

## Synthesis of Some Aldoxime Derivatives of 4*H*-Pyran-4-ones<sup>†</sup>

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

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

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### Introduction

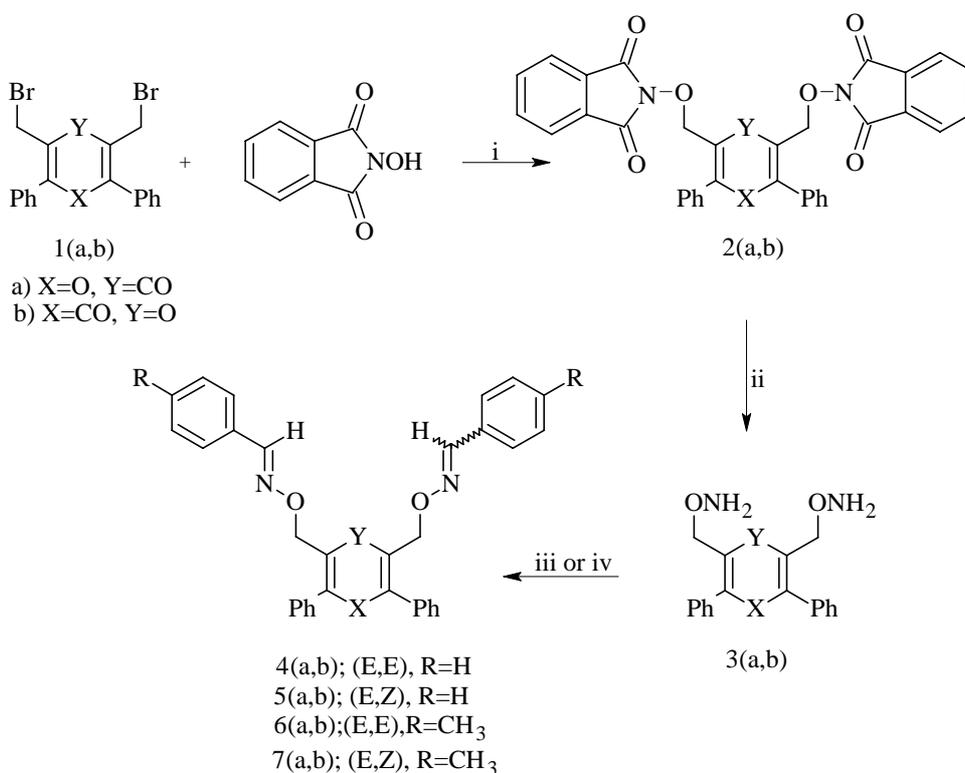
4*H*-pyran-4-one derivatives constitute an useful class of heterocyclic compounds which are widely distributed in nature [1,2]. These compounds display diverse biological activities, acting as fungicides and herbicides and a variety of pharmacological actions, which could be useful in the treatment of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

Several synthetic routes to 4*H*-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-4*H*-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 4*H*-pyran-4-ones, which have been prepared by the condensation of di(aminoxymethyl) derivatives of 4*H*-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) 4*H*-pyran-4-one derivatives **2a,b** in 82.5 and 52% yields, respectively, which were hydrazinolysed 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



- i) Et<sub>3</sub>N, DMF, r.t.  
ii) H<sub>2</sub>N-NH<sub>2</sub>, MeOH, 0°C  
iii) C<sub>6</sub>H<sub>5</sub>CHO, CH<sub>2</sub>Cl<sub>2</sub>, 0°C ( 4-5a,b )  
iv) 4-MeC<sub>6</sub>H<sub>4</sub>CHO, CH<sub>2</sub>Cl<sub>2</sub>, 0°C ( 6-7a,b )

The <sup>1</sup>H-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,  $^1\text{H-NMR}$  and MS) and elemental analyses.

## Conclusions

Several new aldoxime derivatives of 4*H*-pyran-4-ones **4-7a,b** were synthesized and characterized for the first time. These compounds were prepared by condensation of di(aminoxymethyl) 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.  $^1\text{H-NMR}$  spectra were recorded for  $\text{CDCl}_3$  solutions on a FT-NMR Bruker 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*-phthalimidoxymethyl) pyranones **2a,b**.

A mixture of di(bromomethyl)diphenyl-4*H*-pyran-4-one **1a** [9] or **1b** [10] (6.0 g, 13.8 mmol), *N*-hydroxyphthalimide (4.8 g, 29 mmol),  $\text{Et}_3\text{N}$  (4.2 g, 41 mmol) 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-phthalimidoxymethyl)-2,6-diphenyl-4H-pyran-4-one (2a)*. Colourless crystals (82.5% yield), m.p. 233-235°C;  $^1\text{H-NMR}$   $\delta$ : 4.9 (s, 4H,  $-\text{CH}_2\text{O}-$ ), 7.15-7.85 (m, 18H, phenyl-**H**). IR: 3075, 2950, 2875, 1790, 1730, 1670, 1635, 1575  $\text{cm}^{-1}$ ; MS:  $m/z$  598; Anal. Calcd. for  $\text{C}_{35}\text{H}_{22}\text{N}_2\text{O}_8$ : C, 70.23; H, 3.70; N, 4.68. Found: C, 69.80; H, 3.80; N, 4.57.

*2,6-Di(N-phthalimidoxymethyl)-3,5-diphenyl-4H-pyran-4-one (2b)*. Colourless crystals (52% yield), m.p. 228-229.5°C;  $^1\text{H-NMR}$   $\delta$ : 4.95 (s, 4H,  $-\text{CH}_2\text{O}-$ ), 7.1-7.3 (m, 10H, phenyl-**H**), 7.7 (s, 8H, phenyl-**H**); IR: 3094, 2925, 2853, 1790, 1740, 1631, 1620, 1579  $\text{cm}^{-1}$ ; MS:  $m/z$  598; Anal. Calcd. for  $\text{C}_{35}\text{H}_{22}\text{N}_2\text{O}_8$ : 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(aminoxymethyl) 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; <sup>1</sup>H-NMR δ: 4.65 (s, 4H, -CH<sub>2</sub>O-), 5.3 (br, 4H, -NH<sub>2</sub>), 7.35-7.55 (m, 10H, phenyl-H); IR: 3300, 3150, 3050, 2950, 2872, 1643, 1495, 1448 cm<sup>-1</sup>; MS: m/z 338; Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: 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; <sup>1</sup>H-NMR δ: 4.64 (s, 4H, -CH<sub>2</sub>O-), 5.37 (br, 4H, -NH<sub>2</sub>), 7.23 (m, 10H, phenyl-H); IR: 3300, 3250, 3140, 3050, 2960, 1640, 1622, 1570, 1413 cm<sup>-1</sup>; MS: m/z 338; Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: 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 (1.5g) 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); <sup>1</sup>H-NMR δ: 5.1 (s, 4H, -CH<sub>2</sub>O-), 7.2-7.85 (m, 20H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3050, 3017, 2983, 2875, 1644, 1607, 1500, 1446 cm<sup>-1</sup>; MS: m/z 514; Anal. Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: 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); <sup>1</sup>H-NMR δ: 5.1 (s, 4H, -CH<sub>2</sub>O-), 7-7.6 (m, 20H, phenyl-H), 8.1 (s, 2H, -N=CH-); IR: 3050, 3010, 2950, 2900, 1630, 1470, 1405 cm<sup>-1</sup>; MS: m/z 514; Anal. Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: 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); <sup>1</sup>H-NMR δ: 5.1 (s, 4H, -CH<sub>2</sub>O-), 7.1-7.8 (m, 20H, phenyl-H; 1H, -N=CH-), 8.1 (s, 1H, -N=CH-); IR: 3050, 3010, 2980, 2872, 1640, 1600, 1480, 1440 cm<sup>-1</sup>; MS: m/z 514; Anal. Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: 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); <sup>1</sup>H-NMR δ: 5.15 (s, 4H, -CH<sub>2</sub>O-), 7-7.6 (m, 20H, phenyl-H; 1H, -N=CH-), 8.1 (s, 1H, -N=CH-); IR: 3050, 3010, 2985, 1640, 1600, 1480, 1440 cm<sup>-1</sup>; MS: m/z 514; Anal. Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 77.03; H, 5.09; N, 5.44. Found: C, 77.29; H, 5.01; N, 5.32.

(*E,E*)-4-Methylbenzal[(2,6-diphenyl-3,5-4*H*-pyran-4-one-diyl)bis(methylene)]dioxime (**6a**). Colourless crystals (60% yield), m.p. 128°C; <sup>1</sup>H-NMR δ: 2.2 (s, 6H, -CH<sub>3</sub>), 5.1 (s, 4H, -CH<sub>2</sub>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<sup>-1</sup>; MS: m/z 542; Anal. Calcd. For C<sub>35</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: 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-2,6-4*H*-pyran-4-one-diyl)bis(methylene)]dioxime (**6b**). Colourless oil (61.5% yield); <sup>1</sup>H-NMR δ: 2.15 (s, 6H, -CH<sub>3</sub>), 5.2 (s, 4H, -CH<sub>2</sub>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<sup>-1</sup>; MS: m/z 542; Anal. Calcd. for C<sub>35</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: 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-3,5-4*H*-pyran-4-one-diyl)bis(methylene)]dioxime (**7a**). Colourless crystals (11.2% yield), m.p. 138°C; <sup>1</sup>H-NMR δ: 2.3 (s, 6H, -CH<sub>3</sub>), 5.2 (s, 4H, -CH<sub>2</sub>O-), 6.9-7.9 (m, 18H, phenyl-H; 1H, -N=CH-), 8.1 (s, 1H, -N=CH-); IR: 3050, 3020, 2940, 2880, 1630, 1570, 1500 cm<sup>-1</sup>; MS: m/z 542; Anal. Calcd. for C<sub>35</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: 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-2,6-4*H*-pyran-4-one-diyl)bis(methylene)]dioxime (**7b**). Colourless oil (12.3% yield); <sup>1</sup>H-NMR δ: 2.2 (s, 6H, -CH<sub>3</sub>), 5.2 (s, 4H, -CH<sub>2</sub>O-), 6.9-7.5 (m, 18H, phenyl-H; 1H, -N=CH-), 8.1 (s, 1H, -N=CH-); IR: 3050, 3010, 2930, 2890, 1645, 1620, 1480 cm<sup>-1</sup>; MS: m/z 542; Anal. Calcd. for C<sub>35</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.43; H, 5.39; N, 5.18.

## References and Notes

- † Presented in part at the 13<sup>th</sup> International Conference on Organic Synthesis. (Warsaw, Poland), 2000. Book of Abstracts, p. 192.
1. Moriguchi, T.; Matsuura, H.; Itakura, Y.; Katsuki, H.; Saito, H.; Nishiyama, N. Allixin, a phytoalexin produced by garlic, and its analogs as novel exogenous substances with neurotrophic activity. *Life Sci.* **1997**, *61*, 1413-1420.
  2. Murrar, R. D. H. Naturally occurring oxygen-ring compounds. *Aromat. Heteroaromat. Chem.* **1978**, *5*, 472-501.
  3. Clark, B. P.; Ross, W. J.; Todd, A. 6-Substituted pyranone compounds for pharmaceutical uses. *Ger Offen.*, 3,012,584; [*Chem. Abstr.*, **1981**, *94*, P121322f].
  4. Clark, B. P.; Ross, W. J.; Todd, A. 5-Substituted pyranone compounds for pharmaceutical uses. *Ger Offen.*, 3,012,597; [*Chem. Abstr.*, **1981**, *94*, P83945b].
  5. Shahrissa, A.; Tabrizi, R.; Ahsani, H. R. A novel method for the synthesis of 4*H*-pyran-4-one derivatives. *Org. Prep. & Proced. Int.* **2000**, *32*, 47-55.
  6. Shahrissa, A.; Tabrizi, R. Synthesis and characterization of new macrocyclic polyether-diester ligands containing a 4*H*-pyran-4-one subcyclic unit. *Iran. J. Chem. & Chem. Eng.* **1999**, *18*, 91-97.

7. Yamamura, S.; Nishiyama, S. Synthetic studies on polypropionate-derived 4-pyrone-containing marine natural products. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025-2037.
8. Naito, T.; Kobayashi, H.; Ogura, H.; Zama, K. Preparation of pyranone compounds as intermediate for cephalosporin derivatives. *Jpn. Kokai Tokkyo Koho JP 04 91,088*; [*Chem. Abstr.*, **1992**, *117*, 131069m].
9. Allowhn, J.; Brumm, M.; Frenking, G.; Hornivius, M.; Massa, W.; Steubert, F. W.; Wocadlo, S. Synthese und konformationsanalysen von pyranophanonen und pyrylophanium-verbinding mit intraannularen substituenten. *J. Prakt. Chem.* **1993**, *335*, 503-514.
10. Massa, W.; Schween, M.; Steuber, F. W.; Wocadlo, S. Konformationsanalysen von pyrolytisch erzeugten [2.2] phanen des 4-pyranons. *Chem. Ber.* **1990**, *123*, 1119-1128.
11. Girard, A. In *Organic Synthesis Collective*; John Wiley & Sons: Chichester (U.K.), 1943; Vol.2, p. 86.

*Sample Availability:* Available from the authors.

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