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One-pot Synthesis of 4*H*-Pyran-4-one Carboxaldehyde Derivatives by Using Selenium Dioxide as a Reusable Oxidant

M. HABIBI[1,*], Y. BAYAT[2], R. MARANDI[1], A.A. MEHRDADSHARIF[1] and S. SALAHI[2]

[1]Department of Applied Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Department of Chemistry, Faculty of Chemistry, Malek-Ashtar University of Technology, Tehran, Iran

*Corresponding author: Fax: +98 21 229777861; Tel: +98 21 229777932; Email: m_habibi@gorganiau.ir

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A simple, fast, efficient and basic method for synthesis of symmetrical 4*H*-pyran-4-one carboxaldehyde derivatives from 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one derivative has been reported. The reaction time is effectively reduced from 72 h to 1 min with the yield increase over 30 %.

Key Words: 4*H*-Pyran-4-one, Carboxcaldehyde derivatives, One-pot, Microwave-assisted, Selenium dioxide.

INTRODUCTION

Functionalized heterocycles are often used for synthesis of target organic compounds in the production of dyes, drugs and a variety of pharmacological applications, which can be useful in the treatment of asthma, allergies, tumors and convulsants[1-6]. 4*H*-Pyran-4-one derivatives are useful as flavouring agents, food preservatives, fungicides and herbicides[7-14]. For example, phenoxan has an anti-HIV activity. The structural study of phenoxan shows that it is closely related to other microbial metabolites that contain a 4*H*-pyran-4-one system (Fig. 1)[15].

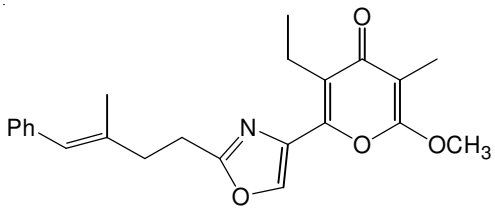
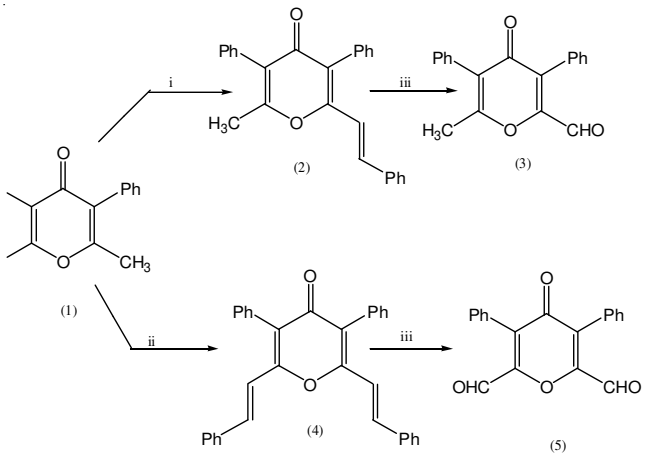


Fig. 1. Structure of phenoxan

Some carboxaldehyde derivatives of 4*H*-pyran-4-ones were prepared by oxidation of hydroxymethyl group in acid derivatives[16,17], by formylation of pyrones in presence of trifluoroacetic acid[18]. Ghandi and co-workers prepared some mono- and dicarboxlaldehyde derivatives of 4*H*-pyran-4-one substituted at position 2 and 6 by the condensation of mono and dimethyl derivatives of 4*H*-pyran-4-one with benzaldehyde, followed by the oxidation of corresponding mono and distryl derivatives in presence of the osmium tetroxide and potassium periodate in overall[19] yield of 60 % (**Scheme-I**).



Scheme-I:. (i) PhCHO, NaOEt, (ii) 2PhCHO, 2NaOEt, (iii) OsO_4, KIO_4

In this method we need to use osmium tetroxide, which is highly toxic, harmful and expensive. In addition method, total yield is less than 60 % and Teimuri and co-workers prepared carboxaldehyde derivatives of 4*H*-pyran-4-ones from their corresponding bromomethyl derivatives by treatment with silver acetate followed by hydrolysis and oxidation[20,21]. In all these methods the final product were prepared by four steps with maximum total yielding of 57 %.

We wish to report a convenient, one-pot preparation, safe method with higher yield by reclaimable compound for the synthesis of mono and dicarboxylaldehyde derivatives.

EXPERIMENTAL

Melting points were determined with an electro thermal instrument model 9100 and are uncorrected. Infrared (FT-IR) spectra were run on a shimadzu 8010 M spectrophotometer as KBr disks or as smears between salt plates. The ^{1}H NMR spectra were recorded on a Varian-EM 390 spectrometer. Chemical shifts are reported in δ (ppm) with TMS as an internal standard. Mass spectra were taken by a Shimadzu MS-QP 1100 EX mass spectrometer. Elemental analyses were performed on a Heareus CHN-0-RAPID analyzer. Starting materials were purchased from commercial sources. Column chromatography was performed using merck kieselgel 60 (0.063-0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Typical procedure for the synthesis of 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one (1): A mixture of 12.5 mL (0.02 mol) acetic anhydride and 20 g (0.02 mol) polyphosphoric acid and 2.1 g (0.01 mol) of 1,3-diphenyl-2-propanone subjected to microwave irradiation for 2 min to achieve 2,6-dimethyl-3,5-diphenyl- 4*H*-pyran-4-one (**2**). The cooled mixture was diluted with ice-water and was extracted with dichloromethane for several times. The combined organic phase was dried over anhydrous $MgSO_4$ and eflavourated under vacuum according to the previously reported procedure[22]. The mixture was recrystallized in absolute ethanol and 1.93 g (70 %) of yellow pale crystal of (**1**) was obtained; m.p. 202.8-203.7 ºC (L,[19] m.p. 203.2-203.9 ºC); ^{1}H NMR (100 MHz, DMSO): δ 2.3 (6 H, s, 2 CH_3), 7.25 -7.49 (10H, m, phenyl-H).

Synthesis of 3,5-diphenyl-2-carboxaldehyde-6-methyl-4*H*-pyran-4-one (2): A solution of 2.76 g (0.01 mol) 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one (**1**) and 1.11 g (0.01 mol) SeO_2 in 10 mL dioxane was refluxed for 32 h under N_2 atmosphere. Black precipitate was collected and washed several times by dichloromethane. The mixture solution was concentrated under reduced pressure and the mixture of (**1**), (**2**) was extracted by 3 × 10 mL dichloromethane and the solvent was eflavourated and parts of mixture was separated by column chromatography and 1.86 g (65 %) of yellow pale crystals **3**, 5-diphenyl-2-carboxaldehyde-6-methyl-4*H*-pyran-4-one (**2**) was obtained; m.p. 188.8-189.4 ºC (L,[19] m.p. 189-189.6 ºC); IR (KBr, ν_{max}, cm^{-1}): 3021, 2962, 2884, 1706, 1642, 1248, 971 and 800. ^{1}H NMR (DMSO): δ 2.40 (3H, s, -CH_3), 7.40 (10H, m, phenyl-H), 9.80 (1H, s, -CHO). MS (EI, 70 eV): 290 (M^+). Anal. calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.41; H, 4.90.

Synthesis of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one (3) by selenium dioxide: A solution of 2.76 g (0.01 mol) 2,6-dimethyl-3, 5-diphenyl-4*H*-pyran-4-one (**1**) and 3.33 g (0.03 mol) SeO_2 in 10 mL dioxane was refluxed for 72 h under N_2 atmosphere. Black precipitate was collected and washed several times by dichloromethane. The organic layer was flavourated under reduced pressure and was separated by column chromatography and 2.05 g (60 %) of pale yellow crystals 2,6-dicarboxaldehyde 3,5-diphenyl-4*H*-Pyran-4-one (**3**) was obtained; m.p. 196 -196.9 ºC, IR (KBr, ν_{max} cm^{-1}): 3031, 2879, 1708 and 1648. ^{1}H NMR (DMSO): δ 7.40s, 10H, phenyl-H), 9.69 (s, 2H,-CHO). MS (EI, 70 eV): 304 (M^+). Anal. calcd. For $C_{19}H_{12}O_4$: C 74.99; H 3.98; found: C, 75.15; H, 4.08.

Synthesis of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one (3) by selenous acid: A solution of 2.76 g (0.01 mol) 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one (**1**) and 3.33 g (0.03 mol) of reclaimed SeO_2 in 10 mL dioxane was refluxed for 60 h under N_2 atmosphere. Black precipitate was collected and washed several times by dichloromethane. The mixture solution was concentrated under reduced pressure and the mixture was extracted by 3 × 10 mL dichloromethane and the solvent was eflavourated and parts of mixture was separated by chromatography column and 2.46 g (72 %) of yellow pale crystals 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one (**3**) was obtained; m.p. 195.9 -196.7 ºC, IR (KBr, ν_{max}, cm^{-1}): 3052, 2884, 1706 and 1642. ^{1}H NMR (DMSO): δ 7.40s, 10H, phenyl-H), 9.6 (s, 2H,-CHO). MS (EI, 70 eV): 304 (M^+). Anal. calcd. for $C_{19}H_{12}O_4$: C 74.99; H 3.98; Found: C, 75.12; H, 4.10.

Solvent free preparation of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one (3) by selenium dioxide: 1.38 g (5 mmol) of 2,6-dimethyl -3,5-diphenyl-4*H*-pyran-4-one and 5.55 g (50 mmol) of SeO_2 was mixed and were reacted with each other under microwave irradiation for 15 min. The mixture was washed several times by dichloromethane, parts of mixture was separated by column chromatography and 1.28 g (75 %) of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one was obtained.

Solvent free preparation of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one (3) by selenous acid: 1.38 g (5 mmol) of 2,6-dimethyl-3,5-diphenyl-4H-pyran-4-one and 5.55 g (50 mmol) of reclaimed SeO_2 was mixed and were reacted with each other under microwave irradiation for 1 min. The mixture was washed several times by dichloromethane and parts of mixture was separated by chromatography column and 1.37 g (80 %) of 2,6-dicarboxaldehyde-3,5-diphenyl-4*H*-pyran-4-one was obtained.

Reclaiming of SeO_2: The black precipitate is selenium, which was solved in nitric acid and the mixture was heated to flavourate the solvent and selenous acid was prepared by this reaction.

$$3Se + 4HNO_3 + H_2O \rightarrow 3H_2SeO_3 + 4NO$$

$$H_2SeO_3 \rightleftharpoons SeO_2 + H_2O$$

RESULTS AND DISCUSSION

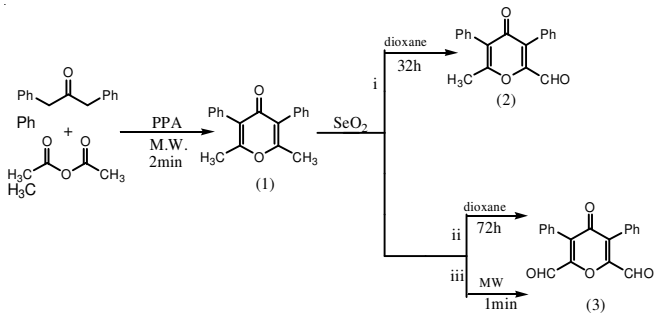
Selenium dioxide is a useful reagent for allylic oxidation of alkenes[23-24], oxidation of β-methyl-substituted δ-lactones[25], oxidation of methyl groups in preparation of caerulomycin E[26], dicarboxaldehyde naphthyridine derivatives[27] and 1,10-dicarboxaldehyde phenathroline[28,29].

We synthesized mono and dicarboxaldehyde derivatives of 4*H*-pyran-4-one by two different methods by using selenium dioxide as a methyl group oxidant with a suitable yield (**Scheme-II**).

In this process selenium dioxide was reduced to selenium which we reclaimed all of selenium by reaction with nitric acid. It seems that selenium reacted with nitric acid and selenous acid (H_2SeO_3) produced. Selenous acid was used for this oxidation in order to give higher yield in shortest time (Table-1).

Benzene selenic anhydrate was used for preparation of aldehyde and ketone derivatives from alcohols and benzilic

hydrocarbons as a good reagent with the yield higher than selenium dioxide in shorter time[24,25,29]. Some 4*H*-pyran-4-ones derivatives were prepared by solvent free method by using microwave irradiation[30].



Scheme-II: (i), (ii) by solvent (iii) by solvent free methods

TABLE-1
OPTIMIZATION OF 4H-PYRAN-4-ONE CARBOXALDEHYDE DERIVATIVES PREPARATION

Entry	Conditions	Time	Yield (%)
2	SeO_2 (1 equiv), dioxane + reflux	32 h	65
3	SeO_2 (2 equiv), dioxane + reflux	72 h	60
3	SeO_2 (5 equeiv), (m.w. assisted)	15 min	70
3	H_2SeO_3 (5 equeiv), (m.w. assisted)	1 min	80

Recently, the wide applicability of microwave irradiation in chemical reaction enhancement is due to the high reaction rate with the formation of more pure cleaner products and simple operation[31-35].

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