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N-Vinylation of Imidazole and Benzimidazole with a Paramagnetic Vinyl Bromide

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Abstract: An *N*-vinylation of imidazole and benzimidazole with a paramagnetic vinyl bromide was investigated. Among the tested procedures, Pd-catalyzed reaction was the most powerful one. The *N*-vinylation of 2-aminobenzimidazole with a β-bromo-α,β-unsaturated pyrroline nitroxide aldehyde offered 1,1,3,3-tetramethyl-1*H*-benzimidazo[1,2-*a*]pyrrolo[3,4-*e*]pyrimidin-2(3*H*)-yloxyl radical and the corresponding non-cyclized Schiff base. The reaction of a β-bromo-α,β-unsaturated pyrroline nitroxide aldehyde with imidazole gave β-imidazo-α,β-unsaturated pyrroline nitroxide aldehyde, which was reduced to the alcohol and converted to an unstable allyl chloride.

Keywords: imidazole; benzimidazole; nitroxide; cross coupling reactions

1. Introduction

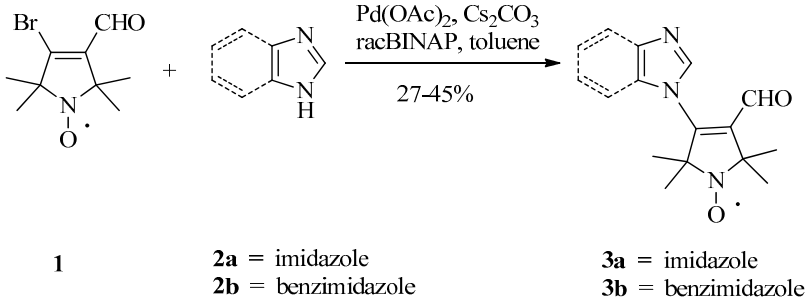
Nitroxides belong to a group of stable organic radicals, containing the nitroxyl group as a part of aliphatic, aromatic, bicyclic, or heterocyclic scaffolds. The most commonly used nitroxides are piperidine, pyrrolidine, pyrroline, isoindoline, oxazolidine, imidazoline, and imidazolidine nitroxides with a broad range of applications. They are used as co-oxidants in organic chemistry [1], spin labels on biomolecules [2], as antioxidants and antiproliferative drugs [3,4], mediators of polymerization [5], redox active materials in batteries [6], sensor molecules [7], and as magnetic imaging (MRI) [8] and electron paramagnetic imaging (EPRI) [9] contrast agents, just to name a few examples.

To fulfill these various requirements, a broad range of different nitroxides with miscellaneous substitution patterns need to be prepared, sometimes by using complex synthetic procedures. In the last two decades, transition-metal-catalyzed cross-coupling reactions have proven to be a powerful tool in modifications of vinyl or aryl halide derived stable nitroxide free radicals [10–12] including Heck-, Sonogashira-, and Suzuki-type cross-coupling reactions. In our laboratory, we used these reactions to introduce new substituents onto the pyrroline or tetrahydropyridine ring and to construct nitroxide-condensed heterocycles as well [13,14]. Very recently, we have reported Buchwald-Hartwig amidation procedures for nitroxide-condensed lactam and pyrimidine ring constructions [15] starting from β-bromo-α,β-unsaturated pyrroline nitroxide aldehyde. In this paper, we report the extension of the Buchwald-Hartwig cross-coupling for the *N*-vinylation of imidazoles and benzimidazoles with paramagnetic vinyl bromides.

2. Results and Discussion

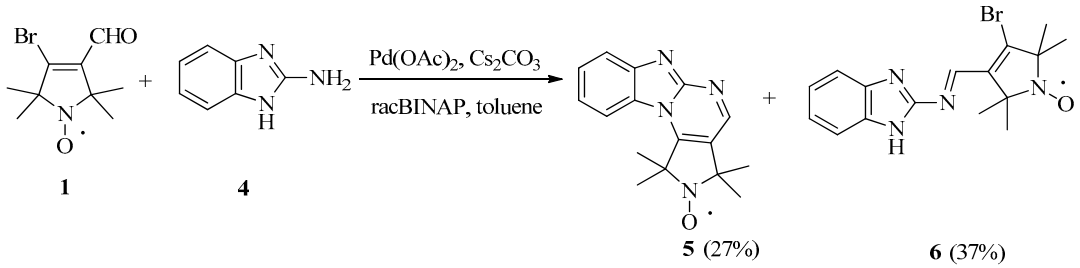
Treatment of compound **1** [16] with imidazole (**2a**) or benzimidazole (**2b**) (1.0 equiv.) in the presence of Cs_2CO_3 (1.2 equiv.), $Pd(OAc)_2$ (3 mol %), and racemate 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

(racBINAP) (4 mol %) in anhyd. toluene at reflux temperature [17] yielded compound **3a** in 45% yield and compound **3b** in 27% yield, respectively (Scheme 1). We note that our optimization attempts, based on reports from Mao [18] and Ho [19], to utilize CuI catalysis or microwave assisted synthesis have furnished, at best, only trace amounts of the desired products.



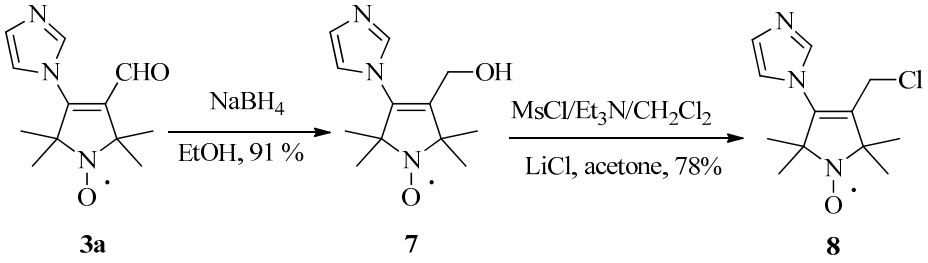
Scheme 1. Cross-coupling reaction of β-bromo-α,β-unsaturated pyrroline nitroxide aldehyde with imidazole and benzimidazole.

In order to explore the scope of the coupling reactions, *N*-vinylation of 2-aminobenzimidazole **4** with compound **1** was conducted under Pd-catalyzed conditions, as mentioned above, yielding the desired polycondensed heterocyle **5** in 27% yield and Schiff base **6** in 37% yield as a by-product (Scheme 2). The formation of Schiff base was revealed by mass spectrometry measurements, which showed molecular ion peaks at 361/363 with 1/1 intensity.



Scheme 2. Cross-coupling reaction of 2-aminobenzimidazole with β-bromo-α,β-unsaturated pyrroline nitroxide.

To achieve reactive spin label compounds [20,21] aldehyde, **3a** was reduced with $NaBH_4$ in EtOH at 0 °C to give alcohol **7,** which was converted to allylic chloride **8** via mesylate by nucleophilic substitution with LiCl in acetone (Scheme 3). However, this compound proved to be unstable, as decomposition products appeared after several days despite low temperature (−18 °C) storage. The freshly prepared chloromethyl compound **8** can be applied for irreversible SH specific labeling of proteins.



Scheme 3. Synthesis of 3-chloromethyl-4-imidazol-1-yl-pyrroline nitroxide compound.

3. Materials and Methods

Melting points were determined with a Boetius micro-melting point apparatus (Franz Küstner Nachf. K. G., Dresden, Germany) and were uncorrected. Elemental analyses (C, H, N, and S) were performed with a Fisons EA 1110 CHNS elemental analyzer (Fisons Instruments, Milan, Italy). Mass spectra were recorded on an Automass Multi spectrometer (ThermoQuest, CE, Instruments, Milan, Italy) in EI mode. NMR spectra were recorded on a Bruker Avance III Ascend 500 spectrometer (Bruker BioSpin Corp., Karsluhe, Germany); chemical shifts are referenced to TMS. The paramagnetic compound was reduced to *N*-hydroxylamine with five equivalents of hydrazobenzene (DPPH)/radical. Measurements were performed at a probe temperature of 298 K in $CDCl_3$ or DMSO-d_6 solution. ESR spectra were recorded on a Miniscope MS 200 (Magnettech Gmbh., Berlin, Germany) in $CHCl_3$ solution. All monoradicals gave a triplet line at 14.4–15.6 G. IR spectra were recorded with a Bruker Alpha FT-IR instrument (Bruker Optics, Ettlingen, Germany) with ATR support (ZnSe plate). Flash column chromatography was performed on a Merck (Darmstadt, Germany) Kieselgel 60 (0.040–0.063 mm). Compound **1** [16] was prepared as described previously; compound **5** was reduced to diamagnetic NH form by Fe/AcOH [22]. Other reagents were purchased from Sigma Aldrich (St. Louis, MO, USA), Alfa Aesar (Karlsruhe, Germany), Acros (Geel, Belgium), and TCI (Tokyo, Japan).

Pd-Catalyzed N-Vinylation, General Procedure (**3a, 3b, 5, 6**)

A round-bottomed flask was charged under argon with compound **1** (1.0 mmol), imidazole **2a** or benzimidazole **2b** or 2-aminobenzimidazole **4** (1.0 mmol), anhyd. toluene (5 mL), Cs_2CO_3 (391 mg, 1.2 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol) and racBINAP (25 mg, 0.04 mmol). The mixture was stirred and heated at reflux temperature for 20 h under Ar. After cooling down to room temperature, the mixture was diluted with THF (10 mL), filtered through Celite, and the solvents were evaporated. The residue was dissolved in $CHCl_3$ (15 mL), and then washed with brine (5 mL). The organic phase was separated, dried ($MgSO_4$), and then activated MnO_2 (17 mg, 0.2 mmol) was added. To re-oxidize the hydroxylamine traces, O_2 (200 cm^3/min) was bubbled through the mixture for 15 min. The mixture was filtered, evaporated and purified by flash column chromatography with hexane/EtOAc, followed by $CHCl_3/Et_2O$ to give compounds **3a** or **3b** or **5** and **6.**

3-Formyl-4-(1H-imidazol-1-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-1-yloxyl Radical (**3a**)*:* 105 mg (45%), yellow solid, m.p. 92–93 °C, R_f 0.54 ($CHCl_3/Et_2O$/MeOH) (4:1.5:0.5). IR: 1653, 1626 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 8.58 (s, 1H), 7.66 (s, 1H), 7.29 (s, 1H), 7.14 (s, 1H), 1.50 (s, 6H), 1.38 (s, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 186.1, 153.4, 138.0, 136.9, 130.8, 120.2, 68.8, 67.6, 24.2 (2 C), 23.7 (2 C). MS (EI): *m*/*z* (%) = 234 (29) $[M]^+$, 220 (29), 204 (22), 108 (54), 42 (100). Anal. calcd. for $C_{12}H_{16}N_3O_2$: C, 61.52; H, 6.88; N, 17.94; Found: C, 61.44; H, 6.80; N, 17.90.

3-Formyl-4-(1H-benzimidazol-1-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-1-yloxyl Radical (**3b**)*:* 76 mg (27%), deep yellow solid, m.p. 156–157 °C, R_f 0.30 ($CHCl_3/Et_2O$) (2:1). IR: 1688, 1634, 1604 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 9.30 (s, 1H), 8.50 (s, 1H), 7.82 (d, 1H, *J* = 6.0 Hz), 7.41–7.34 (m, 3H), 1.45 (m, 6H), 1.33–1.20 (m, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 187.3, 152.7, 143.4, 143.2, 139.3, 136.2, 124.7, 123.3, 120.4, 110.6. 69.3, 67.0, 24.8, 24.0 (3C). MS (EI): *m*/*z* (%) = 284 (33) $[M]^+$, 254 (11), 239 (25), 211 (27), 127 (100). Anal. calcd. for $C_{16}H_{18}N_3O_2$: C, 67.59; H, 6.38; N, 14.78; Found: C, 67.64; H, 6.20; N, 14.71.

1,1,3,3-Tetramethyl-1H-benzimidazo[1,2-a]pyrrolo[3,4-e]pyrimidin-2-yloxyl Radical (**5**)*:* 76 mg (27%), yellow solid, m.p. 251–252 °C, R_f 0.27 ($CHCl_3/Et_2O$) (2:1). IR: 1645, 1539, 1510 cm^{-1}. ^{1}H-NMR of **5** NH-form (500 MHz, DMSO-d_6): δ = 9.47 (s, 1H), 8.25 (d, 1H, *J* = 8.0 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.50 (t, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 1.92 (s, 1H), 1.52 (s, 6H), 1.46 (s, 6H), ^{13}C-NMR of **5** NH-form (125 MHz, DMSO-d_6): δ = 178.5, 151.6, 144.4, 129.2, 128.0, 127.8, 125.9, 121.3, 119.5, 112.4,

62.3, 58.7, 32.5 (2 C), 30.2 (2 C). MS (EI): *m*/*z* (%) = 281 (27) $[M]^+$, 251 (71), 236 (42), 219 (55), 133 (100). Anal. calcd. for $C_{16}H_{17}N_4O$: C, 68.31; H, 6.09; N, 19.91; Found: C, 68.25; H, 6.10; N, 19.80.

3-[(1H-Benzimidazol-2-yl)iminomethyl]-4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (**6**): 134 mg (37%), yellow solid, m.p. 122–123 °C, R_f 0.32 (hexane/Et_2O) (1:1). IR: 1583, 1514 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 9.22 (s, 1H), 7.67 (br s, 3H), 7.23 (d, 1H, *J* = 9.0 Hz), 1.50 (s, 6H), 1.28 (s, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 159.0, 155.8, 143.6, 139.8, 71.1, 69.6, 24.9 (2 C), 24.8 (2 C). Remark: 2 quaternary carbons and 4 CH carbons are missing because of overlap with DPPH signals. MS (EI): *m*/*z* (%) = 363/361 (7/7) $[M]^+$, 333/331 (2/2), 252 (67), 41 (100). Anal. calcd. for $C_{16}H_{18}BrN_4O$: C, 53.05; H, 5.01; N, 15.47; Found: C, 53.10; H, 4.98; N, 15.41.

3-(Hydroxymethyl)-4-(1H-imidazol-1-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (**7**): To a stirred solution of compound **3a** (234 mg, 1.0 mmol) in dry EtOH (5 mL), $NaBH_4$ (46 mg, 1.5 mmol) was added in one portion at 0 °C. After consumption of the starting material (~15 min), the reaction mixture was quenched with aq. NH_4Cl solution (3 mL), and the mixture was immediately diluted with $CHCl_3$ (10 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography ($CHCl_3$/Et_2O) to provide the title alcohol as a pale yellow solid 215 mg (91%), m.p. 129–130 °C, R_f 0.32 ($CHCl_3$/Et_2O/MeOH) (4:1.5:0.5). IR: 3260, 1654, 1617 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 7.67 (s, 1H), 7.20 (s, 1H), 7.07 (s, 1H), 3.86 (s, 2H), 1.31 (s, 6H), 1.14 (s, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 139.0, 138.4, 136.2, 129.1, 120.8, 68.1, 67.3, 54.2, 25.1 (2 C), 24.4 (2 C). MS (EI): *m*/*z* (%) = 236 (20) $[M]^+$, 222 (12), 206 (3), 191 (16), 41 (100). Anal. calcd. for $C_{12}H_{18}N_3O_2$: C, 61.00; H, 7.68; N, 17.78; Found: C, 60.92; H, 7.70; N, 17.72.

3-Chloromethyl-4-(1H-imidazol-1-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (**8**): To a stirred solution of compound **7** (118 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) and Et_3N (60 mg, 0.6 mmol), methanesulfonyl chloride (69 mg, 0.6 mmol) was added in one portion at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was washed with brine (5 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was immediately dissolved in dry acetone LiCl (42 mg, 1.0 mmol) was added and the mixture was stirred at 40 °C for 30 min. After cooling, the solvent was evaporated, the residue dissolved in $CHCl_3$ (10 mL) washed with water (5 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$/Et_2O) to furnish compound **8**, 99 mg (78%) as a yellow solid, mp 105–107 °C, R_f 0.41 ($CHCl_3$/Et_2O/MeOH) (4:1.5:0.5). IR: 1682 cm^{-1}. (EI): *m*/*z* (%) = 254/256 (40/13) $[M]^+$, 239/241 (20/6), 224/226 (5/2), 189 (74), 42 (100). Anal. calcd. for $C_{12}H_{17}ClN_3O$: C, 56.58; H, 6.73; N, 16.50; Found: C, 56.62; H, 6.75; N, 16.43.

4. Conclusions

The *N*-vinylation of imidazole and benzimidazole with activated paramagnetic vinyl bromide (β-bromo-α,β-unsaturated pyrroline nitroxide aldehyde) was accomplished by Pd-catalyzed Buchwald-Hartwig cross-coupling reaction, offering the desired products with moderate yields. As far as we know, this is the first report on *N*-vinylation of heterocycles with nitroxide free radicals. Currently, extending the scope of the developed methodology on other heterocycles, such as nucleic bases [23], is being pursued in our laboratory.

Supplementary Materials: Copies of the ^{1}H-NMR, ^{13}C-NMR spectra are available online http://www.mdpi.com/1422-8599/2018/1/M980/s1.

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Author Contributions: Gy.U.: experimental synthetic work; G.G.F.: NMR recording and interpretation, K.H.: synthesis planning, writing of the manuscript; T.K.: recording MS spectra, writing of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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