Pertanika 11(1), 87–90 (1988)

Synthesis of N-methoxy-N-methylaminocarbonyl-1, 4-benzoquinone: the First Quinone Carrying an N-methoxy-N-methylamino Group

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Key words: Quinone synthesis N-methoxy-N-methylaminocarbonyl-1; 4-benzoquinone.

ABSTRAK

Di sini kami laporkan satu penyediaan sebatian yang disebutkan di atas sebanyak empat peringkat. Asid gentisik (1) pada permulaannya telah ditukarkan kepada asetatnya (2) dengan tindak balas asetik anhidrida dengan kehadiran asid sulfurik pekat. Tindakbalas diasetat ini dengan oksalil klorida dalam pelarut diklorometana dengan kehadiran dimetilformamida diikuti dengan N-O-dimetilhidroksiamina hidroklorida dan piridina menghasilkan 2, 5-diasetoksi-N-metoksi-N-metilbenzamida (3) satu sebatian yang diperlukan bagi sintesis kuinon yang disebutkan di atas. Tindak balas sebatian terakhir ini dengan natrium hidrogen karbonat bagi menghasilkan hidrokuinon (4) diikuti dengan pengoksidaan oleh perak oksida menghasilkan kuinon (5) yang diperlukan.

ABSTRACT

We report herein a four-step preparation of the title compound. Gentisic acid (1) was firstly converted into its diacetate (2) by treatment with acetic anhydride in the presence of concentrated sulfuric acid. Treatment of the diacetate with oxalyl chloride in dichloromethane in the presence of dimethylformamide followed by N-O-dimethyl-hydroxyamine hydrochloride and pyridine gave 2, 5-diacetoxy-N-methoxy-N-methylbenzamide (3). Reaction of this with sodium hydrogen carbonate to generate the hydroquinone (4) followed by oxidation with silver oxide gave the desired quinone (5).

INTRODUCTION

Acetyl-1, 4-benzoquinone (6) is well documented (Bruce, 1981). Addition of buta-1, 3-diene to this quinone occurs with great ease at –70 to –50°C in dichloromethane containing a little trifluoroacetic acid and gives adduct (7) almost exclusively. Treatment of this adduct with a 1:1 mixture of pyridine and methanol at room temperature gives a quantitative yield of its isomer (9) (Sabetian, 1978). This isomerisation involves a [1,5]–acetyl shift in the intermediate enol (8) (Ahmad, *et al.* 1981) (Scheme 2).

Interestingly, addition of buta-1, 3-diene to oximinoquinone (10), an oxime of quinone (6), has been reported (Kishi, *et al.* (1970). The addition can be controlled by complexing with stannic chloride in acetonitrile, addition of the diene then occurring exclusively at the side carrying the oximino group, to give the adduct (11).

To our knowledge, *N*-methoxy-*N*-methylaminocarbonyl-1, 4-benzoquinone (5) has not been reported in the literature. Therefore it was of in-

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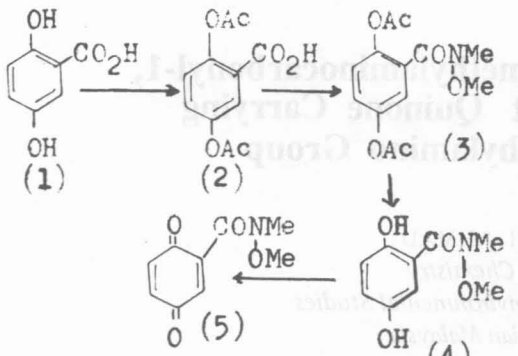


Scheme 1.

terest to synthesise it in order to determine whether the adduct (12) would be formed on addition of buta-1, 3-diene. Reaction of the adduct with pyridine and methanol could then be examined.

MATERIALS AND METHODS

Proton magnetic resonance (p.m.r.) spectra are quoted in p.p.m. with respect to internal tetramethylsilane, and were measured on a Perkin-Elmer R12B instrument at 60MHz, a Perkin-Elmer R34 instrument at 220 MHz, and a Varian SC300 instrument at 300 MHz as stated. Multiplicities of peaks are denoted by s, d and dd indicating singlet, doublet and double doublet; a prefix b indicates broadening of the signal. Coupling constants *(J)* are in Hz. Resonances assigned to hydroxyl groups were removed by addition of D_2O.

Mass spectra (m.s.) were recorded on A.E.I. MS 25 and MS 30 instruments. The relative abundances (% of base peak) of fragments are quoted in parentheses after *m/z* values. Melting points (m.p.) were recorded on a Kofler block and are uncorrected.

Infrared (i.r.) spectra were recorded on a Perkin-Elmer FTIR 1710 spectrometer as films or solutions as stated. Intensities are expressed by s and m to indicate strong and medium, respectively.

2, 5-Diacetoxybenzoic Acid (2)

To a stirred solution of gentisic acid (7.5g, 5 mmole) in acetic anhydride (12 ml) was added concentrated sulphuric acid (10 drops) and the reaction mixture was then heated for 1 hr at 70°C. The solution was then cooled, water (100 ml) added, and the suspension shaken vigorously for several minutes. The product allowed to crystallise at 0°C and collected by filtration to afford white crystals (9.0 g, 78%), m.p. 120–121°C (m.p. 116–119°C, Pardasani, 1982). It had δ(60 MHz, $CDCl_3$) 2.30 (3H, s, 2x OAc), 7.10 (1H, d, *J* 9, H–3), 7.40(1H, dd, *J* 9, *J* 3, H-4), 7.90(1H, d, *J* 3, H-6), and *m/z* CI(NH_3)332 [100, $(M + 18)^+$], , 290[15, $(M + 16 - CH_2CO)^+$], 221 (42, $[C_6H_3CO(OAc)_2]^+$).

2, 5-Diacetoxy-N-methoxy-N-methylbenzamide (3)

To a stirred solution of gentisic acid diacetate (3.20 g, 15 mmole) in dichloromethane (40 ml), was added oxalyl chloride (2.10 g, 16 mmole), and DMF (15 drops). Effervescence occurred and the reaction was allowed to continue for about 40 min. To this solution was then added *N, O*-dimethylhydroxylamine hydrochloride (1.6 g, 16 mmole) followed by pyridine (2.52 g, 2.6 ml, 32 mmole). The mixture was stirred at room temperature for 1.5 hr. Brine (40 ml) was then added and the organic layer separated. The aqueous layer was extracted with a 1:1 mixture of ether and dicholoromethane (4 x 20 ml). The combined extracts were washed with brine (1 x 30 ml) and dried. Removal of the solvent gave the desired product (2.24 g, 78%) as a sticky colourless oil which was then distilled (bulb-to-bulb) at 76–78 °C/0.1 mmHg (Found C, 55.6; H, 5.6; N, 4.9, $C_{13}H_{15}NO_6$ requires C, 55.5 H, 5.4 N, 5.0%). It had δ(60 MHz, $CDCl_3$) 2.20 (3H, s, Ac), 2.50 (3H, s, Ac), 3.24 (3H, s, NMe), 3.47(3H, s, OMe), 7.21(3H, bs, H–3+H–4+H–6) *m/z* CI(NH_3) 299 [9, $(M + 18)^+$], 282[100, $(M + 1)$], 252 [18, $(M + 1-2Me)$], 210 [79, $(M + 1 - CH_2 = C = O - 2Me]$, and γ_{max}(film) 1640s, 1760s cm^{-1}

2, 5-Dihydroxy-N-methoxy-N-methylbenzamide (4)

To a stirred solution of the foregoing diacetate (160 mg, 0.57 mmole) in methanol (10 ml) under nitrogen at room temperature was added saturated sodium hydrogen carbonate (6 ml). After stirring for 2 hr the mixture was acidified with 10% hydrochloric acid, extracted with ethyl acetate (4 x 20 ml), and dried (Na_2SO_4). Evaporation of

the solvent gave the desired product as a brownish oil (73 mg, 66%) which was purified by distillation (bulb-to-bulb) at 74–80°C/0.1 mmHg (Found: C, 54.6; H, 5.8; N, 6.4, $C_9H_{11}NO_4$ requires C, 54.8; H, 5.6; N, 7.1%). Elemental analysis persistently showed a low nitrogen content. The above data were obtained using freshly distilled material, (Found: M^+, 197.0690, $C_9H_{11}NO_4$ requires M, 197.0688). It had δ (300 MHz, $CDCl_3$) 3.40 (3H, s, NMe), 3.64 (3H, s, OMe), 6.80–7.10 (1H, bs, HO-5), 6.92(1H, 3d, J 9, H–3), 6.98 (1H, dd, J_1 9. J_2 3, H–4), 7.50 (1H, d, J 3, H–6), 13.30–13.40 (1H, b, HO-2), m/z 197 (8, m^+), 168 [8, $(M-NMe)^+$], 167[17, $(M\text{-}OMe + 1)^+$], 137 [100, M-CO.NMe.OMe^+], and γ_{max} (CH_2Cl_2) 3680–3580b, 1575s cm^{-1}.

N-Methoxy-N-methylaminocarbonyl-1, 4-benzoguinone (5)

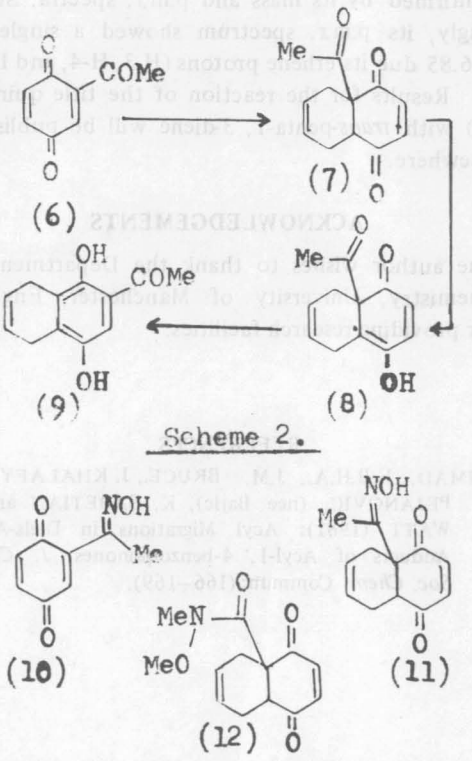
A mixture of 2.5-dihydroxy-*N*-methoxy-*N*-methylbenzamide (20 mg, 0.1 mmole), silver oxide (80 mg, 0.3 mmole), and anhydrous sodium sulphate (150 mg) in dry dichloromethane (5 ml) was shaken for 5 hr in a flask covered with aluminium foil, at room temperature. The suspension was then filtered through Celite, and washed with dichloromethane until the washings had no colour.

Solvent evaporation gave an orange sticky oil (16 mg, 81%), which was distilled at 60–68°C/0.1 mmHg (Found: M^+, 195.0532. $C_9H_9O_4N$ requires M, 195.0534). It had δ (220 MHz, $CDCl_3$) 3.32 (3H, s, NMe), 3.51 (3H, s, OMe), 6.85 (3H, s, H–3 + H–4 + H–6), m/z 195 (32, M^+), 135[72, $(M\text{-}NMe.OMe)^+$], 107[92, $(M\text{-}CO.NMe.OMe)^+$], and γ_{max} (film) 1664s cm^{-1}).

RESULTS AND DISCUSSION

The first synthesis of the title quinone (5) is shown in Scheme 1. Treatment of gentisic acid (1) with acetic anhydride in the presence of sulfuric acid at 70°C gave the desired gentisic acid diacetate (2) in 75% yield as white crystals, m.p 120–121°C; identical (m.p., mixed m.p) with the compound previously reported by Pardasani, (1982).

Reaction of gentisyl chloride diacetate [formed *in situ* by treatment of the diacetate (2) with oxalyl chloride] and *N-O*-dimethylhydroxylamine hydrochloride in dichloromethane containing pyridine at room temperature gave the desired diacetate (3) in 79% yield as a colourless stickly oil. Its structure was confirmed by its elemental analysis, mass and p.m.r. spectra. Its mass spectrum CI(NH_3) showed that diacetate (3) easily lost ketene and two methyl groups. Suprisingly, it was unchanged on treatment with 2M hydrochloric acid in acetone at room temperature overnight. In this connection Nahm and Weinreb (1981) reported that *N*-methoxy-*N*-methylamides showed normal tertiary amide stability and hence required no special handling.



Treatment of diacetate (3) with saturated sodium hydrogen carbonate under nitrogen in methanol gave the desired hydroquinone (4). Its structure was confirmed by its mass and p.m.r. spectra. Its mass spectrum (EI) showed that the hydroquinone easily lost the CO.(NMe). OMe group to give the base peak. However, it was difficult to obtain a good elemental analysis: the nitrogen value was always low, although several attempts were made using freshly distilled material. The desired quinone (5) was easily prepared by oxidation of hydroquinone (4) using silver oxide in dichloromethane at room temperature, and was an orange stickly oil. Its structure was

confirmed by its mass and p.m.r. spectra. Suprisingly, its p.m.r. spectrum showed a singlet at δ 6.85 due its ethene protons (H-3, H-4, and H-6).

Results for the reaction of the title quinone (5) with *trans*-penta-1, 3-diene will be published elsewhere.

ACKNOWLEDGEMENTS

The author wishes to thank the Department of Chemistry, University of Manchester, England for providing research facilities.

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(Received 14 November, 1987)