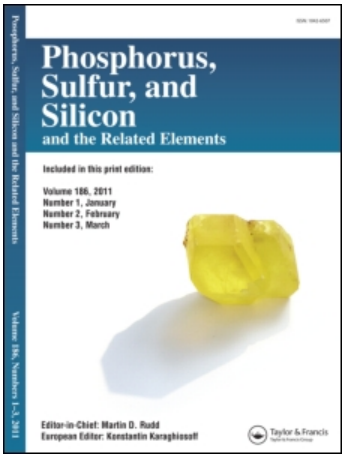

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Selenocyclofunctionalization of β-Ketoamides: Synthesis of Substituted Dihydrofurans

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Selenocyclofunctionalization of ß-Ketoamides: Synthesis of Substituted Dihydrofurans

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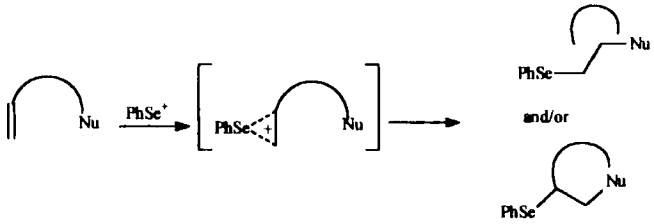
Selenocyclofunctionalization of α-substituted β-ketoamides obtained from the aminolysis of the ethyl acetoacetate yielded dihydrofurans in moderate to good yields.

Keywords: selenocyclofunctionalization; α-substituted β-ketoamides; dihydrofurans

1. INTRODUCTION

Several biologically active natural products are characterized by the presence of heterocyclic rings in their structure.[1] Furans and their derivatives have been the key intermediates in the synthesis of many natural products which have a variety of applications as pharmaceutical, flavour and fragrance compounds.[2] A large variety of heterocyclic compounds, with different ring sizes, can be obtained by using cyclofunctionalization reaction which shows considerable theoretical and practical interest.[3]

Phenylselenofunctionalization reactions, i.e. the phenylselenium induced cyclization of alkenes bearing an internal nucleophile, is a well known chemical procedure (Scheme 1).



SCHEME 1

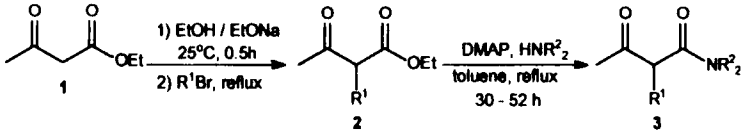
Since the first example described by the selenolactonization of 4-pentenoic acids,[4] this methodology has been widely explored in organic synthesis over the last decades. Several cyclization reactions hat lead to oxygen heterocycles are widely described in the literature as convenient pathways for the synthesis of natural products and related compounds. In particular, cyclization of unsaturated alcohols and carboxylic acids leads to cyclic ethers and lactones. Depending upon the nature of the internal

nucleophile, a variety of 5- and 6-membered ring heterocycles can be prepared showing the versatility of this methodology.

It must be emphasized that different regioisomers can be produced, in some cases, by simply choosing conditions favoring a kinetic or a thermodynamic control. Under many aspects, selenocyclofunctionalization can be compared to the corresponding halo- or thiocyclization. However, the selenium protocol might have advantages compared to these other methodologies for introducing the heteroatom, such as, the manipulation of the products and the removal of the function are facilitated by the simple and mild conditions required, namely, oxidation followed by a *syn*-selenoxide elimination, hydrogenolysis or nucleophilic substitution.

2. RESULTS AND DISCUSSION

The main concern of this communication is to report the selenocyclofunctionalization of α-substituted-β-ketoamides **3**. These compounds were prepared following the literature procedure, which consists in the alkylation of the ethyl acetoacetate **1**, followed by aminolysis of the obtained product **2** catalyzed by DMAP[5] (Scheme 1). The yields are presented in Table 1.



SCHEME 1

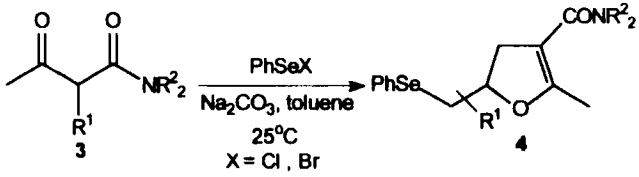
TABLE 1: Aminolysis of α-substituted ethyl acetoacetate

Compound	R^2	R^1	Yield (%)
3a	$-CH_2CH_2-O-CH_2-CH_2$	$-CH_2-CH=CH_2$	84
3b	$-CH_2-(CH_2)_2-CH_3$	$-CH_2-CH=CH_2$	92
3c	$-CH_2-(CH_2)_3-CH_2-$,	$-CH_2-(CH_3)C=CH_2$	83
3d	$CH_2-(CH_2)_3-CH_2-$	$-CH_2-CH=CH-CH_3$	84[a]
3e	$-CH_2-(CH_2)_2-CH_3$	$-CH_2-CH=CH-(CH_2)_3-CH_3$	90[b]
3f	$-CH_2-(CH_2)_2-CH_3$	$-CH_2-CH=CH-C_6H_5$	85[c]

[a]**3d** *E/Z* ratio(85:15) [b]**3e** *E/Z* ratio (10:90) [c]**3f** *E/Z* ratio (100:0)

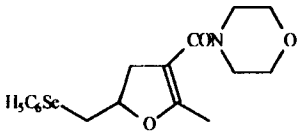
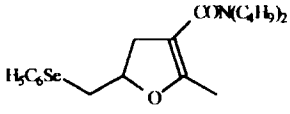
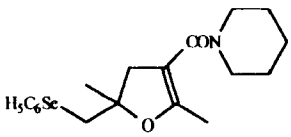
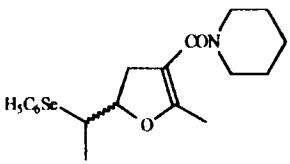
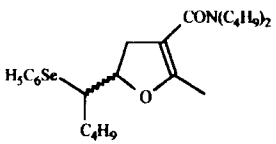
The aminolysis reaction did not occur when primary amines were used and only the starting materials were recovered. Compound **3d** was obtained as a mixture of *E/Z* isomers, even when a pure *Z* double bond isomer was used in the reaction. With **3f** no isomerization was observed.

Treatment of α-substituted β-ketoamides **3** with two equivalents of phenylselenenyl chloride in toluene yielded the corresponding dihydrofurans **4** in moderate to good yields (Scheme 2, Table 2).



SCHEME 2

TABLE 2: Selenocyclofunctionalization of α-substituted β-ketoamides **3**

	Product	Reaction time (h)	Yield (%)
4a		3.5	67
4b		4.0	73
4c		4.5	65
4d		4.5	51
4e		5.0	84

When **3f** was used as the starting material no reaction was observed, probably due to the conjugation of the double bond with the aromatic

ring. In all cases, the reaction was monitored by TLC and gas chromatography and it was observed that when PhSeCl was used as an electrophilic source the reaction was faster than that with PhSeBr. In addition, the reactions with PhSeBr required reflux. However, when PhSeCl was used, the reaction occurred at room temperature. In some cases, it was observed the formation of a lactone as a minor product.

The addition of sodium carbonate increased the yield in 10% and the reaction occurred with other solvents like MeCN, CH_2Cl_2 and THF. However, longer reaction times were required.

The diasteromeric ratios of **4d** (5:1) and **4e** (6:1) were determined by gas chromatography analysis and corroborated by NMR. It also shows that for these compounds, the same isomer ratio of the corresponding α-substituted β-ketoamides used as starting materials (**3d** and **3e**) was observed. All new compounds were characterized by ^1H and ^{13}C NMR, MS and IR.

In conclusion, the methodology described in this communication for the preparation of substituted dihydrofurans appears to be a good and efficient procedure, mainly due to its technical simplicity, smooth and mild conditions and good yields. Further studies in this area will be reported in due course.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 at 300 MHz and 75 MHz respectively, using tetramethylsilane as a internal standard in $CDCl_3$. IR spectra were recorded on a Bomen spectrometer

(film). The products and starting reagents were analyzed on a Hewlett Packard-6890 chromatograph with a flame-ionization detector using a HP-1 capillary column (30 m x 0.32 mm x 0.25 μm). Mass spectra were recorded on Shimadzu GCMS-QP5050A spectrometer.

Preparation of α-substituted ethyl acetoacetate **2**

Ethanol (5.0 mL, 85.0 mmol) and snips of sodium (0.025g, 1.0 mmol) were added to a two-necked round-bottom flask equipped with a reflux condenser and a magnetic stirring bar under nitrogen atmosphere. The reaction was stirred until all sodium was consumed and then ethyl acetoacetate (0.127 mL, 1.0 mmoL) was added dropwise. After 0.5 hour at room temperature, the appropriate alkyl halide (1.0 mmol) was added and the mixture was refluxed. The reacion was monitored by TLC and at the end of reaction the solvent was evaporated. Ethyl acetate (30.0 mL) was added and the organic phase was washed with water and dried over $MgSO_4$. The solvent were removed *in vacuo* and the residue was purified by distillation under reduced pressure.

Preparation of α-substituted-β-ketoamides: 3a-f

A round-bottom flask equipped with a reflux condenser and a magnetic stirring bar under nitrogen atmosphere and containing a mixture of the appropriate amine (2.0 mmol), α-substituted ethyl acetoacetate (1.0 mmol) and DMAP (0.036g, 0.3 mmol) in toluene (3.0 mL) was heated to reflux. The reaction was monitored by TLC and at the end of reaction the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography column using a mixture of hexane/ethyl acetate as eluent. The yields are described on Table 1.

Compound **3a**

^{1}H NMR δ (ppm): 2.17 (3H, s), 2.58-2.74 (2H, m), 3.54-3.75 (9H, m), 5.06 (1H, dd, J_1 = 1.25 Hz, J_2 = 10 Hz), 5.11 (1H, dd, J_1 =1.20 Hz, J_2 = 17 Hz), 5.74 (1H, m). ^{13}C NMR δ (ppm): 26.85, 32.70, 42.35, 46.15, 57.05, 66.36, 66.56, 117.17, 134.25, 166.95, 203.79. LRMS *m/z* (%): 86.15 (100), 168.20 (95), 81.15 (86), 153.20 (79), 70.15 (53), 57.00 (53), 114.05 (49), 169.20 (47), 83.15 (28), 88.15 (26), 154.20 (24), 211.20 (6, [M^+]). IR (cm^{-1}): 1116, 1437, 1639, 1720, 2858, 2921, 2971.

Compound **3b**

^{1}H NMR δ (ppm): 0.93 (3H, t, J=7.3 Hz), 0.96 (3H, t, J=7.3 Hz), 1.24-1.40 (4H, m), 1.46-1.61 (4H, m), 2.17 (3H, s), 2.56-2.71 (2H, m), 3.16-3.45 (4H, m), 3.61 (1H, t, J=7.3 Hz), 5.03 (1H, dd, J_1 =1.3 Hz, J_2 = 10 Hz), 5.11 (1H, dd, J_1 = 1.3 Hz, J_2 = 17 Hz), 5.74 (1H, m). ^{13}C NMR δ (ppm): 13.81, 13.85, 20.05, 20.22, 27.16, 29.72, 31.49, 33.65, 46.22, 47.93, 57.61, 117.24, 134.82, 168.27, 204.43. LRMS *m/z* (%): 85.15 (100), 91.15 (54), 157.05 (24), 253.15 (10, [M^+]). IR (cm^{-1}): 1444, 1638, 1717, 2929, 2965.

Compound **3c**

^{1}H NMR δ (ppm): 1.50-1.71 (6H, m), 1.74 (3H, s), 2.16 (3H, s), 2.55-2.65 (2H, m), 3.47-3.66 (4H, m), 3.86 (1H, d, J=7 Hz), 4.92 (1H, s), 4.78 (1H, s). ^{13}C NMR δ (ppm): 22.70, 24.46, 25.67, 26.43, 26.95, 36.49, 43.37, 46.99, 56.07, 112.04, 142.36, 166.88, 204.46. LRMS *m/z* (%): 43.10 (100), 84.15 (98), 95.15 (25), 112.15 (32), 152.00 (13), 180.25 (96), 223.35 (6, [M^+]). IR (cm^{-1}): 1442, 1636, 1718, 2859, 2937.

Compound **3d**

^{1}H NMR δ (ppm): 1.51-1.69 (9H, m), 2.15 (3H, s), 2.56 (2H, t, J= 7Hz), 3.40-3.67 (5H, m), 5.35 (1H, dt, J_1 = 7 Hz, J_2 = 15 Hz), 5.52 (1H, dqua, J_1 = 6.5 Hz, J_2 = 15 Hz). ^{13}C NMR δ (ppm): 17.91, 24.48, 25.71, 26.48, 27.24, 43.34, 47.06, 57.87, 127.32, 127.75, 167.05, 204.54. LRMS *m/z* (%): 43.05 (52), 55.10 (19), 69.15 (29), 84.15 (50), 95.15 (30), 112.15 (18), 126.15 (8), 152.20 (11), 180.25 (100), 223.30 (8, [M^+]). IR (cm^{-1}): 1442, 1634, 1721, 2858, 2937.

Compound **3e**

^{1}H NMR δ (ppm): 0.85-0.98 (9H, m), 1.23-1.39 (8H, m), 1.46-1.60 (4H, m), 1.93-2.01 (2H, m), 2.17 (3H, s), 2.53-2.66 (2H, m), 3.13-3.44 (4H, m), 3.52 (1H, t, J = 7.4 Hz), 5.21-5.36 (1H, m), 5.41-5.56 (1H, m). ^{13}C NMR δ (ppm): 13.71, 13.86, 19.94, 20.10, 22.25, 26.87, 26.92, 27.31, 29.62, 31.36, 31.65, 46.17, 47.81, 57.90, 125.00, 132.70, 168.34. LRMS *m/z* (%): 43.05 (43), 57.10 (25), 86.15 (28), 156.20 (19), 266.35 (100), 309.40 (2, [M^+]). IR (cm^{-1}): 1431, 1640, 1721, 2869, 2931, 2959.

Compound **3f**

^{1}H NMR δ (ppm): 0.90 (6H, t, J = 7 Hz), 1.25-1.36 (4H, m), 1.43-1.58 (4H, m), 2.70-2.88 (2H, m), 3.15-3.43 (4H, m), 3.66 (1H, t, J = 7 Hz), 6.11 (1H, dt, J_1 = 7 Hz, J_2 = 16 Hz), 6.46 (1H, d, J = 16 Hz), 7.17-7.38 (5H, m). ^{13}C NMR δ (ppm): 13.95, 14,00, 20.22, 20.38, 27.45, 29.88, 31.65, 33.16, 46.41, 48.11, 58.11, 126,18, 127.50, 128.68, 132.72, 137.22, 168.43, 204.67. LRMS *m/z* (%): 43.00 (32), 57.05 (19), 91.05 (11), 117.05 (14), 129.05 (11), 157.05 (33), 286.20 (100), 329.30 (7, [M^+]). IR (cm^{-1}): 750, 971, 1445, 1634, 1718, 2867, 2929, 2960.

Selenocyclofunctionalization: compounds **4a-e**

To a suspension of sodium carbonate (1.0 mmol) and α-substituted β-ketoamide **3** (1.0 mmol) in toluene (4.0 mL) under nitrogen atmosphere at room temperature was added the phenylselenenyl halide (2.0 mmol) in toluene (1.0 mL). The reaction was monitored by TLC and at the end of reaction, ethyl acetate (20.0 mL) was added. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography column using a mixture of hexane/ethyl acetate as eluent. The yields are described on Table 2.

Compound **4a**

^{1}H NMR δ (ppm): 1.82 (3H, s), 2.72 (1H, dd, J_1 = 7.3 Hz, J_2 = 15 Hz), 3.09 (1H, dd, J_1 = 12 Hz, J_2 = 15 Hz), 3.01-3.12 (2H, m), 3.20 (1H, dd, J_1 = 5 Hz, J_2 = 12.5 Hz), 3.48-3.77 (8H; m), 4.75-4.80 (1H, m), 7.25-2.38 (3H, m), 7.51-7.54 (2H, m).^{13}C NMR δ (ppm): 13.50, 32.77, 37.84, 45.16, 66.99, 80.20, 103.06, 127.31, 129.18, 129.38, 132.97, 157.25, 167.43. LRMS *m/z* (%): 43.05 (45), 81.10 (27), 123.10 (100), 210.30 (69), 367.25 (4, [M^+]). IR (cm^{-1}): 739, 1109, 1444, 1630, 1716, 1769, 2856, 2919, 2965, 3054.

Compound **4b**

^{1}H NMR δ_H (ppm): 0.92 (3H, t, J = 7 Hz), 0.98 (3H, t, J = 7 Hz), 1.22-1.58 (8H, m), 2.14 (3H, s), 2.60-265 (1H, m), 2.83-2.92 (2H, m), 3.05-3.36 (5H, m), 4.58-4.65 (1H, m), 7.27-7.30 (3H, m), 7.48-759 (2H, m). ^{13}C NMR δ_C (ppm): 13.51, 13.60, 19.90, 27.86, 29.36, 31.26, 45.95, 79.85, 104.18, 127.42, 129.10, 132.67, 158.19, 172.37. LRMS *m/z* (%):

43.10 (79), 57.15 (31), 81.10 (30), 123.10 (100), 128.20 (37), 210.35 (40), 252.35 (36), 409.35 (5, [M^+]). IR (cm^{-1}): 744, 1237, 1434, 1631, 1724, 2866, 2928, 2965.

Compound **4c**

^1H NMR δ_H (ppm): 1.50 (3H, s), 1.36-1.72 (6H, m), 1.75 (3H, s), 2.78 (1H, d, J = 14.5 Hz), 2.93 (1H, d, J = 14.5 Hz), 3.17 (1H, d, J = 12.5 Hz), 3.25 (1H, d, J = 12.5 Hz), 3.42-3.53 (4H, m), 7.22-7.27 (3H, m), 7.51-7.55 (2H, m). ^{13}C NMR δ_C (ppm): 14.19, 24.43, 24.65, 26.86, 39.29, 43.63, 45.61, 86.15, 103.41, 126.93, 129.05, 129.12, 132.58, 155.18, 167.25. LRMS *m/z* (%): 43.10 (65), 84.15 (100), 112.10 (23), 137.10 (36), 157.00 (8), 208.30 (10), 222.25 (36), 379.35 (6, [M^+]). IR (cm^{-1}): 739, 1234, 1274, 1434, 1610, 1738, 2856, 2939, 3057.

Compound **4d**

^1H NMR δ_H (ppm): 1.44 (3H, d, J = 6 Hz), 1.59-1.68 (6H, m), 2.17 (3H, s), 2.85-2.94 (1H, m), 3.17-3.30 (1H, m), 3.38-3.71 (4H, m), 4.37-4.50 (1H, m), 4.58-4.74 (1H, m), 7.22-7.29 (3H, m), 7.57-7.62 (2H, m). ^{13}C NMR δ_C (ppm): 16.53, 17.84, 25.02, 26.63, 32.71, 37.44, 45.80, 81.97, 104.03, 126.34, 129.77, 129.92, 132.85, 159.11, 166.51. LRMS *m/z* (%): 43.10 (100), 55.10 (69), 69.15 (22), 84.20 (51), 112.20 (18), 137.15 (32), 180.35 (15), 222.40 (88), 379.50 (4, [M^+]). IR (cm^{-1}):): 739, 1239, 1280, 1434, 1615, 1725, 2856, 2939, 2975, 3048.

Compound **4e**

^1H NMR δ_H (ppm): 0.84-0.96 (9H, m), 1.23-1.74 (12H, m), 1.86-2.01 (2H, m), 2.15 (3H, s), 2.52-2.67 (1H, m), 2.86-2.99 (1H, m), 3.14-

3.51 (4H, m), 4.45-4.53 (1H, m), 4.71-4.79 (1H, m), 7.23-7.26 (3H, m), 7.51-7.56 (2H, m). ^{13}C NMR δ_C (ppm): 13.19, 13.86, 13.99, 20.08, 22.37, 30.39, 31.71, 32.15, 32.73, 47.11, 50.67, 82.68, 104.44, 125.07, 129.07, 129.10, 130.50, 132.84, 163.05, 173.58. LRMS *m/z* (%): 43.05 (100), 57.10 (18), 128.15 (26), 266.30 (5), 308.40 (34), 465.40 (2, $[M^+]$). IR (cm^{-1}): 735, 1446, 1630, 2880, 2928, 2959.

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