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

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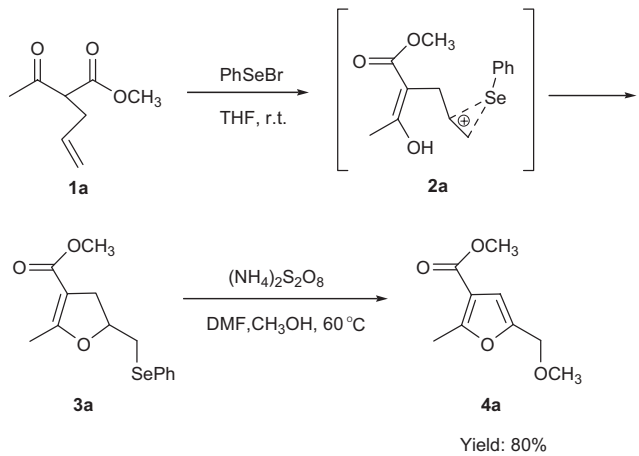
Trisubstituted furans have been synthesised efficiently by an alcohol substitution and dehydrogenation reaction of selenocyclic enol ethers which were prepared by organoselenium-induced regioselective electrophilic intramolecular cyclisation of allyl-substituted 1,3-dicarbonyls.

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

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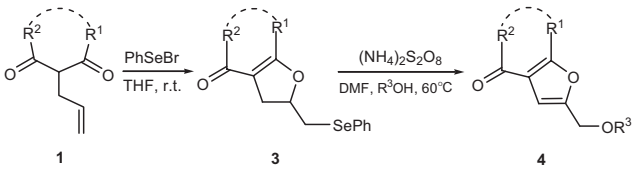
Table 1 Preparation of substituted furans



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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