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Synthesis of 2-(*o*-hydroxyaryl)-4-arylthiazoles by regioselective Pd(0)-catalyzed cross-coupling

Thorsten Bach * and Stefan Heuser

Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

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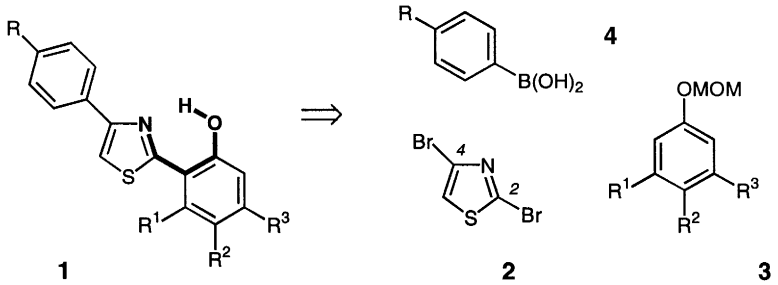
Abstract

The difunctional substrate 2,4-dibromothiazole **2** was transformed into the title compounds **1** by consecutive Pd(0)-catalyzed cross-coupling reactions. Aryl zinc reagents which were prepared by *ortho*-lithiation of compounds **3** and subsequent transmetalation were used as carbon nucleophiles in the first coupling reaction. By this means, an aryl substituent was attached to the 2-position (50–62% yield). A succeeding cross-coupling with arylboronic acids **4** occurred at the 4-position of the intermediate 4-bromothiazoles **5** (76–97% yield). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium; palladium compounds; catalysis; coupling reactions; thiazoles.

2-(*o*-Hydroxyaryl)-4-arylthiazoles **1** can be considered as heteroanalogous β-hydroxyenones (Scheme 1). Based on this analogy they should be able to dissipate the energy of absorbed UV-light by an intramolecular hydrogen transfer,[1] a property which would make them promising candidates to be used in cosmetic sunscreens.[2] Due to our continuing interest in the development of new UV-A-absorbers[3] we sought a facile entry into this class of compounds.



Scheme 1.

* Corresponding author.

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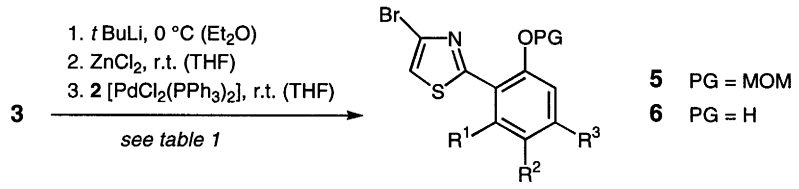
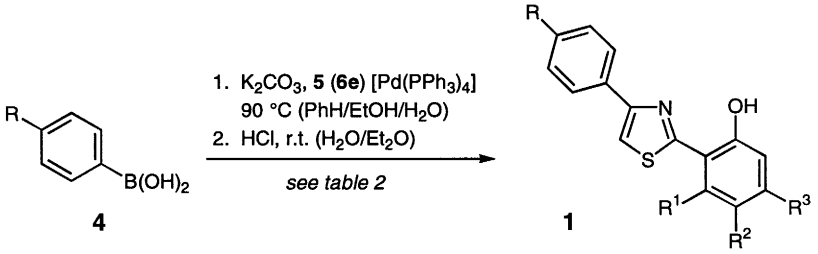
Since it was desirable to investigate the influence of various substituents R, R^1, R^2 and R^3 on the chromophore, a versatile synthetic strategy was mandatory to achieve the neccessary scope. Initial attempts employing classic heterocyclic chemistry[4] (Hantzsch synthesis) failed in this respect and we, therefore, looked into regioselective bond constructions starting from the readily available 2,4-dibromothiazole **2**.[5] The possibility to prepare *ortho*-metalated *O*-methoxymethyl (MOM) protected phenols by directed metalation of arenes **3**[6–8] led us to consider a regioselective coupling reaction at the more electron-deficient 2-position of thiazole **2** (Scheme 2). Subsequent Suzuki cross-coupling[9] at C(4) with arylboronic acids **4** was expected to yield the target compounds after deprotection (Scheme 3). Although precedence for regioselective cross-coupling reactions of this type in the thiazole series was rare[10–12] we attempted to use a Negishi cross-coupling[13] to establish the aryl–C(2) bond. To this end, the MOM-protected phenols **3** were treated with *t*-butyllithium at 0°C in ether and the lithiated arenes were transmetalated by treatment with $ZnCl_2$ in THF. The species so obtained underwent a regioselective Pd(0)-catalyzed C–C bond formation with substrate **2** to yield the desired intermediates **5**. Some examples for the described transformation are summarized in Table 1.[14] The yields of the 4-bromothiazoles **5** were reliably in the range of 60% irrespective of the substitution pattern at the benzene ring. In the case of substrate **3e** the primary product **5e** was deprotected in the course of the reaction (entry 5) and the phenol **6e** was isolated as the final product. Proof for the regioselectivity of the cross-coupling was obtained by comparing the ^{13}C NMR data of substrate **2** with those of the products **5**. The aryldebromination leads to a significant downfield shift of the carbon atom at which the substitution occurs.[15] In the transformation **2**→**5** the carbon atom C(2) clearly showed the expected shift to lower field ($\Delta\delta \cong 25$ ppm).



Scheme 2.



Scheme 3.

As in previous examples,[15,16] we ascribe the pronounced regioselectivity to the oxidative addition step, i.e. to the insertion of Pd(0) into the carbon–bromine bond. At room temperature the insertion into the more electron-deficient C(2)–Br bond is fast and there is no competitive reaction at C(4). The succeeding Suzuki cross-coupling of the thiazoles **5** and **6e** proceeded in high yield (76–97%).[17] The higher reaction temperature facilitates the oxidative addition of Pd(0) at the less electrophilic 4-position. Compound **6e** gave direct access to the free phenol **1e**. For all other substrates, the MOM group was removed in a final deprotection step and the desired target compounds **1** were isolated (Table 2).

Table 1
Pd(0)-Catalyzed cross-coupling of *ortho*-metalated MOM-protected phenols **3** with thiazole **2**

Entry	Substrate	R^1	R^2	R^3	Product	Yield [%]
1	**3a**	H	H	H	**5a**	58
2	**3b**	H	*t*-Bu	H	**5b**	55
3	**3c**	H	Cl	H	**5c**	62
4	**3d**	H	H	*t*-Bu	**5d**	55
5	**3e**	OMe	H	OMe	**6e**	50
6	**3f**	H	OBu	H	**5f**	61

Table 2
Yields of target compounds **1** obtained by cross-coupling of arylboronic acids **4** with thiazoles **5** and subsequent deprotection

Entry	R	R^1	R^2	R^3	Product	Yield[a] [%]
1	H	H	H	H	**1a**	60
2	H	H	*t*-Bu	H	**1b**	76
3	H	H	Cl	H	**1c**	78
4	H	H	H	*t*-Bu	**1d**	85
5	H	OMe	H	OMe	**1e**	97[b]
6	H	H	OBu	H	**1f**	81
7	Cl	H	H	H	**1g**	74
8	*t*-Bu	H	H	H	**1h**	77

[a] Total yield over two steps. [b] No deprotection step, compound **6e** was used as starting material.

In summary, a regioselective access to 2,4-disubstituted thiazoles has been established. The Negishi cross-coupling of aryl zinc halides with 2,4-dibromothiazole **2** proceeded exclusively at the more electron-deficient position thus permitting the selective installation of an aryl fragment at C(2). In preliminary experiments, we have found that alkyl and alkenyl zinc reagents behave similarly and the use of the described methodology for the construction of biologically active thiazoles is currently being pursued in our laboratory.

Acknowledgements

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14. Representative procedure: A 1.34 M solution of *t*-BuLi in pentane (8.3 mL, 11 mmol) was added dropwise to a stirred solution of 1.36 g *O*-methoxymethylphenol **3a** (1.30 mL, 10 mmol) in 50 mL of ether at 0°C. The mixture was stirred for another 10 min at 0°C. A 0.5 M solution of $ZnCl_2$ in THF (30 mL, 15 mmol) was subsequently added and the resulting solution was warmed to ambient temperature. After another 30 min at rt the solution of the aryl zinc reagent so prepared was added dropwise to a suspension of 2.43 g 2,4-dibromothiazole[5] **2** (10 mmol) and 350 mg $PdCl_2(PPh_3)_2$ (0.5 mmol, 5 mol%) in 50 mL of THF. The mixture was stirred at room temperature for 16 h and subsequently quenched with a saturated aqueous solution of NH_4Cl (100 mL). After extraction with ether (3×200 mL) the organic layers were combined, washed with brine and dried over Na_2SO_4. After removal of the solvent the residue was purified by flash chromatography (4×20 cm silica gel; pentane/*t*-butylmethyl ether=98:2) to yield 1.72 g of compound **5a** (58%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=3.51 (s, 3 H), 5.37 (s, 2 H), 7.10–7.37 (m, 4 H), 8.40 (dd, *J*=8.0 Hz, *J*=1.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 57.0 (q), 94.6 (t), 114.6 (d), 118.2 (d), 122.1 (s), 122.4 (d), 125.6 (s), 128.9 (d), 131.6 (d), 154.5 (s), 163.7 (s). $C_{11}H_{10}BrNO_2S$ (300.17) calcd: C, 44.02; H, 3.36; N, 4.67; found: C, 43.78; H, 3.23; N, 4.80.
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17. Representative procedure: A solution of 1.74 g K_2CO_3 (12.3 mmol) in 5 mL of water and a solution of 732 mg phenylboronic acid (**4**, R=H) (6.15 mmol) in 5 mL of EtOH were added successively to a solution of 1.24 g 4-bromothiazole **5a** (4.1 mmol) and 140 mg $Pd(PPh_3)_4$ (0.16 mmol, 4 mol%) in 20 mL of benzene at ambient temperature. The mixture was heated to 90°C and kept at this temperature for 72 h. Upon cooling to rt the mixture was extracted with ether (3×150 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography (3×30 cm silica gel; pentane/*t*-butylmethyl ether=98:2) to yield 1.02 g of the *O*-MOM-protected derivative of compound **1a** (82%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=3.49 (s, 3 H), 5.34 (s, 2 H), 6.88–7.50 (m, 8 H), 7.65 (dd, *J*=7.7 Hz, *J*=1.5 Hz, 1 H), 7.88 (dd, *J*=8.0 Hz, *J*=1.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 57.0 (q), 94.7 (t), 114.6 (d), 114.8 (d), 122.6 (d), 123.5 (s), 126.9 (d), 128.4 (d), 129.2 (d), 129.3 (d), 131.0 (s), 135.4 (s), 154.5 (s), 154.8 (s), 162.4 (s). $C_{17}H_{15}NO_2S$ (297.37) calcd: C, 68.66; H, 5.08; N, 4.71; found: C, 68.99; H, 4.91; N, 4.36.