Synthesis of Some Aldoxime Derivatives of 4H-Pyran-4-ones†

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Abstract: Aldoxime derivatives of 4H-pyran-4-ones 4-7a,b have been synthesized by the reaction of di(aminoxymethyl) pyranones 3a,b with aromatic aldehydes.

Keywords: 4H-pyran-4-one, N-hydroxyphthalimide, Condensation reaction.

Introduction

4H-pyran-4-one derivatives constitute an useful class of heterocyclic compounds which are widely distributed in nature [1,2]. These compounds display diverse biological activities, acting as fungicides and herbicides and a variety of pharmacological actions, which could be useful in the treatment of asthma and allergies [3,4].

Several synthetic routes to 4H-pyran-4-one derivatives have been reported in the literatures [5-7]. However, the synthesis of their aminoxymethyl derivatives have not developed. 2-Aminoxymethyl-5-benzyloxy-4H-pyran-4-one, which was prepared by Natio and co-workers, has been used as an intermediate in the synthesis of cephalosporin derivatives [8]. As a followup of their work, we report here the synthesis of some aldoxime derivatives of 4H-pyran-4-ones, which have been prepared by the condensation of di(aminooxymethyl) derivatives of 4H-pyran-4-ones with aromatic aldehydes.
Results and Discussion

The reaction of di(bromomethyl) pyranones 1a,b and N-hydroxyphthalimide gave the di(N-phthalimidoxymethyl) 4H-pyran-4-one derivatives 2a,b in 82.5 and 52% yields, respectively, which were hydrazinolysized to produce the corresponding di(aminoxymethyl) pyranones 3a,b in 91 and 67.6% yields. The condensation of the compounds 3a or 3b with benzaldehydes at 0°C led to mixtures of isomeric pairs of aldoximes 4a,b, 5a,b and 6a,b, 7a,b formed in 9.7-72% yields, which were the mixture of (E,E) and (Z,Z) isomers of each compound (Scheme 1). Characterization of these compounds indicated that in each case, the major product was the (E,E) isomer.

Scheme 1

The 1H-NMR spectra of the (E,E) isomers 4a,b and 6a,b and the (E,Z) isomers 5a,b and 7a,b were not identical. The two azomethine protons in the (E,E) isomers 4a,b and 6a,b appeared as a singlet around 8.1 ppm while in the (E,Z) isomers 5a,b and 7a,b one of these protons appeared in the aromatic
area. The proposed structures have been confirmed by the spectral data (IR, ¹H-NMR and MS) and elemental analyses.

Conclusions

Several new aldoxime derivatives of 4H-pyran-4-ones 4-7a,b were synthesized and characterized for the first time. These compounds were prepared by condensation of di(aminooxymethy) pyranones 3a,b with aromatic aldehydes.

Experimental

General

Melting points were determined with an Electrothermal Instrument model 9100 and are uncorrected. IR spectra (KBr disks) were taken on a Shimadzu 8010M spectrophotometer. ¹H-NMR spectra were recorded for CDCl₃ solutions on a FT-NMR Brucker 100 MHz spectrometer. Chemical shifts are reported in ppm values relative to TMS used as the internal standard. Mass spectra were obtained on a Shimadzu GC MS-QP 1100 EX. Elemental analyses were performed on a Heareus, CHN-O-RAPID analyzer.

General procedure for preparation of di(N-phthalimidoxyethyl) pyranones 2a,b.

A mixture of di(bromomethyl)diphenyl-4H-pyran-4-one 1a [9] or 1b [10] (6.0 g, 13.8 mmol), N-hydroxyphthalimide (4.8 g, 29 mmol), Et₃N (4.2 g, 41mmol) and DMF (50 mL) was stirred at room temperature for 24 hrs. To this mixture was added water (20 mL) and the resulting solid was filtered and washed with water. The crude product 2a,b was used without any purification in the next step.

3,5-Di(N-phthalimidoxyethyl)-2,6-diphenyl-4H-pyran-4-one (2a). Colourless crystals (82.5% yield), m.p. 233-235°C; ¹H-NMR δ: 4.9 (s, 4H, -CH₂O-), 7.15-7.85 (m, 18H, phenyl-); IR: 3075, 2950, 2875, 1790, 1730, 1670, 1635, 1575 cm⁻¹; MS: m/z 598; Anal. Calcd. for C₃₅H₂₂N₂O₈: C, 70.23; H, 3.70; N, 4.68. Found: C, 69.80; H, 3.80; N, 4.57.

2,6-Di(N-phthalimidoxyethyl)-3,5-diphenyl-4H-pyran-4-one (2b). Colourless crystals (52% yield), m.p. 228-229.5°C; ¹H-NMR δ: 4.95 (s, 4H, -CH₂O-), 7.1-7.3 (m, 10H, phenyl-); IR: 3094, 2925, 2853, 1790, 1740, 1631, 1620, 1579 cm⁻¹; MS: m/z 598; Anal. Calcd. for C₃₅H₂₂N₂O₈: C, 70.23; H, 3.70; N, 4.68. Found: C, 70.12; H, 3.67; N, 4.62.

General procedure for preparation of di(aminooxymethyl) pyranones 3a,b.

Hydrazine hydrate (97%, 1.7 mL) was added dropwise over 20 min. to a stirred suspension of compound 2a or 2b (4.0 g, 6.6 mmol) in absolute methanol (40 mL) [11] at 0°C under nitrogen. The mixture was stirred at the same temperature for 1h, then allowed to reach room temperature, and the
residue was dissolved in dichloromethane. The mixture was cooled, stirred, and filtrated. After removing of the remaining phthalhydrazide, the filtrate was evaporated to give the crude crystalline solid 3a,b.

3,5-Di(aminoxymethyl)-2,6-diphenyl-4H-pyran-4-one (3a). Colourless crystals (91.5% yield), m.p. 127-129°C; 1H-NMR δ: 4.65 (s, 4H, -CH$_2$O-), 5.3 (br, 4H, -NH$_2$), 7.35-7.55 (m, 10H, phenyl-H); IR: 3300, 3150, 3050, 2950, 2872, 1643, 1495, 1448 cm$^{-1}$; MS: m/z 338; Anal. Calcd. for C$_{19}$H$_{18}$N$_2$O$_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.28; H, 5.23; N, 8.30.

2,6-Di(aminoxymethyl)-3,5-diphenyl-4H-pyran-4-one (3b). Colourless crystals (67.6% yield), m.p. 131.5-133°C; 1H-NMR δ: 4.64 (s, 4H, -CH$_2$O-), 5.37 (br, 4H, -NH$_2$), 7.23 (m, 10H, phenyl-H); IR: 3300, 3250, 3140, 3050, 2960, 1640, 1622, 1570, 1413 cm$^{-1}$; MS: m/z 338; Anal. Calcd. for C$_{19}$H$_{18}$N$_2$O$_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 66.97; H, 5.27; N, 8.20.

General procedure for preparation of aldoxime derivatives of 4H-pyran-4-ones 4-7a,b.

To a stirred suspension of compound 3a or 3b (0.5 g, 1.47 mmol) and 4Å molecular sieves (1.5 g) in dry dichloromethane (15 mL) at 0°C under nitrogen was slowly added benzaldehyde (0.31 g, 2.9 mmol) or 4-methylbenzaldehyde (0.36 g, 2.9 mmol). When the addition of aldehyde was complete, the mixture was stirred at room temperature overnight. After filtration, the solvent was evaporated. The resulting crude product was purified by column chromatography on silicagel, using 9:1 petroleum ether - ethyl acetate as an eluent.

(E,E)-Benzal[(2,6-diphenyl-3,5-4H-pyran-4-one-diyl)bis(methylene)]dioxime (4a). Yellow oil (70.1% yield); 1H-NMR δ: 5.1 (s, 4H, -CH$_2$O-), 7.2-7.85 (m, 20H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3050, 3017, 2983, 2875, 1644, 1607, 1446 cm$^{-1}$; MS: m/z 514; Anal. Calcd. for C$_{33}$H$_{26}$N$_2$O$_4$: C, 77.03; H, 5.09; N, 5.44. Found: C, 77.18; H, 5.10; N, 5.38.

(E,E)-Benzal[(3,5-diphenyl-2,6-4H-pyran-4-one-diyl)bis(methylene)]dioxime (4b). Yellow oil (68% yield); 1H-NMR δ: 5.1 (s, 4H, -CH$_2$O-), 7-7.6 (m, 20H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3050, 3010, 2950, 2900, 1630, 1470, 1405 cm$^{-1}$; MS: m/z 514; Anal. Calcd. for C$_{33}$H$_{26}$N$_2$O$_4$: C, 77.03; H, 5.09; N, 5.44. Found: C, 76.92; H, 5.10; N, 5.30.

(E,Z)-Benzal[(2,6-diphenyl-3,5-4H-pyran-4-one-diyl)bis(methylene)]dioxime (5a). Yellow oil (10.5% yield); 1H-NMR δ: 5.1 (s, 4H, -CH$_2$O-), 7.1-7.8 (m, 20H, phenyl-H), 8.1 (s, 1H, -N=CH-); IR: 3050, 3010, 2980, 2872, 1640, 1480, 1440 cm$^{-1}$; MS: m/z 514; Anal. Calcd. for C$_{33}$H$_{26}$N$_2$O$_4$: C, 77.03; H, 5.09; N, 5.44. Found: C, 77.20; H, 4.92; N, 5.34.

(E,Z)-Benzal[(3,5-diphenyl-2,6-4H-pyran-4-one-diyl)bis(methylene)]dioxime (5b). Yellow oil (10% yield); 1H-NMR δ: 5.15 (s, 4H, -CH$_2$O-), 7-7.6 (m, 20H, phenyl-H), 8.1 (s, 1H, -N=CH-); IR: 3050, 3010, 2985, 1640, 1600, 1480, 1440 cm$^{-1}$; MS: m/z 514; Anal. Calcd. for C$_{33}$H$_{26}$N$_2$O$_4$: C, 77.03; H, 5.09; N, 5.44. Found: C, 77.29; H, 5.01; N, 5.32.
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(E,E)-4-Methylbenzal[(2,6-diphenyl-3,5-4H-pyran-4-one-diyl)bis(methylene)]dioxime (6a). Colourless crystals (60% yield), m.p. 128°C; $^1$H-NMR $\delta$: 2.2 (s, 6H, -CH$_3$), 5.1 (s, 4H, -CH$_2$O-), 6.9-7.9 (m, 18H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3060, 3035, 2940, 2890, 1640, 1620, 1570, 1480 cm$^{-1}$; MS: m/z 542; Anal. Calcd. For C$_{35}$H$_{30}$N$_2$O$_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.34; H, 5.47; N, 5.02.

(E,E)-4-Methylbenzal[(3,5-diphenyl-2,6-4H-pyran-4-one-diyl)bis(methylene)]dioxime (6b). Colourless oil (61.5% yield); $^1$H-NMR $\delta$: 2.15 (s, 6H, -CH$_3$), 5.2 (s, 4H, -CH$_2$O-), 6.9-7.5 (m, 18H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3050, 3020, 2975, 2880, 1640, 1600, 1480, 1440 cm$^{-1}$; MS: m/z 542; Anal. Calcd. for C$_{35}$H$_{30}$N$_2$O$_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.27; H, 5.49; N, 5.11.

(E,Z)-4-Methylbenzal[(2,6-diphenyl-3,5-4H-pyran-4-one-diyl)bis(methylene)]dioxime (7a). Colourless crystals (11.2% yield), m.p. 138°C; $^1$H-NMR $\delta$: 2.3 (s, 6H, -CH$_3$), 5.2 (s, 4H, -CH$_2$O-), 6.9-7.9 (m, 18H, phenyl-H; 1H, -N=CH-); IR: 3050, 3020, 2940, 2880, 1630, 1570, 1500 cm$^{-1}$; MS: m/z 542; Anal. Calcd. for C$_{35}$H$_{30}$N$_2$O$_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.51; H, 5.42; N, 5.12.

(E,Z)-4-Methylbenzal[(3,5-diphenyl-2,6-4H-pyran-4-one-diyl)bis(methylene)]dioxime (7b). Colourless oil (12.3% yield); $^1$H-NMR $\delta$: 2.2 (s, 6H, -CH$_3$), 5.2 (s, 4H, -CH$_2$O-), 6.9-7.5 (m, 18H, phenyl-H; 1H, -N=CH-); IR: 3050, 3010, 2930, 2890, 1645, 1620, 1480 cm$^{-1}$; MS: m/z 542; Anal. Calcd. for C$_{35}$H$_{30}$N$_2$O$_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.43; H, 5.39; N, 5.18.

References and Notes

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