Synthesis of Isoindoline Nitroxides by Electrocyclic Reactions

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Abstract: The Suzuki reaction of the pyrroline nitroxide, 3-bromo-4-formyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yl-oxyl radical, with vinylboronic acids and subsequent Horner–Wadsworth–Emmons reaction followed by electrocyclic reaction of the thus formed 1,3,5-triene and oxidation offers a new route for the synthesis of 5,6-disubstituted 1,1,3,3-tetramethylisoindolin-2-yloxyl radicals. The alternative Diels–Alder reaction pathway sometimes resulted in poor yields. Starting from 5-(ethoxycarbonyl)-1,1,3,3-tetramethyl-6-phenylisoindolin-2-yl-oxyl radical we obtained a spin-labeled fluorenone.

Key words: cross-coupling, Diels–Alder reaction, electrocyclic reaction, free radical, Wittig reaction

Nitroxide stable free radicals are used in many areas of chemistry and biology,1 for example, as spin labels,2 spin traps,3 antioxidants,4 co-oxidants,5 and mediators of radical polymerization,6 to mention but a few. Beyond pyrroline and piperidine nitroxides, isoindoline-type nitroxides condensed with a heterocycle have become more widespread in the past decade thanks to the recognition of their enhanced thermal and chemical stability, superior EPR line widths, and their structural variability expanded by changing the heterocycle7,8 and by aromatic substitution on the benzene ring.9

To the best of our knowledge there are two main approaches to the synthesis of isoindoline nitroxides: treatment of N-benzylphthalimide with a Grignard reagent followed by deprotection and oxidation10 and the Diels–Alder reaction of the diene 1 with methyl propynoate or diethyl acetylenedicarboxylate to give 5-monosubstituted or 5,6-disubstituted isoindoline nitroxides, respectively followed by oxidative aromatization.11 The weakness of the latter approach is the multistep synthesis of diene 1 and sometimes the long heating period for the Diels–Alder reaction which causes degradation or polymerization of the starting materials and, hence, low yields of products.

The synthesis of compound 2 was improved by performing the reaction of diene 1 with ethyl propynoate in 5 M ethereal lithium perchlorate solution12 followed by oxidation with activated manganese dioxide, however reaction of ethyl but-2-ynoate and diene did not furnish compound 3 under these conditions. Heating the mixture of diene 1 and ethyl but-2-ynoate in toluene followed by oxidation of the adduct with activated manganese(IV) oxide offered the 5-(ethoxycarbonyl)-1,1,3,3,6-pentamethylisoindoline nitroxide 3 in poor yield (12%) (Scheme 1).

For the construction of six-membered carbocycles not only cycloadditions but electrocyclic reactions are also used. The electrocyclic reaction of 1,3,5-hexatriene provides a six-membered ring that can be dehydrogenated to an aromatic ring. The central double bond Z-geometry is required for successful electrocyclization, which can be a thermally or a photochemically induced cyclization or this process can be supported with a Lewis acid catalyst.13 The 6π-electrocyclization is involved in the biosynthesis of vitamin D,14 and this process is often used for the synthesis of complex, not readily accessible organic molecules such as 3-nitroindoles,15 natural products such as coralydine16 and hyellazole,17 and, in our laboratory, we also experienced that 1,3,5-hexatriene formation from unsaturated 1,4-dicarbonyl compounds also led to aromatic ring formation.18 In this paper we report the study of this electrocyclization reaction as a new method for the synthesis of isoindoline nitroxides.
The Suzuki–Miyaura reaction of 2-substituted vinylboronic acids in dioxane and aqueous sodium carbonate solution in the presence of tetrakis(triphenylphosphine)palladium(0) under nitrogen gave aldehydes with vinyl 5, prop-1- enyl 6, oct-1-enyl 7, styryl 8, and 3-thienylvinyl substituents 9. The Horner–Wadsworth–Emmons reaction of these aldehydes with triethyl phosphonoacetate in toluene 19 in the presence of sodium hydroxide solution in methanol and the isolated aldehyde 4 was cyclized by an intramolecular Friedel–Crafts reaction 25 by treatment with sulfuric acid to give pyrroline nitroxide annulated fluorenone 17 (Scheme 4).

In conclusion, we have extended the repertoire for the synthesis of isoidole nitroxides starting from 3-bromo-4-formylpyrroline nitroxide by successive application of Suzuki–Miyaura couplings, Horner–Wadsworth–Emmons reactions, and electrocyclic reactions. The obtained 3,4-disubstituted isoidole nitroxides can be used for further transformation reactions, such as to an isoidole nitroxide annulated fluorenone.

The activation energy for hexatriene electrocyclization is well supported by our observation that the triene obtained 3,4-disubstituted isoidole nitroxides can be used for further transformation reactions, such as to an isoindole nitroxide annulated fluorenone.
Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 85) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on a Thermoquest AutoMass Multi and VG TRIO-2 instruments and in the El mode. 

1H NMR spectra were recorded with Varian Unity Inova 400 WB spectrometer. Chemical shifts are referenced to TMS; measurements were run at 298 K probe temperature in CDCl3, soln.

ESR spectra were taken on Miniscope MS 200 in 10−5 M CHCl3 soln and all monoradicals gave triplet line $\Delta v = 14.4$ G. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.2 cm) coated with Merck Kieselgel GF254. Compounds 11 and 14 were prepared according to published procedures. Compounds 15 were published earlier and compound 10 was reduced to its diamagnetic derivative for NMR study as published earlier.23 Boronic acids and other reagents were purchased from Aldrich.

5-(Ethoxycarbonyl)-1,1,3,3-tetramethyl-1,3-dihydro-2H-isooindol-2-2-yloxy Radical (2)

To a stirred soln of 1 (830 mg, 5.0 mmol) in anhyd Et2O (10 mL) containing LiClO4 (5.30 g, 50.0 mmol), ethyl propynoate (540 mg, 5.5 mmol) was added and the mixture was concentrated at r.t. for 24 h. The mixture was poured into ice-water (100 mL). EtOAc (20 mL) was added, the organic phase was separated, the aqueous phase was washed with EtOAc (10 mL), and the combined organic phases were dried (MgSO4), filtered, and evaporated. The residue was dissolved in CHCl3 (30 mL), activated MnO2 (870 mg, 10.0 mmol) was added and the mixture was stirred and refluxed for 30 min. The MnO2 was filtered off, the soln was concentrated at vacuo and the residue was purified by flash column chromatography (hexane–Et2O, 2:1). 

Yellow solid; yield: 900 mg (72%); mp 117–119 °C; $\Delta v$ = 0.03 (acetone–Et2O, 2:1).

IR (Nujol): 1655 (C=O), 1615, 1575, 1540 cm−1 (C=C).

Anal. Calcd for C15H18NO2S: C, 65.19; H, 6.56; N, 5.07; S, 11.60. Found: C, 67.26; H, 7.73; N, 5.23.

5-(Ethoxycarbonyl)-1,1,3,3,6-pentamethyl-1,3-dihydro-2H-isooindol-2-yloxy Radical (3)

A soln of 1 (830 mg, 5.0 mmol) and ethyl but-2-ynoate (616 mg, 5.5 mmol) in toluene (30 mL) was heated under reflux for 48 h. The mixture was cooled, the solvent was evaporated off, the residue was dissolved in CHCl3 (30 mL), activated MnO2 (870 mg, 10.0 mmol) was added and the mixture was stirred and refluxed for 1 h. The MnO2 was filtered off, the solvent was evaporated, and the residue was purified by flash column chromatography (hexane–Et2O, 2:1) to yield 3 (165 mg, 12%) as a second band; $\Delta v$ = 118–120 °C; $R_f$ = 0.32 (hexane–Et2O, 2:1).

IR (Nujol): 1725 (C=O), 1630, 1570 cm−1 (C=C).

Anal. Calcd for C17H20NO2: C, 75.53; H, 7.46; N, 5.18. Found: C, 75.47; H, 7.48; N, 5.34.

4-Substituted 3-Formyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxy Radicals 5–9 and 13 by Suzuki–Miyaura Coupling; General Procedure

To a deoxygenated soln of 4 (1.25 g, 5.0 mmol) in dioxane (30 mL) was added Pd(PPh3)4 (150 mg, 0.15 mmol) and the mixture was stirred at r.t. for 10 min, then the appropriate boronic acid (5.50 mmol) and 10% aq Na2CO3 (10 mL) were added and the mixture was stirred and refluxed under N2 until the starting materials had been consumed (~3 h). The mixture was cooled, the solvents were evaporated in vacuo, and the residue was partitioned between H2O (20 mL) and CHCl3 (40 mL). The organic phase was separated, dried (MgSO4), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et2O, 2:1) to yield the aldehydes 5, 6, 8, 9, and 13 as yellow solids and 7 as an orange oil in 55–73% yields.
IR (Nujol): 1655 (C=O), 1615 cm⁻¹ (C=C).

MS (EI, 70 eV): m/z (%): 250 (M⁺, 100), 235 (31), 220 (22), 205 (24), 149 (64).


5-[(Ethoxycarbonyl)-1,1,3,3-tetramethyl-1,3-dihydro-2H-isindol-2-yl]xy Radical (1)

Yellow solid; yield: 0.23 g (85%); mp 167–170 °C; Rf = 0.23 (hexane–Et₂O, 2:1).

IR (Nujol): 1695 (C=O), 1630, 1585 cm⁻¹ (C=C).

MS (EI, 70 eV): m/z (%): 344 (M⁺, 22), 314 (32), 299 (31), 41 (100).


3-[2-(Ethoxycarbonyl)vinyl]-2,2,5,5-tetramethyl-1,3-dihydro-2H-pyrrol-1-yl Radical (14)

Yellow solid; yield: 1.08 g (68%); mp 88–90 °C; Rf = 0.30 (hexane–Et₂O, 2:1); no cyclization occurred.

IR (Nujol): 1705 (C=O), 1630 cm⁻¹ (C=C).

MS (EI, 70 eV): m/z (%): 320 (M⁺, 100), 305 (30), 290 (10), 231 (65).

Anal. Calcd for C₁₅H₂₀NO₃: C, 63.72; H, 6.92; N, 4.37; S, 9.01. Found: C, 63.52; H, 6.87; N, 4.50; S, 9.82.
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Anal. Calcd for C19H20NO3: C, 73.53; H, 6.05; N, 4.51. Found: C, 73.39; H, 6.21; N, 4.31.

1,1,3,3-Tetramethyl-9-oxo-3,9-dihydroindeno[1,2-f]isoindol-2(1H)-yloxyl Radical (17)

Carboxylic acid 16 (676 mg, 2.0 mmol) was dissolved in 96% H2SO4 (8 mL) at 0 °C with stirring. The dark brown soln was stirred at r.t. for 30 min and then poured into ice-water (50 mL). The soln was cautiously neutralized with solid NaHCO3 (intense foaming!). The aqueous soln was extracted with EtOAc (2 × 20 mL), the organic phase was separated and dried (MgSO4), activated MnO2 (87 mg, 1.0 mmol) was added and O2 was bubbled through the soln for 10 min. The mixture was filtered, the solvent was evaporated off and the residue was purified by flash column chromatography (hexane–EtOAc, 4:1) to yield 17 (333 mg, 57%) as a yellow solid; mp 257–259 °C; Rf = 0.22 (hexane–Et2O, 2:1).

IR (Nujol): 1700 (C=O), 1605, 1590, 1570 cm–1 (C=C).

MS (EI, 70 eV): m/z (%) = 292 (M+, 28), 278 (91), 262 (100), 247 (38).

Anal. Calcd for C19H18NO2: C, 78.06; H, 6.21; N, 4.79. Found: C, 78.00; H, 6.25; N, 4.71.

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