SYNTHESIS OF SUBSTITUED 5-(2-HYDROXYPHENYL)-1,3-THIAZOL- 4-OLES AS pH SWITCHABLE FLUOROPHORES

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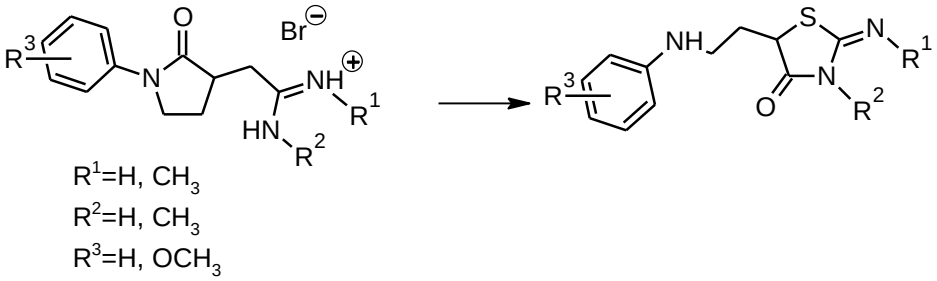
Abstract: Present work is a continuation of our previous research done in the field of transformation reaction of isothiuronium salts derived from various lactones and lactames giving substituted 2-iminothiazolidin-4-ones or 2-aminothiazolin-4-ones. These compounds are known e.g. for their significant biological activity but they do not possess any fluorescence behaviour. On the other hand some substituted 1,3-thiazol-4-oles are good fluorophores in solutions and sometimes also in solid state. It is also known that the presence of some ionizable groups (OH, NH_2 etc.) can significantly affect the shift of their UV absorption/fluorescence band. Therefore we have prepared a new set of substituted 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles and studied their spectral properties under various conditions.

Keywords: Thioamide, rearrangement, 1,3-thiazol-4-ole, fluorophore, transformation, 3-Bromocoumaran-2-one

Introduction

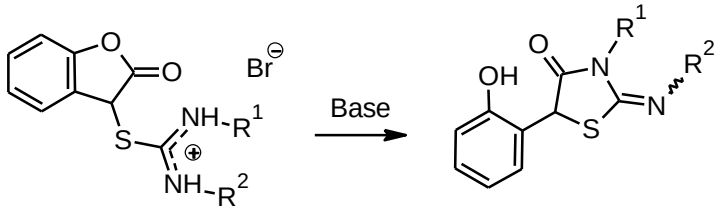
In organic chemistry have great significance rearrangements of heterocyclic compounds. In this way we can prepare otherwise difficult-to-prepare biologically active compounds. The possibility of preparing heterocycles has recently been widely used[1-3] and in many cases such transformations proceed by 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) isothiuronium 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

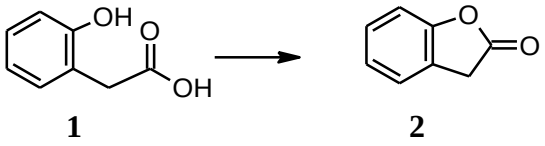
Recently our group studied rearrangement[9] of substituted *S*-(1-benzofuran-2(3*H*)-one-3-yl) isothiuronium bromides to substituted 5-(2-hydroxyphenyl)-2-imino-1,3-thiazolidine-4-ones. In this rearrangement acid-base catalysis under very mild conditions is applied.



Scheme 2

Methods/experimental

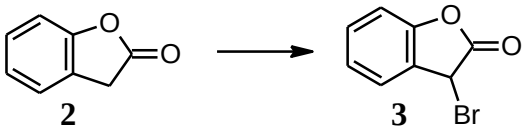
In the first step the cyclic lactame coumaran-2-one (**2**) must be created by dehydration[10] of (2-hydroxyphenyl)acetic acid (**1**) (***Scheme 3***).



Scheme 3

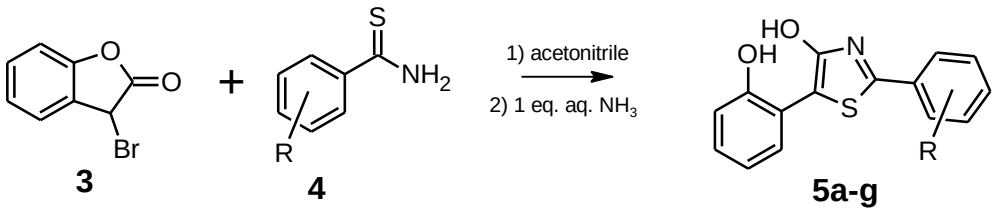
(2-Hydroxyphenyl)acetic acid (**1**) is lactonized by azeotropic distillation of mixture xylene/water. Coumaran-2-one (**2**) was purified by vacuum distillation.

The next step is bromination of this lactone to position 3. We were looking for a good brominating[11] agent and as the best of all appeared dioxane complex of bromine in ether at laboratory temperature (***Scheme 4***).



Scheme 4

3-Bromocoumaran-2-one (**3**) reacts easily with aromatics thioamides (**4**). This reaction give hydrobromide of substituted 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles which have been subsequently converted to 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles using suitable base (aq. NH_3). Substituted 1,3-thiazol-4-oles have been obtained as solid in very good yield (73 - 87 %) (***Scheme 5***).



Scheme 5

	R	Yield[%]	m.p. [°C]
a	H	75	221-226
b	4-CH_3	83	238-250
c	4-CF_3	79	229-235
d	4-CH_3O	69	228-235
e	4-tBu	87	252-256
f	4-Cl	68	245-250
g	3-Cl	73	223-230

Results and discussion

Lactonization (2-hydroxyphenyl)acetic (**1**) acid was not problematic step. 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.

Substituted 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles were prepared by reacting 3-bromo-1-benzofuran-2(3*H*)-one (**3**) with differently substituted aromatic thioamides in acetonitrile. After several hours of standing at room temperature, the crystals of hydrobromide of substituted 1,3-thiazol-4-oles have been excluded (***Scheme 5***). Hydrobromides were filtered off and then were suspended in water and this suspension was added an equivalent amount of aqueous ammonia. Less than one hour substituted 1,3-thiazol-4-oles have been excluded in very good yields (73 - 87 %). 1,3-Thiazol-4-oles were purified by crystallization in toluene and were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analyzes and HRMS.

For these substituted 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles was fluorescence observed in solution. In the structures of substituted 5-(2-hydroxyphenyl)-1,3-thiazol-4-oles are two hydroxyl groups and it is possible to convert them with a base to anionic form. This anionic form has different color of solution.

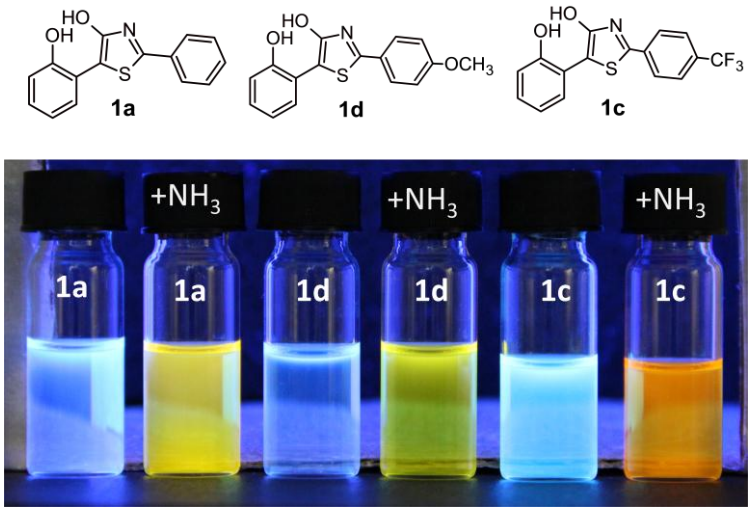


Figure 1. *Fluorescence of three thiazololes in acetone at 366 nm. In every second solution was added aq. ammonia.*

For these compounds the UV-VIS spectra, fluorescence spectra were measured and quantum yield calculated.

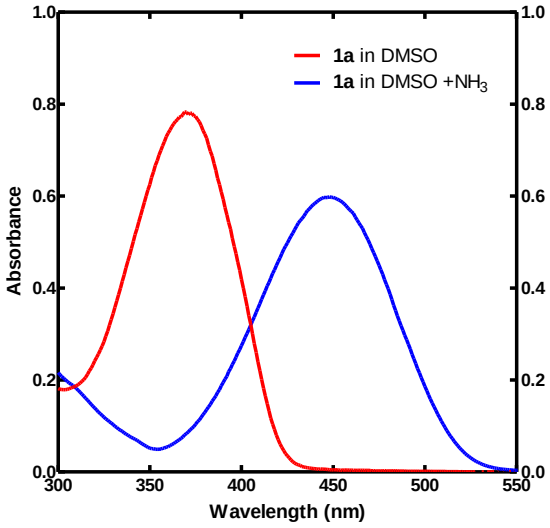


Figure 2. (left) *UV-VIS spectrum of* ***1a*** *in DMSO (RED) and in DMSO with small amount of aq ammonia (BLUE)*

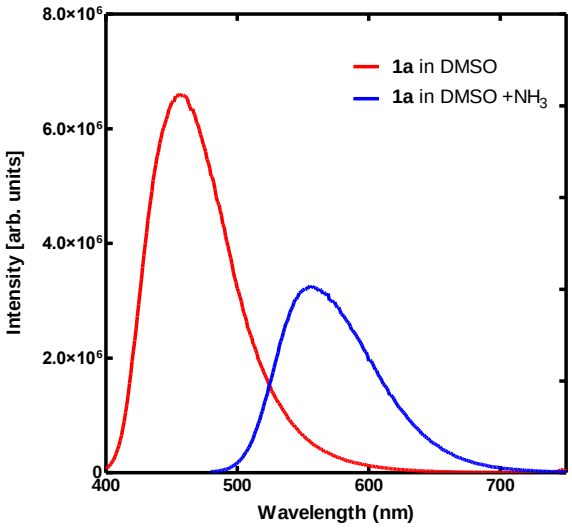


Figure 3. (right) *Fluorescence spectrum of* ***1a*** *in DMSO (RED) and in DMSO with small amount of aq. ammonia (BLUE)*

Table 1 Absorption and emission wavelength of thiazoles measured in DMSO and calculated quantum yield.

	a	b	c	d	e	f	g
A_{max} [nm]	373	372	390	372	373	380	382
A_{max} (+NH_3) [nm]	448	447	476	439	448	459	463
F_{max} [nm]	455	455	480	455	455	465	468
F_{max} (+NH_3) [nm]	555	555	590	550	555	570	575
Φ (quantum yield)	0.98	0.75	0.90	0.30	0.95	~1	0.92
Φ (+NH_3)	0.37	0.24	0.16	0.20	0.28	0.26	0.25

References

1 Vivona N., Buscemi S., Frenna V., Cusmano G., *Adv. Heterocycl. Chem.,* **1993**, *56*, 49–154.

2 van der Plas H. C., *Adv. Heterocycl. Chem.,* **1999**, *74*, 153–221.

3 Hajós G., Riedl Z., Kollenz G., *Eur. J. Org. Chem.,* **2001**, 3405–3414.

4 Hanusek J., Sedlák M., Drabina P., Růžička A., *Acta Crystallogr., Sect. E,* **2009**, *65*, 411-412.

5 Hanusek J., Sedlák M., Drabina P., Růžička A., *Acta Crystallogr., Sect. E* **2009**, *65*, 413.

6 Sedlák M., Hejtmánková L., Hanusek J., Macháček V., *J. Heterocycl. Chem.,* **2002**, *39*, 1105–1107.

7 Sedlák M., Hanusek J., Hejtmánková L., Kašparová P., *Org. Biomol. Chem.,* **2003**, *1*, 1204–1209.

8 Hanusek J., Hejtmánková L., Štěrba V., Sedlák M., *Org. Biomol. Chem.,* **2004**, *2*, 1756–1763.

9 Kammel R., Hanusek J. *Heterocycles* **2014**, 89, 1183–1194.

10 Kadin S. B.: *J. Med. Chem.* **1972,** *15,* 551–552.

11 Abramenko P. I., Zhiryakov V. G.: *Chem. Heterocycl. Comp.* **1977**, *13*, 1194–1197.