SYNTHESIS OF BENZIMIDAZO[2,1-*a*]ISOQUINOLINES AND 5,6-DIHYDROBENZIMIDAZO[2,1-*a*]ISOQUINOLINES

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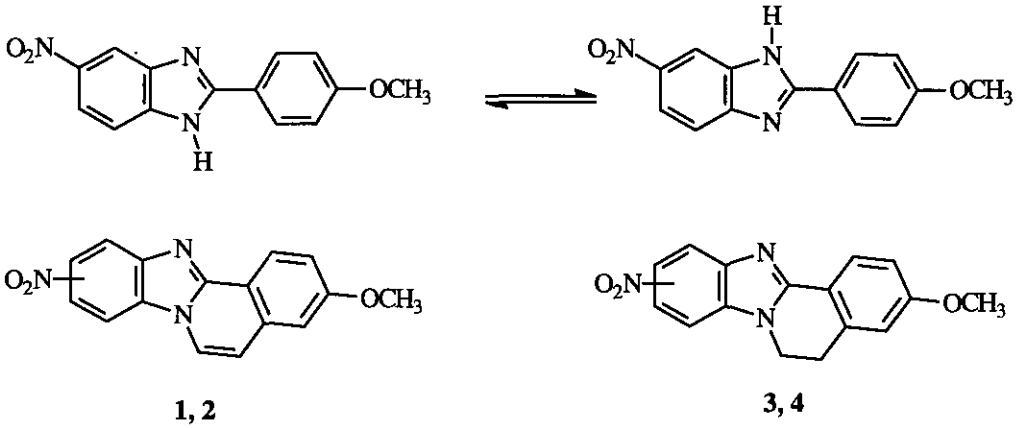
Abstract - The formation of substituted benzimidazo[2,1-*a*]isoquinolines by the palladium-catalyzed intramolecular cyclization of 2-[2-(2-trimethylsilyl-ethynyl)-phenyl]-1*H*-benzimidazole is described. 5,6-Dihydrobenzimidazo[2,1-*a*]isoquinolines were formed directly during the condensation of a 1,2-phenylenediamine with an *o*-vinylbenzaldehyde. These synthetic routes represent useful approaches for the preparation of pharmacologically-active benzimidazo[2,1-*a*]isoquinolines.

There has been intense interest in the identification of novel mammalian topoisomerase I inhibitors in view of their potential use as cancer chemotherapeutic agents.[1-3] Recently it has been reported that 2-aryl-1*H*-benzimidazoles that have substituents attached to their 5-position capable of acting as hydrogen bond acceptors do exhibit activity as topoisomerase I inhibitors.[4] 5-Nitro-2-(4-methoxyphenyl)-1*H*-benzimidazole is among the more active analogs which were evaluated for activity as a topoisomerase I inhibitor. Tautomerization of this benzimidazole makes it indistinguishable from 6-nitro-2-(4-methoxyphenyl)-1*H*-benzimidazole (**Scheme 1**). In order to elucidate the biologically active conformation of this benzimidazole derivative, two groups of structurally restricted analogs, 9-nitro- and 10-nitrobenzimidazo[2,1-*a*]isoquinoline (**1**, **2**) and their 5,6-dihydro derivatives (**3**, **4**) were designed and synthesized as outline in **Scheme 1**.

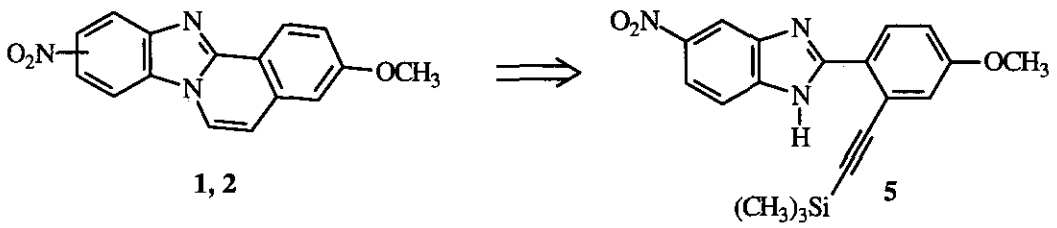
Pd-catalyzed synthesis has been reported to be a useful method for synthesizing heterocyclic compounds.[5-13] Larock *et al.* have reported that coupling iodoanilines with internal acetylenes to give



1, 2 **3, 4**

Scheme 1

2,3-disubstituted indoles using palladium catalysis.[5] Palladium-catalyzed conversion of alkyne derivatives has also been used in the syntheses of hetero-condensed pyrroles,[6] tryptophans,[7] benzofurans,[8,9] benzopyrans,[9] furopyridines,[10] isocoumarins,[9,11] 1,2-dihydroisoquinolines,[9] and nucleoside derivatives.[12,13] However, the application of Pd chemistry to the synthesis of benzimidazo[2,1-*a*]isoquinolines has not been reported previously. Here, we report a procedure to prepare 9-nitro- and 10-nitrobenzimidazo[2,1-*a*]isoquinolines from 2-[2-(2-trimethylsilylethynyl)phenyl]-1*H*-benzimidazole (**5**) by the palladium-catalyzed intramolecular cyclization as shown in the retrosynthetic scheme shown in **Scheme 2**.

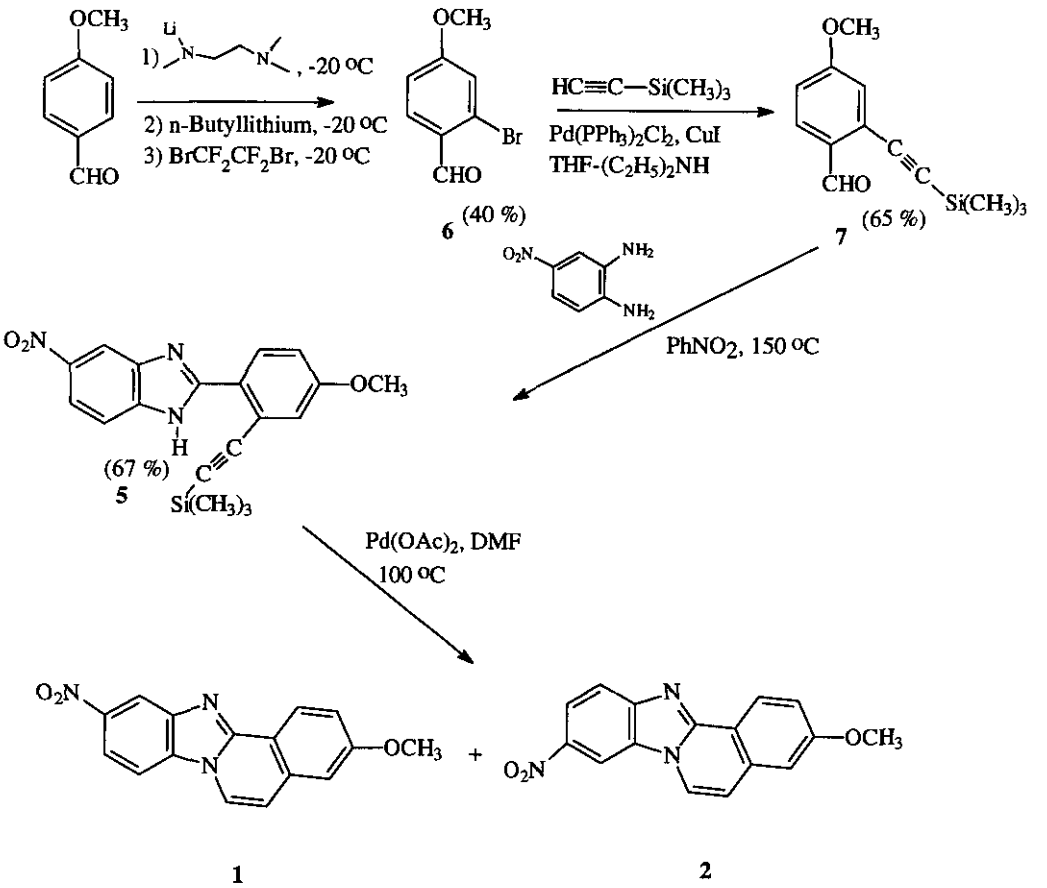


1, 2 **5**

Scheme 2

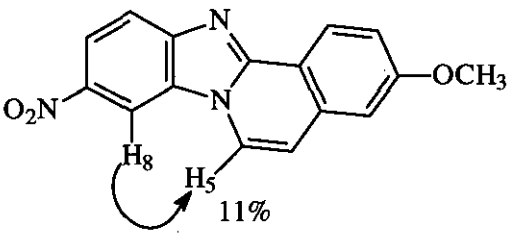
As shown in **Scheme 3**, *ortho*-lithiation of *p*-anisaldehyde followed by quenching with 1,2-dibromotetrafluoroethane provided **6**.[14,15] Palladium-catalysed coupling of this bromo derivative with

trimethylsilylacetylene using CuI as co-catalyst gave **7**.[16] Coupling **7** with 4-nitrophenylenediamine in nitrobenzene at 150 °C provided **5**.[17] A mixture of **5** (195 mg, 0.53 mmol) and palladium acetate (12 mg, 0.053 mmol) in DMF (5 ml) was heated at 100 °C under N_2 overnight to provide a mixture of **1** and **2** in 89% yield in a ratio of 1:2, which was separated by flash column chromatography with silica gel (40-63 μm) using 10-30% ethyl acetate in hexanes.[18]

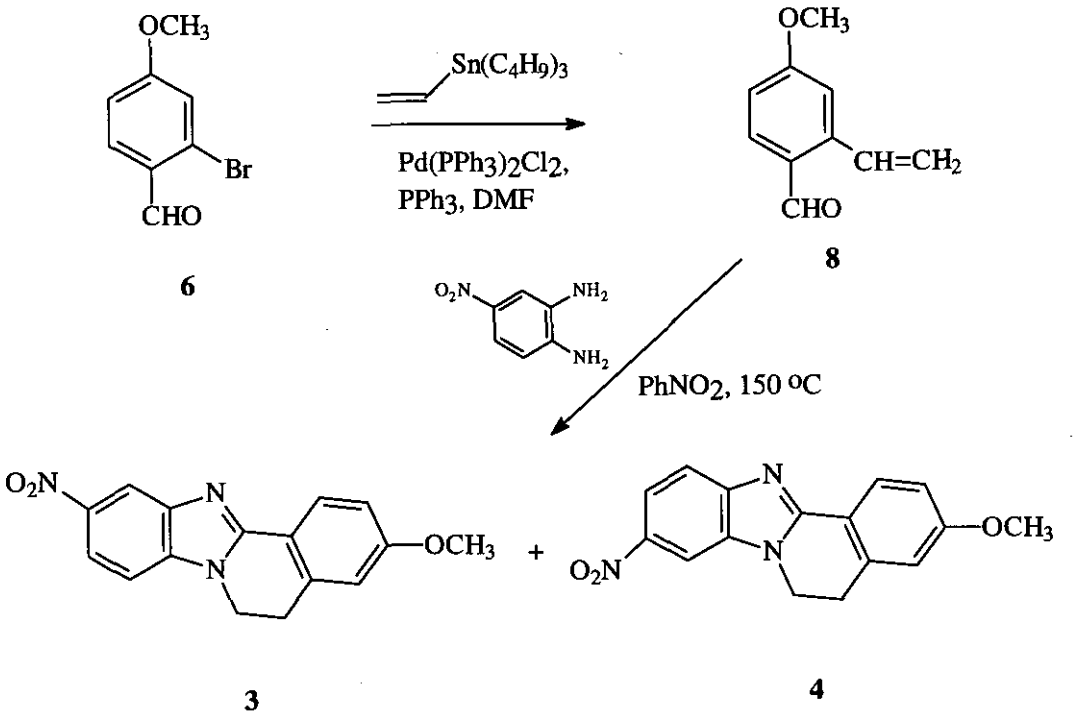


Scheme 3

The structural assignment for the isomer formed in higher quantity was based on ^{1}H nmr spectra.[18] Using NOE, it was evident that only for this isomer, which eluted earlier during chromatography, upon irradiation of H-8 resulted in an enhancement (11%) for the signal for H-5, consistent with its structural assignment as **2**.



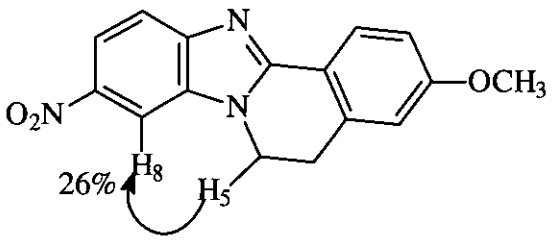
As shown **Scheme 4**, palladium-catalyzed coupling of tributylvinyltin with **6** gave 2-vinyl-*p*-anisaldehyde, **8**, in 97% yield.[19] A mixture of **8** (757 mg, 4.95 mmol) and 4-nitrophenylenediamine (802 mg, 4.95 mmol) in nitrobenzene (20 ml) was heated at 150 °C under N_2 overnight to afford a mixture of **3** and **4**, in 57% yield in a ratio of 1:9.[20] This mixture was separated using flash column chromatography



Scheme 4

using silica gel (40-63 μm) and 10-30% ethyl acetate in hexanes.[20] This reaction presumably occurs through the initial formation of 5(6)-nitro-2-[2-vinyl-4-(methoxyphenyl)]benzimidazole followed by cyclization to the mixture of 9- and 10-nitro-5,6-dihydro-1*H*-benzimidazo[2,1-*a*]isoquinolines. The

increased nucleophilicity of the 6-nitrobenzimidazole tautomer is likely to be responsible for the higher ratio of **4,** which eluted earlier during column chromatography, present in this mixture of products. The structures were consistent with their nmr spectra.[20] The basis for the structural assignment of these isomers was the NOE with the dominant isomer wherein a 26% enhancement was observed for H-8 upon irradiation of H-5, consistent with its structural assignment as **4**.



Similar topoisomerase I inhibition was observed with each pair of isomers (**1** vs. **2**) and (**3** vs. **4**). All four compounds exhibited similar topoisomerase I inhibition as 5-nitro-2-(4-methoxyphenyl)-1*H*-benzimidazole.

ACKNOWLEDGMENT

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18. Physical Data on Compounds (**1** and **2**)

1: mp 265-267 °C (ethyl acetate); ir (KBr): 3091, 2929, 1645, 1519, 1478, 1340, 1269; uv: 270, 295 nm (log ε 4.12, 4.04); ^{1}H nmr (DMSO-d_6) δ 3.97 (3H, s), 7.38-7.44 (2H, m), 7.55 (1H, d, J = 2.5), 8.31 (1H, dd, J = 8.9, 2.1), 8.48 (1H, d, J = 8.9), 8.62 (1H, d, J = 9.0), 8,73 (1H, d, J = 2.0), 8.90 (1H, d, J = 7.3); HRms (EI) calcd for $C_{16}H_{11}N_3O_3$ 293.0800, found 293.0797. Ms: 293.1 (M^+, 100), 247.1 (45), 232.1 (13), 204.1 (15), 177.1 (24).

2: mp > 270 °C; ir (KBr): 3449, 3087, 2921, 1622, 1521, 1475, 1339, 1275, 1227; uv: 210, 270, 385 nm (log ε 4.14, 4.37, 3.92); ^{1}H nmr (DMSO-d_6) δ 3.98 (3H, s), 7.43 (1H, dd, *J* = 8.9, 2.6), 7.45 (1H, d, *J* = 7.3), 7.56 (1H, d, *J* = 2.5), 8.00 (1H, d, *J* = 9.0), 8.37 (1H, dd, *J* = 9.0, 2.3), 8.63 (1H, d, *J* = 8.9), 9.08 (1H, d, *J* = 7.3), 9.37 (1H, d, *J* = 2.1); ^{13}C nmr (DMSO-d_6 + 3 drops CF_3COOH) δ 56.3, 109.2, 110.4, 115.6, 115.8, 120.4, 122.6, 127.2, 128.6, 136.6, 139.1, 143.4, 146.7, 163.6; HRms (EI) calcd for $C_{16}H_{11}N_3O_3$ 293.0800, found 293.0804. Ms: 293.1 (M^+, 100), 263.1 (18), 247.1 (38), 204.1 (15), 192.1 (33), 177 (32).

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20. Physical data on Compounds (**3** and **4**)

3: mp 242-244 °C (ethyl acetate); ir (KBr): 3443, 2926, 1614, 1513, 1473, 1339, 1274; uv: 200, 280, 360 nm (log ε 4.56, 4.27, 4.26); ^{1}H nmr (DMSO-d_6) δ 8.52 (1H, d, *J* = 2.2), 8.19 (1H, dd, *J* = 8.9, 2.2), 8.11 (1H, d, *J* = 8.4), 7.80 (1H, d, *J* = 9.0), 7.09-7.03 (2H, m), 4.49 (2H, t, *J* = 6.8), 3.88 (3H, s), 3.32 (2H, t, *J* = 7.00); ^{13}C nmr (DMSO-d_6) δ 161.9, 152.9, 143.1, 143.0, 139.6, 138.2, 127.6, 118.2, 117.9, 114.7, 113.93, 113.89, 110.6, 55.8, 27.6; HRms (EI) calcd for $C_{16}H_{13}N_3O_3$ 295.0957, found 295.0959. Ms: 295.1 (M^+, 100), 249.1 (35), 85.1 (57), 71.1 (74).

4: mp 259-260 °C (ethyl acetate); ir (KBr): 2952, 2836, 1619, 1510, 1454, 1333, 1263, 1231, 1081; uv: 205, 280, 360 nm (log ε 4.51, 4.19, 4.23); ^{1}H nmr (DMSO-d_6) δ 8.61 (1H, d, *J* = 2.1), 8.13 (1H, dd, *J* = 8.9, 2.3), 8.10 (1H, d, *J* = 8.5), 7.80 (1H, d, *J* = 8.9), 7.10-7.02 (2H, m), 4.53 (2H, t, *J* = 7.0), 3.88 (3H, s), 3.31 (2H, t, *J* = 7.0); ^{13}C nmr (DMSO-d_6) δ 162.0, 154.1, 148.7, 142.3, 138.5, 134.5 127.7, 118.7 118.2, 117.9, 113.94, 113.88, 107.3, 55.8, 27.6; Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.01; H, 4.32; N, 14.31.

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