# Alcohol substitution and dehydrogenation of selenium compounds: a convenient preparation of trisubstituted furans from allyl-substituted 1,3-dicarbonyls

**E Tang[a,*] and Xian Huang[b]**

[a]*Department of Applied Chemistry, Yunnan University, Kunming 650091, P.R. China*

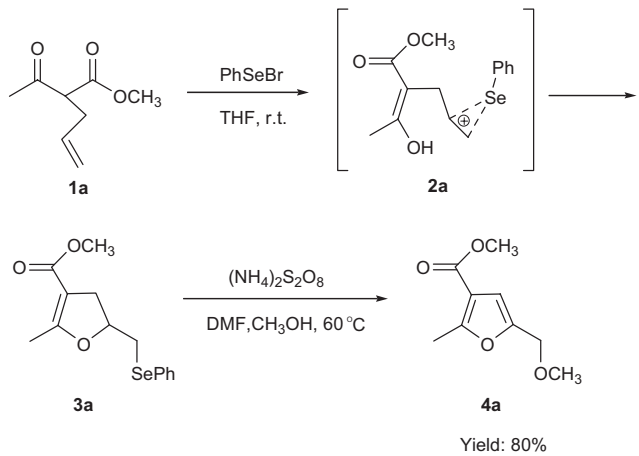
[b]*Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, P.R. China*

Trisubstituted furans have been synthesised efficiently by an alcohol substitution and dehydrogenation reaction of selenocyclic enol ethers which were prepared by organoselenium-induced regioselective electrophilic intramolecular cyclisation of allyl-substituted 1,3-dicarbonyls.

**Keywords:** selenium-mediated intramolecular cyclisation, allyl-substituted 1,3-dicarbonyls, trisubstituted furan, alcohol substitution, dehydrogenation, ammonium persulfate

Furans are an important class of heterocycle which occur widely in nature.[1-5] Possessing a variety of biological activities, they are used as pharmaceutical, flavouring, insecticidal and fish antifeedant agents.[6-8] Furthermore, furans are useful synthetic intermediates.[9] In principle, furans are synthesised either by cyclisation of acyclic precursors or by derivatisation reaction of the furan ring.[10-12] In the latter case, the introduction of substituents at the 2- or 5-position is usually relatively easy, while a similar operation at the 3- or 4-position is difficult. Cyclisations of acyclic precursors are the most important synthetic methods for substituted furans.[1-5,13-31] Among them, the classic acid-catalysed cyclocondensation of 1,4-dicarbonyl compounds has some limitations in the case of acid-sensitive substrates.[16] In catalytic approaches, palladium catalysed cycloisomerisation can proceed under rather mild or neutral conditions.[28-31] However, it is limited mostly to the synthesis of aryl- or heteraryl-substituted furans and allows for the preparation of the furan derivatives in moderate yields[28,30] or accompanied by a trace to notable amounts of dimeric products.[29] Organoselenium reagent-induced electrophilic cyclisation of allyl substituted 1,3-dicarbonyl compounds can also proceed under rather mild and neutral conditions.[32] However, only 5-methyl substituted furans can be obtained by the classic deselenenylation with $H_2O_2$ and DBU.[33] Here, an efficient preparation method of trisubstituted furans is reported by organoselenium reagent-induced electrophilic cyclisation of allyl substituted 1,3-dicarbonyl compounds, followed by alcohol substitution, accompanied with a dehydrogenation reaction of selenocyclic enol ethers, using ammonium persulfate and alcohol. Although ammonium persulfate is widely used in the deselenenylation process either in the substitution[34] or the elimination,[35] to the best of our knowledge, this is the first deselenenylation method involving substitution by an alkoxyl group and elimination of hydrogen at one time to form 2, 3, 5-trisubstituted furans.

A 1,3-dicarbonyl compound bearing an allyl substitutent **1a** was treated with phenylselenenyl bromide**.** After attack on the double bond by the electrophilic selenium moiety, an intramolecular addition occurred between the resulting seleniranium ion and the enolate **2a** to form 5-(phenylselenylmethyl)-4,5-dihydrofuran compound **3a.** When **3a** was treated with 30% hydrogen peroxide, *m*-chloroperoxybenzoic acid or ammonium persulfate in $CH_3CN$, no elimination product was obtained. To our excitement, in the presence of methanol, treatment of **3a** with ammonium persulfate in DMF at 60°C gave the 5-methoxyl methyl substituted trisubstituted furan **4a** in a yield of 80%. (Scheme 1) Apparently, selenocyclic enol ether **3a** could react with ammonium persulfate suffering alcohol substitution deselenenylation and dehydrogenation in the presence of methanol to afford **4a**, the product of substitution and dehydrogenation, and phenylselenyl sulfate. The deselenenylation method involves selenium radical cation or selenonium ion intermediate[36, 37] and a similar dehydrogenation reaction has already been observed by Tiecco *et al*.[38]




**Scheme 1**

In order to extend this result, various selenocyclic enol ethers **3**, which could be easily prepared under mild conditions by organoselenium-induced electrophilic intramolecular cyclisation of allyl-substituted 1, 3-dicarbonyl compounds **1**,[7] were treated with various alcohols and ammonium persulfate in DMF. The results are summarised in Table 1. We found that in the presence of methanol and ethanol, 5-alkoxyl methyl-substituted trisubstituted furans **4** were obtained in good yields (Table 1, entries 1–8). When allylol, ethanediol and benzyl alcohol were used, no 5-alkoxyl methyl-substituted trisubstituted furans were obtained.

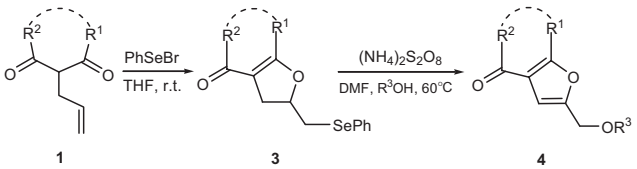
In conclusion, we have developed a facile and efficient method for the synthesis of trisubstituted furans by electrophilic selenium-induced intramolecular cyclisation followed by alcohol substitution, dehydrogenation of selenocyclic enol ethers with the advantages of readily available starting materials, simple procedure, mild reaction conditions and good yields.

## Experimental

1H NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra (EI, 70 eV) were recorded on an HP5989B mass spectrometer. IR spectra were recorded on a Bruker Vector 22 infrared spectrometer and measured

* Correspondent. E-mail: tange@ynu.edu.cn

**Table 1** Preparation of substituted furans




1 3 4

| Entry | $R^1$ | $R^2$ | $R^3$ | Products/ yields[a]/% |
|---|---|---|---|---|
| 1 | $CH_3$ | $OCH_3$ | $CH_3$ | **4a**/80 |
| 2 | $CH_3$ | $OCH_3$ | $C_2H_5$ | **4b**/76 |
| 3 | $CH_3$ | $OC_2H_5$ | $CH_3$ | **4c**/82 |
| 4 | $CH_3$ | $OC_2H_5$ | $C_2H_5$ | **4d**/76 |
| 5 | $-CH_2CH_2CH_2-$ | | $CH_3$ | **4e**/84 |
| 6 | $-CH_2C(CH_3)_2CH_2-$ | | $CH_3$ | **4f**/83 |
| 7 | $CH_3$ | Ph | $CH_3$ | **4g**/70 |
| 8 | $CH_3$ | Ph | $C_2H_5$ | **4h**/68 |

[a]All products were identified by $^1$H NMR, IR, MS and elemental analysis. [b]Isolated yield.

on thin film or in KBr. Elemental analyses were performed on a Flash EA1112 instrument. DMF was dried with calcium hydride. THF was distilled from sodium/benzophenone immediately prior to use. Compounds **3** were prepared as previously described.[32]

*Typical procedure for the preparation of 5-methoxymethyl-2-methylfuran-3-carboxylic acid methyl ester* **(4a):** To a solution of selenocyclic enol ether **3a** (1 mmol) in dry DMF (5 ml) was added ammonium persulfate (2 mmol) and methanol (1 ml). The mixture was stired at 60°C for 3 h. Ethyl acetate (5 ml) and water (5 ml) were added and the water layer was separated and extracted with ethyl acetate (5 ml × 3). The organic layers were combined, washed with brine and water and dried over $MgSO_4$. After evaporation of solvent, the oily residue was subjected to preparative TLC on silica gel with ethyl acetate and light petroleum (1:9) as eluent to give 148 mg of **4a** (80% isolated yield). yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ6.57 (1H, s), 4.33 (2H, s), 3.82 (3H, s), 3.36 (3H, s), 2.58 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ164.3, 159.7, 149.3, 113.8, 110.2, 66.0, 57.8, 51.3, 13.8; MS: *m/z* 184 ($M^+$, 8%), 43 (100); IR (neat) 2951, 1719, 1617, 1581, 1443, 1231, 1083, 778 cm$^{-1}$; Anal. calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.6; H, 6.5.

*5-Ethoxymethyl-2-methylfuran-3-carboxylic acid methyl ester* **(4b):** $^1$H NMR (400 MHz, $CDCl_3$) δ6.58 (1H, s), 4.39 (2H, q, *J* = 7.0 Hz), 3.82 (3H, s), 3.49 (2H, s), 2.60 (3H, s), 1.13 (3H, t, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ165.9, 160.6, 155.9, 111.0, 106.3, 67.0, 64.1, 51.7, 14.9, 14.0; MS: *m/z* 198 ($M^+$, 12%), 43 (100); IR (neat) 2985, 2823, 1716, 1608, 1581, 1410, 1377, 1232, 1210, 779 cm$^{-1}$; Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: 60.7; H, 7.0.

*5-Methoxymethyl-2-methylfuran-3-carboxylic acid ethyl ester* **(4c):** $^1$H NMR (400 MHz, $CDCl_3$) δ6.58 (1H, s), 4.33 (2H, s), 4.28 (2H, q, *J* = 7.1 Hz), 3.36 (3H, s), 2.57 (3H, s), 1.34 (3H, t, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ163.9, 159.5, 149.3, 114.0, 110.3, 67.0, 60.1, 57.7, 14.3, 13.8; MS: *m/z* 198 ($M^+$, 29%), 43 (100); IR (neat) 2984, 2931, 2823, 1715, 1607, 1581, 1411, 1377, 1230, 1208, 1080, 779 cm$^{-1}$; Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: 60.5; H, 7.2.

*5-Ethoxymethyl-2-methylfuran-3-carboxylic acid ethyl ester* **(4d):** $^1$H NMR (400 MHz, $CDCl_3$) δ6.58 (1H, s), 4.39 (2H, s), 4.30–4.25 (4H, m), 2.58 (3H, s), 1.35 (3H, t, *J* = 6.8 Hz), 1.14 (3H, t, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ166.1, 160.6, 155.8, 111.7, 105.7, 67.1, 64.3, 60.4, 14.9, 14.1, 13.9; MS: *m/z* 212 ($M^+$, 16%), 43 (100); IR (neat) 3060, 2931, 2866, 1717, 1601, 1578, 1493, 1453, 1370, 1069, 759, 697 cm$^{-1}$; Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.2; H, 7.7.

*2-Methoxymethyl-6,7-dihydro-5H-benzofuran-4-one* **(4e):** $^1$H NMR (400 MHz, $CDCl_3$) δ6.59 (1H, s), 4.38 (2H, s), 3.38 (3H, s), 2.89 (2H, t, *J* = 6.3 Hz), 2.49 (2H, t, *J* = 6.1 Hz), 2.20–2.14 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ194.4, 167.6, 151.8, 121.7, 105.9, 66.1, 58.0, 37.6, 23.4, 22.5; MS: *m/z* 180 ($M^+$, 25%), 149 (100); IR (neat) 2924, 1638, 1219, 757 cm$^{-1}$; Anal. calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.7; H, 6.8.

*2-Methoxymethyl-6,6-dimethyl-6,7-dihydro-5H-benzofuran-4-one* **(4f):** $^1$H NMR (400 MHz, $CDCl_3$) δ6.58 (1H, s), 4.38 (2H, s), 3.38 (3H, s), 2.75 (2H, s), 2.37 (2H, s), 1.14 (6H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ195.4, 166.2, 153.4, 122.5, 106.8, 65.9, 58.9, 50.9, 38.8, 34.4, 29.4, 27.5; MS: *m/z* 208 ($M^+$, 48%), 177 (96), 152 (100); IR (neat) 2922, 1637, 1217, 757 cm$^{-1}$; Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.3; H, 7.8.

*(5-Methoxymethyl-2-methylfuran-3-yl)phenylmethanone* **(4g):** $^1$H NMR (400 MHz, $CDCl_3$) δ7.79 (2H, d, *J* = 7.2 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.48 (2H, t, *J* = 7.2 Hz), 6.52 (1H, s), 4.37 (2H, s), 3.40 (3H, s), 2.54 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ191.2, 160.0, 149.3, 139.1, 132.2, 128.9, 128.9, 128.4, 128.4, 121.1, 111.3, 66.1, 58.1, 14.3; MS: *m/z* 230 ($M^+$, 8%); IR (neat) 3028, 2974, 2926, 1673, 1601, 1557, 1453, 1370, 1234, 733 cm$^{-1}$; Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.0; H, 6.2.

*(5-Ethoxymethyl-2-methylfuran-3-yl)phenylmethanone* **(4h):** $^1$H NMR (400 MHz, $CDCl_3$) δ7.80 (2H, d, *J* = 7.2 Hz), 7.59 (1H, t, *J* = 7.2 Hz), 7.49 (2H, t, *J* = 7.2 Hz), 6.53 (1H, s), 4.36 (2H, s), 3.49 (2H, q, *J* = 6.8 Hz), 2.52 (3H, s), 1.13 (3H, t, *J* = 6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ193.2, 160.8, 149.5, 139.2, 132.8, 129.1, 129.1, 128.5, 128.5, 122.0, 111.5, 66.5, 64.2, 15.0, 14.4; MS: *m/z* 244 ($M^+$, 12%); IR (neat) 3026, 2974, 2924, 1674, 1600, 1557, 1455, 1235, 734 cm$^{-1}$; Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.8; H, 6.5.

We thank the Natural Science Foundation of Yunnan University (No. 2007Q007A) for financial support.

*Received 1 February 2008; accepted 21 April 2008*
*Paper08/5080 doi: 10.3184/030823408X320629*

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