Tetrahedron Letters 50 (2009) 6751–6754

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sodium borohydride or potassium carbonate-mediated intramolecular Michael addition: a general method for the synthesis of fused dihydrofuran and furan derivatives

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ARTICLE INFO

Article history:
Received 6 August 2009
Revised 9 September 2009
Accepted 13 September 2009
Available online 17 September 2009

Keywords:
Sodium borohydride
Michael addition
Dihydrofuran
Furan

ABSTRACT

A simple and convenient method for the synthesis of fused dihydrofuran derivatives using $NaBH_4$-mediated reductive cyclization and fused furan derivatives by K_2CO_3-mediated intramolecular Michael addition followed by acid-catalyzed methanol elimination has been developed.

1. Introduction

Five-membered oxygen-containing heterocyclic compounds, a key structural subunit present in many naturally occurring compounds, exhibit remarkable biological activities.[1] Figure 1 highlights several natural biologically active molecules which contain dihydrofuran or furan as a subunit.[2,3] The intramolecular Michael addition has been proven to be a widely employed method for C–C and C–O bond formation with numerous applications in the synthesis of carbocyclic and heterocyclic compounds of biological significance.[4] Sudhakar et al.[3] have synthesized an alkaloid, Isoferbenfugine, which contains tetrahydrofuran ring as a subunit, and they have used intramolecular Michael addition in one of the steps.

In continuation of our work on palladium chemistry,[5] we have been able to prepare fused furan and dihydrofuran derivatives by Heck reaction followed by an intramolecular Michael addition reaction. A number of methods have been reported for the synthesis of substituted furan and dihydrofuran. For example, Du and his group[6] synthesized substituted furans and dihydrofurans via gold-catalyzed cyclization of (*Z*)-2-en-4-yn-1-ols. These ring systems can also be synthesized by transition-metal-catalyzed reactions including cyclization of allenyl ketones[7] and 3-alkyn-1-ones,[8] cycloisomerizations of (*Z*)-2-en-4-yn-1-ols[9] and Pd(II)-catalyzed tandem cyclization reaction of 1,ω-Bisallenols[9d]. Ru-catalyzed metathesis reactions can also be useful for terminal alkene–alkyne systems.[10] The marine natural product euryfuran which contains a 3,4-disubstituted-fused furan ring system as the subunit has been synthesized by using an intramolecular Diels–Alder reaction. However this strategy[11] requires high temperature.

Herein, we report mild and efficient methodologies for the preparation of dihydrofuran and furan derivatives from the ester of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid by $NaBH_4$-mediated reductive cyclization[12] and base-mediated intramolecular Michael addition reaction followed by acid-catalyzed elimination, respectively.

The starting materials for the intramolecular Michael addition were prepared by the nano palladium-catalyzed intermolecular Heck reaction.[13] Thus 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic esters were synthesized in 80–90% yield by treating β-bromovinyl aldehydes with various acrylate derivatives in the presence of palladium chloride, sodium carbonate and tetrabutylammonium bromide in water at room temperature (Scheme 1) within 2–3 h. The substrate **1** was found to be more effective towards the Heck reaction with acrylate derivatives under this reaction condition than the simple aromatic halo compounds that require more vigorous condition[14] and high temperature.[13b]

The substrate **2** was treated with $NaBH_4$ in acetonitrile to get the dihydrofuran derivatives (Table 1, entries 1–10) in 70–80% yield under ambient condition (25–30 °C) within 2–3 h. During the course of our reactions, no reduced product, that is, alcohol, could be isolated. This indicates that the aldehyde first gets reduced to the corresponding alcohol which immediately undergoes

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doi:10.1016/j.tetlet.2009.09.071

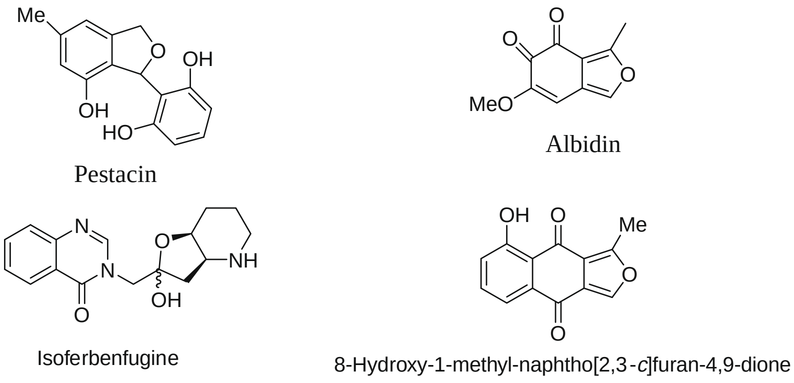


Figure 1. Biologically active dihydrofuran and furan.

intramolecular Michael addition to form the dihydrofuran derivatives in one pot (Scheme 2).

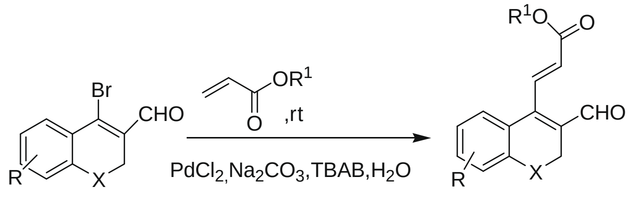
We next examined the scope of this reaction with different substituted esters of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid. In the case of substrates **2a**–**h** we obtained moderate to good yield except in the case of **2i** and **2j**. Then we also studied the effects of polar protic and polar aprotic solvents on this reductive cyclization reaction. In the case of methanol, cyclization product was lower in yield than when the solvent was acetonitrile. So, acetonitrile was found to be a better solvent for this cyclization.

We have also prepared the furan derivatives from the corresponding dihydrofurans as depicted in Scheme 3. The fused furan derivatives were obtained from substrate **2** on treatment with potassium carbonate and methanol in dichloromethane at room temperature with stirring for 2–3 h followed by an acidic work-up. The formation of the furan could be explained by a two-step mechanism (Scheme 3). At first the substrate **2** undergoes intramolecular Michael addition to form a diastereomeric mixture of dihydrofuran derivatives which on acidic work-up via an elimination of methanol produces fused furan derivatives **4** in good yield (70–80%) (Table 2, entries 1–5). The driving force for the elimination of methanol is aromatization.

In conclusion, we have developed a general method for the synthesis of dihydrofuran and furan derivatives by intramolecular Michael addition. In the future we will try to synthesize naphtho [2,3-*c*] furan-4,9-diones related to natural products using this methodology.

2. Typical experimental procedure for reductive cyclization

Compound **2** (1 mmol) and $NaBH_4$ (2 mmol) were placed in a two-necked round-bottomed flask. After the system had been



1

2

R=H, -OMe, -Br
X=-O, $-CH_2$, -CHMe
R^1= -Me, -Et, -^{t}Bu

Scheme 1. Preparation of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid ester.

Table 1
Preparation of fused furan derivative by $NaBH_4$ mediated reductive cyclization

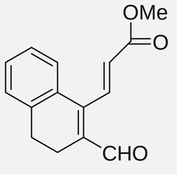
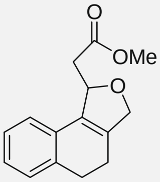
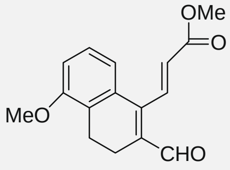
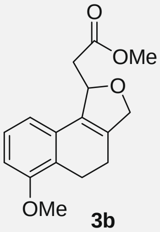
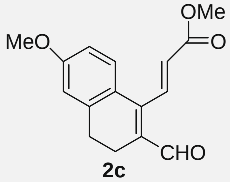
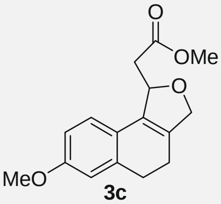
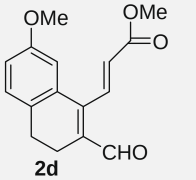
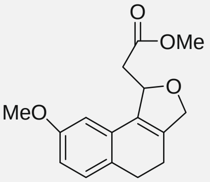
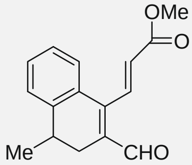
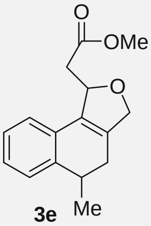
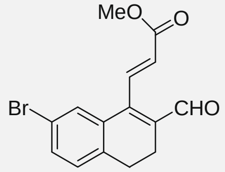
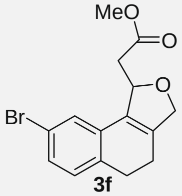
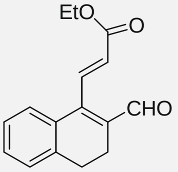
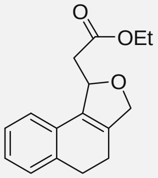
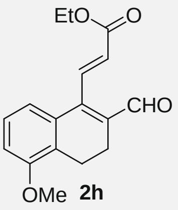
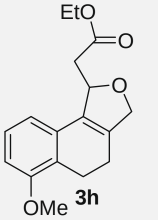
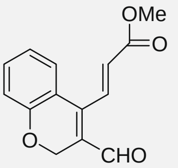
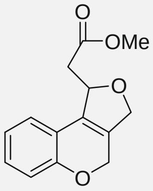
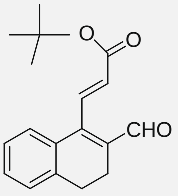
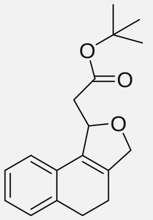
Entry	Substrate	Product	Yield (%)
1	 **2a**	 **3a**	75
2	 **2b**	 **3b**	80
3	 **2c**	 **3c**	78
4	 **2d**	 **3d**	76
5	 **2e**	 **3e**	65

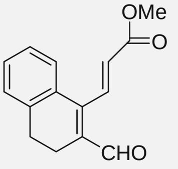
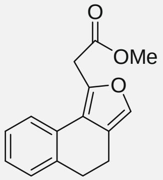
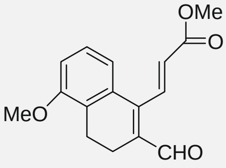
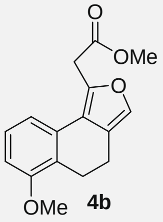
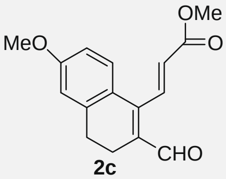
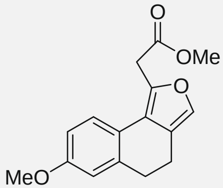
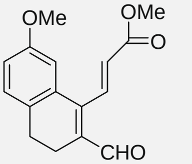
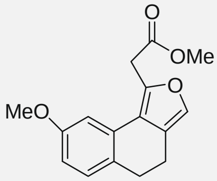
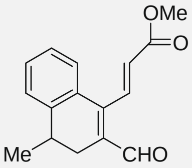
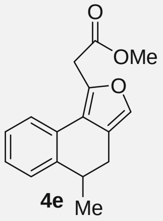
Table 1 (*continued*)

Entry	Substrate	Product	Yield (%)
6	 **2f**	 **3f**	60
7	 **2g**	 **3g**	70
8	 **2h**	 **3h**	70
9	 **2i**	 **3i**	30
10	 **2j**	 **3j**	40

Reagent and conditions: **2a–j** (1 mmol), $NaBH_4$ (2 mmol), CH_3CN (8 mL), room temperature, 2–3 h.

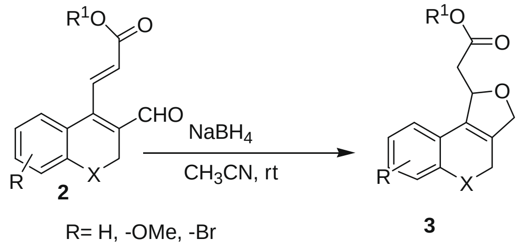
Table 2

Preparation of fused furan derivative by potassium carbonate mediated intramolecular Michael addition

Entry	Substrate	Product	Yield (%)
1	 **2a**	 **4a**	80
2	 **2b**	 **4b**	75
3	 **2c**	 **4c**	70
4	 **2d**	 **4d**	72
5	 **2e**	 **4e**	75

Reagent and conditions: **2a–e** (1 mmol), K_2CO_3 (2 mmol), methanol (1 mL), dichloromethane (5–6 mL), room temperature, 2–3 h.

flushed with nitrogen, 8 mL of acetonitrile was added and the reaction mixture was allowed to stir at room temperature and the progress of the reaction was monitored by TLC. After the disappearance of the starting material, the reaction was quenched with water and the reaction mixture was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography on Silica Gel (60-120).

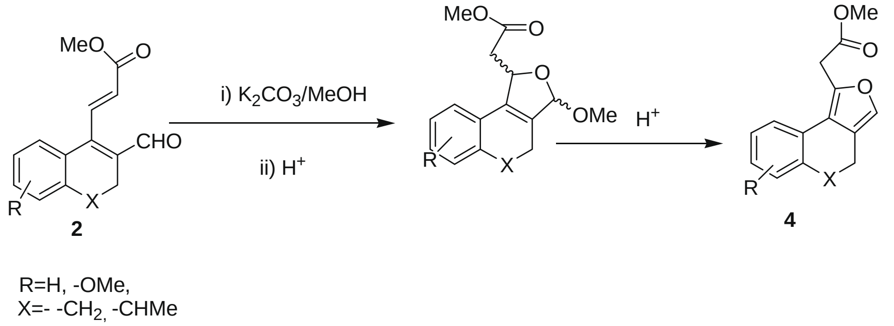


R= H, -OMe, -Br
X= O, -CH$_2$, -CHMe
R^1= -Me, -Et, -^{t}Bu

Scheme 2. $NaBH_4$-mediated reductive cyclization of 3-(2-formyl-3,4-dihydronaphthalen-1-yl)-acrylic acid ester.

3. Typical experimental procedure for fused furan

Compound **2** (1 mmol) and K_2CO_3 (2 mmol) were placed in a two-necked flask and combined with 5 mL of dichloromethane. Then 1 mL of methanol was added and the reaction mixture was stirred at room temperature until the starting material disappeared. After evaporating the solvent of the reaction mixture, 10 mL of diethyl ether was added to it and it was stirred with 2 mL of concd HCl for 30 min. After completion of the reaction, it was diluted with water and extracted with diethyl ether. Removal of the solvent after drying (anhydrous Na_2SO_4), afforded the crude product, which was chromatographed on Silica Gel (60-120).



Scheme 3. Preparation of fused furan derivative from the ester of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid.

4. Spectral data of representative compounds

Compound **3c**: Colourless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.30–2.34 (m, 2H), 2.48–2.54 (m, 1H), 2.82–2.96 (m, 3H) 3.73 (s, 3H) 3.80 (s, 3H) 4.62 (d, 1H, J = 13.2 Hz), 4.80 (dd, 1H, J_1 = 13.2 Hz, J_2 = 2.6 Hz), 5.57–5.60 (m, 1H), 6.67–6.71 (m, 1H), 6.77 (s, 1H) 6.87 (d, 1H, J = 8.4 Hz) ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 20.76, 29.04, 40.78, 52.02, 55.51, 76.31, 81.53, 111.11, 114.96, 123.27, 126.04, 132.49, 133.89, 137.53, 158.98, 172.09. IR ν_{max} ($CHCl_3$): 2950, 1735, 1611, 1280, 1216, 1046, 808, 756, 668 cm^{-1}. MS-ESI: m/z = 275.1150 (100%) [M$^+$+H]. HRMS calcd for $C_{16}H_{19}O_4$ [M$^+$+H]: 275.1285; found 275.1150.

Compound **4c**: Colourless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.67 (t, 2H, J = 7.2 Hz) 2.83 (t, 2H, J = 7.2 Hz), 3.75 (s, 3H) 3.81 (s, 3H), 3.93 (s, 2H), 6.81–6.84 (m, 2H), 7.18 (s, 1H), 7.43 (d. 1H, J = 8 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.25, 30.83, 34.12, 52.34, 55.19, 112.15, 114.40, 119.44, 122.26, 122.71, 125.19, 135.34, 138.50, 140.37, 158.25, 169.93. IR ν_{max} ($CHCl_3$): 2951, 1736, 1611, 1578, 1247, 1043, 757, 611 cm^{-1}. MS-ESI: m/z = 295.01 (100%) [M$^+$+Na].

Acknowledgement

Financial support from CSIR (New Delhi) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.071.

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