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Formation of a Carbon-Nitrogen Bond via a 5-Exo-Trig Radical Cyclization onto the Nitrogen of an Imidate Ester

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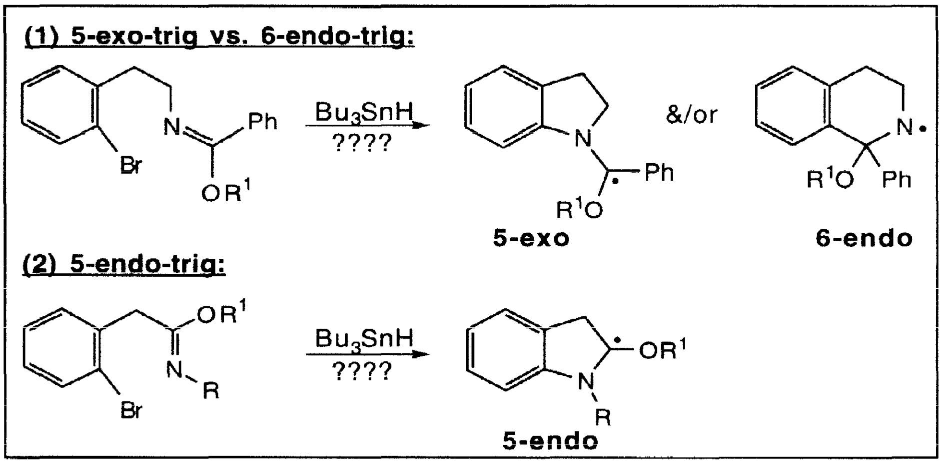
Abstract: Intramolecular addition of an aryl radical to the nitrogen of an imidate ester cyclized in the 5-exo-trig mode to form the C-N bond, with no 6-endo-trig product being detected.

Keywords: *Imidic acid esters; radical cyclization.*

Introduction

We are exploring several different synthetic methods for the preparation of the nitrogen heterocyclic substructures of alkaloids. One method we are investigating is the addition of radicals to the nitrogen end of the C=N in an imidate ester to form a new carbon-nitrogen bond under non-ionic conditions. Radical cyclizations have been shown to be a valuable method in the production of mono-, bi- and tricyclic carbocycles.[3] Nitrogen heterocyclic compounds have also been formed using radical cyclizations with the carbon of oximes[4], nitriles[5] and imines.[6-8] There are only a few reports, however, on the formation of carbon-heteroatom bonds via radical cyclizations to produce either oxygen[9] or nitrogen[7,8,10]

Scheme 1



Dedicated to our colleague and friend Professor Madeleine M. Joullié in celebration of forty years of distinguished teaching and research at the University of Pennsylvania

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heterocycles. At the time this work began, examples of a carbon radical adding to the nitrogen of nitrogen-carbon unsaturation were limited to azo groups[10a] and isonitriles.[10b]

Two possible modes of cyclization need to be considered: (a) the 5-exo-trig vs. the 6-endo-trig, and (b) the "unfavorable" 5-endo-trig (**Scheme 1**).[11] Cyclizing onto an imidate ester would yield a very stable radical[3,12] which could be trapped at the aminal stage, reduced further with an excess of hydride, or oxidized via oxygen or palladium chemistry to the amide.[13] In this paper, we report our initial findings on the first mode of cyclization.

While our work was in progress, several reports of the additions of radicals to C=N double bonds appeared. Warkentin and coworkers cyclized an aryl radical to both the nitrogen and carbon ends of aldimines and ketimines to produce either the 5-exo or 6-endo products, respectively.[7] The 6-endo product was the major product unless the carbon was too sterically hindered for attack by the radical. In that case, the major product was reduction of the bromide. Takano and coworkers saw a similar trend in their cyclizations.[8] Again, 6-endo cyclization to the carbon of the C=N bond predominated unless the carbon was sterically encumbered. These observations are unusual when compared to the all-carbon systems. Cyclization with an alkene prefers the 5-exo mode, unless sterics slow the rate of cyclization enough to make the 6-endo mode competitive.[3] To date, cyclization with an imidate ester remains unreported in the literature.

Results and Discussion

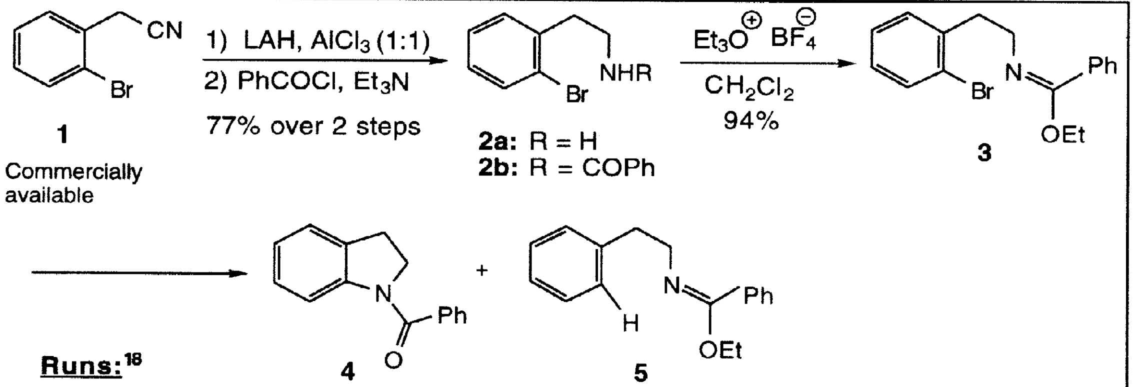
Our radical cyclization studies on the imidate ester system shown in **Scheme 2** has yielded exciting and encouraging results. The benzimidate ester **3** was easily prepared starting with the commerically available 2-bromophenylacetonitrile, **1**. Reduction[14a] of the nitrile to 2-(2-bromophenyl)ethylamine[14b] (**2a**), followed by benzoylation produced the benzamide **2b** in good yield. Subsequent treatment of **2b** with ethyl Meerwein's reagent[15] produced the ethyl benzimidate **3** in excellent yield.

Reaction of the imidate ester **3** with either tributyltin hydride or tris(trimethylsilyl)-silane did indeed form the desired 5-exo product **4** from addition to the nitrogen in 33% and 48% isolated yields, respectively. No 6-endo cyclization product could be detected in the different cyclization reactions via any analytical method used (NMR, GC/MS, chromatography). We initially followed the reactions by NMR and GC/MS, and subsequently increased the scale of the reactions in order to isolate the cyclized product **4**. Correlation of the exact structure of the amide was by independent synthesis of **4** from indoline and benzoyl chloride.[16] The other products isolated from the reactions in **Scheme 2** included reduction product **5**[17], ethyl benzoate (produced by hydrolysis of the imidate ester from either starting material or the reduction product), and starting imidate **3**.[18]

Thus, imidate esters as radical acceptors apparently do not behave the same as aldimines (6-endo-trig) in the addition of an aryl radical to the C=N bond, but behave more like alkenes (5-exo-trig). Formation of the benzamide product **4** and not the expected aminal could arise from trapping of the radical in the cyclized product with oxygen. Alternatively, a tin or silyl radical could abstract the ethyl group in the intermediate aminal radical to form the carbonyl C=O bond.

We have also utilized the iodoaryl derivative in these cyclizations.[19] Preparation of this imidate ester proceeded in lower yield than the bromo derivative presumably due to alkylation of the iodo group with the Meerwein reagent. The cyclization with this iodo derivative yielded results similar to the bromo compound, **3**.

Scheme 2



Runs:[18]	**4**	**5**
1) Bu_3SnH, AIBN PhH, 80 °C	30%	40%
2) $((CH_3)_3Si)_3SiH$, BEt_3, PhH, RT	0%	55%
3) $((CH_3)_3Si)_3SiH$, AIBN, PhH, 78 °C	48%	0%

Warkentin and coworkers proposed that the orbital coefficients of the LUMO of the C=N bond dictated which end of the bond was attacked by the radical.[7a] However, the calculations of these coefficients were performed at a very low level of theory (AM1). We have performed the same calculations on both our imidate ester system and Warkentin's aldimines at the RHF-6-31G* level of theory using the *Spartan*™ program, and found very little difference in the orbital coefficients of the LUMO's in our system relative to his. Therefore, the use of these orbital coefficients in these predictions is not entirely reliable. The complete details of these calculations, along with the calculations of the transition states and intermediate radicals will be published elsewhere.

Thus, the radical cyclization of a carbon radical to the carbon-nitrogen double bond of an imidate ester proceeds by addition to the nitrogen via the 5-exo-trig mode. This result is in contrast to addition to most imine C=N bonds which proceed via a 6-endo trig mode.

Experimental Section

General Methods. All experiments were carried out under an atmosphere of dry argon in oven and/or flame dried glassware. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-300 or a Bruker AM-250 spectrometer using $CDCl_3$ as solvent unless noted otherwise. Chemical shifts are reported in ppm downfield from the internal reference tetramethylsilane. Substances for which combustion analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Infared spectra were taken on a Bruker IFS25 series FTIR spectrometer and are reported in cm^{-1}. GC/MS mass spectra were obtained on a Hewlett Packard model 5970 set at 70 eV. High resolution mass spectra were obtained on a VG 70E_HF double-focusing mass spectrometer. Gas chromatography was performed on a Hewlett Packard model 5890A using a 30 m DB-5 column (0.25 mm i.d., 0.25 mm film thickness), He flowrate 30 cm/sec calibrated at 200°C, (start 50°C hold 5 min, ramp 10°C/min to 300°C, hold until complete). Column chromatography was performed using either Aldrich 22,719-6 silica gel or Acros 18999-0010 activated, basic aluminum oxide. The solvent mixtures used for column chromatography are reported as vol/vol mixtures. R_f values refer to thin layer chromatography on Analtech 2.5 x 10 cm, 250M analytical plates coated with silica gel GF or on Alltech 4 x 8 cm, ALOX (basic alumina) analytical plates. Melting points were taken on a Lab Device Mel-Temp and are uncorrected. CH_2Cl_2 was distilled from CaH_2 under argon. Benzene and diethyl ether were distilled from sodium benzophenone ketyl before use.

Preparation of 2-(2-bromophenyl)ethylamine (2a).[14b] In a dry, 250 mL rbf was placed $LiAlH_4$ (1.89 g, 49.8 mmol) under Ar. The flask was cooled to 0°C, dry ether (50 mL) added slowly, and the mixture stirred for 30 min. A separate 100 mL rbf flushed with Ar was charged with $AlCl_3$ (7.18 g, 53.9 mmol), cooled to 0°C, and dry ether (70 mL) was added slowly. The mixture was stirred until the $AlCl_3$ was dissolved. The $AlCl_3$/ ether solution was transferred to the cooled $LiAlH_4$/ether via cannula under Ar. After 75 min of stirring at 0°C, 2-bromophenylacetonitrile (5.40 mL, 41.6 mmol) in dry ether (5 mL) was added dropwise. After 10 min of stirring at 0 °C, the mixture was allowed to warm to rt and stirring was continued for 2 h. The mixture was recooled to 0°C, conc. aq. ammonia (80 mL) added very slowly, and the mixture stirred overnight. The mixture was filtered, the layers separated, and the aqueous layer was extracted with ether (4 x 40 mL). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo* to yield a yellow oil (9.24 g). Distillation (80-88°C, 2.6 mm Hg) yielded the amine as a colorless oil (7.24 g, 36.2 mmol, 87 %). ^{1}H NMR: 7.46 (d, 1H, J = 8.0 Hz), 7.16 (m, 2H), 7.02-6.96 (m, 1H), 2.92-2.79 (m, 4H), 1.02 (s, 2H). ^{13}C NMR: 139.0, 132.8, 130.7, 127.8, 127.3, 124.5, 42.0, 40.2.

Preparation of *N*-2-(2-bromophenyl)ethylbenzamide (2b). In a dry 25 mL rbf was placed amine **2a** (0.8414 g, 4.205 mmol), Et_3N (1.80 mL, 12.91 mmol), and dry CH_2Cl_2 (20 mL). The mixture was cooled to 0°C, and benzoyl chloride (0.540 mL, 4.65 mmol) was added dropwise with stirring. The mixture was allowed to warm to rt, stirred for 2 h, poured into 10% aqueous HCl (20 mL), the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo* to yield a pink solid (1.561 g). Column chromatography (15% EtOAc/ hex) yielded a clear oil (R_f = 0.45, 40% EtOAc/hex) which solidified upon standing (1.240 g, 4.07 mmol, 97%), mp 93.4-94.2°C (toluene). ^{1}H NMR: 7.71-7.68 (m, 2H), 7.55 (d, 1H, J = 7.8 Hz), 7.50-7.37 (m, 3H), 7.27-7.21 (m, 2H), 7.12-7.06 (m, 1H), 6.18 (bs, 1H), 3.73 (app q, 2H, *J* = 6.7 Hz), 3.09 (t, 2H, *J* = 6.9 Hz). ^{13}C NMR: 167.5, 138.3, 134.5, 133.0, 131.4, 131.1, 128.5, 128.3, 127.7, 126.8, 124.6, 39.9, 35.7. IR (KBr): ν 3269, 3063, 2966, 1636, 1541, 1491, 1382, 757, 709. HRMS calculated for $C_{15}H_{14}BrNO$: 303.025875; found: 303.024704. GC/MS (R_t = 27.4 min): 304 (1), 224 (50), 183 (8), 181 (8), 162 (5), 134 (13), 105 (100), 77 (40), 51 (14).

Preparation of ethyl *N*-2-(2-bromophenyl)ethylbenzimidate (3). In a dry 25 mL rbf was place **2b** (0.110 g, 0.362 mmol) and CH_2Cl_2 (10 mL). The solution was cooled to 0°C, and ethyl Meerwein's reagent[15] (0.55 mL, 1.0 M) was added. The mixture was stirred at 0°C for 4 h, warmed to rt, stirred for 36 h, poured into 10% aqueous $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo* to yield a yellow oil (0.130 g). Column chromatography (10% EtOAc/hex.) using basic alumina yielded a colorless oil (R_f = 0.51, 40% EtOAc/hex), (0.111 g, 0.344 mmol, 95%). ^1H NMR: 7.46 (d, 1H, *J* = 7.8 Hz), 7.40-7.32 (m, 3H), 7.20-7.13 (m, 4H), 7.06-6.99 (m, 1H), 4.24 (q, 2H, *J* = 7.1 Hz), 3.51 (t, 2H, *J* = 7.3 Hz), 2.96 (t, 2H, *J* = 7.3 Hz), 1.32 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR: 161.5, 139.7, 132.7, 131.4, 130.0, 129.2, 128.3, 127.8, 127.7, 127.1, 124.8, 61.2, 51.7, 38.5, 14.5. IR (KBr): ν 3059, 2977, 2900, 1668, 1442, 1030, 750, 700. HRMS calculated for $C_{17}H_{18}BrNO$: 331.0572; found: 331.0596. GC/MS (R_t = 25.4 min): 333 (11), 331 (11), 252 (37), 224 (10), 183 (5), 162 (52), 118 (68), 105 (100), 77 (66), 51 (20).

General Procedures for Radical Cyclization. Method A: A solution of AIBN (6.1 mg, 0.037 mmol) and tributyltin hydride (98.6 μL, 0.348 mol) was prepared in benzene (10 mL), degassed under a stream of Ar for 20 min, and taken up in a 10 mL syringe. In a 50 mL rbf was placed the ethyl benzimidate **3** (100 mg, 0.301 mmol) and benzene (25 mL). The flask was fitted with a reflux condenser and flushed with Ar. After heating to reflux, the AIBN/tributyltin hydride solution was added to the reaction mixture via syringe pump at a rate of 0.6 mL/h . After 18h of reflux, the reaction mixture was cooled to rt, and the solvent removed *in vacuo*. Flash chromatography (100% hexane until high R_f compounds were removed, then 10% EtOAc/hex until finished) yielded *N*-benzoyl-2H,3H-indole, **4**, as an oil (22.2 mg, 0.099 mmol, 33%), R_f = 0.21 (20% EtOAc/Hex). The spectral data were consistent with the literature values.[16] ^1H NMR: 7.55 - 7.00 (m, 9H), 4.12 - 3.95 (m, 2H), 3.10 (t, 2H, *J* = 8.2 Hz). ^{13}C NMR: 168.9, 130.3, 128.5, 127.1, 124.9, 123.9, 50.0, 28.0. IR (KBr): ν 3062, 2988, 1636, 1595, 1482, 1404, 757, 700. GC/MS (R_t = 27.0 min.): 224 (52), 184 (12), 171 (6), 134 (17), 105 (100), 77 (50), 51 (17).

Also isolated was the reduced product ethyl *N*-(2-phenylethyl)benzimidate, **5**, (16.7 mg, 0.069 mmol, 23%); R_f = 0.60 (20% EtOAc/Hex). ^1H NMR: 7.27 (dd, 2H, *J* = 5.7, 1.5 Hz), 7.18-7.01 (m, 8H), 4.16 (q, 2H, *J* = 7.1 Hz), 3.42 (t, 2H, *J* = 7.3 Hz), 2.76 (t, 2H, *J* = 7.3 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR: 161.1, 140.3, 132.8, 129.6, 129.1, 129.0, 128.2, 127.8, 125.9, 61.2, 51.7, 38.5, 14.5. IR (neat): ν 3060, 2976, 2900, 1667, 750, 699. HRMS calculated for $C_{17}H_{19}NO$: 253.1467; found: 253.1475. GC/MS (R_t = 27.6 min): 253 (4), 252 (8), 224 (3), 208 (6), 162 (58), 118 (74), 105 (100), 91 (17), 77 (54), 51 (14).

Method B: In a 100 mL rbf was placed the ethyl benzimidate **3** (77.8 mg, 0.24 mmol) and benzene (50 mL). The flask was then fitted with a drying tube packed with Drierite and stirred under an atmosphere of dry air. To this mixture was added triethylborane (0.30 mL, 1.0 M in hexanes) followed by tris-(trimethylsilyl)silane (0.12 mL, 0.38 mmol). The mixture was stirred at rt for 16 h, and the reaction followed by GC/MS. See **Scheme 2** for the ratio of the products isolated.

Method C: A flame-dried 100 mL rbf under Ar was charged with ethyl benzimidate **3** (0.052 g, 0.156 mmol), tris(trimethylsilyl)silane (0.090 mL, 0.29 mmol), and benzene (50 mL). The solution was brought to reflux as a solution of AIBN (10.1 mg, 0.062 mmol) in benzene (10 mL) was added via syringe pump at a rate of 0.58 mL/hr. After the addition was complete, the solution was allowed to reflux for an additional hour. The solvent was removed *in vacuo* to yield **4** as a yellow oil (0.102 g). Column chromatography (100% Hex to 20% EtOAc/Hex) yielded a colorless oil (R_f = 0.21 20% EtOAc/Hex), which solidified upon standing (0.0189 g, 0.085 mmol, 48%), mp 99.5-100.6°C (toluene).[16]

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References and Notes

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