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Reactions of nitroxides. Part VIII [1]: nitroxides with a cyanato substituent

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Abstract Nitroxides bearing a cyanato group were synthesized from nitroxides containing a phenolic hydroxyl group using both cyanogen chloride and bromide.

Keywords Cyanate esters · Nitroxyl radicals · Cyanogen chloride · Cyanogen bromide

Introduction

Cyanate esters (R–O–C≡N) may be regarded as organic compounds with a reactive cyanato functional group [2, 3]. Dicyanate esters (in general, commercially available derivatives of bis(4-cyanatoaryl)methane) undergo polycyclotrimerisation. The resulting cyanate resins have excellent dielectric properties and good flammability characteristics [4–8].

Synthesis of the cyanate esters involves the reaction of compounds bearing a phenolic hydroxyl group with cyanogen halides in the presence of triethylamine [2, 3, 6, 7, 9, 10]. The reaction is realized at −10 to −15 °C in acetone [11, 12] or DMF [13]. In some preparations preliminary reaction of triethylamine with a phenol derivative is suggested. The resulting salt is added dropwise to the solution of cyanogen bromide in methyl isobutyl ketone at +40 °C [10].

Nitroxides with reactive functional groups can be used for modification of biologically active synthetic or natural molecules or macromolecules, and for investigation of their properties with EPR spectroscopy (spin labelling).

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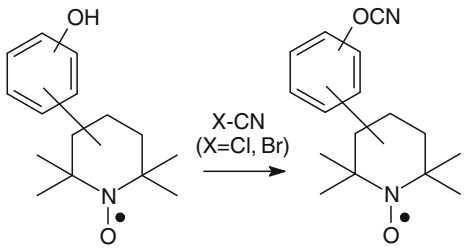
To the best of our knowledge, nitroxyl radicals with a cyanato function are unknown. Herein we report the synthesis of nitroxides bearing the cyanato group (Scheme 1).

Results and discussion

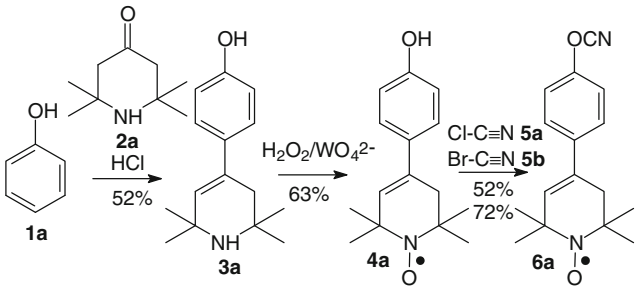
Triacetonamine (**2a**) and 2,2,6,6-tetramethyl-4-piperidinol (**2b**) were chosen as precursors of the two structures containing a nitroxyl fragment (2,2,6,6-tetramethylpiperidin-1-oxyl) and a phenolic hydroxyl functional group, which in turn were assumed to be starting materials to target compounds bearing a cyanato group. The synthesized phenols and cyanates containing the nitroxyl fragment are presented in Schemes 2 and 3.

Condensation of phenol (**1a**) with triacetonamine (**2a**) in the presence of hydrochloric acid leads to amine **3a**. Oxidation of **3a** with hydrogen peroxide leads to the nitroxyl radical **4a** containing a phenolic hydroxyl group [14–16]. **4a** was converted into the corresponding cyanate **6a** with both cyanogen chloride (**5a**) and cyanogen bromide (**5b**). There is no essential difference between the results obtained with **5a** and **5b**. As expected, use of **5b** is more convenient because of easier manipulation of **5b** which is solid at rt. However, a cyanate obtained in this way may be contaminated with the starting **5b**, because of poor chromatographic separation.

Direct transesterification of methyl 4-hydroxybenzoate (**1b**) with 2,2,6,6-tetramethyl-4-piperidin-1-oxyl using either sodium methoxide or potassium hydroxide as catalysts failed. This result is consistent with the literature observation [17] that esterification of 2,2,6,6-tetramethyl-4-piperidin-1-oxyl with 4-hydroxybenzoic acid using either PCl_3 or $SOCl_2$ in the presence of NEt_3 was unsuccessful.



Scheme 1



Scheme 2

Transesterification with methyl 4-hydroxybenzoate (**1b**) in the presence of magnesium methoxide also failed [17].

Because the synthesis of **4b** by direct transesterification of methyl 4-hydroxybenzoate (**1b**) with 2,2,6,6-tetramethyl-4-piperidin-1-oxyl was unsuccessful, a two-step method was applied. In the first step, methyl 4-hydroxybenzoate (**1b**) was transesterified with 2,2,6,6-tetramethyl-4-piperidinol (**2b**). Three transesterification catalysts were tested: titanium butanoate [17], sodium methoxide [18], and potassium hydroxide [18]. Transesterification in the presence of titanium butanoate [17] and sodium methoxide [18] failed. When potassium hydroxide was used in the melt at about 200 °C, **3b** was obtained [18]. In the second step **3b** was oxidized with hydrogen peroxide to the expected corresponding nitroxyl radical **4b** which, in turn, was converted with cyanogen bromide into the corresponding cyanate **6b**.

The structures of synthesized nitroxyl radicals bearing a cyanato functional group (**6a**, **6b**) were characterized by use of MS, HR MS, and IR spectroscopy.

To synthesize compounds bearing both a nitroxyl moiety and a cyanato group, we also attempted to use 4-isocyanato [19] and 4-isothiocyanato-2,2,6,6-tetramethylpiperidinyl-1-oxyl [20]. The iso(thio)cyanates were converted into the corresponding (thio)ureas with amines such as 4-aminophenol, 4-amino-4-acetoxybenzene, and tyramine (4-(2-aminoethyl)phenol). The resulting ureas and thioureas bearing both nitroxyl and phenolic fragments were subsequently treated with cyanogen halides, but no expected cyanates were obtained; this was likely to be because of the possible tautomerism of ureas and thioureas and the creation of the second possible reaction centre [R$^{\bullet}$–NH–C(=X)–NH–Ar–OH ⇄ R$^{\bullet}$–NH–C(–XH)=N–Ar–OH, R$^{\bullet}$ = nitroxyl moiety, X = O, S].

Conclusion

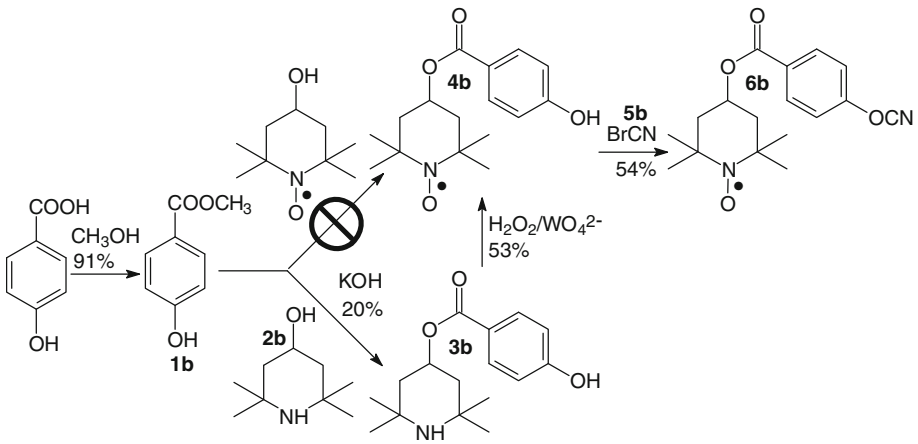
The synthesized compounds **6a** and **6b** are the first nitroxyl radicals bearing a cyanato functional group.

Experimental

General

Both cyanogen chloride (**5a**) and cyanogen bromide (**5b**) were manufactured at the Institute of Industrial Organic Chemistry. Thin-layer and column chromatography were done on silica gel—Merck Alurolle 5562, Alufolien 5554 and Merck 1.09385.1000 (0.040–0.063 mm, 230–400 mesh), respectively. Visualization: UV 254 nm and/or I_2 vapour. The following abbreviations for mobile phases are used throughout the text: BM3, BM9, BM95 = benzene–

Scheme 3



methanol 3:1, 9:1, 95:5, respectively; BA9, BA95 = benzene–ethyl acetate 9:1, 95:5, respectively; ClM1 = chloroform–methanol 1:1 (all *v*/*v*). MS (EI, 70 eV) data were recorded using AMD 604 and Agilent 5975 B mass spectrometers. HR-MS (EI, 70 eV) data were recorded using an AMD 604 mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker WP 100 SY (100 and 25 MHz for proton and carbon, respectively) and a Varian UNITYplus 200 spectrometer. IR data were recorded using a Jasco 420 FTIR spectrophotometer. UV–Vis spectra were recorded on a Pye–Unicam SP-8 100 spectrometer in methanol as solvent. EPR measurements were recorded on a Radiopan spectrometer (9.3 GHz—X band) in chloroform as solvent (3.7×10^{-4} mol/dm^3) using diphenylpicrylhydrazyl as standard.

4-(1,2,3,6-Tetrahydro-2,2,6,6-tetramethyl-4-pyridinyl)-phenol (**3a**)

Concentrated hydrochloric acid (70 cm^3) was placed in a reactor of 1 dm^3 capacity, equipped with a heating mantle, a bottom valve, a mechanical stirrer, a reflux condenser, and a thermometer. Triacetonamine (**2a**, 60.2 g, 0.387 mol), phenol (**1a**, 73 g, 0.777 mol), and additional hydrochloric acid (30 cm^3) were added with vigorous stirring. Hot water (70 °C) was introduced into the heating mantle. The reaction mixture was stirred and heated to 70 °C for 10 h, then cooled to rt. Benzene (100 cm^3) was added. An efficiently stirred precipitate was transferred through a bottom valve into a funnel with a sintered glass disk. The precipitate was isolated by filtration under reduced pressure, pressed, copiously washed with benzene, and finally pressed again. The precipitate was gradually added into a 20% potassium carbonate solution (300 g) in a beaker. After all the carbon dioxide had evolved, the precipitate was isolated by filtration, pressed, washed with cold water, pressed again, and air-dried. Crude **3a** (62 g, 69%, m.p. > 240 °C) was obtained. **3a** (10 g) was dissolved in a dilute solution of sodium hydroxide (28 g in 350 cm^3 water) then 10% hydrochloric acid solution was added until a titration curve measured with a pH meter showed an inflection point at pH 10. The precipitate (13.7 g) was isolated by filtration. After drying, 7.5 g purified **3a** (52%, m.p. 190–192 °C) was obtained. A sample of purified **3a** (1 g) was crystallized from 6.5 cm^3 methanol–benzene 5:1 (*v*/*v*) affording fine colourless crystals of **3a**. M.p.: 192–194 °C (196–197 °C [15], 193–195 °C [16]); $R_f = 0.06$ (BM9), 0.20 (BM3), 0.20 (ClM1); ^{1}H NMR (100 MHz, $CDCl_3$): $\delta = 1.24$ (s, 6H, 2 × CH_3), 1.28 (s, 6H, 2 × CH_3), 2.23 (d, 2H, $J = 1.57$ Hz, CH_2), 3.02 (s, 1H, OH), 5.88 (t, 1H, $J = 1.57$ Hz, $(CH_3)_2C$-C<u>H</u>=), 6.76–6.85 and 7.23–7.32 (m, 4H, C_6<u>H_4</u>OH) ppm; ^{13}C NMR (25 MHz, $CDCl_3$): $\delta = 155.37$ (C), 134.28 (C), 131.62 (CH=C), 129.73 (CH=C), 126.42 (CH), 115.48 (CH), 51.82 (C), 50.04 (C), 40.08 (CH_2), 31.49 (2 × CH_3), 30.09 (2 × CH_3) ppm; IR (KBr): $\bar{\nu} = 3{,}410$ (OH), 1,270, 1,230 (C–O) cm^{-1}; UV–Vis (MeOH): λ_{max} (ε) = 204 (20,970), 254 (17,250) nm (mol^{-1} dm^3 cm^{-1}); MS (70 eV): *m*/*z* = 231 (M$^+$, 2), 216 (M$^+$ − CH_3, 100), 200 (6), 199 (5), 159 (15), 149 (5), 131 (4), 115 (4), 107 (5), 105 (3), 100 (6), 93 (5), 91 (5), 81 (5), 77 (4), 71 (3), 69 (3), 58 (7), 57 (6), 56 (4), 55 (6), 43 (8), 42 (16), 41 (8).

3,6-Dihydro-4-(4-hydroxyphenyl)-2,2,6,6-tetramethylpyridin-1(2H)-oxyl (**4a**)

4-(1,2,3,6-Tetrahydro-2,2,6,6-tetramethyl-4-pyridinyl)phenol (**3a**, 3 g, 0.013 mol), sodium tungstate (0.24 g), and triethylbenzylammonium chloride (0.24 g) were placed in a conical flask of 200 cm^3 capacity equipped with a magnetic stirring bar. Methanol (52 cm^3) and water (4.8 cm^3) were added. A solution of 30% hydrogen peroxide (4.2 g) in methanol (9.3 cm^3) was added. The reaction mixture was stirred for 6 days. Methanol was evaporated under reduced pressure. Dichloromethane (30 cm^3) and water (50 cm^3) were added. The aqueous layer was acidified with hydrochloric acid solution (1:1, *v*/*v*) to pH 2. The dichloromethane layer was separated, washed with water, and dried with anhydrous magnesium sulfate. After filtration to remove the magnesium sulfate and evaporation of the dichloromethane, brick precipitate (2.9 g) of crude **4a** was obtained. The crude **4a** was subjected to column chromatography (BA95) to afford a yellow precipitate of 2.02 g (63%) purified **4a**. M.p.: 138-140 °C (134–135 °C [16]); $R_f = 0.15$ (BA95), 0.47 (BM9), 0.65 (BM3), 0.93 (ClM1); ^{1}H NMR (200 MHz, $CDCl_3$, after reduction with phenylhydrazine in $CDCl_3$, aliphatic part of the spectrum, in fact the spectrum of the corresponding hydroxylamine [21]): $\delta = 1.37$ (s, 6H, 2 × CH_3), 1.44 (s, 6H, 2 × CH_3), 2.58 (s, 2H, CH_2), 5.20 (s, 2H, 2 × OH), 5.72 (s, 1H, $(CH_3)_2$C–CH=) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, after reduction with phenylhydrazine in $CDCl_3$, aliphatic part of the spectrum, in fact the spectrum of the corresponding hydroxylamine [21]): $\delta = 59.22$ (C), 58.11 (C), 42.50 (CH_2), 26.21 (2 × CH_3), 25.31 (2 × CH_3) ppm; IR(KBr): $\bar{\nu} = 3{,}260$ (OH), 1,290, 1,240, 1,210 (C–O) cm^{-1}; UV–Vis (MeOH): λ_{max} (ε) = 204 (21,490), 254 (19,000) nm (mol^{-1} dm^3 cm^{-1}); EPR (3.7×10^{-4} mol/dm^3, $CHCl_3$): $g = 2.0060$, $a = 1.576$ mT; MS (70 eV): *m*/*z* = 246 (M$^+$, 17), 232 (6), 216 (20), 201 (100), 186 (5), 173 (26), 159 (90), 145 (25), 141 (11), 131 (18), 115 (20), 107 (25), 105 (9), 91 (20), 77 (23), 65 (13), 56 (26), 41 (39).

4-(4-Cyanatophenyl)-3,6-dihydro-2,2,6,6-tetramethylpyridin-1(2H)-oxyl (**6a**, $C_{16}H_{19}N_2O_2$)

From Br-CN: In a three necked flask of 5 cm^3 capacity equipped with a magnetic stirring bar **4a** (0.246 g, 1 mmol) was dissolved in 1 cm^3 anhydrous acetone (dried over magnesium sulfate). Cyanogen bromide (**5b**, 0.110 g,

1.04 mmol) was added at <0 °C. Anhydrous triethylamine (150 mm^3) was added dropwise with a syringe (ice–salt bath). A copious precipitate of triethylamine hydrochloride was formed. The reaction mixture was stirred at ~0 °C for 2 h. The precipitate of triethylamine hydrochloride was removed by filtration and washed with acetone. The filtrate was evaporated. The residue (0.4388 g) was subjected to column chromatography (BA95) to give 0.1958 g (72%) **6a** as a red oil.

From Cl-CN: In a three necked flask of 5 cm^3 capacity equipped with a magnetic stirring bar **4a** (0.246 g, 1 mmol) was dissolved in anhydrous acetone (1 cm^3, dried over magnesium sulfate). Excess cyanogen chloride (**5a**, 1.2–2.4 g, 1–2 cm^3, 20–40 mmol) was added at <0 °C. Anhydrous triethylamine (140 mm^3) was added with a syringe in three portions at about −20 °C. A copious precipitate of triethylamine hydrochloride was formed. The reaction mixture was stirred at 0 °C for 0.5 h. The precipitate of triethylamine hydrochloride was removed by filtration and washed with acetone. The filtrate was evaporated. The dark residue was subjected to column chromatography (BA95) to give 0.14 g (52%) **6a** as a red solid.

M.p.: 75–78 °C; $R_f = 0.36$ (BA9); IR (KBr): $\bar{\nu}$ = 2,983, 2,265, 2,231, 1,504, 1,356, 1,190, 1,168 cm^{-1}; MS (70 eV): m/z = 271 (M^+, 53), 257 (13), 241 (15), 226 (100), 184 (43), 156 (13), 142 (20); HR-MS: calc. for $C_{16}H_{19}N_2O_2$: 271.14465, found: 271.14378.

Methyl 4-hydroxybenzoate (**1b**)

4-Hydroxybenzoic acid (13.8 g, 0.1 mol) and methanol (100 cm^3) were placed in a round-bottomed flask of 0.5 dm^3 capacity. Concentrated sulfuric acid (2 g, 1.08 cm^3) was added dropwise. The solution was heated under reflux for 6.5 h and allowed to cool to rt. The excess methanol was removed by evaporation under reduced pressure and the residue was transferred to a separation funnel filled with a saturated sodium bicarbonate solution (50 cm^3) and diethyl ether (50 cm^3). The organic layer was washed with water and dried with anhydrous magnesium sulfate. Removal of the drying agent by filtration and evaporation of diethyl ether afforded 13.8 g (91%) colourless, crystalline **1b**. M.p.: 121–124 °C (127.7–128.3 °C [22]).

2,2,6,6-Tetramethylpiperidin-4-yl 4-hydroxybenzoate (**3b**)

Methyl 4-hydroxybenzoate (**1b**, 0.608 g, 4 mmol), 1.57 g 2,2,6,6-tetramethyl-4-piperidinol (**2b**, 10 mmol), and potassium hydroxide (0.056 g, 1 mmol) were triturated in a mortar and placed in a two-necked flask equipped with a distillation condenser. The mixture was magnetically stirred and heated to about 200 °C for 35 min. The condenser was occasionally connected to a vacuum line to remove, by distillation, the methanol formed. The reaction mixture was cooled to 70 °C. The content of the flask was dissolved in a small amount of methanol (about 2 cm^3). The solution was subjected to chromatographic filtration (mobile phase: methanol) to give a solid residue (1.55 g). The residue was dissolved in methanol, silica gel was added, and the suspension was evaporated to dryness. The residual powder was placed on the top of the silica bed of a chromatography column. Two column chromatographic separations gave 0.22 g (20%) **3b**. M.p.: 245–248 °C (252 °C [17]); $R_f = 0.37$ (MeOH); IR (KBr): $\bar{\nu}$ = 3,272, 1,694, 1,607, 1,279 cm^{-1}; MS (70 eV): m/z = 277 (M^+, 1), 262 (M^+—15, 10), 140 (5), 124 (100), 121 (10), 107 (5), 93 (4), 65 (4), 58 (21).

4-(4-Hydroxybenzoyloxy)-2,2,6,6-tetramethylpiperidin-1-oxyl (**4b**)

2,2,6,6-Tetramethylpiperidin-4-yl 4-hydroxybenzoate (**3b**, 0.1394 g, 0.5 mmol), sodium tungstate (0.07 g), triethylbenzylammonium chloride (0.01 g), and sodium versenate (0.01 g) were suspended in a mixture of methanol (5–6 cm^3) and water (0.2 cm^3) in a flask of 5 cm^3 capacity. Hydrogen peroxide (50%, 0.715 cm^3) was added to the reaction mixture. The suspension was magnetically stirred for 27 h at rt. The oxidation was monitored by use of TLC (BM9). The precipitate was isolated by filtration directly into a separation funnel and washed with dichloromethane (2 × 5 cm^3) and 20 cm^3 water. The organic layer was separated and dried over anhydrous magnesium sulfate. After filtration and evaporation crude **4b** was obtained (0.1012 g, 69%). The crude product **4b** was subjected to column chromatography (BM95) to give 0.0778 g (53%) **4b** as a red solid. M.p.: 179–180 °C (175 °C [17]), $R_f = 0.44$ (BM9); IR (KBr): $\bar{\nu}$ = 3,296, 1,699, 1,609, 1,280 cm^{-1}; MS (70 eV): m/z = 292 (M^+, 9), 278 (1), 262 (7), 206 (3), 155 (5), 154 (18), 140 (11), 139 (13), 124 (71), 121 (100), 109 (57), 93 (10), 82 (8), 81 (6), 69 (6), 68 (5), 67 (7), 65 (7), 56 (3), 55 (4), 41 (8), 39 (5).

4-(4-Cyanatobenzoyloxy)-2,2,6,6-tetramethylpiperidin-1-oxyl (**6b**, $C_{17}H_{21}N_2O_4$)

In a flask of 5 cm^3 capacity, **4b** (0.0778 g, 0.266 mmol) was dissolved in anhydrous acetone (0.5 cm^3, dried over magnesium sulfate). The reaction mixture was cooled to 0 °C. A cooled solution of **5b** (0.055 g, 0.52 mmol) in acetone (0.5 cm^3) was added with a syringe. Then, triethylamine (40 mm^3) was added dropwise using a syringe. A precipitate was formed. The reaction mixture was magnetically stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC (BM9, BA9). The reagents were warmed to rt. A precipitate (0.0327 g) was isolated by filtration. The filtrate was evaporated, and the residue (0.0790 g) was subjected to column chromatography (BA95) to give 0.046 g (54%) **6b** as a red solid. M.p.: 115–118 °C, $R_f = 0.38$ (BA9), 0.76 (BM9); IR (KBr): $\bar{\nu}$ = 2,285, 2,258, 2,239, 1,717 (C=O), 1,600, 1,498,

1,280 cm^{-1}; MS (70 eV): $m/z = 317$ (M^+, 12), 154 (24), 146 (100), 140 (7), 139 (11), 124 (90), 109 (77), 82 (15), 81 (12), 76 (5), 69 (11), 68 (12), 56 (6), 55 (10), 41 (19); HR-MS: calc. for $C_{17}H_{21}N_2O_4$: 317.15013, found: 317.14892.

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References

1. Zakrzewski J, Krawczyk M (2008) Heteroat Chem 19:549
2. Martin D, Bacaloglu R (1980) Organische Synthesen mit Cyansaeureestern. Akademie-Verlag, Berlin
3. Prejzner J (1968) Wiad Chem 22:187
4. Hamerton I (ed) (1994) Chemistry and technology of cyanate ester resins. Blackie Academic & Professional, London
5. Office of Aviation Research, Washington, DC, 20591, US Department of Transportation, Federal Aviation Administration (2001), Thermal decomposition of cyanate ester resins. http://www.tc.faa.gov/its/worldpac/techrpt/ar01-32.pdf. Accessed March 2010
6. Pankratov VA, Vinogradova SV, Korshak VV (1977) Usp Khim 46:530, Russ Chem Rev 46:278
7. Hamerton I, Hay JN (1998) Polym Int 47:465
8. Hamerton I, Hay JN (1998) High Perform Polym 10:163
9. Snow AW (1994) In: Hamerton I (ed) Chemistry and technology of cyanate ester resins. Blackie Academic & Professional, London, pp 7–57
10. Jackson RJ (1991) US Patent 4981994, European Patent 411707
11. Chaplin A, Hamerton I, Howlin BJ, Barton JM (1994) Macromolecules 27:4927
12. Anuradha G, Sarojadevi M (2008) Polym Bull 61:197
13. Anuradha G, Sarojadevi M (2006) High Perform Polym 18:1003
14. Zakrzewski J, Szymanowski J (2000) Polym Degrad Stab 67:279
15. Skripko LA, Popova ZG, Filina RD, Pankova TA, Tretjakova GN (1978) SSSR Patent 631516; Chem Abstr 90:54839
16. Randell DR, Smith MJ (1975) British Patent 1395159
17. Zhang Y-K, Shen D-K (1993) Z Naturforsch B 48:849
18. Murayama K, Morimura S, Yoshioka T, Horiuchi H, Higashida S (1972) DE Patent 2204659, US Patent 3840494; Chem Abstr 77:165545
19. Zakrzewski J, Krawczyk M (2006) Heteroat Chem 17:393
20. Zakrzewski J, Hupko J, Kryczka K (2003) Monatsh Chem 134:843
21. Lee TD, Keana JFW (1975) J Org Chem 40:3145
22. Buehler CA, Gardner TS, Clemens ML (1937) J Org Chem 2:167