAP and the reaction was monitored by HPLC. We observed that DMAP caused the disappearance of N-1 acylated product with an accompanying marked increase of C-10 acylated product (Figure 1).

Figure 1  Rearrangement of compound 2 to compound 9 isomers via DMAP catalysis

Acylation reactions employing acid chlorides and catalyzed by DMAP are known to proceed via acylation of pyridine ring to afford highly reactive pyridinium species. This entity then undergoes facile nucleophilic attack affording the acylated product and regenerating the catalyst.\textsuperscript{12,13} We propose that a similar species is operative in our migration reaction; the sequence is depicted in Scheme 2 as example. N-Acylation is kinetically favored, a nucleophilic attack by DMAP on carbonyl group would afford the acylated pyridinium ion 2a, expelling the anion 2b in the process. Subsequent attack by the rearranged 2c would afford the carbon-functionalized isomer 9 (Scheme 2).

DMAP retained its efficacy in halogenated solvents. Both, dichloromethane and chloroform allowed a faster and complete rearrangement than the more polar dimethylformamide. DMF slowed the reaction considerably, consistent with solvation and partial separation of the ionic species. In the non-polar solvent hexane a mixture was obtained without any rearrangement. A series of 15 derivatives employing sulfonyl, alkyl and aryl acyl chloride were obtained in good to excellent yields (Scheme 3).

In conclusion, we have synthesized the starting heterocycle with a novel and efficient method. We prompted the acylation reaction by two methods: Schotten-Baumann reaction and DMAP as catalyst. Inclusion of DMAP seems to be a regioselective reaction. Migration of N-acyl product to C-isomer was monitored by HPLC.

Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are uncorrected. IR spectra were recorded with a FT Perkin-Elmer Spectrum One from KBr discs. UV spectra were measured with a Jasco V-5570 UV/Vis/NIR spectrophotometer. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were obtained with a Bruker spectrometer (200 MHz) at r.t. The chromatographic system was performed using preparative centrifugally accelerated chromatography (Chromatotron\textsuperscript{®}) and silica gel Merck 60 PF-254. The HPLC chromatograms were obtained in a Konik-500-A SERIES chromatograph, using spherisorb silica 5-\mu (250 \times 4.6 mm) alltech. The purity of all compounds was checked using HPLC, employing ODS Hypersil column (5 \mu, 200 \times 4.6 mm) Hewlett Packard. Microwave-assisted reaction was carried out in a household MW oven (BGH-QUICK Chef 15240). The apparatus was modified for laboratory applications with an external reflux condenser.

Scheme 2
2,3-Dihydroimidazo[1,2-b]isoquinoline-5(1H)-one and Derivatives

A suspension of homophthalic acid (Aldrich, 5 g, 24 mmol) and ethylenediamine (Merck, 35 mL, 48 mmol) was stirred and subjected to microwave irradiation operating at 240 Watts for 6 min, using a household MW oven. The product was collected by filtration and crystallized from EtOH to yield 1 (4.8 g, 96%) as yellow needles; mp 217–218 °C (Lit.3 mp 210–211 °C).

IR (KBr): 3213, 1664, 1531, 767, 690 cm–1.

$^{1}$H NMR (DMSO-$d_6$): $\delta = 7.93$ (ddd, $J = 8.11, 1.28, 0.72$ Hz, 1 H, H-6), 7.39 (t, $J = 8.11$ Hz, 1 H, H-7), 7.26 (t, $J = 8.11$ Hz, 1 H, H-8), 7.00 (dd, $J = 8.0, 1.28$ Hz, 2 H, H-9, NH, exchangeable with D$_2$O), 5.53, (s, 1 H, H-10), 4.05 (t, $J = 7.9$ Hz, 2 H, H-2), 3.6 (t, $J = 7.18$ Hz, 2 H, H-3).

$^{13}$C NMR (CCl$_3$D): $\delta = 160, 148.9, 140.9, 132.1, 126.6, 123, 121.0, 119.2, 77.6, 43.9, 41.9$. Anal. Calcd for C$_{11}$H$_{10}$N$_2$O: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.16; H, 5.72; N, 14.87.

Acylation of Compound 1 with Acyl Chlorides and Sulfonyl Chlorides; (Schotten–Baumann Reaction); General Procedure Method I: To a magnetically stirred mixture of compound 1 (0.5 g, 2.7 mmol) in CH$_2$Cl$_2$ (15 mL) and 20% aq solution KOH (5 mL), was slowly added dropwise a solution of acyl or sulfonyl chloride in CH$_2$Cl$_2$ (10 mL, 3.3 mmol) at 0–5 °C and the mixture was then allowed to warm to r.t. for an additional 2 h. The organic layer was separated, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The products were purified by an appropriate method.

1-[(4-Nitrophenyl)carbonyl]-2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one (2)

4-Nitrobenzoyl chloride and compound 1 afforded an N-acyl and C-acyl isomer mixture. The crude product was purified using Chromatotron® and EtOAc–hexane (60:40) as eluent to give 2 (0.27 g, 30%); mp 192–194 °C.

IR (KBr): 3130–3052, 1616, 1599, 836, 761–693 cm–1.

$^{1}$H NMR (DMSO-$d_6$): $\delta = 8.4$ (dd, $J = 6.91, 1.9$ Hz, 2 H, arom), 8.14 (d, $J = 7.9$ Hz, 1 H, H-7), 7.94 (dd, $J = 6.92, 1.9$ Hz, 2 H-9, 2 H, H-10), 7.64–7.92 (m, 2 H, H-7, H-9), 7.36–7.41 (m, 1 H, H-8), 7.1 (s, 1 H, H-10), 4.0–4.1 (m, 4 H, H-2, H-3).

Anal. Calcd for C$_{18}$H$_{13}$N$_3$O$_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.83; H, 4.29; N, 12.18.

1-(Phenylcarbonyl)-2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one (3)

Method I: Benzoyl chloride and compound 1 afforded only compound 3 which was crystallized from EtOH; yield: 0.62 g (80%); white powder; mp 180–181 °C (Lit.3 mp 178–180 °C).

IR (KBr): 3130, 3052, 1706, 1614, 1548, 761, 700, 693 cm–1.
\[ \text{Method 2: To a suspension of compound 1 (0.5 g, 2.7 mmol) in CH}_2\text{Cl}_2 (5 \text{ mL}), were added dropwise pyridine (0.5 mL, 6.7 mmol) and benzoyl chloride (1.4 mL, 3.3 mmol) with stirring at 0–5 °C. The temperature of the reaction was allowed to rise to r.t. and the mixture was stirred overnight. The pyridine was evaporated under reduced pressure. The solid product was crystallized from EtOH to give 3 (0.23 g, 30%), whose physical properties and elemental analysis are identical with the product obtained by Method 1.} \\

\[ \text{Method 3: Compound 1 (0.5 g, 2.7 mmol) and DMAP (0.6 g, 4.4 mmol) were suspended in CH}_2\text{Cl}_2 (5 \text{ mL}). After 5 min, benzoyl chloride was added over a period of several min with stirring at 0–5 °C for 2 h. The organic layer was dried (MgSO}_4\), filtered, and evaporated under reduced pressure. The solid was crystallized from EtOH to give 3 (0.18 g, 23%), whose physical properties and elemental analysis are identical with the product obtained by Method 1.} \\

\[ \text{1-Acetyl-2,3-dihydroimidazol-1,2-b}-\text{isoquinoline-5(1H)-one (4) Method 1: Acetyl chloride and compound 1 afforded the title compound 4, which was crystallized from benzene yield: 0.24 g (40%); mp 180–182 °C.} \\

\[ \text{1H NMR (CDCl}_3\): } \delta = 8.12 (d, J = 6.7 Hz, 1 H, H-6), 7.53–7.56 (m, 1 H, H-6), 7.35–7.37 (m, 2 H, H-7, H-9), 7.19 (s, 1 H, H-4). \text{IR (KBr): 1660, 1624, 1596, 1360, 752, 668 cm}^{-1}. \text{Anal. Calcd for C}_12\text{H}_12\text{N}_2\text{O}_3\text{S: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.65; H, 4.93; N, 10.35.} \\

\[ \text{Method 2: To a suspension of compound 1 (0.5 g, 2.7 mmol) in pyridine (5 mL) were added dropwise methanesulfonyl chloride (0.5 mL, 3.1 mmol) with stirring at 0–5 °C. The reaction temperature was allowed to rise to r.t. and the mixture was stirred overnight. The pyridine was evaporated under reduced pressure and the residual viscous oil obtained was triturated with EtOH to give 0.11 g (15%) of product 7, whose physical properties and elemental analysis are identical with the product obtained by Method 1.} \\

\[ \text{1-[4-(Methylphenyl)sulfonyl]-2,3-dihydroimidazol-1,2-b}-\text{isoquinoline-5(1H)-one (8) Method 1: Tosyl chloride and compound 1 afforded the title compound 8. It was crystallized from CH}_2\text{Cl}_2–\text{MeOH; yield: 0.32 g (35%); mp 207–210 °C.} \text{ IR (KBr): 1660, 1596, 1360, 752, 668 cm}^{-1}. \text{Anal. Calcd for C}_16\text{H}_16\text{N}_2\text{O}_3\text{S: C, 54.51; H, 4.74; N, 8.23. Found: C, 54.63; H, 4.82; N, 8.12.} \\

\[ \text{C-Acylation of Compound 1 via DMAP Catalysis; General Procedure} \\

\[ \text{To a suspension of compound 1 (0.5 g, 2.7 mmol) in CH}_2\text{Cl}_2 (10 \text{ mL}) was added DMAP (0.6 g, 4.4 mmol) with stirring. After 5 min, the acyl chloride (3.5 mmol) was added over a period of several min and the mixture was stirred at 0–5 °C for 2 h. The organic layer was washed with H}_2\text{O (20 mL) and then with 10% aq solution of K}_2\text{CO}_3 (20 mL). The product was purified by chromatotron® using EtOAc–hexane (60:40) as eluent to give 6 (0.17 g, 20%); mp 168–170 °C.} \\

\[ \text{1-(4-(4-Nitrophenyl)carbonyl)-2,3-dihydroimidazol-1,2-b}-\text{isoquinoline-5(1H)-one (9) 4-Nitrobenzoyl chloride and compound 1 afforded the title compound 9. The red powder was triturated with EtOH; yield: 0.72 g (80%); mp 280–281 °C.} \text{ IR (KBr): 3303, 1651, 1558, 758, 668 cm}^{-1}. \text{Anal. Calcd for C}_16\text{H}_16\text{N}_2\text{O}_3\text{S: C, 54.51; H, 4.74; N, 8.23. Found: C, 54.63; H, 4.82; N, 8.12.} \\

10-[(4-Methylphenyl)carbonyl]-2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one (10)

4-Methylbenzoyl chloride and compound 1 afforded the title compound 10. The crude product was crystallized from EtOH; yield: 0.41 g (50%); mp 201–202 °C.

IR (KBr): 3197, 1672, 720, 690 cm⁻¹.

1H NMR (DMSO-d₆): δ = 8.47 (s, 1 H, NH), 7.91 (d, J = 7.2 Hz, 1 H, H-6), 7.63 (m, 2 H, H-7, H-8), 7.45 (m, 1 H, H-9), 7.32 (m, 2 H, H-3, H-4), 4.18 (t, J = 7.8 Hz, 2 H, H-2), 3.91 (s, 2 H, H-3).

Anal. Calcd for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.03; H, 5.41; N, 9.17.

10-(2,4-Dichloro-5-fluorophenyl)carbonyl]-2,3-dihydroimidazo[1,2-b]isoquinoline-5(1H)-one (11)

A solution of compound 10 in CH₂Cl₂ was added to a 100 mL two-necked flask, fitted with rubber septum, and NaOH (3 mol L⁻¹). The heterogeneous mixture was allowed to react overnight and the organic layer was washed with 10% aq solution of NaOH (3 x 15) and then with H₂O (20 mL). The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure to afford the crude product. Purification was effected as noted below for each case.

1H NMR (DMSO-d₆): δ = 8.21 (s, 1 H, NH), 8.06 (d, J = 7.4 Hz, 1 H, H-6), 7.91 (m, 1 H, H-9), 7.47–7.0 (m, 5 H, H-7, H-8, H-9), 4.55 (t, J = 8.32 Hz, 2 H, H-2), 4.17 (t, J = 7.4 Hz, 2 H, H-3).


C-Acylation with Sulfonyl Derivatives of Compound 1 via DMAP Catalysis; General Procedure

A solution of compound 1 (0.5 g, 2.7 mmol) in CH₂Cl₂ (10 mL) was added to a 100 mL two-necked flask, fitted with rubber stopper, and N₂ inlet. A solution of tosyl chloride (667 mg, 3.5 mmol) in CH₂Cl₂ (5 mL) was added dropwise with stirring at 0–5 °C. After 5 min, a solution of DMAP (4.9 mmol) in CH₂Cl₂ (5 mL) was added over a period of several min. The heterogeneous mixture was allowed to react overnight and the organic layer was washed with 10% aq solution of NaOH (3 x 15) and then with H₂O (20 mL). The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure to afford the crude product.
Equation 1

\[
\text{\% C-isomer}_{\text{time } n} = \frac{\text{Area C-isomer}_{\text{time } n} \times 100}{(\text{Area C-isomer} + \text{Area N-isomer})_{\text{time } n}}
\]

\[
\text{\% N-isomer}_{\text{time } n} = \frac{\text{Area N-isomer}_{\text{time } n} \times 100}{(\text{Area C-isomer} + \text{Area N-isomer})_{\text{time } n}}
\]

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