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Decarboxylative Bromination of Thiazole Core and Consecutive Cross-Coupling Reactions

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Abstract

The 2,5-substituted 4-hydroxythiazoles form a fluorescent dye class with wide-range-tunable absorption and emission wavelengths. The insights gained on these heterocyclic fluorescence systems are intended to contribute to the development of alternative applications of such molecules in the various areas of biology, chemistry and technology. Therefore, a synthesis strategy for the bromination of the thiazole core was developed, which allows the implementation of various cross-coupling reactions on thiazoles. Furthermore, the so formed conjugated cross-coupling products are highly fluorescent and were investigated in terms of their spectroscopic properties.

Keywords

etherification**;** fluorescence; heterocycles; Hunsdiecker reaction; thiazole.

Introduction

The 2,5-substituted 4-hydroxythiazoles are currently intensive investigated molecules [1]. Especially, their fluorescent properties like large Stokes Shifts as well as high quantum yields make them interesting for many applications, e.g. as light-harvesting antenna molecules for DSSC (dye sensitized solar cells) [2] or ion detecting systems [3]. Recently, Habenicht *et al*. describes the opportunities of the synthesis of long-wavelength fluorophores (LWF´s) based on 4-hydroxythiazols with push-pull character [4]. The small size of the thiazole molecule implies their usage as fluorescent markers for assays in molecular biology [5]. Also known are investigations on 1,3-thiazoles, without OH-moiety, as a novel class of angiogenesis inhibitors for

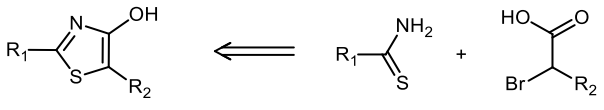
cancer treatment [6], since molecules containing thiazole moiety are often associated with biological activity. Moreover, some of arylthiazoles are investigated in terms of their photo-protective activity *in vitro* and *in vivo* [7].

The variation of the substitution patterns in the positions 2 and 5, but also the etherification of the phenolic hydroxyl group, lead to wide-range-tunable fluorescence, which is beneficial for technical and biological implementations. Basically, the synthesis of thiazole core proceeds according to Hantzsch. The 2-pyridyl substituent in the 2-position of the thiazol is known to enhance the fluorescence [3], while the ester group in the 5-position acts as leaving group in the planned modification.

We were interested in the synthesis of 5-bromo substituted thiazoles which would give raise to the introduction of numerous building blocks, containing olefinic or even triple bond structures using cross-coupling reactions, like Suzuki, Heck or Sonogashira. We hoped that the spectroscopic analysis of the behavior of such novel conjugated thiazols could give a deeper inside in the fluorescence characteristics of 5-bromo substituted thiazoles. Furthermore, such building blocks can be considered to be useful "fluorescence tags" in many applications.

Results and Discussion

Due to the synthesis of **1** via Hantzsch Thiazol Synthesis R^1 and R^2 are of (hetero)-aromatic or aliphatic nature or an ester function (Scheme 1). Thus, the one step introduction of a halogen substituent is not possible.

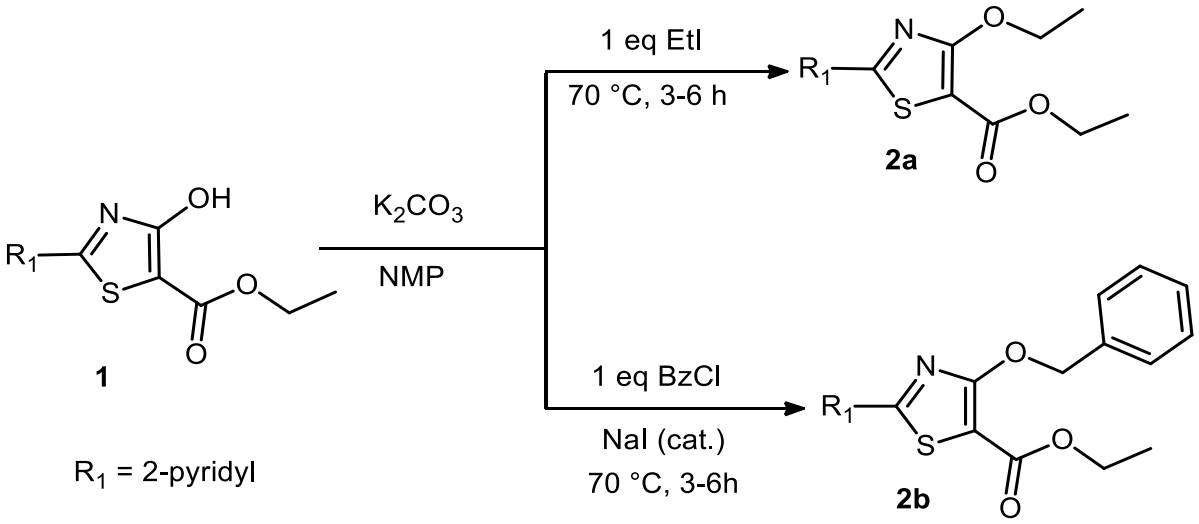


1

R_1 = 2-pyridyl, R_2 = CO_2Et

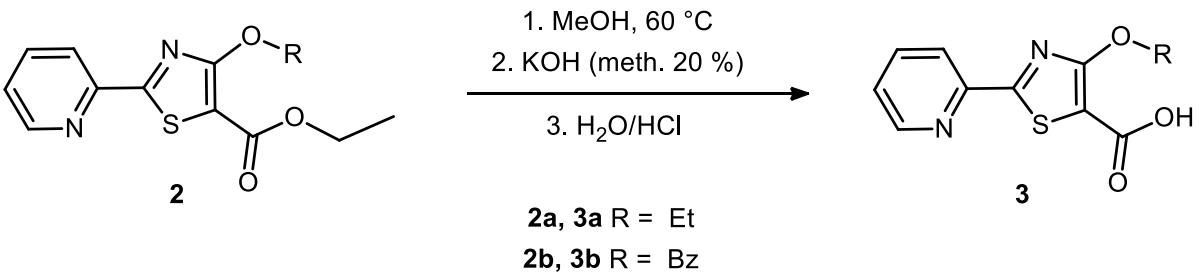
Scheme 1: Retrosynthetic view of Thiazole synthesis according to Hantzsch

However, since the synthesis of the 5-ester functionalised thiazoles like **2a**, **2b** is already described in the literature [8] we considered them as staring material. The reaction conditions for the Williamson ether formation was optimised by using NMP as a solvent, which led to better yields. Moreover, the reaction time could be significant reduced. Using NMP also simplifies the work-up, the addition of water causes the precipitation of the desired compound. Both ester **2a**, **2b** were obtained after recrystallisation in good yields (Scheme 2).



Scheme 2: Etherification of **1**

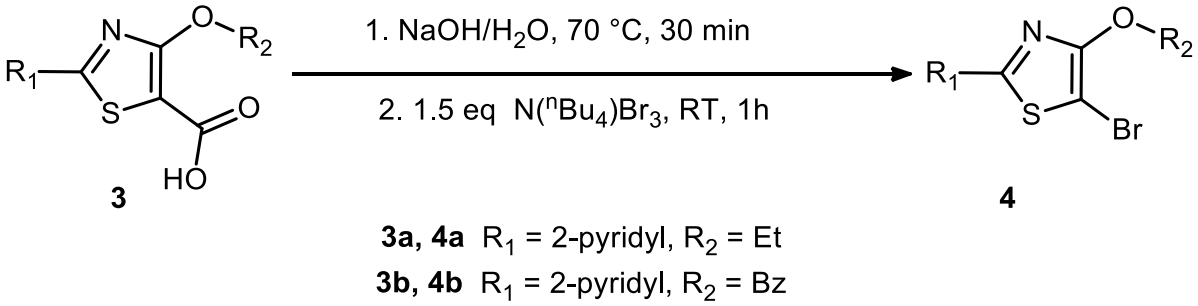
They are easily hydrolysed (Scheme 3), by saturated methanolic potassium hydroxide solution, after reprotonation with diluted HCl, the desired thiazole carboxylic acid **3a** and **3b**, were obtained in very good yields.



Scheme 3: Synthesis of thiazole carboxylic acid **3a** and **3b** via based-catalysed hydrolysis.

Introduction of the bromine was carried out by the Hunsdiecker Reaction. Usually, the presence of silver or mercury salts of the carboxylic acids and the use of toxic environmental dangerous organic solvents like carbon tetrachloride are required [9]. In the present work we applied a transition metal free synthesis, starting from thiazole carboxylic acids **3** under a mild conditions, according to a green and environmentally friendly procedure.

In the search for alternative solvents for this reaction we noted good solubility of thiazole carboxylic acid in sodium hydroxide/water mixture, which was already used for Hunsdiecker reaction on perylene dyes [10]. However, the application of pure bromine as described was far from satisfactory. Nevertheless, traces of desired product were determined. Quibell *et al.* employed *tetra*-butylammonium tribromide as an effective bromine source for the bromination of aromatic carboxylic acids [11]. The implementation of those reaction conditions led to the desired brominated product but with moderate yields of 40 %. By combining both synthesis types: the usage of sodium hydroxide/water mixture as solvent and *tetra*-butylammonium tribromide as bromine source resulted in a highly efficient synthesis (Scheme 4).



Scheme 4: Decarboxylative bromination of thiazole core.

To achieve complete conversion 1.5 eq of the bromination reagent are needed. The total reaction time is about one hour. Upon cooling to the room temperature the analytically pure product precipitated and could be removed by convenient filtration in very high yields.

After recrystallisation from methanol single crystals of **4a** were obtained, suitable for X-ray single crystal analysis (Figure 1, see Supporting information file S3 for full crystallographic data of **4a**).

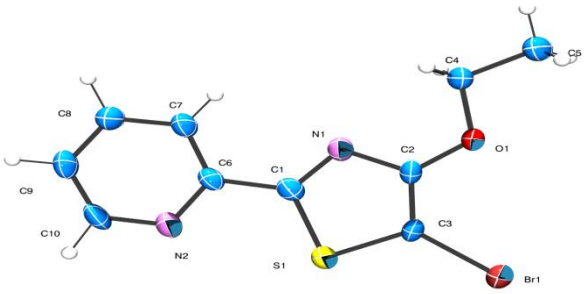
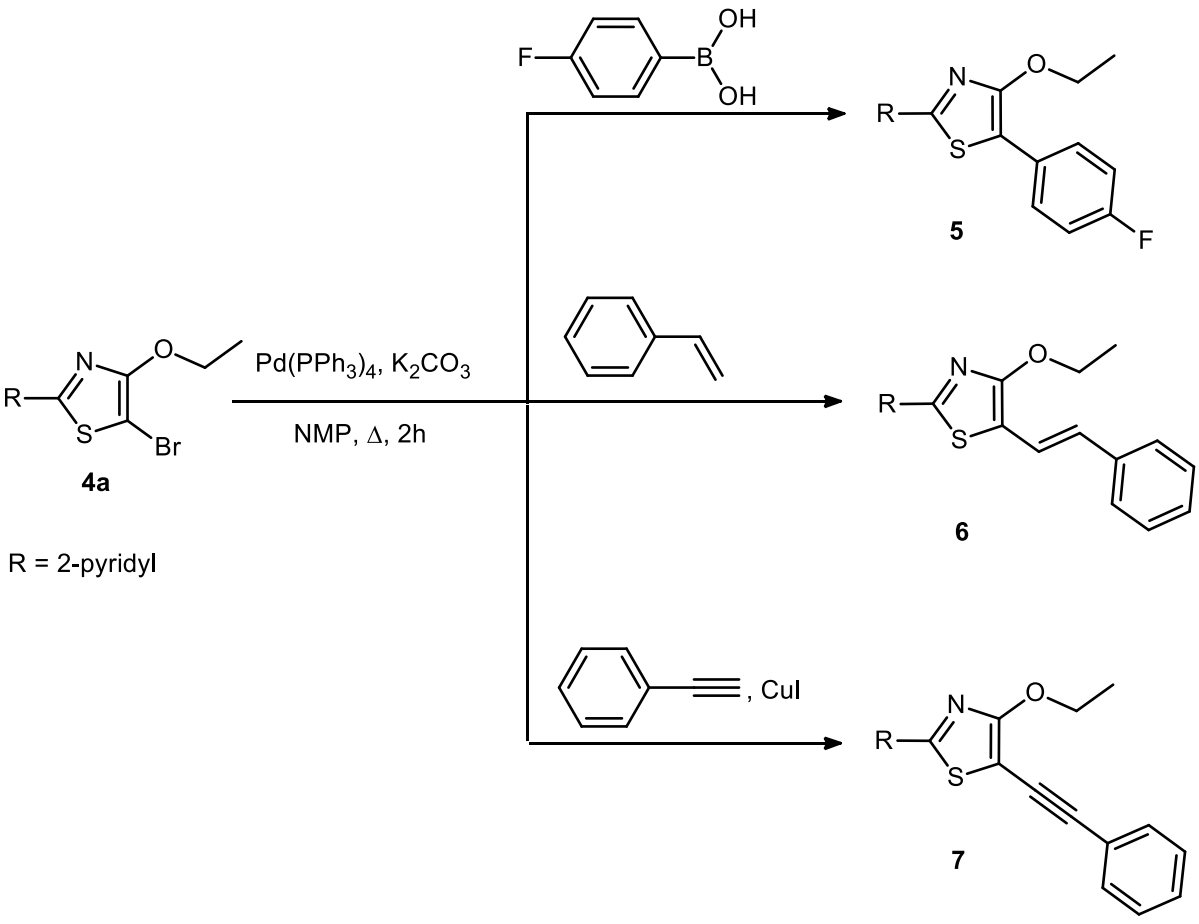


Figure 1: ORTEP plot. X-ray crystal structure of **4a**. Selected bond lengths [Å] and angles [°]: C3-Br1: 1.864, C1-S1: 1.724, S1-C3: 1.722, C1-C6: 1.472, C6-C7: 1.384, C2-O1: 1.334, C1-N1: 1.312, C3-S1-C1: 88.3, C1-N1-C2: 110.6,C2-C3-Br1: 126.2.

We now were curious to investigate cross- coupling behaviour of the 5-bromothiazoles. For this purpose, a general procedure for all three reaction types - Suzuki, Heck and Sonogashira was developed. NMP is a well-known solvent for Suzuki reactions [12] and also a good solvent for **4.** It was found that it is suitable for all tested cross-coupling reactions. The standard catalyst tetrakis(triphenylphosphine)-palladium(0) was used in all reactions. The general procedure was carried out under inert conditions considering the reaction-specific details, like temperature and required reactants beside catalyst, base and solvent (Scheme 5).



Scheme 5: Consecutive cross-coupling reactions on **4a.**

For the Suzuki and Heck reactions the optimum temperature was at 120 °C. In contrast, the Sonogashira reaction was more efficient if the temperature did not exceed 80 °C, because of possible polymerisation of phenylacetylene [13].

All desired products were synthesised in good yields between 43 and 60% and investigated in terms of their fluorescent properties. The thiazole derivative **5** shows the highest quantum yield about 86 % (using quinine as standard). This product occurs as amber-coloured needles, which shows intensively light blue solid-state fluorescence.

The obtained product **6** from the Heck reaction could be determined in only one isomeric form as *E*-configuration, which was confirmed by ^{1}H-NMR spectra with a coupling constant of J = 16.2 Hz between associated vicinal protons. Compared to the other derivatives, the absorption and emission maxima of **6** with λ_{max}(abs.) = 406 nm and λ_{max}(em.) = 492 nm are slightly shifted to the higher wavelengths (Table 1).

Table 1: UV-VIS and fluorescence data of all synthesised products.

substance	λ_{max}(abs.) [nm]	λ_{max}(em.) [nm]	Φ (DMSO) [%]
2a	349	418	13.97
2b	344	417	6.61
3a	345	418	15.41
3b	346	415	4.19
4a	348	430	17.41
4b	346	418	15.51
5	368	452	86.12
6	406	492	40.11

7	382	463	69.39

Therefore, strong yellow-greenish fluorescence is already visible in daylight. The fluorescence spectra of products **4**-**7** are shown in Figure 2. The full experimental data of all synthesized products is given in Supporting Information file S1 “Experimental section”.

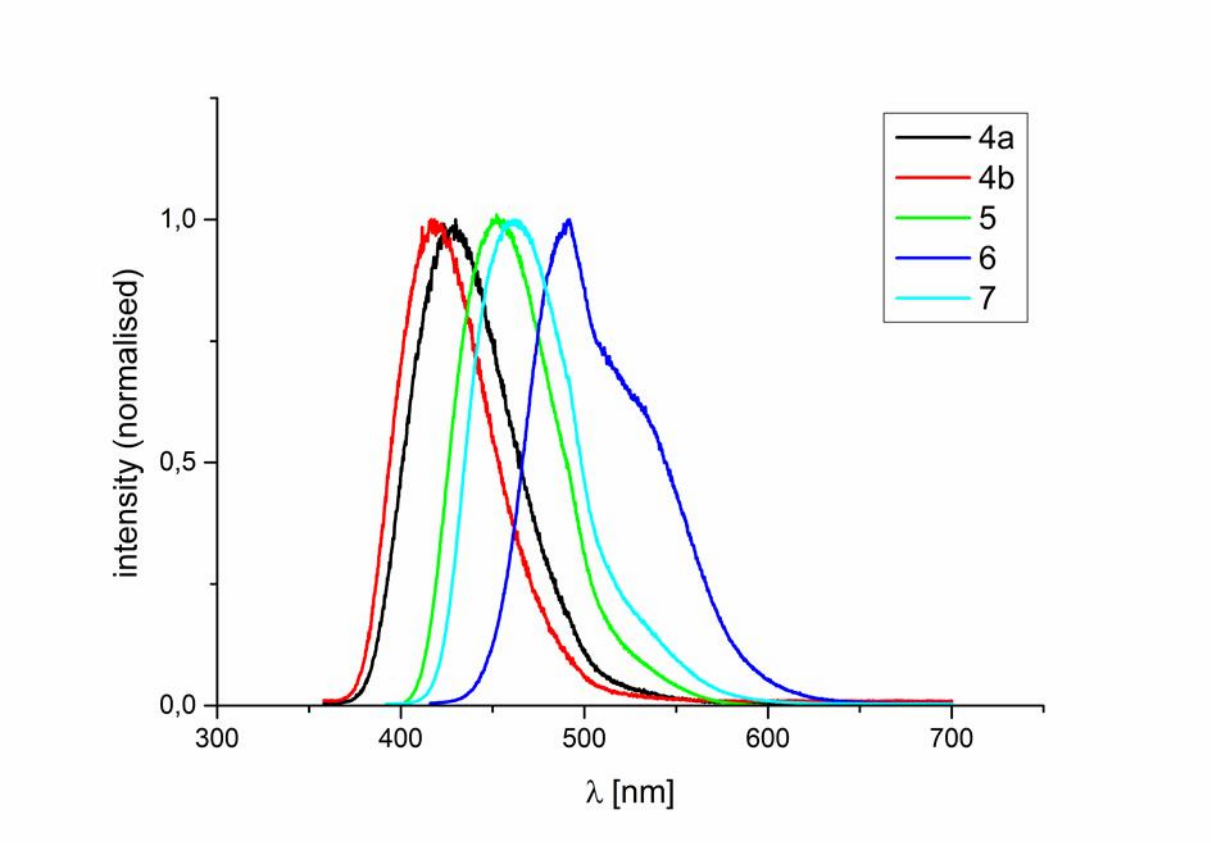


Figure 2: Normalised fluorescence spectra of synthesised products

Supporting Information

Supporting information features Experimental section (S1), copies of ^{1}H and ^{13}C NMR spectra of compounds **2**-**7** (S2), plus crystallographic data of compound **4a** (S3).

Supporting Information File 1:

File Name: S1

File Format: Microsoft Word

Title: Experimental section

Supporting Information File 2:

File Name: S2

File Format: Microsoft Word

Title: NMR spectra of compounds **2**-**7**

Supporting Information File 3:

File Name: S3

File Format: Microsoft Word

Title: Crystallographic data of compound **4a**

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