The Thermal Instability of 2,4 and 2,6-*N*-Alkylamino-disubstituted and 2-*N*-Alkylamino-substituted Nitrobenzenes in Weakly Alkaline Solution: *sec*-Amino Effect

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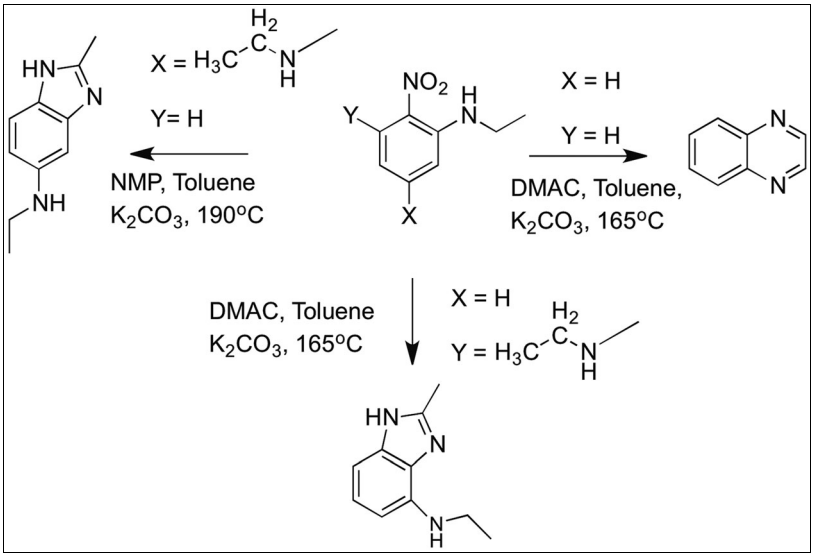

We report herein the preparation of two families of secondary amines by the reactions of two equivalents of monoamines with either 2,4 or 2,6-difluoronitrobenzenes in *N*,*N*-dimethylacetamide in the presence of anhydrous potassium carbonate, as precursors of biologically important nitric oxide donating *N*-nitrosamines. In both instances, these compounds could be prepared in quantitative yield when the reaction temperature was held below 130°C. Above this reaction temperature, an unexpected cyclization reaction between the nitro and newly formed adjacent secondary amine group leads to the formation of benzimidazole or quinoxaline rings in low yields. Reasonable reaction mechanisms for the cyclization reaction are proposed.

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INTRODUCTION

Nitric oxide (NO), a small diatomic gaseous molecule, produced *in vivo*, plays a critical role in cell signaling [1]. We have reported the preparation of a variety of low and high molecular weight exogenous NO donors, *N*-nitrosoamines, and their effects on the proliferations of human aortic smooth muscle cells. These *N*-alkyl-*N*-aryl nitrosamines release NO in a slow and sustained manner. This NO release pattern is in contrast to the commercially available NO donors, which release NO in a single burst of high concentration. Furthermore, the synthesized NO donors exhibit longer half-lives ranging from 60 to 140 h, significantly longer than the commercial materials [2–5]. In the course of our investigations, we were successful in preparing low molecular weight secondary amines as precursors to *N*-nitrosoamines, by the reactions of 2,4 and 2,6-difluoronitrobenzenes (2,4-DFNB and 2,6-DFNB) with homologous aliphatic primary amines (from n-hexyl to n-decyl amines) [5]. The low molecular weight secondary amines were prepared in *N*,*N*-dimethylacetamide (DMAc) at 120°C in the presence of anhydrous potassium carbonate. Any one of these reactions at reaction temperatures above 130°C failed to yield the desired products in high yield. Analysis of the reaction mixture by TLC and GC–MS showed the presence of the desired product, and numerous other compounds along with one major component. The presence of the disubstituted secondary amine in the complex reaction mixture indicated the following: the secondary amine forms at a lower temperature and then decomposes at elevated temperatures. In addition, the molecular weight of each major side product was 34 Da less than its corresponding starting material, indicative of the loss of a molecule of hydrogen peroxide.

In order to understand the possible origin of these side products, lower molecular weight secondary amines, *N*,*N*′-diethyl-4-nitrobenzene-1,3-diamine (**1**) and *N*,*N*′-diethyl-2-nitrobenzene-1,3-diamine (**2**), were prepared under carefully controlled reaction conditions, by the reactions of each of the two dihalides, 2,4-DFNB and 2,6-DFNB, *via* nucleophilic substitution with ethylamine, respectively (Scheme 1). In this report, we propose a possible reaction pathway leading to the formation of the unexpected products *via* the formation of a nitrene intermediate, based upon the structural elucidation of the major isolable side product.

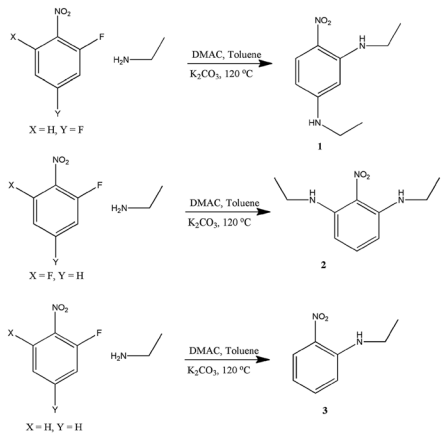
RESULTS AND DISCUSSIONS

In order to identify unambiguously the major component formed at elevated temperature, (**1**) and (**2**) were dissolved in *N*-methylpyrrolidinone (NMP) and DMAC, respectively. These solutions were heated with potassium carbonate and toluene to simulate the reaction conditions used for the formation of the secondary amines (Scheme 2). The major component from each of these two reactions, 5-*N*-ethylamino-2-methyl-1*H*-benzimidazole (**4**) and 4-*N*-ethylamino-2-methyl-1*H*-benzimidazole (**5**), were isolated and identified. As expected, the molecular weights of these cyclized species were 34 Daltons less than the respective starting materials. Furthermore, the mass spectral analyses of the starting materials, (**1**) and (**2**), revealed the formation of fragments ($(M–H_3O_2)^{+\cdot}$); *m*/*z* values 35 units less than the *m*/*z* of the molecular ions. It is important to point out that in the absence of anhydrous potassium carbonate compounds (**1**) and (**2**) remained unaffected.

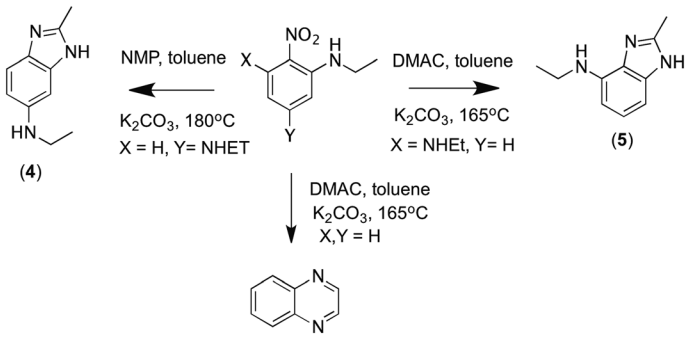
From an examination of Scheme 2, there appears to be a reaction between the secondary amino group (ortho to the nitro group) and the adjacent methylene unit reacts with the nitro group. This results in the formation of an imidazole ring with the concurrent loss of hydrogen peroxide, as the major side product in addition to a series of other compounds, which were not identified. To the best of our knowledge, this is the first instance where such a reaction has been observed. It is important to point out that this cyclization reaction is somewhat similar to the cyclization observed in the case of nitrobenzenes with ortho-substituted tertiary *N*-alkylamine moieties. This known cyclization reaction, called "*tert*-Amino Effect", was reported as far back as 1895 by Pinnow [6,6b),6c),6d),6e),6f),7–9], and served as an influence to name the observed cyclization (Scheme 2), the "*sec*-Amino Effect". Essentially all reactions falling under *tert*-amino-effect, proceed through ionic intermediates. For example, 2-nitrophenyl sarcosine is transformed to *N*-hydroxyquinoxaline-2-3-dione in aqueous alkaline medium [6e]. *N*,*N*-Dialkyl-2-nitroanilines cyclize thermally to form 1,2-disubstituted benzimidazoles or their *N*-oxides depending on the reaction conditions [7]. Formation of the cyclized products were observed during mass spectral analyses of these *N*,*N*-dialkyl-2-nitroanilines [6f].

The IR, ^{1}H-NMR and the ^{13}C-NMR spectra of (**5**) are displayed in Figure 1a, b, and c, respectively. The X-ray diffraction data of (**5**) has been reported earlier [10]. From an examination of the IR spectrum (Fig. 1a), the broad band centered around 3366 cm^{-1} illustrates the acidic nature of the hydrogen atom attached to one of the nitrogen atoms located in the ring of (**5**) and is confirmed further by the absence of an absorbance due to this hydrogen atom in the ^{1}H-NMR [11]. The absorbances due to the various

Scheme 1. Preparation of (**1**)–(**3**).



Scheme 2. Thermal cyclization of (**1**)–(**3**).



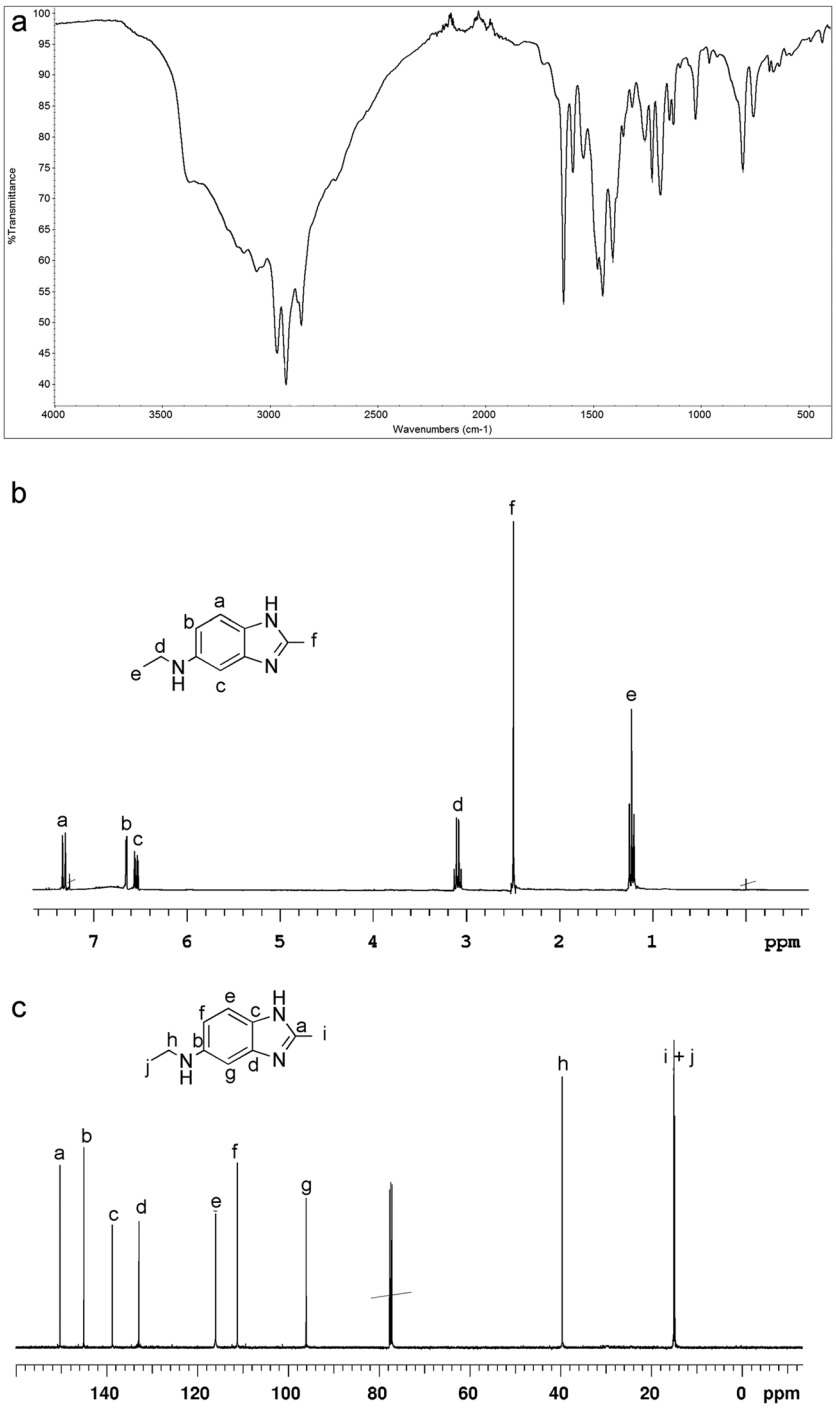
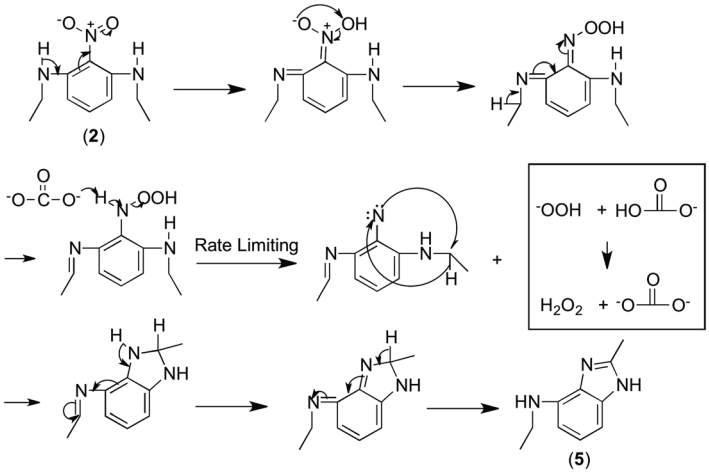


Figure 1. (a) IR (neat) spectrum of (**5**). (b) ^{1}H-NMR ($CDCl_3$) spectrum of (**5**). (c) ^{13}C-NMR (CDCl3) spectrum of (**5**).

carbon atoms in the ^{13}C spectrum are consistent with the calculated values from chemical shifts contributions [12].

As mentioned in the experimental section, the benzimidazoles derived from (**1**) and (**2**) were the only compounds that could be isolated from the myriad of other products. This suggests the formation of a reactive intermediate with the ability to produce a variety of products. It is well known that aromatic nitro groups can be converted to nitrenes either thermally [13,14] or in the presence of catalysts including triethyl phosphite and tributyl phosphine [14–16]. Proposed in the succeeding text is a possible reaction pathway (Scheme 3) for the cyclization reactions of (**1**) and (**2**) (pathway for (**2**) is shown) involving a nitrene intermediate with the concurrent loss of a molecule of

Scheme 3. Proposed reaction pathway for the formation of benzimidazole derivative.



hydrogen peroxide. The nitrene intermediate forms by the intra-molecular reaction between the nitro group and the *N*-ethylamino moiety in either ortho or para orientation. This reactive nitrene group then inserts into the C–H bond of the methylene unit α to the remaining ortho ethylamine group to form a five-membered ring [17]. Nitrenes are known to insert into a secondary α-ethereal C–H bond as well, akin to what is observed in the present instance [18]. The stability of the nitrene intermediate is enhanced by the presence of a secondary amine group in para and ortho orientations for (**1**) and (**2**), respectively. The positioning of substituents in (**2**) enhances the probability of ring closure leading to the formation of (**5**) at 160°C and (**4**) at 180°C.

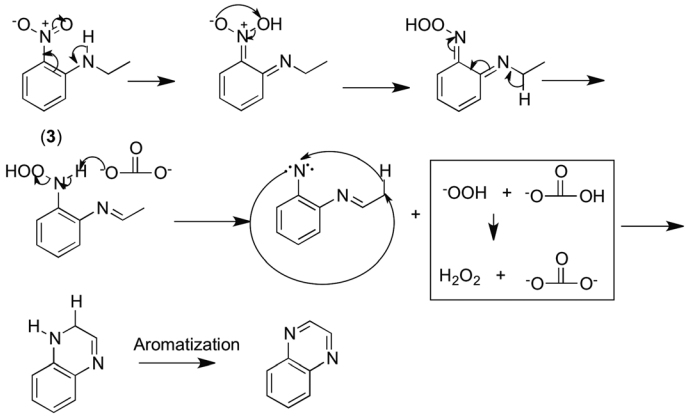
An examination of Scheme 3 indicates the proposed involvement of two *N*-ethylamino substituents. Therefore, the question arises as to how the cyclization reaction would progress in the presence of only one *N*-ethylamino substituent. In order to address this issue, 2-nitro-*N*-ethylaniline, (**3**), was prepared from the reactions of ethylamine and 2-fluoronitrobenzene (Scheme 1) and was subjected to the thermal cyclization reaction conditions (Scheme 2). The ^{1}H-NMR of the cyclized product, quinoxaline, obtained from (**3**) in approximately 5% yield (after column chromatographic separation), was identical to that of the ^{1}H-NMR spectrum of commercially available material. The progress of this reaction was monitored by GC–MS analyses, which indicated the concomitant formation of a species with molecular weight 2 amu higher than that of quinoxaline in addition to residual starting material and a host of other products. The higher molecular weight species co-eluted with the starting material when hexane was used as the eluent during chromatographic separation. We speculate this compound to be 1,4-dihydro-2*H*-quinoxaline, the precursor to quinoxaline formation. These observations suggest that the nitrene intermediate (formed after the loss of hydrogen peroxide) inserts into a C–H bond of the methyl group α to the –N═CH– moiety (Scheme 4) to form 1,4-dihydro-2*H*-quinoxaline, which subsequently aromatizes to quinoxaline. The lack of formation of quinoxaline during the cyclization reactions of (**1**) and (**2**) can be explained by a significantly lower heat of formation of benzimidazoles, 83.1 kJ/mole [19] compared with that of quinoxaline, 240.3 kJ/mole [20]. These observations lend further credence to the proposed electron deficient nitrene intermediate for the cyclization reactions. We are presently investigating the possible inhibitory effects of electron withdrawing substituents including nitro and nitrile groups on the cyclization reactions of 2-nitro-*N*-ethylaniline in different orientations with respect to the nitro group. Theoretical quantum mechanical modeling studies in support of the proposed mechanism involving a nitrene intermediate will be reported elsewhere.

In summary, we have identified a possible reaction pathway through which 2,4 and 2,6-di-*N*-alkylamino as well as 2-*N*-alkylamino substituted nitrobenzenes decompose at elevated reaction temperatures in a weakly basic dipolar aprotic solvent medium. The formation of a nitrene intermediate is proposed for compounds with *N*-alkylamino substituent(s) containing at least two carbon atoms.

EXPERIMENTAL

General. Dimethylacetamide, NMP (Aldrich), and toluene (Fisher) were dried over calcium hydride and distilled at reduced pressure. All other reagents were used as received. NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer and a Varian INOVA 500 MHz spectrometer with $CDCl_3$ (7.26 ppm for ^{1}H-NMR), $CDCl_3$ (77.0 ppm for ^{13}C-NMR). TMS was used as the internal standard for these measurements. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). Standard abbreviations for NMR spectra are: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. IR

Scheme 4. Proposed reaction pathway for the formation of quinoxaline from 2-nitro-*N*-ethylaniline.



spectra were recorded on a Nicolet 20DXB FTIR spectrometer, covering the range of 500–4000 cm^{-1}. IR samples were prepared by depositing a thin film of sample on a sodium chloride plate. Mass spectra were obtained using a Waters GCT Premier 7890 GC–MS with an ionization potential of 70 eV. All mass spectral data is reported in Daltons.

Syntheses of *N,N′*-diethyl-4-nitrobenzene-1,3-diamine (1) and *N,N′*-diethyl-2-nitrobenzene-1,3-diamine (2). Anhydrous potassium carbonate (5.09 g, 0.036 mol) and a solution of ethylamine (11.34 g, 0.253 mol; 70% in water) in DMAc (8 mL) were combined in a 100 mL three-necked round-bottom flask fitted with a nitrogen inlet, thermometer, magnetic stirring bar, and a Dean-Stark trap fitted with a condenser. To the stirring solution, 2,4-difluoronitrobenzene (2.35 g, 0.0148 mol) in DMAc (5 mL) was added. Additional DMAc (8 mL) was used to wash the transfer container and this was added to the reaction mixture, followed by toluene (20 mL). The color of the reaction mixture turned orange within a minute. The reaction was allowed to stir at room temperature for 4 h, while the temperature of the reaction mixture was gradually increased to 120°C over a 2-h span. Water, the by-product of the reaction, was removed *via* azeotropic distillation with toluene. On completion of the reaction, the reaction mixture was allowed to cool to room temperature and diluted with dichloromethane (30 mL). The reaction mixture was then filtered through celite under reduced pressure to remove remaining potassium carbonate. The filtrate was then transferred to a rotary evaporator to remove dichloromethane. The residual DMAc was then removed by short path distillation, at reduced pressure and at a temperature below 100°C using a hot oil bath as the heat source. The red crude product was dissolved in dichloromethane (30 mL), transferred to a separatory funnel and washed repeatedly with deionized water. The organic layer was collected, dried over anhydrous magnesium sulfate, filtered, and the filtrate was evaporated using a rotary evaporator to yield a bright yellow solid, (**1**): Yield: 2.17 g, 70%; mp 108–110°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.4 (br s, 1H), 8.0 (d, J = 9.60 Hz, 1H), 5.9 (dd, J_1 = 9.60 Hz, J_2 = 2.40 Hz, 1H), 5.6 (d, J = 2.18 Hz, 1H), 4.4 (br s, 1H), 3.3 (two overlapping q, 4H), 1.34 (t, J = 7.20 Hz, 3H), 1.28 (t, J = 7.20 Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 200.59, 154.52, 148.70, 129.47, 104.90, 90.10, 38.10, 37.76, 14.61, 14.42 ppm. IR (NaCl, $v > 1400\ cm^{-1}$): v = 3340, 3307, 2973, 1623,1551, 1460 cm^{-1}. HRMS *m/z* Calcd for $C_{10}H_{15}N_3O_2$ 209.1161, found 209.1176 (TOF MS EI), 174.1033 (98%).

The synthesis of the isomeric form, *N,N*'-diethyl-2-nitrobenzene-1,3-diamine, (**2**), was conducted in a similar manner. Crystals suitable for X-ray diffraction were obtained by recrystallization from ethanol/dichloromethane, (**2**): Yield: 2.01 g, 65%; mp 63–65°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.6 (br s, 2H), 7.1 (t, J = 8.7 Hz, 1H), 5.9 (d, J = 9.60 Hz, 2H), 3.2 (q, J = 8.40, 4H), 1.3 (t, J = 7.20 Hz, 6H), ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): 148.51, 137.06, 121.01, 98.01, 38.34,14.42 ppm. IR (NaCl, v 1400 cm^{-1}): v = 3347, 2980, 2860, 1582, 1515,1472 cm^{-1}. HRMS *m/z* Calcd for $C_{10}H_{15}N_3O_2$ 209.1161, found 209.1165 (TOF MS EI), 174.1032 (100%).

Synthesis of 2-nitro-*N*-ethylaniline (3). The reaction vessel consisted of a 100 mL, three-necked round-bottomed flask fitted with thermometer, a magnetic stirrer, and Dean-Stark apparatus fitted with a condenser. The reaction vessel was charged with 2-fluoronitrobenzene (0.94 g, 0.0066 mol), 70% aqueous solution of ethylamine (3 mL, excess), anhydrous potassium carbonate (3.53 g, excess), DMAc (10 mL), and toluene (10 mL). The reaction vessel was heated with an external oil bath, and the reaction was allowed to continue under reflux for 1 h. An additional 2 mL of ethylamine solution was added and the reaction was allowed to continue for an additional 1.5 h. Water was continuously removed *via* the Dean-Stark apparatus. At the completion of the reaction, the reaction mixture was diluted with dichloromethane (20 mL) and filtered. Dichloromethane, residual ethylamine, and toluene were removed from the filtrate using a rotary evaporator at reduced pressure. The residue was subjected to high vacuum distillation to remove DMAc. The residue was dissolved in dichloromethane, washed with water twice, and the organic layer was dried over anhydrous magnesium sulfate. Dichloromethane was removed from the filtrate using a rotary evaporator. The residue was distilled using high vacuum to obtain the pure desired compound (**3**). Yield: 0.80 g, 73%; bp 125–127°C/0.9 mmHg. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.2 (dd, J_1 = 8.70 Hz, J_2 = 1.50 Hz, 1H); 8.0 (br s, 1H); 7.4(m, 1H) 6.8 (dd, J_1 = 8.70 Hz, J_2 = 1.20 Hz, 1H); 6.6 (m, 1H); 3.4 (dq, J_1 = 5.45 Hz, J_2 = 9.21 Hz, 2H); 1.4 (t, J = 8.40 Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.57; 37.87; 113.99; 115.30; 127.01, 131.72, 136.45, 145.70 ppm. IR (NaCl, $v > 1400\ cm^{-1}$): v = 3382; 2974; 2873; 1617; 1573; 1441 cm^{-1}. HRMS *m/z* Calcd for $C_8H_{10}N_2O_2$ 166.0730, found 166.0732 (TOF MS EI), 151.0494 (100).

5-*N*-ethylamino-2-methyl-1*H*-benzimidazole (4). A three-necked, 50 mL, round-bottomed flask containing a magnetic stir bar and fitted with a nitrogen inlet, a thermometer and a condenser was used as the reaction vessel. The reaction vessel was charged with anhydrous potassium carbonate (0.65 g, 0.0046 mol). (**1**) (0.66 g, 0.003 mol), was weighed into a one-dram glass vial, dissolved in NMP (5 mL) and then transferred to the reaction vessel. The vial was subsequently washed with 12 mL of NMP, which was then added to the reaction vessel to ensure complete transfer. The reaction mixture was stirred, while the vessel was heated using an external temperature-controlled oil bath. The reaction was allowed to continue at 180°C for 14 h. Upon the extraction process, (**4**) was found in the aqueous layer. The aqueous layer was filtered through a celite bed to remove all solids, and the filtrate was cooled in a dry-ice/acetone bath and was then lyophilized for 48 hours using a Labconco Freeze Dry System. The crude residue was dissolved in methanol, mixed with silica gel (60–100 mesh), and then dried to remove methanol. The desired compound, 5-ethylamino-2-methyl-1*H*-benzimidazole was eluted with ethanol/ethyl acetate (10/90 v/v) on a silica gel column. GC–MS analysis indicated a pure product. However, in spite of repeated attempts, we were unable to recrystallize this compound to obtain crystals of sufficient quality for X-ray diffraction studies. (**4**), Yield: 0.8 g, ~15%. mp 122–124°C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.3$ (d, $J = 8.40$ Hz, 1H), 6.7 (d, $J = 2.40$ Hz, 1H), 6.5 (dd, $J_1 = 8.10$ Hz, $J_2 = 2.40$ Hz, 1H), 3.1 (q, $J = 8.10$ Hz 2H), 2.5 (s, 3H), 1.2 (t, $J = 8.70$ Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 150.29$, 145.05, 138.76, 132.95, 116.03, 111.21, 96.05, 39.67, 15.08, 14.84 ppm. IR (NaCl, $\nu > 1400\,cm^{-1}$): $\nu = 3349$, 3199, 2969, 1637, 1593, 1456, 1408 cm^{-1}. HRMS *m/z* Calcd for $C_{10}H_{13}N_3$ 175.1107, found 175.1101 (TOF MS EI), 160.0867 (100).

4-*N*-ethylamino-2-methyl-1*H*-benzimidazole (5). The cyclization reaction was carried out similar to that of compound (**1**). DMAc, instead of NMP was used as the solvent in the presence of anhydrous potassium carbonate. The dark-red reaction mixture was stirred, while the vessel was heated using an external temperature-controlled oil bath. The reaction was allowed to continue at 160°C for 24 h. During this period, multiple aliquots were withdrawn from the reaction mixture at increasing time intervals to monitor the progress of the reaction using GC–MS analyses. Upon the conclusion of the reaction, the reaction mixture turned black and opaque. The external heating source was removed and the reaction was allowed to cool to room temperature. The reaction mixture was diluted with dichloromethane (30 mL) and filtered through a celite bed to remove potassium carbonate and other residual solids. The filtrate was distilled at reduced pressure to remove all solvents. The crude product mixture was dissolved in a minimal amount of dichloromethane and transferred to a separatory funnel, and washed three times with deionized water. The organic layer was collected, dried over magnesium sulfate, and filtered. The filtrate was evaporated using a rotary evaporator at reduced pressure to yield a sticky dark brown solid. 4-Ethylamino-2-methyl-1*H*-benzimidazole, (**5**), the major component of the mixture, was identified by GC–MS and isolated using an alumina column with dichloromethane and ethyl acetate (70:30 v/v) as the eluent. The solution was evaporated at reduced pressure and the blue-green solid residue was recrystallized using dichloromethane. (**5**), Yield: 0.5 g, 10%. mp 63–65°C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.1$ (t, $J = 9.00$ Hz, 1H), 6.7 (dd, $J_1 = 10.50$ Hz, $J_2 = 1.50$ Hz, 1H), 6.3 (d, $J = 7.50$ Hz, 1H), 3.3 (q, $J = 6.90$ Hz, 2H), 2.6 (s, 3H), 1.3 (t, $J = 7.50$ Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 148.81$, 139.63, 134.31, 131.14, 124.11, 101.88, 100.53, 38.56, 15.06 ppm. IR (NaCl, $\nu > 1400\,cm^{-1}$): $\nu = 3366$, 2961, 1607, 1540, 1422 cm^{-1}. HRMS *m/z* Calcd for $C_{10}H_{13}N_3$ 175.1107, found 175.1108 (TOF MS EI), 160.0879 (100).

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