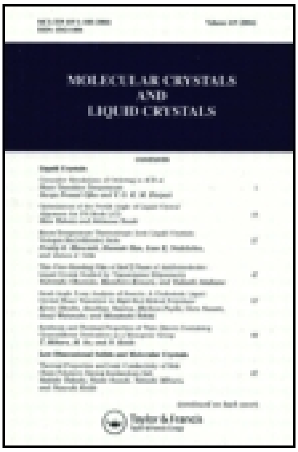

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4, 4′-(butadiyne-l, 4-diyl)-bis-(2, 2, 6, 6-tetramethyl-4-hydroxypiperidin-1 -oxyl): A Convenient Synthesis and a Polymorphic Transformation Induced by Ionizing Radiation

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4,4'-(BUTADIYNE-1,4-DIYL)-BIS-(2,2,6,6-TETRAMETHYL-4-HYDROXYPIPERIDIN-1-OXYL): A CONVENIENT SYNTHESIS AND A POLYMORPHIC TRANSFORMATION INDUCED BY IONIZING RADIATION

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Abstract A new convenient synthesis of the diacetylenic nitroxide 4,4'-(butadiyne-1,4-diyl)-bis-(2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl) (1) has been achieved by oxidative coupling of the relevant monoacetylene. In the presence of air, polycrystalline samples of the beta phase of 1 are converted to the alpha polymorph on exposure to radiation from Cu Kα or ^{60}Co sources. This polymorphic transformation is conveniently monitored by observing the x-ray powder diffraction pattern in the 2θ range 6-13°. New synthetic procedures to the diacetylenic nitroxides 2,4-hexadiyn-1,6-diyl-bis-(2,2,5,5-tetramethyl-1-oxyl-3-pyrolline-3-carboxylate) (3) and 5-(2,2,6,6-tetramethyl-1-oxyl-1,2,5,6-tetrahydropyridin-4-yl)penta-2,4-diyn-1-ol (4) are reported.

Keywords: polymorphic transformation by radiation, diacetylenic nitroxides, synthesis of diacetylene nitroxides

INTRODUCTION

Previous investigators have studied 4,4'-(butadiyne-1,4-diyl)-bis-(2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl) (1) in connection with possible spin-spin exchange[1] and as a possible precursor to a ferromagnetic polymer.[2-4] In connection with our previous studies for the latter purpose,[5,6] the shortcomings of the existing[1a] synthetic method, namely, the length of time (1.5 months!) required and the presence of the bis-piperidine precursor (2) in the reaction mixture and the isolated product, motivated us to seek a more convenient synthesis.

Two polymorphic forms of (1) have been crystallographically characterized: needles of the alpha-phase in centrosymmetric space group Pccn[2d] and orange parallelopiped crystals in noncentrosymmetric space group Pca2_1.[4] In the course of our solid state characterization of samples of (1), we observed that exposure of polycrystalline samples of the beta-phase to Cu Kα x-rays convert it to the alpha-phase. We subsequently found that ^{60}Co gamma radiation brought about the same polymorphic phase transformation.

These studies are detailed herein. Our studies of magnetism in samples of (1) and polymeric materials obtained by heating of (1) by static susceptibility[5] and by electron spin resonance[6] have been separately reported. In the course of these studies, we also synthesized other diacetylenic nitroxides. Our procedures for the synthesis of two of these compounds, 2,4-hexadiyn-1,6-diyl-bis-(2,2,5,5-tetramethyl-1-oxyl-3-pyrolline-3-carboxylate) (3), and 5-(2,2,6,6-tetramethyl-1-oxyl-1,2,5,6-tetrahydropyridin-4-yl)penta-2,4-diyn-1-ol (4), are given in the Experimental Section, with emphasis on observations unique to our studies.

RESULTS AND DISCUSSION

Synthesis

The original[1a] synthesis of (1) involved tungstate oxidation of (2) over a period of 1.5 months. We found that the synthesis of (1) via the reported[1a] method did not give reproducible yields, and that unreacted (2) was always found in the reaction mixtures and the samples of (1). Accordingly, we sought an alternative synthesis of (1).

The oxidative coupling of monoacetylenes using the procedure of Hay[7] is a standard method of synthesis for conjugated diynes. Accordingly, this approach was used with (5) as starting material. In view of the reported crystal structure of (5),[8] which reveals the -OH group in an equatorial position, while it is in an axial position in the reported[2d,4] structures of (1), this synthetic strategy anticipates the expected low barrier to nitrogen inversion in nitroxides.[9] Our isolation and characterization of (1) confirms this strategy.

Both the literature[1a] and our synthetic routes to (1) are summarized in Figure 1. As detailed below in Experimental, we routinely isolated (1) in yields in excess of 40% by the Hay coupling of (5) at 0°C. When the Hay coupling of (5) was attempted at 20-25°C, the presence of (1) could not be detected in the reaction mixture.

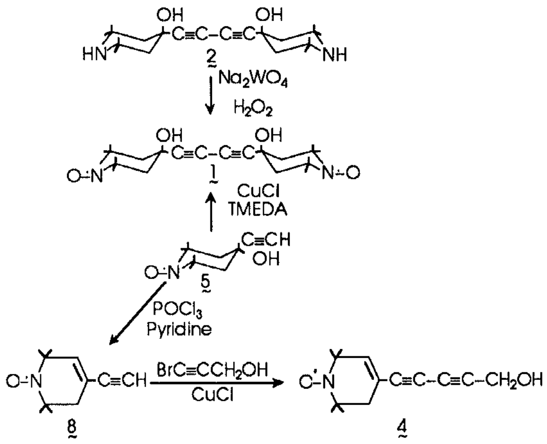

Figure 1. Synthetic routes to the diacetylenic nitroxides 1 and 4.

There has been some uncertainty concerning the thermal behavior of (1). The initial report[1a] gave a decomposition point above 220°C, and a subsequent report[4a] gave a decomposition temperature of approximately 140°C. Our initial observations during relatively rapid heating in a capillary tube indicated a decomposition temperature in the 150–160°C range. Our studies via differential scanning calorimetry[5] indicated a decomposition temperature of 139° for a heating rate of 2°/min, while a decomposition temperature of 160° was noted for a heating rate of 13°/min.

Single crystals of the beta phase of (1) were obtained from ethyl acetate solution, as previously described[4]. We obtained single crystals of the alpha polymorph of (1) by crystallizing a mixture of (1) and (2) in a molar ratio of 3.74:1 from aqueous methanol.[5]

Our synthesis of (3) involves the use of the carboxylate (6) in N,N-dimethylformamide(DMF) as a nucleophile to displace tosylate in PTS monomer (7) and is shown in Figure 2. Also shown in Figure 2 is the reported synthesis of (3) involving esterification of the acid related to (6) and the appropriate diol brought about by dicyclohexylcarbodiimide.[10]

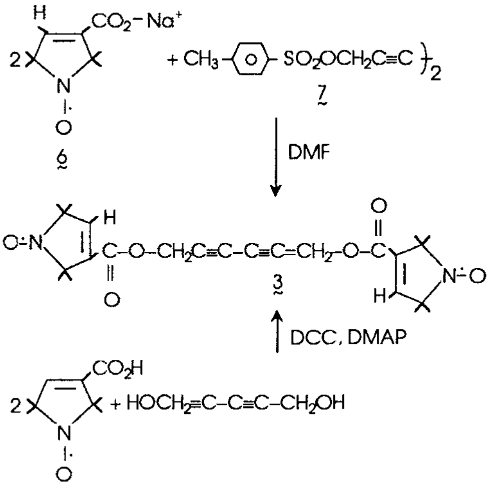

Figure 2. Synthetic routes to the diacetylenic nitroxide 3.

There have been two reports concerning (4) and its crystal structure and solid state reactivity. In one report,[11] the structure of a monoclinic form of (4) was reported, and its synthesis via a Cadiot-Chodkiewicz coupling was claimed, but no experimental detail was given. A second publication[12], submitted after publication of reference 11, reported the synthesis of (4) from a coupling of the dehydration product of (5), namely (8), and propargyl alcohol; (4) was described as unstable, and a satisfactory elemental analysis was not obtained. This paper[12] also reported the same crystal structure for (4), as previously reported[11]. Both publications concluded that topochemical polymerization of (4) was unlikely for structural reasons. Our synthesis of (4) via Cadiot-Chodkiewicz coupling of (8) and 3-bromo-2-propyn-1-ol is given in the Experimental Section and shown in Figure 1. We obtained a satisfactory elemental analysis of (4) and confirm the lack of topochemical solid state reactivity. We isolated both the previously reported[11,12] phase of (4) as well as a different solid form, as revealed by x-ray powder diffraction.

A Radiation-Induced Polymorphic Transformation of (1)

In the course of our routine identification of the phase of (1) by x-ray powder diffraction, it was noted that the observed diffraction pattern continued to change on prolonged exposure to the Cu Kα radiation, and that the observed changes were consistent with the conversion of the beta phase of (1) to the alpha phase. We have found that this polymorphic transformation is conveniently monitored by careful observation of the diffraction pattern in the 2θ range 6-13°, as illustrated in Figure 3. The initial scan of a sample of the beta phase of (1) is shown in Figure 3(a), revealing, in increasing values of 2θ, the reflections (0,0,2); (–2,0,0); (-1,-1,0); (-2,0,-1). A subsequent scan of this sample is exhibited in Figure 3(b). The intensity of the reflections shown in Figure 3(a) is decreased in Figure 3(b), and the following reflections, in increasing value of 2θ, of the alpha phase are observed: (-2,0,0); (1,-1,1); (-1,0,2).

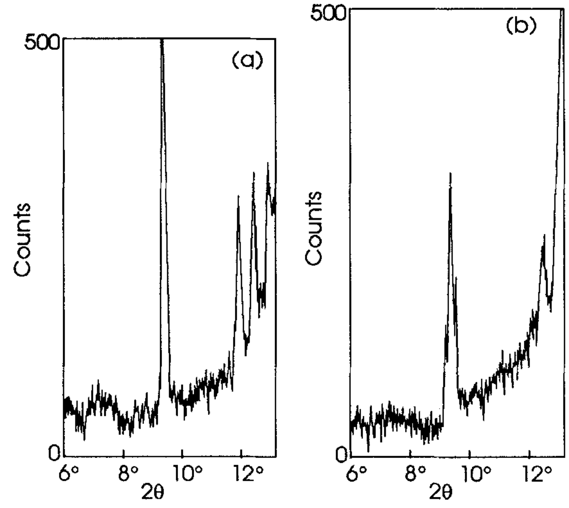

Figure 3. X-ray diffractometer tracing (2θ = 6–13°) for (a) β-phase of 1, initial scan; (b) same sample of 1, subsequent scan, revealing reflections of both α- and β-phases.

The data summarized in Figure 3 are not representative of all samples of the beta phase of (1). Such data are found only in polycrystalline samples of (1), as exposure of single crystals of beta-(1) to Cu Kα radiation for 16 hr did not result in detectable changes in rotation or Weissenberg photographs. Additionally, data of the type shown in Figure 3 are not found in samples of beta-(1) which have not been exposed to atmospheric conditions. For example, a sample of beta-(1) was sealed in a sample holder in an inert atmosphere glove box. The diffraction patterns for repeated scans of this sample revealed no change. However, on exposure of the sample to the ambient atmosphere, the pattern immediately began to change, analogously to that illustrated in Figure 3. The changes shown in Figure 3 are found in samples synthesized either as described previously[1a] or by the Hay coupling procedure described herein.

It was also of interest to learn if other forms of ionizing radiation could bring about the polymorphic transformation. We found that if a sample of beta-(1) in an ampoule sealed under vacuum was exposed to ^{60}Co gamma radiation (>30 Mrad over 31 days), the sample did not undergo the transformation. However, if a sample is divided into two parts, one of which was shown to undergo the polymorphic transformation, the second was exposed, in the presence of air, to a similar dose of gamma radiation, the polymorphic transformation occurred. Using samples of beta-(1), divided into two parts, as above, and shown to be reactive toward Cu Kα radiation, we have not yet observed the polymorphic transformation with Fe Kα radiation.

EXPERIMENTAL

General

Melting points are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Synthesis of 4-Ethynyl-4-hydroxy-2,2,6,6-tetramethyl-1-oxyl (5). This procedure is patterned after Method B of Rauckman, *et al.*[13] Powdered 4-ethynyl-4-hydroxy-2,2,6,6-tetramethylpiperidine[14] (10.0 g, 55.2 mmol) was dissolved in warm methanol (400 ml). The solution was allowed to cool, and acetonitrile (7ml), sodium bicarbonate (3.65 g, 43.5 mmol), and sodium tungstate (0.551 g, 1.67 mmol) were added. To this solution was added 30% hydrogen peroxide (20.4 ml, 666 mmol) over a period of one hour. The mixture was kept in the dark at ambient temperature for 4-5 days. It was then filtered, the filtrate was diluted with saturated sodium chloride (400 ml), and the pH was adjusted to 3-4 with concentrated hydrochloric acid. This solution was exhaustively extracted with dichloromethane, and the organic layer was dried over $MgSO_4$ and evaporated to give an orange solid. Vacuum sublimation gave (3), 4.62 g (43% yield), mp 125°C (lit.[15] mp 125-126°C). X-ray powder diffraction of the solid exhibited the following reflections (2θ, degrees): 7.5, 13.8, 14.0, 15.1, 15.8, 17.7, 18.1, 18.9, 19.1, 19.7, 20.5, as expected for the reported[8] crystal structure of (3).

Synthesis of 4,4'-(Butadiyne-1,4 diyl)-bis-(2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl) (1). A mixture of cuprous chloride (174 mg, 1.76 mmol), N,N,N',N'-tetramethylethylenediamine (211 mg, 1.76 mmol) and (3) (495 mg, 2.52 mmol) in acetone (10 ml) was stirred magnetically at 0°C. Oxygen was bubbled into this mixture over a period of 2.5 hr. At this time, water (20 ml) was added, and the mixture was filtered. Crystallization of the solid product from ethyl acetate gave the desired product, 230 mg (47% yield), m.p. 153°(dec.) (capillary tube). X-ray powder diffraction identified the solid as the beta phase of (1).

Anal. Calculated for $C_{22}H_{34}N_2O_4$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.94; H, 8.45; N, 6.94.

Synthesis of 2,4-Hexadiyn-1,6-diyl-bis-(2,2,5,5-Tetramethyl-1-oxyl-3-pyrolline-3-carboxylate, (3). A warm solution of powdered NaOH(0.792 g, 0.02 mole) in N,N-dimethylformamide (DMF, 18 ml) was added to a warm solution of the acid related to (6) (3.31 g, 0.018 mole). To the magnetically stirred cool solution of (6) was added a DMF (18 ml) solution of (7)[16] (2.364 g, 0.006 mole), and the mixture was heated at 50°C for 4 hr. The solution was then poured into ice water and extracted with chloroform. The extracts were washed with water (6 × 100 ml) and saturated Na_2CO_3(2 × 100 ml), dried over $MgSO_4$ and evaporated. A chloroform solution of the residue was chromatographed on silica gel, and the product was crystallized from 8:1 (v/v) hexane-benzene to give (3), 0.98 g (37% yield), m.p. 106–107°C [lit[10] m.p. 104–105°C (alpha phase), 108–109°C (beta phase)]. The mass spectrum exhibited the expected molecular ion at m/e 442. X-ray powder diffraction of this material indicated it to be a mixture of the reported[10] phases.

Anal. Calculated for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6,83; N, 6.33. Found: C, 64.42; H, 6.99; N, 6.22.

Synthesis of 4-Ethynyl-2,2,6,6-tetramethyl^3-dihydro-1-piperidin-1-oxyl, (8). To a solution of (3) (3.92 g, 0.02 mole) in dry pyridine (20 ml) was added $POCl_3$ (3.45g, 2.1 ml, 0.0225 mole), and the solution was magnetically stirred for 24 hr. The solution was diluted with water and extracted with benzene until the washings were colorless. The benzene solution was washed with 0.01M HCl (5–200 ml portions) and water (3–200 ml portions), dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel in benzene and recrystallized from hexane to give (8), 1.76 g (49% yield), m.p. 50–52° (lit.[17] m.p. 47°C). The mass spectrum exhibited the expected molecular ion at m/e 178, and the infrared spectrum (nujol) exhibited the following main absorptions (cm^{-1}): 3320, 3240, 1360, 1255, 940, 910, 880, 870, 820, 800, 640.

Synthesis of 5-(2,2,6,6-Tetramethyl-1-oxyl-1,2,5,6-tetrahydro-pyridin-4-yl)penta-2,4-diyn-1-ol, (4). To a solution of hydroxylamine hydrochloride (1.03 g, 0,015 mole) in water (3.6 ml) was added methanol (10.2 ml), 70% aqueous ethylamine (8.3 ml), and CuCl (0.198 g, 0.002 mole). This mixture was stirred magnetically under argon. To this solution was added (8) (3.88 g, 0.022 mole). 3-Bromo-2-propyn-1-ol (3.46 g, 0. 026 mole) was added over a period of one hour to the mixture kept at 30-35°C. After heating and stirring for 3.5 hr, volatiles were removed under reduced pressure. To the residue was added a solution of KCN (0.513 g, 0.08 mole), NH_4Cl (2.08 g, 0.039 mole) in water (31 ml) with stirring. Ether was used to extract a brown solid, and the ether extract was washed with water, dried over $MgSO_4$, filtered and evaporated. A chloroform solution of the brown residue was chromatographed on silica gel. Recrystallization of the product gave (4), 1.65 g (33% yield), m.p. 122–123°C. Mass spectrometry revealed the expected molecular ion at m/e 232. The main features of the infrared spectrum (nujol) are (cm^{-1}): 3370, 2730, 1360, 1335, 1295, 1260, 1235, 1180, 1140, 1065, 1030, 945, 870, 800. The x-ray powder pattern of (4) crystallized from cyclohexane or aqueous methanol revealed the reported[11,12] phase. Another crystalline form of (4) was obtained by crystallization from a 2:1 v/v hexane-chloroform mixture, m.p. 130–133°. X-ray powder diffraction of this material exhibited the following (d, Å): 7.3, 6.65, 6.50, 6.42, 5.86, 5.31, 4.95, 4.77, 4.41, 4.11, 3.95, 3.74, 3.55.

Anal. Calculated for $C_{14}H_{18}NO_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 71.94; H, 7.57; N, 5.81.

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