A NEW ROUTE TO SYNTHESIS OF 2,5,7-SUBSTITUTED 1,5-BENZOTHIAZEPIN-4(5H)-ONES FROM TERTIARY 3-BENZOYLPROPIONAMIDES

Georgia Tsolomiti, Kyriaki Tsolomiti and Athanase Tsolomitis*

The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens 157 80, Greece

Abstract : Tertiary amides of 3-benzoylpropionic acid have been found to be converted, on reaction with excess thionyl chloride, via the intermediate 3-sulfenyl chlorides of 3-benzoylacrylamides, followed by an intramolecular Friedel-Crafts reaction, to 2,5,7-substituted 1,5-benzothiazepin-4(5H)-ones.

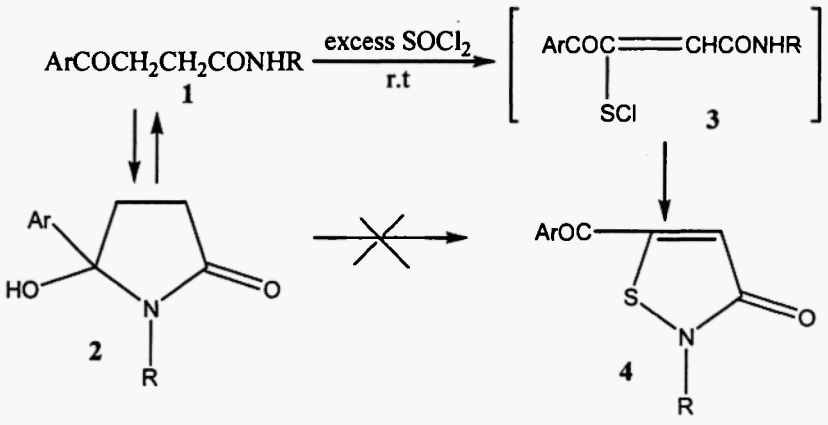
Over the past three decades, substituted 1,5-benzothiazepin-4-ones have exhibited considerable pharmacological interest, primarily as calcium antagonists by interaction with the L-type voltage gated Ca^{2+} channel.[1,2] Nowadays, the 1,5-benzothiazepin-4-one (diltiazem) is among the most widely used drugs in the treatment of cardiovascular disorders.[3] Various benzothiazepin-4-ones have been patented as spasmolytics,[4] as angiotensive converting enzyme inhibitors[5] and as squalene synthetase inhibitors.[6] The importance and utility of benzothiazepinones have led to the development of numerous synthetic routes.[7]

Non classical oxidative reactions of thionyl chloride with different organic substrates are known a long time ago. α-Methyl carbons to aromatic rings,[8] methylene carbons[9] adjacent to an aryl and a carboxylic group, α-methylenes to a carbonyl moiety, ketonic or carboxylic as well as α-methinic carbons to a carboxylic group (e.g. of cinnamic acid) have been also extensively investigated and were presented in a series of interesting papers[10a-g] in which safe proofs were cited that all the referred oxidations occur at the α-carbon atom to a carbonyl function, resulting to the corresponding α-chloro-α-chlorosulfenyl chlorides. Moreover, the former authors in some cases separated the α-chloro-α-chlorosulfenyl derivatives, while in other instances the initially formed sulfenyl chlorides underwent an electrophilic aromatic substitution to form sulfur heterocycles e.g. benzo[b]thiophenes. Furthermore some benzo[b]thiophenes were also prepared by a Friedel-Craafts cyclization of the appropriate sulfenyl chlorides.[10g] In all above mentioned reports an excess thionyl chloride was always used in the presence of a tertiary amine, (usually pyridine), at strong reaction conditions. It is interesting to note that analogous reactions with other active methylenes such as those of arylacetonitriles,[11] aryl alkyl ketones and malonates, have been also reported.[12]

Recently,[13] we have reported the oxidative behavior of thionyl chloride on some secondary amides as those of propionic, phenylacetic and β-phenylpropionic acids, resulting to the corresponding α-chloro-α-chlorosulfenyl-imidoyl chlorides. In all the former reactions excess thionyl chloride was used without any of base.[14]

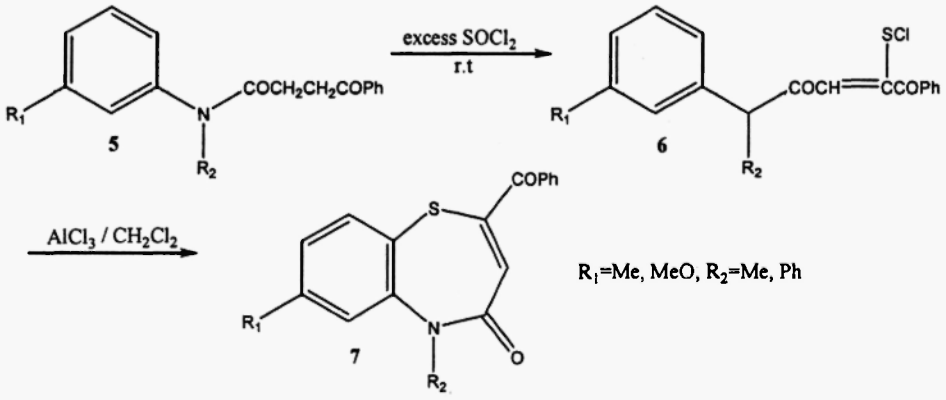
In previous reports,[15a,b] we described the preparation of some 5-aroylisothiazol-3(2H)-ones 4 from the appropriate 3-aroylpropionamides **1** on reaction with excess thionyl chloride. This oxidation-cyclocondensation reaction has been suggested[15a] to proceed

through intermediacy of sulfenyl chlorides **3**, (Scheme 1), resulting from the oxidation of the methylene group adjacent to the aroyl carbonyl, followed by a nucleophilic displacement from the amidic nitrogen, with extrusion of hydrogen chloride. Formation of such an intermediate would only be possible for the open chain γ-keto amides **1**, given[16] that γ-keto amides of the general formula **1** are known to exhibit ring-chain tautomerism **1↔2**, (γ-keto amide↔5-hydroxypyrrolidin-2-one). It must be pointed out that pure cyclic tautomers of the structure **2** did not give the above heterocyclization to the isothiazolones **4**, as anticipated.



Scheme-1

Here, we describe the synthesis of some 2,5,7-substituted 1,5-benzothiazepin-4(5H)-ones **7** starting from tertiary γ-keto amides **5** prepared via a known procedure,[17] using 5-phenylfuran-2(3H)-one and the appropriate secondary amine. Apparently, a ring-chain tautomerism of these γ-keto amides must be excluded, this was proved spectroscopically (see experimental). At the γ-keto amides **5** the amide aryl moiety was chosen so as to have a substituent which increases the reactivity of aromatic nucleus to the aromatic electrophilic substitution by the sulfenyl chloride moiety of **6**, via an intramolecular Friedel-Crafts reaction, resulting to the desired 1,5-benzothiazepin-4(5H)-one **7**, (Scheme-2).



Scheme-2

Although the study of aromatic substitution with sulfenyl chlorides has been well documented[18] a limited number of sulfenyl chlorides were used in the reaction. Almost most of them have electron-withdrawing groups. It is worth noticing that the reaction of activated aromatic nucleus with reactive sulfenyl chlorides can proceed without any of catalyst e.g. a Lewis acid,[19] while for less reactive reagents a catalyst is needed.[20]

Experimental

General. NMR spectra were recorded, at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer in $CDCl_3$. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (in KBr pellets).

General procedure for the preparation of N-methyl-(or N-phenyl-)-4-oxo-4-phenylbutanarylamides **5.**

An equimolar mixture, (0.1 mol of each), of N-methyl- or N-phenyl-arylamine and 5-phenyl-2(3H)-furanone was heated for 3 h on a steam bath, for N-methylarylamines or 6 h for N-phenyarylamines. The resulting resinous mass was dissolved in ethyl ether and washed successively with 10 % hydrochloric acid and 5 % sodium bicarbonate, the formed solid after usual workup and condensation of the solution proved to be, ^{1}H NMR, almost pure γ-ketoamide **5**. After recrystallization from ethanol an analytically pure sample of **5** was received, in yields 74-87 %.

N-Methyl-N-(3-methylphenyl)-4-oxo-4-phenylbutanamide 5a: yield 87 %, mp 81-82 ^{0}C. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 6.72; N, 5.13. IR: 1685, 1654, 1593. ^{1}H NMR: 2.35 (s, 3H, CH_3Ar), 2.47 (t, J=6.5, 2H, 2-CH2), 3.28 (s, 3H, CH_3N), 3.35 ((t, J=6.5, 2H, 3-CH2), 7.23-7.90 (m, 9H, arom.). ^{13}C NMR: 24.30, 28.35, 33.60, 37.20, 118.60, 124.52, 124.63, 128.70, 128.80, 133.25, 136.63, 138.41, 142.33, 171.90, 199.20.

N-Phenyl-N-(3-methylphenyl)-4-oxo-4-phenylbutanamide 5b: yield 82 %, mp 97-98 ^{0}C. Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.57; H, 6.31; N, 3.96. IR: 1683, 1652, 1595. ^{1}H NMR: 2.38 (s, 3H, CH_3Ar), 2.50 (t, J=6.5, 2H, 2-CH2), 3.37 ((t, J=6.5, 2H, 3-CH2), 6.95-7.96 (m, 14H, arom.). ^{13}C NMR: 24.60, 28.58, 33.80, 116.20, 118.50, 118.67, 128.64, 128.75, 129.47, 133.28, 136.33, 139.30, 142.15, 143.37, 172.10, 199.35.

N-Methyl-N-(3-methoxyphenyl)-4-oxo-4-phenylbutanamide 5c: yield 77 %, mp 73-75 ^{0}C. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.86; H, 6.25; N, 4.55. IR: 1685, 1655, 1590. ^{1}H NMR: 2.43 (t, J=6.5, 2H, 2-CH2), 3.26 (s,3H, CH_3N), 3.37 ((t, J=6.5, 2H, 3-CH2), 3.78 (s, 3H, CH_3O), 7.97-7.90 (m, 9H, arom.). ^{13}C NMR: 28.40, 33.55, 37.50, 54.64, 104.67, 109.80, 113.62, 128.45, 128.63, 128.75, 128.73, 130.10, 133.25, 136.42, 143.20, 171.80, 199.45.

N-Phenyl-N-(3-methoxyphenyl)-4-oxo-4-phenylbutanamide 5d: yield 74 %, mp 111-112 ^{0}C. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.98; N, 3.90. Found: C, 76.58; H, 6.05; N, 4.11. IR: 1681, 1650, 1592. ^{1}H NMR: 2.51 (t, J=6.5, 2H, 2-CH2), 3.34 (t, J=6.5, 2H, 3-CH2), 3.73 (s, 3H, CH_3O), 6.65-7.98 (m, 14H, arom.). ^{13}C NMR: 28.40, 33.73, 54.37, 102.20, 103.35, 111.40, 119.22, 128.30, 128.67, 128.81, 129.60, 130.70, 133.45, 136.23, 140.11, 141.55, 161.33, 171.80, 199.27.

General procedure for the preparation of N-methyl-(or N-phenyl)-4-oxo-4-phenylbut-2-ene-arylamide-3-sulfenyl chlorides **6**. A mixture of the appropriate γ-keto amide **5** and 30 ml of freshly distilled thionyl chloride was stirred at room temperature for a day. The resulting dark solution was concentrated under vacuum to a resinous mass which was assigned, ^{1}H NMR, to be pure enough the desired sulfenyl chloride **6**. This intermediate was used without further purification for the synthesis of 1,5-benzothiazepin-4(5H)-ones 7.

N-Methyl-N-(3-methylphenyl)-4-oxo-4-phenylbut-2-ene-3-sulfenyl chloride 6a: ^{1}H NMR: 2.36 (s, 3H, CH_3Ar), 3.33 (s, 3H, CH_3N), 5.73 (s, 1H, H-2), 7.12-7.93 (m, 9H, arom.).

N-Phenyl-N-(3-methylphenyl)-4-oxo-4-phenylbut-2-ene-3-sulfenyl chloride 6b: ^{1}H NMR: 2.40 (s, 3H, CH_3Ar), 5.70 (s, 1H, H-2), 6.68-7.88 (m, 14H, arom.).

N-Methyl-N-(3-methoxyphenyl)-4-oxo-4-phenylbut-2-ene-3-sulfenyl chloride 6c: ^{1}H NMR: 3.25 (s, 3H, CH_3N), 3.76 (s, 3H, CH_3O), 5.70 (s, 1H, H-2), 6.65-7.91 (m, 9H, arom.).

N-Phenyl-N-(3-methoxyphenyl)-4-oxo-4-phenylbut-2-ene-3-sulfenyl chloride 6d: ^{1}H NMR: 3.75 (s, 3H, CH_3O), 5.76 (s, 1H, H-2), 6.61-7.93 (m, 14H, arom.).

General procedure for the preparation of 2,5,7-substituted 1,5-benzothiazepin-4(5H)-ones **7**: To a vigorously stirred solution of 10 mmol of sulfenyl chloride **6** in 100 ml of dry methylene chloride, anhydrous aluminium chloride, 3.5 g, was added over a period of 20 min. at 5-10 ^{0}C. The stirring was continued at this temperature for 2 h and then for additional 2 h at room temperature. The mixture decomposed with 10 % hydrochloric acid, the organic phase after the usual workup was concentrated to yield a crude product which was purified by using silica gel (activity grade III) column chromatography, by elution with ethyl acetate-ethyl ether (10:1) to furnish 57-66 %, (based on **5**), of pure enough, ^{1}H NMR, benzothiazepinone 7. Recrystallization from ethyl acetate/ethyl ether afforded analytically pure benzothiazepinone 7 in yields 51-63 %.

1,5-Benzothiazepin-4(5H)-one-2-benzoyl-5,7-dimethyl 7a: yield 58 %, mp 145-146 ^{0}C. Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53; S, 10.36. Found: C, 70.11; H, 4.68; N, 4.61; S, 10.47. IR: 1680, 1630, 1585. ^{1}H NMR: 2.34 (s, 3H, CH_3Ar), 3.44 (s, 3H, CH_3N), 6.35 (s, 1H, H-3), 6.60-7.87 (m, 9H, arom.). ^{13}C NMR: 24.33, 37.76, 120.31, 121.53, 124.52, 124.90, 129.32, 129.54, 129.85, 135.20, 135.46, 135.63, 156.60, 166.71, 188.41.

1,5-Benzothiazepin-4(5H)-one-2-benzoyl-5-phenyl-7-methyl 7b: yield 51 %, mp 161-162 ^{0}C. Anal. Calcd for $C_{23}H_{17}NO_2S$: C, 74.37; H, 4.61; N, 3.77; S, 8.63. Found: C, 74.56; H, 4.50; N, 3.96; S, 8.49. IR: 1682, 1655, 1595. ^{1}H NMR: 2.38 (s, 3H, CH_3Ar), 6.31 (s, 1H, H-3), 6.60-7.87 (m, 14H, arom.). ^{13}C NMR: 24.43, 118.80, 119.15, 120.50, 129.34, 129.65, 129.90, 131.10, 132.63, 134.60, 136.23, 137.86, 156.70, 166.80, 188.60.

1,5-Benzothiazepin-4(5H)-one-2-benzoyl-5-methyl-7-methoxy 7c: yield 57 %, mp 133-134 ^{0}C. Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30; S, 9.85. Found: C, 66.61; H, 4.47; N, 4.51; S, 10.07. IR: 1682, 1653, 1582. ^{1}H NMR: 3.33 (s, 3H, CH_3 N), 3.76 (s, 3H, CH_3O), 6.37 (s, 1H, H-3), 7.22-7.91 (m, 9H, arom.). ^{13}C NMR: 37.81, 54.73, 105.11, 110.21, 120.33, 129.30, 129.85, 130.57, 130.63, 136.70, 137.90, 157.63, 166.80, 188.70.

1,5-Benzothiazepin-4(5H)-one-2-benzoyl-5-phenyl-7-methoxy 7d: yield 63 %, mp 148-149 ^{0}C. Anal. Calcd for $C_{23}H_{17}NO_3S$: C, 71.30; H, 4.42; N, 3.61; S, 8.28. Found: C, 71.11; H, 4.51; N, 3.49; S, 8.43. IR: 1684, 1648, 1590. ^{1}H NMR: 3.80 (s, 3H,

CH_3O), 6.40 (s, 1H, H-3), 6.75-7.94 (m, 14H, arom.). ^{13}C NMR: 54.85, 102.51, 104.11, 118.27, 119.31, 128.20, 129.33, 129.70, 129.91, 132.10, 134.63, 137.85, 156.73, 166.70, 188.75.

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