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In this paper is described an unreported method employing α-alkenyl β-ketoamides as starting material to give 2,3-dihydrofurans, precursors of substituted furans.

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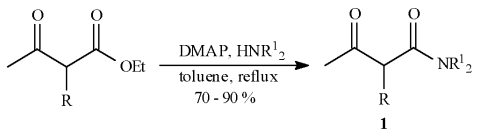
Furan derivatives have received much attention since their structures were identified as important synthons and principal moiety of several bioactive compounds [1]. The synthesis of furans involving cyclizations of substituted 1,3-dicarbonyl compounds have been reported by our group [2] and other authors [3].

The cyclization of unsaturated amides has also been reported leading to lactones and lactams *via* the participation of the O or N atom of the amide group [4].

In this paper we describe a methodology which promotes the formation of iodinated 2,3-dihydrofurans despite the possibility of formation of lactones and lactams by the iodocyclization of α-alkenyl-β-ketoamides. In our methodology only the attack of the enolic hydroxy group at the iodine π-complex was observed, thus maintaining the amide group intact.

Scheme 1



1

(**1a**) R = -CH_2-CH=CH_2 ; R^1 = -$(CH_2)_2$-O-$(CH_2)_2$-
(**1b**) R = -CH_2-CH=CH_2 ; R^1 = -$(CH_2)_3$-CH_3
(**1c**) R = -CH_2-CH=CH_2 ; R^1 = -CH_2-C_6H_5
(**1d**) R = -CH_2-(CH_3)C=CH_2 ; R^1 = -$(CH_2)_2$-O-$(CH_2)_2$-
(**1e**) R = -CH_2-(CH_3)C=CH_2 ; R^1 = -CH_2-C_6H_5
(**1f**) R = -CH_2-CH=CH-CH_3 (*cis*/*trans*) = 15:85); R^1 = -CH_2-$(CH_2)_3$-CH_2-
(**1g**) R = -CH_2-CH=CH-C_6H_5 (*trans*); R^1 = -$(CH_2)_3$-CH_3

The starting β-ketoamides were prepared by the aminolysis of the corresponding β-ketoesters under DMAP catalysis (Scheme 1) [5].

Concerning the iodocyclization reaction, we observed at first that carrying out the process under the usual conditions for 1,3-dicarbonyl compounds (iodine, $NaCO_3$ and CH_2Cl_2 or $CHCl_3$) [2,3] only low yields were obtained even with long reaction times.

Aiming therefore for better results, the system of choice to convert the ketoamides into the 2,3,5-trisubstituted-2,3-dihydrofurans in good yields was iodine and Na_2CO_3 in toluene under reflux. Sonication conditions were used to improve the cyclization yields. Increased yields were obtained in some cases, but disapointly these results can not be generalized (Scheme 2 and Table).

In method A, the reaction conditions of the mixture were maintained until product formation stops, while in method B, the reaction time was no longer than reported in method A for the corresponding entry. Morfolyl (**1a** and **1d**) and dibenzyl (**1e**) amides were converted into the corresponding products in better yields (see Table). No reaction was

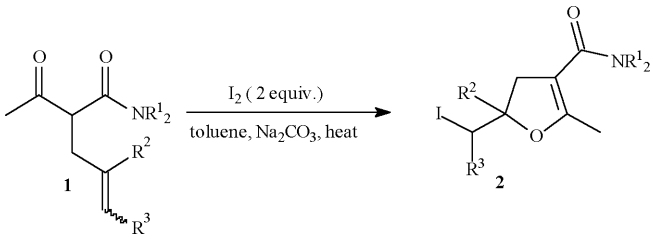
Table

Iodocyclization of α-Substituted β-Ketoamides **1** giving Dihydrofurans **2**

Compound	R^1	R^2	R^3	Reaction Conditions	Reaction Time (h)	Yield (%)
2a	-$(CH_2)_2$-O-$(CH_2)_2$-	H	H	(A)	3	70
				(B)	1	80
2b	-$(CH_2)_3$-CH_3	H	H	(A)	6	60
				(B)	6	35
2c	-CH_2-C_6H_5	H	H	(A)	12	55
				(B)	12	50
2d	-$(CH_2)_2$-O-$(CH_2)_2$-	CH_3	H	(A)	9	70
				(B)	2	85
2e	-CH_2-C_6H_5	CH_3	H	(A)	13	85
				(B)	3	85
2f [a]	-CH_2-$(CH_2)_3$-CH_2-	H	CH_3	(A)	5	65
				(B)	5	40

Reaction conditions: (A) iodine (2 equiv.), Na_2CO_3 (2 equiv.), refluxed toluene; (B) iodine (2 equiv.), Na_2CO_3 (2 equiv.), toluene, sonication, water bath at 60 °C; [a] Diastereomeric ratio measured by GC: **2f** (15/85).

Scheme 2

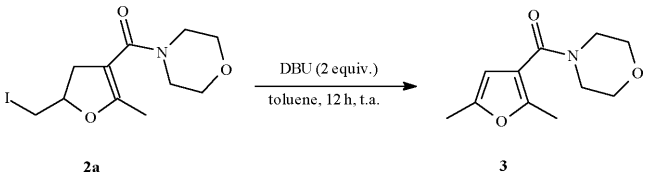


observed when compound **1g** was submitted to both methods of iodocyclization.

When bromine and NBS were used, a mixture of dihydrofurans and α-acetyl-lactone was formed. This result is in agreement with the known behavior of unsaturated amides when submitted to halocyclization conditions. The obtained lactones are not stable enough to be purified or stored. Therefore we were unable to identify accurately these compounds and recognize their isomers. Additional efforts are being directed to achieve further transformations in more stable products.

The synthetic potential of the described methodology was exemplified by the conversion of dihydrofurans (**2a**) into furans (**3**) by dehydrohalogenation reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature [3a,3d,6], as shown in Scheme 3.

Scheme 3



In conclusion, we reported an optional methodology to afford dihydrofurans from α-substituted β-ketoamides, evidencing the versatility of 1,3-dicarbonyl compounds while precursors of heterocyclic rings.

EXPERIMENTAL

NMR data were recorded on a Bruker DPX 300 NMR spectrometer. Shifts are reported as ppm relative to TMS, which was used as internal standard. The chromatographic monitoring of the reactions was made using an Agilent 6890 gas chromatograph equipped with HP-5 column (30 m x 0.32 mm x 0.25 μm film) applying nitrogen as carrier gas with FID detection, and a Shimadzu GCMS-QP5050A low resolution mass spectrometer (IE 70 eV) coupled on a Shimadzu GC-17A gas chromatograph equipped with DB-5 column (30 m x 0.25 mm x 0.25 μm film) applying helium as carrier gas. Infrared spectra were determined by film on KBr in a FTIR Bomem spectrometer. Exact mass spectra were obtained with a VG Autospec high-resolution mass spectrometer (EI 70 eV – direct insertion) at Analytical Center of University of Campinas (UNICAMP), Campinas, SP, Brazil.

General Procedure for Dihydrofurans (**2**).

Method A.

Iodine (2 mmol) and anhydrous sodium carbonate (2 mmol) were added to a solution of α-substituted β-ketoamide **1a-g** (1 mmol) in toluene (5 mL). The mixture was stirred and heated to reflux, and monitored by GC and TLC. Upon completion, the reaction mixture was cooled to room temperature and filtered over silica gel with ethyl acetate as eluent. The solvent was removed under reduced pressure and the residue was purified by chromatography on a silica gel column with EtOAc/hexane as eluent. All compounds were obtained as yellow oil.

Method B.

Iodine (2 mmol) and anhydrous sodium carbonate (2 mmol) were added to a solution of α-substituted β-ketoamide **1a-g** (1 mmol) in toluene (5 mL). The mixture was submitted to sonication in water bath at 60 °C and monitored by GC and TLC. The purification is identical to method A.

(5-Iodomethyl-2-methyl-4,5-dihydrofuran-3-yl)-morpholin-4-ylmethanone (**2a**).

This compound has ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.88 (s,3H), 2.68 (dd, J_1 = 7.00 Hz e J_2 = 15.00 Hz, 1H), 3.11 (dd, J_1 = 10.60 Hz e J_2 = 15.00 Hz, 1H), 3.29 - 3.38 (m, 2H), 3.54 - 3.79 (m, 8H), 4.59 - 4.66 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 9.70, 13.48, 38.52, 45.19 (broad), 66.96, 79.39, 103.09, 156.64, 167.04. IR (cm^{-1}): 972, 1015, 1113, 1213, 1224, 1272, 1379, 1440, 1626, 2856, 2920, 2968. EI-HRMS: calcd. for $C_{11}H_{16}INO_3$ = 337.0175, found *m/z* = 337.0175.

5-Iodomethyl-2-methyl-4,5-dihydrofuran-3-carboxylic Acid Dibutylamide (**2b**).

This compound has ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 0.93 (t, J = 7.24 Hz, 6H), 1.30 (m, 4H), 1.52 (m, 4H), 1.84 (s, 3H), 2.67 (dd, J_1 = 6.20 Hz e J_2 = 15.00 Hz, 1H), 3.07 (dd, J_1 = 9.00 Hz e J_2 = 15.00 Hz, 1H), 3.26 - 3.45 (m, 6H), 4.57 - 4.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 9.78, 13.24, 13.89, 20.15, 30.39, 38.88, 42.80 (broad), 79.40, 104.36, 155.19, 167.73. IR (cm^{-1}): 941, 977, 1075, 1111, 1219, 1425, 1456, 1614, 2832, 2960. EI-HRMS: calcd. for $C_{15}H_{26}INO_2$ = 379.1008, found *m/z* = 379.1007.

5-Iodomethyl-2-methyl-4,5-dihydrofuran-3-carboxylic Acid Dibenzylamide (**2c**).

This compound has ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.91 (s, 3H), 2.68 (dd, J_1 = 6.90 Hz e J_2 = 14.70 Hz, 1H), 3.10 (dd, J_1 = 10.50 Hz e J_2 = 10.45 Hz, 1H), 3.25 (d, J = 6.20 Hz, 2H), 4.43 - 4.64 (m, 5H), 7.15 - 7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 9.52, 13.45, 38.89, 49.50 (broad), 79.55, 103.70, 127.45, 127.68, 128.74, 136.96, 157.14, 168.57. IR (cm^{-1}): 694, 745, 967, 1075, 1150, 1219, 1415, 1451, 1617, 2862, 2919, 3032, 3063. EI-HRMS: calcd. for $C_{21}H_{22}INO_2$ = 447.0695, found *m/z* = 447.0694.

(5-Iodomethyl-2,5-dimethyl-4,5-dihydrofuran-3-yl)-morpholin-4-ylmethanone (**2d**).

This compound has ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.58 (s, 3H), 1.87 (s, 3H), 2.81 (d, J = 15.00 Hz, 1H), 2.92 (d, J = 15.00 Hz, 1H), 3.33 (d, J = 10.00 Hz, 1H), 3.40 (d, J = 10.00 Hz, 1H), 3.55 - 3.72 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 13.86, 16.14, 26.34, 43.81, 45.39 (broad), 67.15, 84.48, 103.07,

156.16, 167.37. IR (cm^{-1}): 972, 1015, 1113, 1224, 1272, 1379, 1440, 1626, 2856, 2920, 2968. EI-HRMS: calcd. for $C_{12}H_{18}INO_3$ = 351.0331, found *m/z* = 351.0332

5-Iodomethyl-2,5-dimethyl-4,5-dihydro-furan-3-carboxylic Acid Dibenzylamide (**2e**).

This compound has ^1H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.53 (s, 3H), 1.91 (s, 3H), 2.79 (d, *J* =15 Hz, 1H), 2.92 (d, *J* =15 Hz, 1H), 3.24 (d, *J* = 10 Hz, 1H), 3.31 (d, *J* = 10 Hz, 1H), 4.38 (d, *J* = 15 Hz, 1H), 4.64 (d, *J* =15 Hz, 2H), 7.15 - 7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 13.64, 15.82, 26.09, 43.97, 48.70 (broad), 84.38, 103.45, 127.50, 127.67, 128.72, 136.97, 156.46, 168.61. IR (cm^{-1}): 969, 1028, 1075, 1147, 1219, 1270, 1420, 1451, 1614, 2857, 2924, 2975, 3032, 3068. EI-HRMS: calcd. for $C_{22}H_{24}INO_2$ = 461.0852, found *m/z* = 461.0821.

[5-(1-Iodo-ethyl)-2-methyl-4,5-dihydrofuran-3-yl]-piperidin-1-ylmethanone (**2f**).

This compound has ^1H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.58 – 1.71 (m, 6H), 1.84 (s, 3H), 1.89 (d, *J* = 6.40 Hz, 3H), 2.70 - 2.77 (m, 1H), 2.99 - 3.09 (m, 1H), 3.48 - 3.53 (m, 4H), 4.24 - 4.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]:13.28, 23.55, 24.65, 26.22, 31.61, 38.29, 45.68 (broad), 84.54, 103.92, 155.18, 166.75. IR (cm^{-1}): 875, 1002, 1122, 1244, 1378, 1447, 1601, 2858, 2935. EI-HRMS: calcd. for $C_{13}H_{20}INO_2$ = 349.0539, found *m/z* = 349.0507.

(2,5-Dimethylfuran-3-yl)-morpholin-4-ylmethanone (**3**).

To a solution of dihydrofuran **2a** (1 mmol) in toluene (5 mL) was added DBU (2 equiv.) and the mixture was stirred at room temperature overnight. Ethyl acetate was added and the solution was washed with brine. The organic layer was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The residual oil was purified through a silica gel column with EtOAc/hexane as eluent; ^1H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.24 (s, 3H), 2.33 (s, 3H), 3.58-3.75 (m, 8H), 5.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 12.71, 13.01, 42.50 (broad), 66.76, 105.63, 115.54, 149.81, 151.60, 165.45. EI-LRMS *m/z*: 209 ($[M]^+$).

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