Synthesis of Imidazo[4,5-*c*]quinolin-4(5*H*)-one *via* Radical Cyclization

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The tributyltin radical-induced cyclization of *N*-(2-bromophenyl)-*N*-butyl-1*H*-1-methylimidazole-4-carboxamide **3** gave 5-butyl-3-methyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **5** *via* [1,2]-acyl rearrangement.

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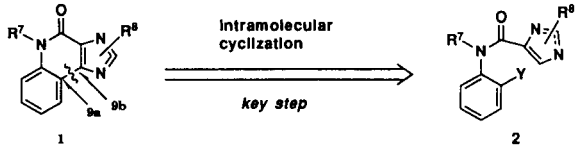
1*H*- or 3*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives **1** have been shown to exhibit potent antiasthmatic activity [1]. This discovery stimulated our efforts to devise an efficient and direct chemical synthesis, which requires the construction of a single bond between C-9a and C-9b (Scheme 1).

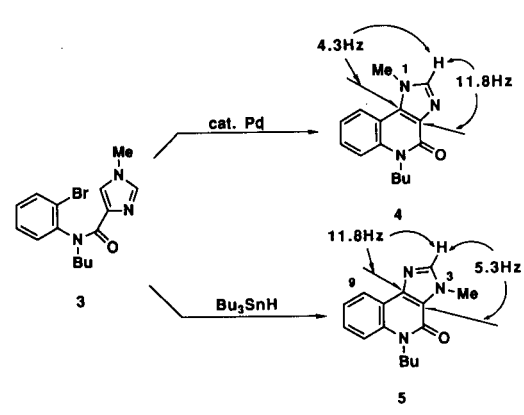
Scheme 1



We recently reported that the target compound **1** could be obtained from **2** *via* the palladium-promoted intramolecular coupling reaction (Scheme 2) [2]. Though many elegant methods using palladium-catalyzed intramolecular or intermolecular aryl-aryl couplings [3,4] have been reported, fewer couplings *via* a radical process have been reported. Togo and Kikuchi reported that the reaction of *N*-allyl-2-bromobenzanilide and ethyl acrylate with tributyltin hydride and catalytic AIBN afforded 5-allylphenanthridin-6(5*H*)-one as an unexpected product instead of 3-ethoxycarbonylpropyl-1-benzoylindole [5]. This interesting reaction prompted us to also test the feasibility of the construction of **1** from **2** *via* a radical-induced cyclization.

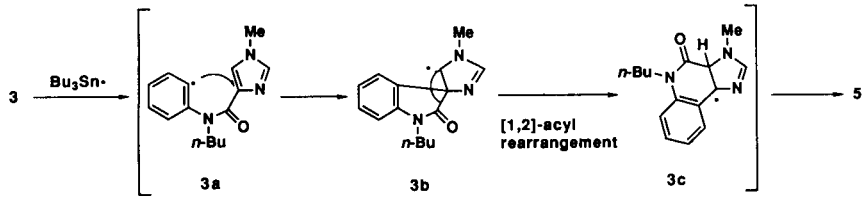
A precursor for the cyclization, **3** was prepared as described before [2]. Treatment of **3** with tributyltin hydride (1.3 equivalents) under the radical conditions [catalytic AIBN, toluene, reflux, 5 hours] gave the cyclized product, 5-butylimidazo[4,5-*c*]quinolin-4(5*H*)-one derivative in 37% yield (50% yield based on the recovered starting material). However the spectral and physical data of the product were different from those of the 1-methyl derivative, **4** [2]. The structure of the product was shown to be the 3-methyl derivative **5** with the aid of nmr spectroscopic analysis. NOE between 3-Me and 2-H was observed but that between 3-Me and 9-H was not. Results of long range coupling based on long range selective proton decoupling experiments were shown in Scheme 1. 1-Methyl derivative **4** and the other regioisomer of **5** were not detected in the reaction mixture.

Scheme 2



Altering the amount of tributyltin hydride and temperature resulted in the same product in low yields. This methyl [1,3]-migration in imidazole is unusual [6], because thermal migrations of substituents on nitrogen of imidazole generally proceed to the carbon atom [7]. In fact, **4** could not be transformed into **5** under these radical reaction conditions. Thus, a possible mechanism to explain the apparent [1,3]-methyl migration is shown in Scheme 3. Phenyl radicals generated by the reaction of **3** with tributyltin radicals undergo intramolecular cyclization to afford a spiro intermediate **3b** [8], which is accompanied by [1,2]-acyl migration of the amide moiety to **3c**, followed by oxidative dehydrogenation to **5**.

Scheme 3



The [1,2-]-acyl migration was observed in the reactions related to coenzyme B_{12} [10] catalyzed rearrangements. Okabe *et al.* [11] and Best *et al.* [12] reported that 2-substituted 2-acylpropyl radicals derived from cobaloximes or halides, provided 2-substituted 3-acylpropenes and the olefin isomers. Furthermore, Tada *et al.* reported that 1-substituted 2-oxocyclopentylmethylcobaloximes were transformed into 3-substituted 2-cyclohexenones by photolysis [13]. A similar example also was recently observed by Boger and Mathvink [14]. However, to our best knowledge, there have been no reports regarding the [1,2]-acyl migration of the amide carbonyl group and the spiro intermediate.

In conclusion, regioselective synthesis of 1-methyl- or 3-methylimidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives **4** or **5** from the common key intermediate **3** has been achieved using palladium [2] or tributyltin radicals, respectively. At present, further application of this methodology in the synthesis of a variety of heterocycles are under way.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (ir) spectra were measured on a JASCO IR-810 spectrometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were measured on a JEOL JNM GX-270 spectrometer or a Hitachi R-90H spectrometer with tetramethylsilane (TMS) as an internal standard. The ^{13}C nmr spectra were recorded on a Bruker AMX400 spectrometer. Mass spectra (ms) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. High resolution EI mass spectra were determined at 70 eV on a JEOL JMS-SX102. Elemental analyses were performed with a Perkin-Elmer 2400CHN. For column chromatography, Silica gel 60 (E. Merck, 0.063-0.200 mm) was used. Silica gel preparative thin layer chromatography was performed with Merck Kieselgel F254S.

N-(2-Bromophenyl)-*N*-butyl-1*H*-1-methylimidazole-4-carboxamide **3** [2].

(a) *N*-(2-Bromophenyl)-1*H*-imidazole-4-carboxamide.

To a suspension of 22 ml (0.20 mole) of 2-bromoaniline in 200 ml of DMF, 8.1 g (0.20 mole) of 60 wt% of sodium hydride was added portionwise with ice cooling. After hydrogen evolution ceased, 9.5 g (0.051 mole) of 5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-5,10-dione [15] was added to the reaction mixture. The mixture was stirred at room temperature for 2 hours. Then, the solvent was evaporated under reduced pressure. Water and chloroform were added to the residue and the mixture was stirred for 30 minutes. The solid was collected by filtration and dried to afford 5.7 g (42%) of *N*-(2-bromophenyl)-1*H*-imidazole-4-carboxamide as gray crystals. An analytical sample was recrystallized from ethanol-water, mp 184-187°; ir (potassium bromide): ν 1665 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform/perdeuteriomethanol = 1/2): 6.80-7.70 (m, 3 H, phenyl 4-, 5-, and 6-H), 7.67 and 7.77 (each d, 2 H, J = 1 Hz, imidazole 2-H and 4-H), 8.40 (dd, 1 H, J = 8, 2 Hz, phenyl 3-H); ms: m/z 265, 267 (molecular ion).

Anal. Calcd. for $C_{10}H_8N_3OBr$: C, 45.14; H, 3.03; N, 15.79. Found: C, 45.36; H, 2.93; N, 15.36.

(b) *N*-(2-Bromophenyl)-1*H*-1-methylimidazole-4-carboxamide.

After 2.6 g (0.010 mole) of the above compound was added to 0.88 g (0.013 mole) of potassium hydroxide in 15 ml of ethanol at room temperature, the mixture was allowed to stand for 30 minutes to 1 hour. Then 3.0 ml (0.021 mole) of methyl iodide was added to the mixture under ice cooling. After the mixture was allowed to stand overnight, 100 ml of water was added and the precipitate was collected by filtration and dissolved in chloroform. The organic layer was washed with water, 1*N* sodium hydroxide aqueous solution, brine, and dried. The solvent was evaporated under reduced pressure to afford 2.0 g (72%) of *N*-(2-bromophenyl)-1*H*-1-methylimidazole-4-carboxamide as yellow crystals. An analytical sample was recrystallized from ethanol, mp 147-149°; ir (potassium bromide): ν 1674 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 3.74 (s, 3 H, CH_3), 7.04 and 7.41 (each br t, 2 H, J = 8 Hz, phenyl 4- and 5-H), 7.68 (dd, 1 H, J = 8, 2 Hz, phenyl 6-H), 7.79 and 7.88 (each d, 2 H, J = 1 Hz, imidazole 2-H and 4-H), 8.38 (dd, 1 H, J = 8, 2 Hz, phenyl 3-H), 9.60 (br s, 1 H, NH); ms: m/z 279, 281 (molecular ion).

Anal. Calcd. for $C_{11}H_{10}N_3OBr$: C, 47.17; H, 3.60; N, 15.00. Found: C, 46.93; H, 3.42; N, 14.62.

(c) *N*-(2-Bromophenyl)-*N*-butyl-1*H*-1-methylimidazole-4-carboxamide **3**.

To a solution of 0.66 g (2.4 mmoles) of *N*-(2-bromophenyl)-1*H*-1-methyliimidazole-4-carboxamide in 15 ml of DMF was added portionwise 0.12 g (3.1 mmoles) of 60 wt% sodium hydride with ice cooling. After stirring for 30 minutes, 0.41 ml (3.60 mmoles) of butyl iodide was added, and the mixture was stirred for 1 hour at 50°. Standard workup afforded a residue that was purified by silica gel column chromatography (eluent: chloroform/methanol = 40/1) to afford 0.72 g (91%) of **3** as pale yellow crystals. An analytical sample was recrystallized from 2-propanol-water, mp 90-92°; ir (potassium bromide): ν 1633 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.91 (t, 3 H, J = 7 Hz, butyl CH_3), 1.23-1.45 and 1.50-1.72 (each m, 4 H, butyl 2-H_2 and 3-H_2), 3.53 (s, 3 H, CH_3), 3.33-4.28 (m, 2 H, butyl 1-H_2), 6.70-7.37 (m, 5 H, phenyl 4-, 5-, 6-H and imidazole 2 H), 7.62 (d, 1 H, J = 8 Hz, phenyl 3-H); ms: m/z 335, 337 (molecular ion).

Anal. Calcd. for $C_{15}H_{18}N_3OBr$: C, 53.58; H, 5.40; N, 12.50. Found: C, 53.70; H, 5.43; N, 12.57.

5-Butyl-1-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **4**.

To a solution of 100 mg (0.30 mmole) of **3** in 2.0 ml of *N*,*N*-dimethylacetamide, was added 6.8 mg (0.030 mmole) of lead acetate, 83 mg (0.30 mmole) of tetrabutylammonium chloride monohydrate, and 63 mg (0.75 mmole) of anhydrous sodium bicarbonate. The mixture was stirred under an argon atmosphere at 150° for 24 hours. The mixture was cooled and a standard workup gave a residue that was purified by silica gel column chromatography (eluent:chloroform/methanol = 50/1) to afford 63 mg (85%) of **4** as white crystals. An analytical sample was recrystallized from 2-propanol/isopropyl ether, mp 208-209°; ir (potassium bromide): ν 1645 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.94 (t, 3 H, J = 7 Hz, butyl CH_3), 1.37-1.45 and 1.55-1.64 (each m, 4 H, butyl 2-H_2 and 3-H_2), 4.17 (s, 3 H, CH_3), 4.34 (t, 2 H, J = 7 Hz, butyl 1-H_2), 7.34 (br t, 1 H, J = 8 Hz, 8-H), 7.55-7.65 (m, 2 H, 6- and 7-H), 8.10 (s, 1 H, 2-H), 8.20 (br d, 1 H, J = 8 Hz, 9-H); ^{13}C nmr (DMSO-d_6): 13.7 (C4'), 19.6 (C3'), 29.4 (C2'), 34.6 (N-Me), 40.9 (C1'), 113.3 (C9a), 115.7 (C6), 121.7 (C8), 121.9 (C9), 128.4 (C7),

131.2 (C3a), 132.6 (C9b), 136.4 (C5a), 143.8 (C2), 157.0 (C4); ms: m/z 255 (molecular ion).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.63; H, 6.73; N, 16.22.

5-Butyl-3-methyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **5**.

To a solution of 0.53 g (1.6 mmoles) of **3** in 100 ml of toluene, was added 0.013 g (0.079 mmole) of 98% AIBN and 0.55 ml (0.021 mmole) of tributyltin hydride. The mixture was refluxed under nitrogen atmosphere for 5 hours. The mixture was cooled, worked up as usual and the residue purified by silica gel preparative thin layer chromatography (eluent:chloroform/methanol = 10/1) to afford 0.15 g (37%) of **5** as white crystals and 0.14 g (26%) of recovered **3**. An analytical sample was recrystallized from 2-propanol/isopropyl ether, mp 151-153°; ir (potassium bromide): ν 1660 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 0.95 (t, 3 H, J = 7 Hz, butyl CH_3), 1.36-1.52 and 1.58-1.71 (each m, 4 H, butyl 2-H_2 and 3-H_2), 4.08 (s, 3 H, CH_3), 4.32 (t, 2 H, J = 7 Hz, butyl 1-H_2), 7.32 (br t, 1 H, J = 8 Hz, 8-H), 7.43 (br d, 1 H, J = 8 Hz, 6-H), 7.56 (br t, 1 H, J = 8 Hz, 7-H), 8.17 (br d, 1 H, J = 8 Hz, 9-H), 8.20 (s, 1 H, 2-H); ^{13}C nmr (DMSO-d_6): 13.7 (C4'), 19.6 (C3'), 29.4 (C2'), 34.6 (N-Me), 40.9 (C1'), 115.3 (C9), 117.4 (C9a), 119.9 (C3a), 122.02 (C8), 122.03 (C9), 128.2 (C7), 136.3 (C5a), 143.4 (C9b), 145.1 (C2), 154.9 (C4); ms: m/z 255 (molecular ion).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 71.05; H, 7.00; N, 16.54.

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* To whom all correspondence should be addressed.

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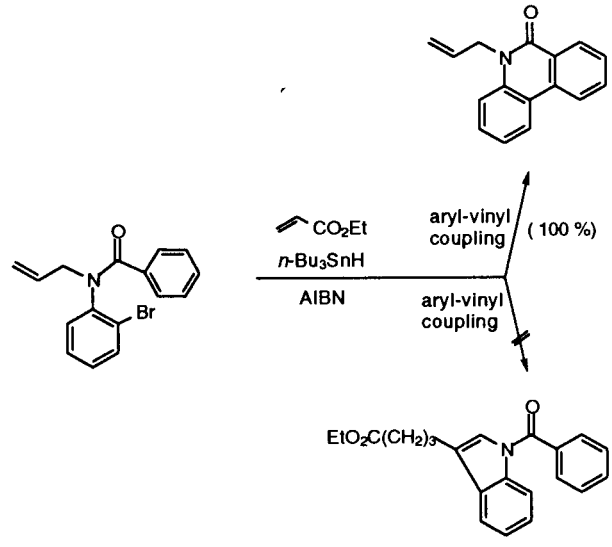

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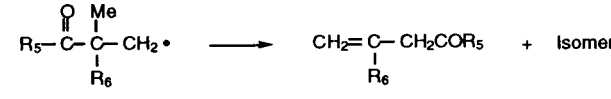

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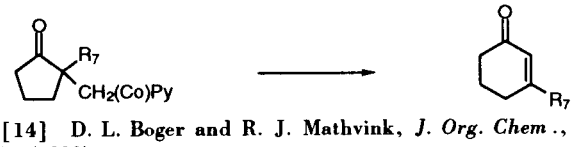

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