SYNTHESIS AND REARRANGEMENT OF SUBSTITUTED S-(1-BENZOFURAN-2(3*H*)-ONE-3-YL) ISOTHIURONIUM-BROMIDES

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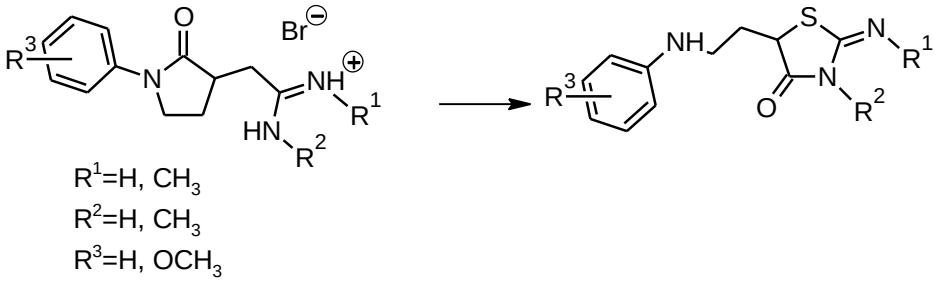
Abstract: Substituted S-(1-benzofuran-2(3*H*)-one-3-yl) isothiuronium bromides are derived from cyclic lactame coumaran-2-one, which is prepared by dehydratation of (2-hydroxyphenyl)acetic acid. Thus prepared lactam is further brominated to position 3, where a good leaving group is needed. In next step 3-bromocoumaran-2-one reacts with different substituted thioureas in the meaning of nucleophilic substitution of atom bromine to atom sulfur and give substituted S-(1-benzofuran-2(3*H*)-one-3-yl) isothiuronium bromide, which was obtained as a solid in good yield. These relatively unstable salts were characterized by ^{1}H and ^{13}C NMR spectra, melting point and elemental analysis. Isothiuronium salts are transformed in base conditions and give substituted 5-(2-hydroxyphenyl)-2-imino-1,3-thiazolidine-4-ones. In this rearrangement acid-base catalysis under very mild conditions is applied. The rearrangement proceeds even at physiological pH, which may have potential importance in the use of these compounds as prodrugs. Next, the kinetics and the mechanism of the rearrangement of *N*-(4-methoxyphenyl)-*S*-(2-oxo-2,3-dihydro-1-benzofurane-3-yl) isothiuronium bromide to 5-(2-hydroxyphenyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-on is studied in aqueous buffers at 25 °C and ionic strength I = 1 mol.l^{-1} under pseudo-first order conditions.

Keywords: Isothiuronium salts, thioureas, rearrangement, transformation reaction, dehydratation, bromination, acid-base catalysis

Introduction

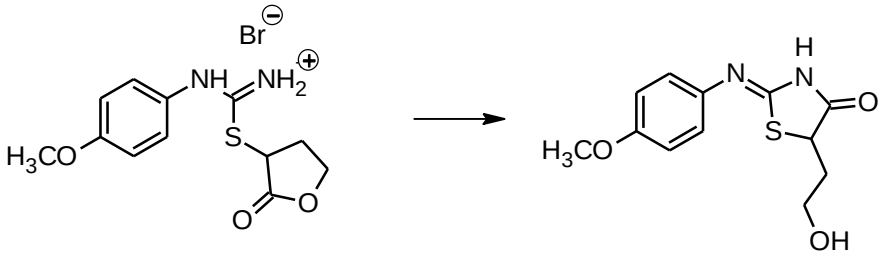
In organic chemistry have great significance rearrangement of heterocyclic compounds. In this way we can prepare otherwise difficult-to-prepare biologically active compounds. The possibility of preparing heterocycles has recently been widely used[1-3] and in many cases such transformations proceed by general acid-base catalysis and under very mild conditions even at physiological pH. These findings have great importance, not only for the synthesis of these compounds but also for their potential application in medicine (prodrug approach).

Our group is engaged in the preparation of isothiuronium salts and their subsequent rearrangement in buffers of different pH. The structure[4,5] and reactivity[6-8] of substituted *S*-(1-phenylpyrrolidin-2-on-3-yl) isothiouronium salts has been studied. The salts undergo in weakly basic medium an intramolecular rearrangement to give substituted 2-imino-5-[2-(phenylamino)ethyl]-1,3-thiazolidin-4-ones (***Scheme 1***).



Scheme 1

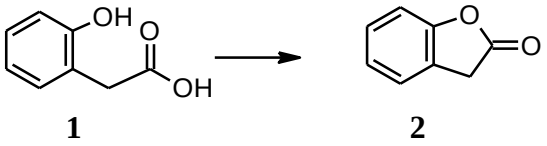
Recently our group studied kinetics and mechanism of rearrangement of *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiouronium bromide into 5-(2-hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (***Scheme 2***)



Scheme 2

Methods/experimental

In the first step the cyclic lactame coumaran-2-one (**2**) must be created by dehydration[9] of (2-hydroxyphenyl)acetic acid (**1**) (***Scheme 3***).

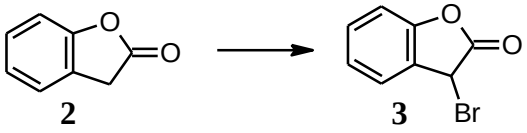


1 **2**

Scheme 3

(2-Hydroxyphenyl)acetic acid (**1**) is lactonized by azeotropic distillation of mixture xylene/water. Coumaran-2-one (**2**) was purified by vacuum distillation.

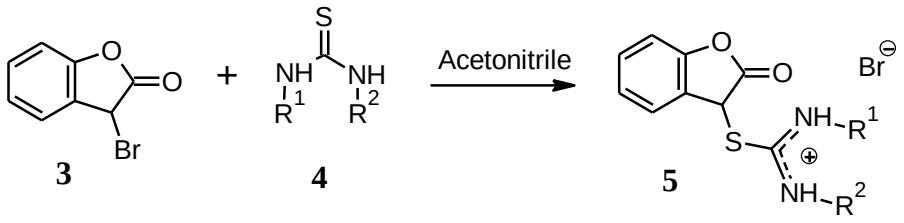
The next step is bromination of this lactone to position 3. We were looking for a good brominating[10] agent and as the best of all appeared dioxane complex of bromine in ether at laboratory temperature (***Scheme 4***).



2 **3**

Scheme 4

3-Bromocoumaran-2-one (**3**) reacts easily with different substituted thioureas. There is nucleophilic substitution of atom bromine to atom sulfur and give substituted S-(1-benzofuran-2(3*H*)-one-3-yl) isothiuronium bromide. Isothiuronium salts are obtained as solid in very good yield (51 - 88 %) (***Scheme 5***).



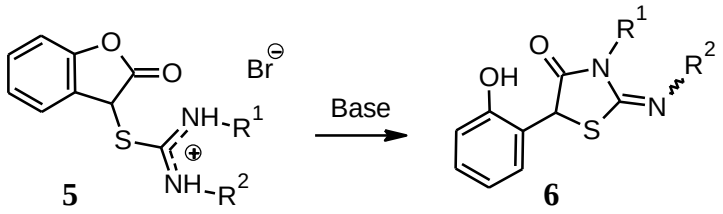
3 **4** **5**

Scheme 5

R^2	R^1	Yield [%]	m.p. [°C]
H	H	87	233-237
CH_3	H	83	181-183
$CH(CH_3)_2$	H	83	223-233
$C(CH_3)_3$	H	67	207-219
Ph	H	65	209-213

4-CH_3Ph	H	71	215-233
4-CH_3OPh	H	85	211-232
4-BrPh	H	85	199-222
4-(CH_3CO)Ph	H	62	208-223
Py(2)	H	82	166-169
Bz	H	51	191-206
CH_3	CH_3	87	231-238
CH_2CH_3	CH_2CH_3	80	195-210
Ph	Ph	65	219-224
4-CH_3OPh	CH_3	58	175-207
CH_2	CH_2	88	181-185

Isothiuronium salts easily rearrangements in a slightly basic medium to substituted 2-imino-1,3-thiazolidin-4-one (***Scheme 6***). In our case isothiuronium salts were suspended in water and an equivalent amount of aqueous ammonia was added to this suspension.



5 **6**

Scheme 6

R^2	**R^1**	**Yield [%]**	**m.p. [°C]**
H	H	83	212-214
CH_3	H	68	155-156
$CH(CH_3)_2$	H	68	200-201
$C(CH_3)_3$	H	95	210-212
Ph	H	82	203-205
4-CH_3Ph	H	91	197-201
4-CH_3OPh	H	86	166-168
4-BrPh	H	88	138-142
4-(CH_3CO)Ph	H	73	179-181
Py(2)	H	75	219-222
Bz	H	93	196-198
CH_3	CH_3	80	139-161
CH_2CH_3	CH_2CH_3	86	140-143
Ph	Ph	88	217-219
4-CH_3OPh	CH_3	69	216-219
CH_2	CH_2	70	126-129

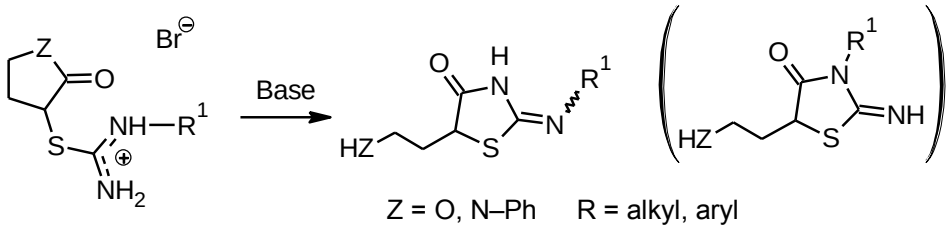
Results and discussion

Lactonization (2-hydroxyphenyl)acetic (**1**) acid was not problematic level. The first problem occurred during brominated lactone. First, we tested the radical bromination lactone (**2**) by *N*-bromosuccinimide in carbon tetrachloride, but the desired 3-bromocoumaran-2-one (**3**) has not been detected (TLC) after the reaction in the reaction mixture. Based on literature[10] research an alternative bromination procedure was found. This method uses bromine dioxane complex in diethyl ether at room temperature. Via this procedure the desired 3-bromo-1-benzofuran-2(3*H*)-one (**3**) (***Scheme 4***) has been achieved in 60% yield. 3-Bromocoumaran-2-one (**3**) is unstable and therefore it was necessary to use it as soon as possible for further reactions, or be temporarily stored in a freezer.

Isothiuronium salts were prepared by reacting 3-bromo-1-benzofuran-2(3*H*)-one (**3**) with differently substituted thioureas in acetonitrile. After several hours of standing at room temperature, the crystals of isothiuronium salts have been excluded (***Scheme 5***). The yields thus obtained salt ranged from 51-88%. The resulting isothiuronium salts are relatively unstable and they tend to rearrange in water to their corresponding derivatives of 2-imino-1,3-thiazolidin-4-one. For this reason, it was necessary to characterize isothiuronium salts by ^{1}H, ^{13}C NMR spectroscopy and elemental analysis almost immediately after their preparation.

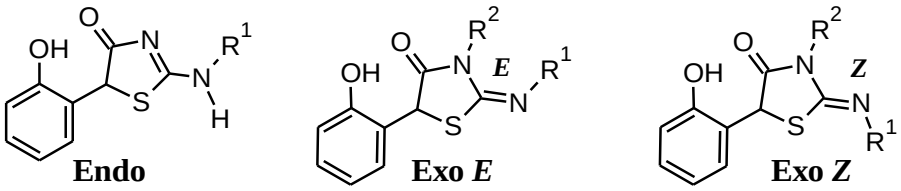
Isolated isothiuronum salts were suspended in water and this suspension was added an equivalent amount of aqueous ammonia. Under these conditions the salts begin to rearrange in less than one hour to 2-substituted imino-1,3-thiazolidin-4-ones in very good yields (68-95 %) (***Scheme 6***). 2-Substituted imino-1,3-thiazolidin-4-ones were purified by crystallization in methanol and were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analyzes and HRMS.

The rearrangement of *N*-substituted isothiuronium salts may be formed formally two isomeric products differing position substituent on the nitrogen atom. As the *N*-fenyl[11] and also *N*-alkylisothiuronium[6,7] salts, it was found that the lactam carbonyl group respectively. Lactone preferentially attacks the unsubstituted nitrogen (*N'*) and alkyl respectively. Aryl substituent is always bound to the imino generated 2-imino-1,3-thiazolidin-4-one (***Scheme 7***).



Scheme 7

The resulting 2-(subst.imino)-1,3-thiazolidine-4-ones can also occur in two tautomeric forms with the endocyclic and exocyclic double bond, from which the exocyclic form can be configured imine bond (*E*) - or (*Z*) - (***Scheme 8***). All three forms (65 % endo, 17.5 % exo-*E* 17.5 % exo-*Z*) have been observed for example, 2-methylimino-5-[2 - (4-nitro-phenylamine)-ethyl]-thiazolidine-4-one[6] in hexadeuteriodimethylsulfoxide solution. In contrast, derivatives of thiazolidine-4-one formed by rearrangement of *N*, *N* disubstituted isothiuronium salts[11] may contain only endocyclic double bond, whose position is fixed disubstituted amino, incapable tautomeric rearrangement.



Scheme 8

In this time we measure the kinetics and the mechanism of the rearrangement of *N*-(4-methoxyphenyl)-*S*2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide to 5-(2-hydroxyphenyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-on. Measurement is performed in aqueous buffers at 25 °C and ionic strength I = 1 mol.l^{-1} under pseudo-first order conditions. When all measurements will be completed, the rearrangement mechanism will be predicted.

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