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Synthesis of β-sulfinyl nitroxides

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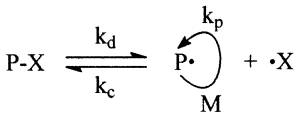
Abstract—Herein we report the synthesis of β-sulfinyl nitroxides via nucleophilic addition of α-lithiated sulfoxides to *N-tert*-butyl-α-phenyl nitrone and subsequent copper^{II}-catalyzed oxidation of the β-sulfinyl hydroxylamine intermediate.

1. Introduction

Nitroxides have been widely studied in polymer science since Rizzardo et al. discovered their ability to control radical polymerization of styrene.[1] The key step of such control is the formation of dormant species (P-X) or alkoxyamines which carry a thermoreversible bond between nitroxides ($X^{\bullet}$) and growing radicals ($P^{\bullet}$) (Scheme 1).

Different studies have shown that both dissociation (k_d) and combination (k_c) rate constants of the alkoxyamine C–O bond, are strongly influenced by the variation of steric or electronic effects of nitroxide substituents, e.g. bulkiness, H bonding or polar groups.[2–4] Therefore, we developed the synthesis of new nitroxides bearing a strongly polar sulfoxide group, as outlined in Scheme 2.

The first step concerns the synthesis of β-sulfinyl hydroxylamines by nucleophilic addition of α-lithiated sulfoxides to a nitrone. This type of reaction, carried out with Grignards, has raised a special interest for the enantioselective synthesis of primary amines.[5] In the case of α-lithiated *p*-tolyl methyl sulfoxide addition to



Scheme 1. Equilibrium between dormant and active species in living/controlled radical polymerization.

Keywords: nitroxide; sulfinyl; radical; living; controlled; polymerization.

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various *N*-alkyl-α-phenyl nitrones, it was shown that the diastereoselectivity increases with the bulkiness of the *N*-alkyl substituent; the best results were obtained with the *tert*-butyl group.[6,7] Therefore, α-lithiated sulfoxides (**2**–**5**) were added to prochiral *N-tert*-butyl-α-phenyl nitrone (**1**) at low temperature (–78°C). The ^{1}H NMR analysis of hydroxylamines (**6**–**9**), in particular the proton borne by the α-carbon atom, has shown that the synthesis of hydroxylamines (**6**–**8**) is highly diastereoselective (>95%). For hydroxylamine (**9**), which implies a tertiary carbanion, the ratio is less favorable (50:50, two peaks for the α-hydrogen atom). An effect of temperature has also been observed for the synthesis of hydroxylamine (**7**). Between –78 and –20°C the diastereoselectivity remains constant, but it increases above this temperature; a 75:25 ratio being obtained at 0°C.

In a second step, β-sulfinyl hydroxylamines (**6**–**9**) were mildly oxidized to β-sulfinyl nitroxides (**10**–**13**) by copper acetate hydrate in methanol.[8] After purification, nitroxides have been characterized by elementary analysis and by ESR spectroscopy. The ESR spectra of nitroxides (**10**–**13**) exhibit the expected doublet of triplet for nitroxides bearing an α-hydrogen atom. The values of hyperfine coupling constants, a_N and a_H are quite similar for these new radicals, suggesting that the spin density on the nitrogen atom is not strongly modified by the variation of steric hindrance around the sulfoxide group.

The use of these new radicals in living/controlled radical polymerization or as intermediates in alkoxyamine synthesis, led us to investigate their thermal stability in benzene solution by electron spin resonance. Nitroxides (**10**, **11**) are relatively unstable and cannot be conserved several days at room temperature, whereas nitroxides

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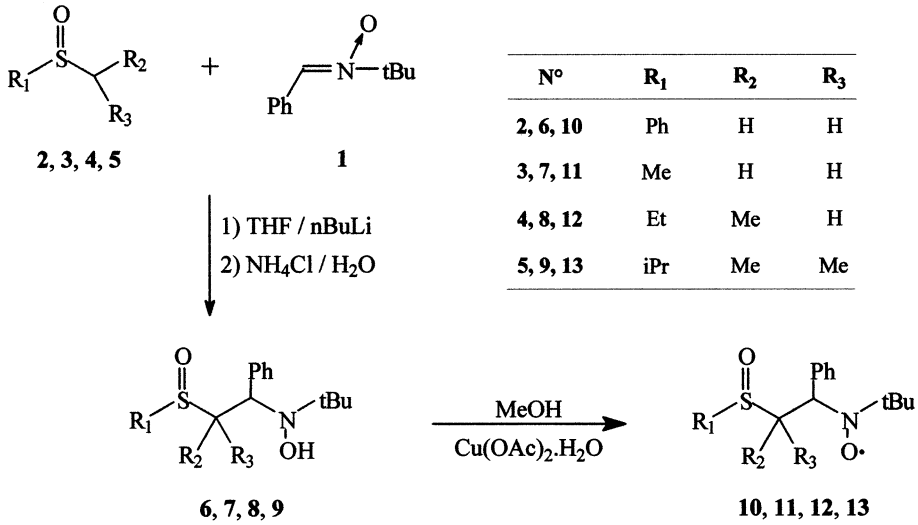

N°	R_1	R_2	R_3
2, 6, 10	Ph	H	H
3, 7, 11	Me	H	H
4, 8, 12	Et	Me	H
5, 9, 13	iPr	Me	Me

Scheme 2. Two-step synthesis of β-sulfinyl nitroxides.

12 and **13** are persistent. At 90°C, only nitroxide (**12**) presents a half time-live sufficiently high ($t_{1/2}$ >20 h) to be engaged in living/controlled radical polymerization of vinyl monomers.

2. General procedure for the synthesis of β-sulfinyl hydroxylamines (6–9)

A solution of *N-tert*-butyl-α-phenyl nitrone (2 mmol) in THF (15 ml) was added dropwise to a cooled (−78°C), stirred solution of α-lithiated sulfoxide prepared from *n*-BuLi (2 mmol) and the appropriate sulfoxide (2 mmol) in THF (10 ml). The mixture was stirred for 2 h maintaining the cooling and quenched with a saturated solution of ammonium chloride (15 ml). The mixture was then allowed to reach room temperature and extracted twice with methylene chloride (15 ml). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and evaporated to give the crude hydroxylamine. This compound was crystallized in pentane to give the pure product or used without further purification in the oxidation step.

3. General procedure for the synthesis of β-sulfinyl nitroxides (10–13)

A solution of a hydroxylamine (2 mmol) and copper^{II} acetate monohydrate (0.1 mmol) in methanol (20 ml) was stirred at room temperature under O_2 (optional) for 2 h. The solvent was evaporated on a rotary evaporator without heating and the pure nitroxide was separated by column chromatography on silica gel eluting with a cyclohexane/ethyl acetate mixture. After evaporation of the solvents, the nitroxide was obtained as pure compound and stored at −20°C.

3.1. *N-tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl) ethyl hydroxylamine (6)

Yield = 69%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (m, 2H), 7.49 (m, 8H), 5.07 (s, 1H), 4.54 (dd, J = 4.3, 11.0 Hz, 1H), 3.57 (dd, J = 11.0, 13.2 Hz, 1H), 2.98 (dd, J = 4.3, 13.2 Hz, 1H), 0.98 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2 (3C), 59.3 (1C), 60.2 (1C), 63.2 (1C), 124.7 (2C), 128.2 (1C), 128.8 (2C), 129.6 (2C), 129.8 (2C), 131.0 (1C), 140.9 (1C), 144.8 (1C). Anal. calcd for $C_{18}H_{23}NO_2S$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.05; H, 7.34; N, 4.34.

3.2. *N-tert*-Butyl-*N*-(1-phenyl-2-methylsulfinyl) ethyl hydroxylamine (7)

Yield = 65%. ^{1}H NMR: δ 7.50 (m, 2H), 7.30 (m, 3H), 4.97 (s, 1H), 4.64 (dd, J = 4.0, 10.6 Hz, 1H), 3.48 (dd, J = 10.6, 13.5 Hz, 1H), 2.91 (dd, J = 4.0, 13.5 Hz, 1H), 2.62 (s, 3H), 1.01 (s, 9H). ^{13}C NMR: δ 27.2 (3C), 27.3 (1C), 59.1 (1C), 60.2 (1C), 60.6 (1C), 128.3 (1C), 128.9 (2C), 129.8 (2C), 140.9 (1C). Anal. calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.48. Found: C, 60.96; H, 8.38; N, 5.51.

3.3. *N-tert*-Butyl-*N*-(1-phenyl-2-methyl-2-ethylsulfinyl) ethyl hydroxylamine (8)

Yield = 76%. ^{1}H NMR: δ 7.50 (m, 2H), 7.31 (m, 3H), 5.34 (s, 1H), 4.10 (d, J = 10.5 Hz, 1H), 3.40 (dd, J = 7.3, 10.5 Hz, 1H), 3.15 (dq, J = 7.5, 12.8 Hz, 1H), 2.62 (dq, J = 7.5, 12.8 Hz, 1H), 1.41 (t, J = 7.5 Hz, 3H), 0.97 (d, J = 7.3 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR: δ 8.7 (1C), 9.5 (1C), 27.1 (3C), 41.6 (1C), 57.5 (1C), 59.7 (1C), 65.8 (1C), 128.2 (1C), 128.8 (2C), 130.3 (2C), 140.0 (1C). Anal. calcd for $C_{15}H_{25}NO_2S$: C, 63.56; H, 8.89; N, 4.94. Found: C, 63.52; H, 8.68; N, 4.79.

3.4. *N-tert*-Butyl-*N*-(1-phenyl-2,2-dimethyl-2-isopropyl-sulfinyl) ethyl hydroxylamine

(Both diastereomers) Yield = 73%. ^{1}H NMR: (**9a**) δ 7.29 (m, 5H), 5.83 (s, 1H), 4.16 (s, 1H), 3.37 (sept, J = 7.0 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H), 1.32 (s, 3H), 1.15 (s, 3H), 0.96 (s, 9H). (**9b**) δ 7.30 (m, 5H), 6.33 (s, 1H), 4.01 (s, 1H), 2.99 (sept, J = 7.0 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.10 (s, 3H), 0.95 (s, 9H). Anal. calcd for $C_{17}H_{29}NO_2S$: C, 65.77; H, 9.19; N, 4.51. Found: C, 65.71; H, 9.40; N, 4.49.

3.5. *N-tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl) ethyl nitroxide (10)

Purification by column chromatography with cyclohexane/ethyl acetate (2:1) as eluant ($R_f = 0.3$). Yield = 95%. ESR (benzene): $a_N = 14.4$ G, $a_H = 3.5$ G, $g = 2.0064$. Anal. calcd for $C_{18}H_{22}NO_2S$: C, 68.32; H, 7.01; N, 4.43. Found: C, 68.11; H, 7.20; N, 4.41.

3.6. *N-tert*-Butyl-*N*-(1-phenyl-2-methylsulfinyl) ethyl nitroxide (11)

Purification by column chromatography with cyclohexane/ethyl acetate (1:4) as eluant ($R_f = 0.3$). Yield = 93%. ESR (benzene): $a_N = 14.3$ G, $a_H = 3.4$ G, $g = 2.0064$. Anal. calcd for $C_{13}H_{20}NO_2S$: C, 61.38; H, 7.92; N, 5.50. Found: C, 61.25; H, 8.12; N, 5.37.

3.7. *N-tert*-Butyl-*N*-(1-phenyl-2-methyl-2-ethylsulfinyl) ethyl nitroxide (12)

Purification by column chromatography with cyclohexane/ethyl acetate (2:3) as eluant ($R_f = 0.3$). Yield = 96%. ESR (benzene): $a_N = 14.5$ G, $a_H = 3.0$ G, $g = 2.0065$. Anal. calcd for $C_{15}H_{24}NO_2S$: C, 63.79; H, 8.56; N, 4.96. Found: C, 63.65; H, 8.42; N, 4.91.

3.8. *N-tert*-Butyl-*N*-(1-phenyl-2,2-dimethyl-2-isopropyl-sulfinyl) ethyl nitroxide (13)

Purification by column chromatography with cyclohexane/ethyl acetate (1:1) as eluant ($R_f = 0.3$). Yield = 93%. ESR (benzene): $a_N = 14.5$ G, $a_H = 2.1$ G, $g = 2.0065$. Anal. calcd for $C_{17}H_{28}NO_2S$: C, 65.98; H, 8.79; N, 4.53. Found: C, 65.86; H, 8.68; N, 4.48.

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