Synthesis of Isoindoline Nitroxides by Electrocyclic Reactions

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Dedicated to Dr. Sándor Berényi on the occasion of his retirement

Abstract: The Suzuki reaction of the pyrroline nitroxide, 3-bromo-4-formyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radical, with vinylboronic acids and subsequent Horner–Wadsworth–Emmons reaction followed by electocyclic 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-yloxyl radical we obtained a spin-labeled fluorenone.

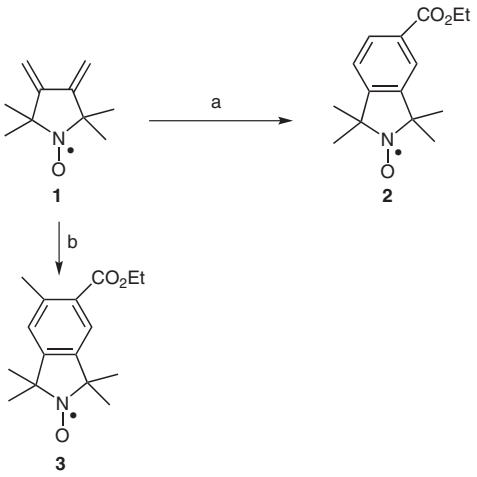
Key words: cross-coupling, Diels–Alder reaction, electrocyclic reaction, free radical, Wittig reaction

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 heterocycle[7,8] 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 oxidation[10] 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 solution[12] 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).



Scheme 1 *Reagents and conditions*: (a) 1. HC≡CCO$_2$Et (1.1 equiv), 5 M LiClO$_4$ in Et$_2$O, r.t., 24 h; 2. MnO$_2$ (2.0 equiv), CHCl$_3$, reflux, 30 min, 88%; (b) 1. MeC≡CCO$_2$Et (1.1 equiv), toluene, reflux, 48 h; 2. MnO$_2$, CHCl$_3$, reflux, 1 h, 12%.

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 coralydine[16] 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.

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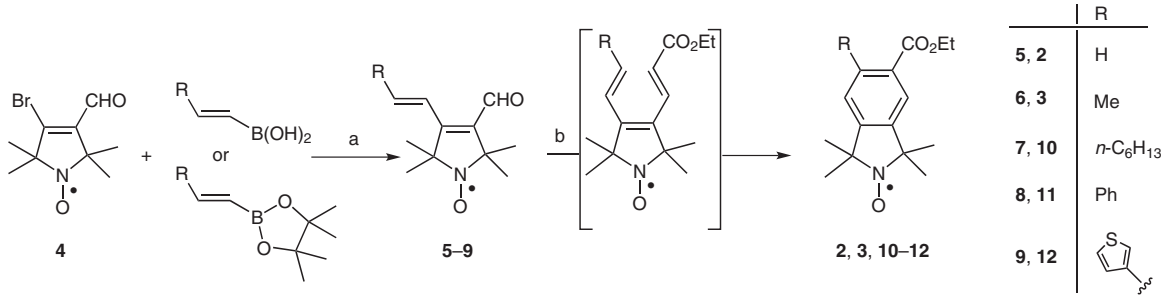


Scheme 2 *Reagents and conditions*: (a) **4** (1.0 equiv), RC=CB(OH)$_2$ (1.1 equiv), Pd(PPh$_3$)$_4$ (0.03 equiv), 10% aq Na$_2$CO$_3$, dioxane, reflux (N$_2$), 3 h, 55–73%; (b) 1. NaH (1.2 equiv), (EtO)$_2$P(O)CH$_2$CO$_2$Et (1.2 equiv), 0 °C, 30 min then **5**–**9** (1.0 equiv), reflux 5 h; 2. MnO$_2$ (2.0 equiv), reflux, 30 min, 78–85%.

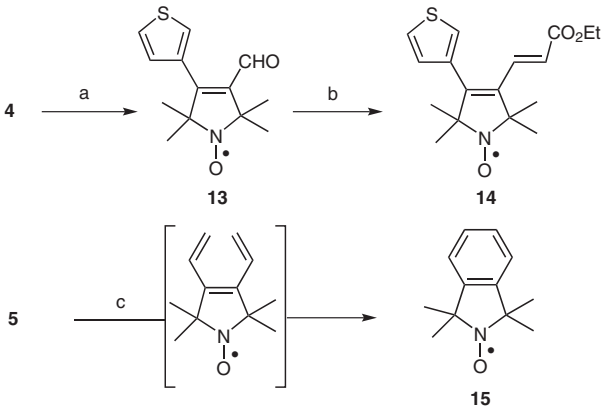
The Suzuki–Miyaura reaction[18] of β-bromo-α,β-unsaturated aldehyde **4** with 2-substituted vinylboronic acids in dioxane and aqueous sodium carbonate solution in the presence of tetrakis(triphenylphosphine)palladium(0) under nitrogen gave aldehydes with vinyl **5**, prop-1-enyl **6**, oct-1-enyl **7**, 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 hydride yielded 1,3,5-trienes. These were not isolated, but the crude product was oxidized with activated manganese(IV) oxide in chloroform to 5,6-disubstituted isoindoline nitroxides **2**, **3**, **10**, **11**, **12** with 45–57% overall yield (Scheme 2). The utility of this process was proven by the identity of products **2** and **3** obtained via Diels–Alder reactions and electrocyclization. The ^{1}H NMR study of a diamagnetic derivative of compound **10** with two singlets at δ = 7.57 and 6.96 also has proven the aromatic ring formation.

To examine the scope and limitations of this reaction, we tested this method on substrates that varied the electronic environments on each polyene. The 3-thienyl derivative **14**, made from compound **4** with Suzuki–Miyaura coupling followed by Horner–Wadsworth–Emmons reactions of **13**, could not be cyclized thermally with the heteroaromatic π-system to the desired thieno[3,2-*e*]isoindole tricycle.

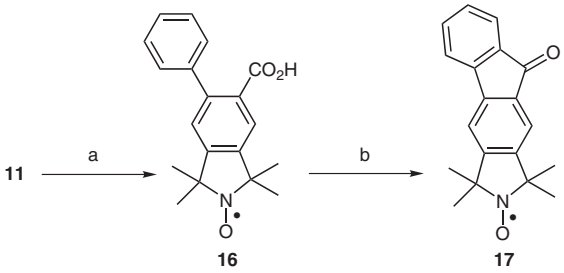
The activation energy for hexatriene electrocyclization is highly influenced by the electron-donor and -acceptor substituents on polyene. Substituents on trienes with 1-donor and 6-acceptor patterns produce a minimal captodative acceleration effect on the electrocyclization.[20] This theory is well supported by our observation that the triene without 1,6-captodative substituents achieved by Wittig reaction of aldehyde **5** and methyltriphenylphosphonium iodide[21] produced compound **15**[10] under more harsh conditions; the crude triene was heated in toluene at reflux temperature for a longer time, and oxidation could be accomplished by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 3).

The 3,4-disubstituted isoindoline nitroxides offer the possibility of synthesizing more complex polycyclic compounds condensed with the pyrroline nitroxide moiety. An example for this is the hydrolysis of ester **11** with aqueous sodium hydroxide solution in methanol and the isolated acid **16** was cyclized by an intramolecular Friedel–Crafts reaction[22] 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 isoindoline 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 isoindoline nitroxides can be used for further transformation reactions, such as to an isoindoline nitroxide annulated fluorenone.



Scheme 3 *Reagents and conditions*: 3-thienylboronic acid (1.1 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), 10% aq Na$_2$CO$_3$, dioxane, reflux (N$_2$), 3 h, 72%; (b) NaH (1.2 equiv), (EtO)$_2$POCH$_2$CO$_2$Et (1.2 equiv), 0 °C, 30 min, then **13** (1.0 equiv), reflux, 5 h, 68%; (c) 1. MePh$_3$PI (1.5 equiv), K$_2$CO$_3$ (1.5 equiv), KOH (0.1 equiv), 18-crown-6 (0.03 equiv), dioxane, reflux, 72 h; 2. toluene, reflux, 2 h, then DDQ (1.0 equiv), reflux, 2 h, 34%.



Scheme 4 *Reagents and conditions*: (a) 10% aq NaOH (excess), MeOH, reflux, 1 h, 91%; (b) 1. H$_2$SO$_4$, 0 °C to r.t., 30 min then neutralize; 2. MnO$_2$ (0.5 equiv), O$_2$ (10 min), 57%.

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 EI mode. ^{1}H 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 $CDCl_3$ soln.

ESR spectra were taken on Miniscope MS 200 in 10^{-4} M $CHCl_3$ soln and all monoradicals gave triplet line a_N = 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 × 0.02 cm) coated with Merck Kieselgel GF_{254}. Compounds **1**[11] and **4**[7] were prepared according to published procedures. Compound **15**[10] was 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-2*H*-isoindol-2-yloxyl Radical (2)

To a stirred soln of **1** (830 mg, 5.0 mmol) in anhyd Et_2O (10 mL) containing $LiClO_4$ (5.30 g, 50.0 mmol), ethyl propynoate (540 mg, 5.5 mmol) was added in one portion and the mixture was stirred 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 ($MgSO_4$), filtered, and evaporated. The residue was dissolved in $CHCl_3$ (30 mL), activated MnO_2 (870 mg, 10.0 mmol) was added and the mixture was stirred and heated under reflux for 30 min The MnO_2 was filtered off, the soln was concentrated in vacuo and the residue was purified by flash column chromatography to yield **2** (1.15 g, 88%) as a yellow solid; mp 98–100 °C; R_f = 0.27 (hexane–Et_2O, 2:1).

IR (Nujol): 1730 (C=O), 1620, 1585 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 262 (M^+, 100), 247 (92), 232 (45), 217 (76), 128 (36).

Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.57; H, 7.73; N, 5.31.

5-(Ethoxycarbonyl)-1,1,3,3,6-pentamethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl 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 $CHCl_3$ (30 mL), activated MnO_2 (870 mg) was added, and the mixture was stirred and refluxed for 1 h. The MnO_2 was filtered off, the solvent was evaporated, and the residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to yield **3** (165 mg, 12%) as a second band; mp 118–120 °C; R_f = 0.32 (hexane–Et_2O, 2:1).

IR (Nujol): 1725 (C=O), 1630, 1570 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 276 (M^+, 62), 261 (100), 246 (43), 231 (90), 128 (34).

Anal. Calcd for $C_{16}H_{22}NO_3$: C, 69.54; H, 8.02; N, 5.07. Found: C, 69.61; H, 7.94; N, 5.20.

4-Substituted 3-Formyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl 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 $Pd(PPh_3)_4$ (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 Na_2CO_3 (10 mL) were added and the mixture was stirred and refluxed under N_2 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 H_2O (20 mL) and $CHCl_3$ (40 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 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.

3-Formyl-2,2,5,5-tetramethyl-4-vinyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (5)

Yellow solid; yield: 591 mg (61%); mp 102–104 °C; R_f = 0.34 (hexane–Et_2O, 2:1).

IR (Nujol): 1655 (C=O), 1565, 1550, cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 194 (M^+, 39), 179 (26), 164 (100), 149 (50).

Anal. Calcd for $C_{11}H_{16}NO_2$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.97; H, 8.25; N, 7.14.

3-Formyl-2,2,5,5-tetramethyl-4-[(1*E*)-prop-1-enyl]-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (6)

Yellow solid; yield: 572 mg (55%); mp 69–71 °C; R_f = 0.38 (hexane–Et_2O, 2:1).

IR (Nujol): 1680 (C=O), 1660, 1635, 1575 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 208 (M^+, 13) 178 (59), 163 (34), 41 (100).

Anal. Calcd for $C_{12}H_{18}NO_2$: C, 69.20; H, 8.71; N, 6.72. Found: C, 69.12; H, 8.80; N, 7.14.

3-Formyl-2,2,5,5-tetramethyl-4-[(1*E*)-oct-1-enyl]-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (7)

Orange oil; yield: 945 mg (68%); R_f = 0.49 (hexane–Et_2O, 2:1).

IR (Nujol): 1680 (C=O), 1630, 1580 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 278 (M^+, 20), 248 (86), 178 (86), 43 (100).

Anal. Calcd for $C_{17}H_{28}NO_2$: C, 73.34; H, 10.14; N, 5.03. Found: C, 73.22; H, 9.95; N, 5.23.

3-Formyl-2,2,5,5-tetramethyl-4-[(*E*)-2-phenylvinyl]-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (8)

Yellow solid; yield: 985 mg (73%); mp 112–114 °C; R_f = 0.29 (hexane–Et_2O, 2:1).

IR (Nujol): 1660 (C=O), 1620, 1580 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 9), 256 (69), 240 (100), 212 (23).

Anal. Calcd for $C_{17}H_{20}NO_2$: C, 75.53; H, 7.46; N, 5.18. Found: C, 75.47; H, 7.48; N, 5.34.

3-Formyl-2,2,5,5-tetramethyl-4-[(*E*)-2-(3-thienyl)vinyl]-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (9)

Yellow solid; yield: 759 mg (55%); mp 125–127 °C; R_f = 0.27 (hexane–Et_2O, 2:1).

IR (Nujol): 1655 (C=O), 1615, 1575, 1540 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 276 (M^+, 6), 246 (17), 231 (6), 41 (100).

Anal. Calcd for $C_{15}H_{18}NO_2S$: C, 65.19; H, 6.56; N, 5.07; S, 11.60. Found: C, 65.20; H, 6.56; N, 5.09; S, 11.42.

3-Formyl-2,2,5,5-tetramethyl-4-(3-thienyl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (13)

Yellow solid; yield: 900 mg (72%); mp 117–119 °C; R_f = 0.35 (hexane–Et_2O, 2:1).

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).

Anal. Calcd for $C_{13}H_{16}NO_2S$: C, 62.37; H, 6.44; N, 5.60; S, 12.81. Found: C, 62.30; H, 6.39; N, 5.52; S, 13.00.

1,1,3,3-Tetramethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radicals 2, 3, 10, 11, 12, and 14 by Horner–Wadsworth–Emmons Reaction, Electrocyclization, and Aromatization; General Procedure

To a stirred suspension of NaH (144 mg, 6.0 mmol) in toluene (20 mL) at 0 °C was added dropwise triethyl phosphonoacetate (1.34 g, 6.0 mmol) in toluene (5 mL). When the addition was complete the mixture was stirred under N_2 for 30 min at this temperature, then the appropriate aldehyde **5**–**9**, **13** (5.0 mmol) was added in toluene (10 mL) and the mixture was heated at reflux temperature for 5 h under N_2 atmosphere. The mixture was cooled, H_2O (20 mL) was added, and the organic phase was separated and the aqueous phase was washed with EtOAc (20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in $CHCl_3$ (30 mL), activated MnO_2 (870 mg, 10.0 mmol) was added and the mixture was stirred at reflux temperature for 30 min. The MnO_2 was filtered off, the solvent was evaporated, and the residue was purified by flash column chromatography to give compounds **2**, **3**, **11**, **12**, and **14** as pale yellow solids, and compound **10** as a pale yellow oil in 68–85% yields.

5-(Ethoxycarbonyl)-1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (2)

Yield: 1.04 g (80%); mp 97–99 °C.

All the spectroscopic data were identical with the sample made by Diels–Alder reaction and aromatization described above.

Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.62; H, 7.55; N, 5.28.

5-(Ethoxycarbonyl)-1,1,3,3,6-pentamethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (3)

Yield: 1.11 g (81%); mp 118–119 °C.

All the spectroscopic data were identical with the sample made by Diels–Alder reaction and aromatization described above.

Anal. Calcd for $C_{16}H_{22}NO_3$: C, 69.54; H, 8.02; N, 5.07. Found: C, 69.50; H, 8.12; N, 5.03.

5-(Ethoxycarbonyl)-6-hexyl-1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (10)

Pale yellow oil; yield: 1.38 g (79%); R_f = 0.54 (hexane–Et_2O, 2:1).

IR (Nujol): 1725 (C=O), 1620, 1570 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 346 (M^+, 93) 331 (100), 316 (45), 301 (38), 43 (41).

Anal. Calcd for $C_{21}H_{32}NO_3$: C, 72.80; H, 9.31; N, 4.04. Found: C, 72.77; H, 9.50; N, 4.00.

Reduced form

^1H NMR (399.9 MHz, $CDCl_3$): δ = 088 (t, 3 H), 1.30 (t, 3 H), 1.35–1.39 (m, 8 H), 1.56 (s, 6 H), 1.61 (s, 6 H), 2.92 (t, 2 H), 4.35 (q, 2 H), 6.96 (s, 1 H), 7.57 (s, 1 H).

5-(Ethoxycarbonyl)-1,1,3,3-tetramethyl-6-phenyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (12)

Yellow solid; yield: 1.31 g (78%); mp 150–152 °C; R_f = 0.29 (hexane–Et_2O, 2:1).

IR (Nujol): 1695 (C=O), 1620, 1600 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) =338 (M^+, 25), 324 (59), 308 (100), 293 (19).

Anal. Calcd for $C_{21}H_{24}NO_3$: C, 74.53; H, 7.15; N, 4.14. Found: C, 74.73; H, 7.11; N, 4.15.

5-(Ethoxycarbonyl)-1,1,3,3-tetramethyl-6-(3-thienyl)-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (13)

Yellow solid; yield: 1.46 g (85%); mp 167–170 °C; R_f = 0.23 (hexane–Et_2O, 2:1).

IR (Nujol): 1695 (C=O), 1620, 1585 cm^{-1} (C=C).

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

Anal. Calcd for $C_{19}H_{22}NO_3S$: C, 66.25; H, 6.44; N, 4.07; S, 9.31. Found: C, 66.12; H6.37; N, 4.10; S, 9.39.

3-[2-(Ethoxycarbonyl)vinyl]-2,2,5,5-tetramethyl-4-(3-thienyl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (14)

Yellow solid; yield: 1.08 g (68%); mp 88–90 °C; R_f = 0.30 (hexane–Et_2O, 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 $C_{17}H_{22}NO_3S$: C, 63.72; H, 6.92; N, 4.37; S, 10.01. Found: C, 63.52; H, 6.87; N, 4.50; S, 9.82.

1,1,3,3-Tetramethyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (15)

To a soln of aldehyde **5** (970 mg, 5.0 mmol) and $MePh_3PI$ (3.03 g, 7.5 mmol) in dioxane (30 mL) was added K_2CO_3 (1.03 g, 7.5 mmol), KOH (28 mg, 0.5 mmol), and 18-crown-6 (40 mg, 0.15 mmol) and the mixture was stirred and heated at reflux temperature for 72 h. The mixture was cooled and filtered and the filtrate was evaporated. The residue was partitioned between Et_2O (30 mL) and H_2O. The aqueous phase was washed with Et_2O (20 mL), the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give a yellow crystalline solid (556 mg) that was dissolved in anhyd toluene and heated under reflux for 2 h, then DDQ (681 mg, 3.0 mmol) was added and the mixture was stirred at reflux temperature for a further 2 h. The mixture was cooled and filtered, the filtrate was washed with 10% aq Na_2CO_3 (20 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography with (hexane–Et_2O, 2:1), to afford **15** as a pale yellow solid; yield: 323 mg (34%); mp 127–128 °C; R_f = 0.48 (hexane–Et_2O, 2:1).

IR (Nujol): 1640, 1535 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 190 (M^+, 75), 160 (41), 145 (100), 128 (26).

Anal. Calcd for $C_{12}H_{16}NO$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.72; H, 8.45; N, 7.26.

5-Carboxy-1,1,3,3-tetramethyl-6-phenyl-1,3-dihydro-2*H*-isoindol-2-yloxyl Radical (16)

To a soln of **11** (1.01 g, 3.0 mmol) in MeOH (15 mL) was added 10% aq NaOH (5 mL) and the mixture was heated at reflux temperature for 1 h. The soln was cooled and diluted with H_2O (20 mL), the half of the solvent was evaporated off in vacuo, and the aqueous soln was acidified with 5% aq H_2SO_4 to pH 2. The precipitated yellow solid was filtered off and air dried, yield: 846 mg (91%); mp 271–273 °C; R_f = 0.37 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 3150 (OH), 1725 (C=O), 1565, 1535 cm^{-1} (C=C).

MS (EI, 70 eV): *m*/*z* (%) = 310 (M^+, 28), 296 (100), 280 (65), 265 (26).

Anal. Calcd for $C_{19}H_{20}NO_3$: 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(1*H*)-yloxyl Radical (17)

Carboxylic acid **16** (676 mg, 2.0 mmol) was dissolved in 96% H_2SO_4 (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 $NaHCO_3$ (intense foaming!). The aqueous soln was extracted with EtOAc (2 × 20 mL), the organic phase was separated and dried ($MgSO_4$), activated MnO_2 (87 mg, 1.0 mmol) was added and O_2 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; R_f = 0.22 (hexane–Et_2O, 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 $C_{19}H_{18}NO_2$: C, 78.06; H, 6.21; N, 4.79. Found: C, 78.00; H, 6.25; N, 4.71.

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