One-Pot Synthesis of Naphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-diones from 2-Amino-3-chloro-1,4-naphthoquinone and Pyridine Derivatives

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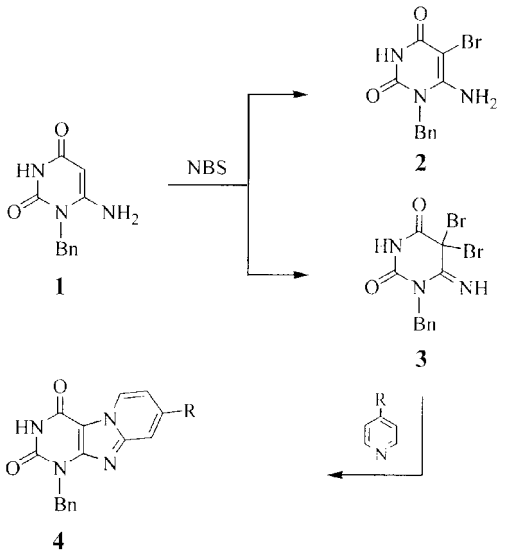
Dioxonaphthalimidazopyridine derivatives such as naphth-[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione and 9-methyl-naphth[1',2':4,5]imidazo[1,2-*a*]pyridine-5,6-dione are interesting chemical entities both as a chromophoric[1] and a pharmacological agent for treating diseases related to venous insufficiency and/or inflammatory edema.[2] Most of the early methods developed for their synthesis are reactions of 2-chloro-3-hydroxy-, 2-chloro-3-ethoxy- and 2-chloro-3-acetoxy-1,4-naphthoquinones with 2-aminopyridines,[3] thermolysis of 3-azido-2-chloro-1,4-naphthoquinone in excess of pyridine[1] and condensation reaction of 2,3-dichloro-1,4-naphthoquinones with 2-aminopyridine using phase transfer catalyst.[4]

Recently, Pérez-Pérez and co-workers reported[5] that the reactions of 6-amino-1-benzyluracil **1** with *N*-bromosuccinimide (NBS) in pyridine at 80 °C afforded 6-amino-1-benzyl-5-bromouracil **2** and 1-benzyl-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **4** *via* intermediate dibromo compound **3** (Scheme 1). With their results in mind, we tried to apply this methodology to the synthesis of naphth[2',3':4,5]imidazo-[1,2-*a*]pyridine-6,11-diones **10** by the reaction of 2-amino-3-chloro-1,4-naphthoquinone **5** with NBS followed by in situ reaction with pyridine derivatives.



Scheme 1

The known 2-amino-3-chloro-1,4-naphthoquinone **5** was easily prepared by the reaction of 2,3-dichloro-1,4-naphthoquinone with ammonim hydroxide.[6] The reaction of **5** with 2 equivalents of NBS in acetonitrile at room temperature for 10 minutes followed by in situ reaction with 5 equivalents of pyridine at reflux for 2 hours led to 55% yield of naphth-[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione together with 15% of unreacted 2-amino-3-chloro-1,4-naphthoquinone. Attempts were made to extend this reaction to other pyridines such as γ-picoline, ethyl isonicotinate, 4-*t*-butylpyridine, 4-pyridinecarboxaldehyde and isoquinoline (Table 1). Introducing excess of NBS (3 equivalents) and pyridine (10 equivalents) to improve the product yield was not successful.

A plausible mechanism for the transformation of **5** into **10** is shown in the Scheme 2.[5] The reaction supposed to be initiated by bromination of **5** with NBS to give dihalo compound **6**.[7] The second step should involve the nucleophilic substitution of bromine atom by pyridine to generate **7**, that, by elimination of BrCl, should give the intermediate

Table 1. Naphth[2',3':4,5]imidazol[1,2-*a*]pyridine-6,11-dione **10a-e** and Naphth[2',3':4,5]imidazo[2,1-*a*]isoquinoline-8,13-dione **10f** Prepared

Substrate	Reaction time (h)	% Yield[a]	Product
Pyridine	2	55 (15)	**10a**
γ-Picoline	1	23 (50)	**10b**
4-*t*-Butylpyridine	4	43 (10)	**10c**
Ethyl isonicotinate	2	22 (50)	**10d**
4-Pyridinecarboxaldehyde	3	20 (52)	**10e**
Isoquinoline	2	32 (30)	**10f**

[a]Parentheses values are yields of recovered starting materials.

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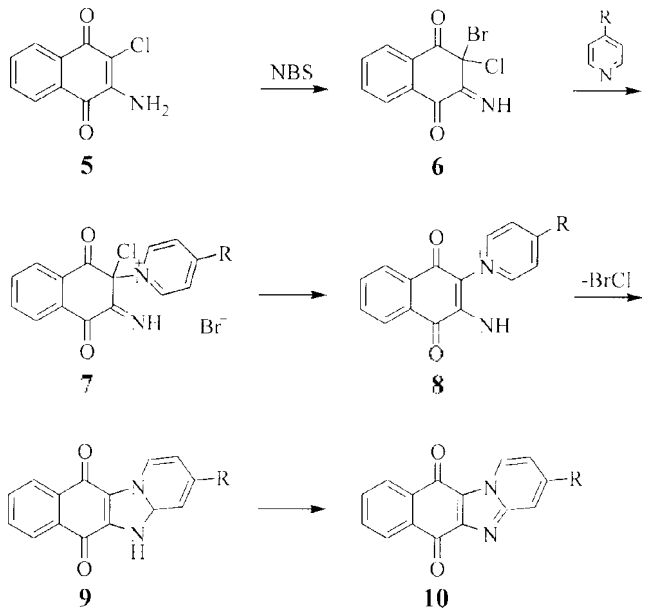

Scheme 2

ylide **8**. The positive charge in the pyridine facilitates a nucleophilic attack in the α-position of the pyridine to generate **9**, that is oxidized to afford the naphth[2',3':4,5]-imidazo[1,2-*a*]pyridine-6,11-diones **10**.

Structural elucidation of **10** was accomplished on the basis of spectral data reported in the literature.[1] In the mass spectra of **10**, the molecular ions (base peak) are observed. The successive lose of carbon monoxide molecules from the molecular ion is suggestive of the presence of two carbonyl groups as part of ring structure and their IR spectra show two carbonyl absorptions.

In summary, an efficient synthesis of naphth[2',3':4,5]-imidazo[1,2-*a*]pyridine-6,11-diones has been performed by the reaction of 2-amino-3-chloro-1,4-naphthoquinone with NBS in the presence of pyridine derivatives.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography was perfomed on silica gel with fluorescent indicator coated on aluminium sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. Mass spectra were obtained using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H NMR spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane.

The 2-amino-3-chloro-1,4-naphthoquinone **5** was prepared following the literature procedure.[6]

General Procedure for the Preparation of Naphth-[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-diones 10. To a solution of 2-amino-3-chloro-1,4-naphthoquinone (**5**, 1.03 g, 5 mmol) in 40 mL of dry acetonitrile was added NBS (1.78 g, 10 mmol). The mixture was stirred at r.t. for 10 min., the corresponding pyridine (25 mmol) was added, and the resulting mixture was heated at reflux for the time indicated in Table 1. After cooling to room temperature the solvent was removed on a rotavapor and the residue was partitioned between aqueous 10% HCl solution and dichloromethane. The dichloromethane layer was washed with water and the solvent was removed after drying over $MgSO_4$, and the residue was chromatographed on silica gel column and eluted with hexane-EtOAc 4 : 1 to give **10** and the recovered starting material **5**. The yields of **10a-10f** are listed in Table 1.

Naphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione (10a). Mp 285-286° (Lit.[1] 290°); IR (KBr) 1685, 1642, 1580, 1506, 1394, 1320, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24-7.28 (m, 1H), 7.59-7.65 (m, 1H), 7.63-7.79 (m, 2H), 7.93-7.96 (m, 1H), 8.24-8.33 (m, 2H), 9.43 (d, J = 6.7 Hz, 1H); MS m/z (rel intensity) 248 (M$^+$, 100), 220 (28), 192 (35), 191 (11).

3-Methylnaphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione (10b). Mp 326-328° (Lit.[1] 330°); IR (KBr) 1679, 1637, 1595, 1507, 1394, 1313, 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$ + TFA) δ 2.81 (s, 3H), 7.71-7.73 (d, J = 6.4 Hz, 1H), 7.98-8.03 (m, 3H), 8.36-8.41 (m, 2H), 9.64 (d, J = 6.7 Hz, 1H); MS m/z (rel intensity) 262 (M$^+$, 100), 234 (23), 233 (13), 206 (18), 205 (23).

3-*t*-Butylnaphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione (10c). Mp 289-290°; IR (KBr) 1689, 1638, 1580, 1506, 1409, 1324, 1277, 1227, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$ + TFA) δ 1.55 (s, 9H), 7.98-8.04 (m, 3H), 8.18 (s, 1H), 8.38-8.43 (m, 2H), 9.68 (d, J = 7.0 Hz, 1H); MS m/z (rel intensity) 304 (M$^+$, 46), 289 (100), 261 (28).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.71; H, 5.12; N, 8.89.

3-Carbethoxynaphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione (10d). Mp 240-243° (Lit.[1] 246°); IR (KBr) 1720, 1685, 1650, 1592, 1514, 1398, 1316, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 7.1 Hz, 3H), 4.49 (q, J = 7.1 Hz, 2H), 7.79-7.83 (m, 3H), 8.25-8.35 (m, 2H), 8.59 (s, 1H), 9.45 (d, J = 7.0 Hz, 1H); MS m/z (rel intensity) 320 (M$^+$, 100), 292 (75), 275 (50), 264 (18), 219 (19), 191 (19).

3-Formylnaphth[2',3':4,5]imidazo[1,2-*a*]pyridine-6,11-dione (10e). Mp 319-322°; IR (KBr) 1774, 1693, 1374, 1297, 1192 cm^{-1}; ^{1}H NMR ($CDCl_3$ + TFA) δ 8.01-8.06 (m, 2H), 8.29 (d, J = 7.0 Hz, 1H), 8.40-8.45 (m, 2H), 8.92 (s, 1H), 9.93 (d, J = 7.3 Hz, 1H), 10.3 (s, 1H); MS m/z (rel intensity) 276 (M$^+$, 100), 275 (45), 219 (17), 191 (29), 164 (13).

Anal. Calcd. for $C_{16}H_8N_2O_3$: C, 69.57; H, 2.92; N, 10.14. Found: C, 69.41; H, 2.80; N, 9.87.

Naphth[2',3':4,5]imidazo[2,1-*a*]isoquinoline-8,13-dione (10f). Mp 314-315° (Lit.[1] 320°); IR (KBr) 1677, 1646, 1596, 1518, 1405, 1347, 1223 cm^{-1}; ^{1}H NMR ($CDCl_3$ + TFA) δ 7.99-8.12 (m, 4H), 8.22 (s, 2H), 8.37-8.43 (m, 2H), 8.81 (d, J =

7.3 Hz, 1H), 9.44 (d, J = 6.7 Hz, 1H); MS m/z (rel intensity) 298 (M^+, 100), 270 (20), 242 (31), 241 (19), 207 (17).

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7. Isolation of dihalo compound **6** was unsuccessful due to rapid decomposition to **5**.