Polysubstituted Thiazole Derivatives via the Halogen-Dance Reaction

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Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday

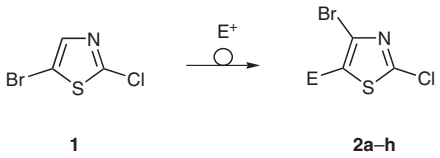
Abstract: A short and efficient method for the synthesis of a series of 5-functionalized 4-bromo-2-chlorothiazole derivatives has been developed by application of the halogen-dance reaction.

Key words: halogen dance, metalation, lithiation, thiazole

Substituted thiazoles are often found in natural products[1] as well as synthetic pharmaceuticals or agrochemicals[2] with interesting biological activity. For the synthesis of new target compounds, functionalized thiazoles are always needed as useful building blocks. Classical approaches to substituted thiazoles, cyclization methods,[3] such as the Hantzsch thiazole synthesis[4] or various electrophilic and nucleophilic substitution sequences[3] are reported in the literature. However, when arylated thiazoles are the targets a more flexible route via transition-metal-catalyzed cross-coupling reactions can be envisaged. Of course, the thiazole system can then either be used as an organometallic species or as the halogenated counterpart. The latter approach is often favorable especially when more than one cross-coupling reaction is to be performed sequentially. In that case the reactivity difference of the three thiazole carbon positions and the reactivity difference of various halides (Cl, Br, I) in cross-coupling reactions can be exploited to increase the selectivity of a cross-coupling process.[5] Additionally, the synthesis of new organometallic thiazole species for each cross-coupling step can be avoided. Therefore, polyhalogenated thiazoles are extremely valuable building blocks and their efficient synthesis is highly desirable since literature disclosures in this area are relatively rare.[3,6]

Within this contribution we report the use of the halogen-dance reaction (HD)[7] for the preparation of various di- and trihalogenated thiazoles. By applying this approach to the easily available 5-bromo-2-chlorothiazole (**1**)[8] a new reactive center is created in the 4-position and additionally, quenching the intermediate with various electrophiles leads to the introduction of different functionalities in the 5-position (Scheme 1), all in a one-pot reaction.

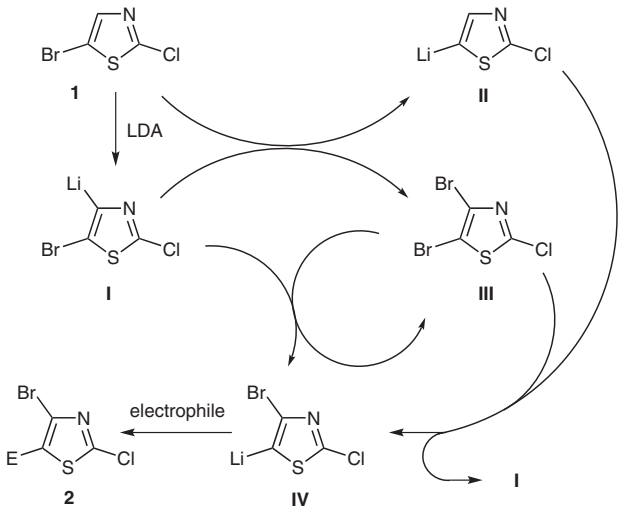
In Scheme 2 the general mechanism of the HD reaction is displayed for the present transformation. Lithiation of 5-bromo-2-chlorothiazole (**1**) in the 4-position generates the lithiated intermediate **I**, which reacts with still available



1 **2a–h**

Scheme 1 Investigated reaction sequence

starting material **1** to form two additional intermediates (**II** and **III**) via metal–halogen exchange. This initiates a cascade reaction where the lithiated species (**I** and **II**) undergo reaction with the dibromo compound **III** to finally form the more stable key intermediate **IV**. Upon quenching of **IV** with various electrophiles the corresponding 5-substituted 4-bromo-2-chlorothiazoles are obtained.



Scheme 2 Mechanism of the HD reaction starting with **1**

The results obtained after quenching intermediate **IV** with different electrophiles are summarized in Table 1. Considering our ambition to decorate thiazoles via cross-coupling reactions, polyhalogenated products, such as 2,4-dihalogenated and 2,4,5-trihalogenated thiazoles, were of special interest. Quenching of **IV** with ethanol gave 4-bromo-2-chlorothiazole (**2a**) in good yield (75%), which demonstrated that the HD reaction is efficient in this system. The introduction of chlorine with hexachloroethane and iodine with I_2 as electrophiles (**2b** in 61% yield and **2d** in 76% yield) worked well. Introduction of bromine was more efficiently achieved with 1,2-dibromo-1,1,2,2-tetrachloroethane in anhydrous THF than with Br_2 leading to

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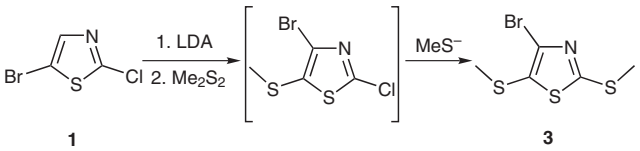
the dibromo product **2c** in good yield (69%). Introduction of alcohol functionalities with benzaldehyde and cyclohexanone generated the corresponding products **2e** and **2f** both in 77% yield. A carbonyl functionality could also be introduced by conversion of **IV** with DMF to give the corresponding aldehyde **2g** in 56% yield. Transformation to the silyl compound **2h** (71%) is a useful option to block position 5 temporarily for further synthetic purposes.

Table 1 Introduction of Electrophiles into the 5-Position[9]

Electrophile	E	Product	Yield (%)[a]
EtOH	H	**2a**	75
Cl_3CCCl_3	Cl	**2b**	61
$BrCl_2CCCl_2Br$	Br	**2c**	69
I_2	I	**2d**	76[10]
benzaldehyde	PhCH(OH)	**2e**	77
cyclohexanone	$C_6H_{10}OH$	**2f**	77
DMF	CHO	**2g**	56[11]
TMSCl	TMS	**2h**	71
DMDS	SMe	**3**[b]	88

[a] Average of two runs.
[b] See Scheme 3.

In an attempt to apply dimethyldisulfide (DMDS) for the introduction of a sulfur electrophile, we did not obtain the expected product. The HD reaction took place as expected and the MeS group was introduced in 5-position, but the methylthiolate formed in situ also replaced the chlorine at the 2-position to form 4-bromo-2,5-bis(methylthio)thiazole (**3**) in excellent yield (88%, Scheme 3).



Scheme 3 Subsequent nucleophilic substitution in 2-position

In conclusion, we have demonstrated the utility of the HD reaction for the synthesis of polyhalogenated thiazoles as precursors for cross-coupling reactions as well as for the introduction of electrophiles in the 5-position. Generally good, although not optimized, yields were obtained (56–88%). Once again it must be emphasized that, via this method, mixed 2,4- and 2,4,5-trihalogenated thiazoles can be easily obtained from readily available 5-bromo-2-chlorothiazole (**1**). Compounds **2a**–**h** offer several possibilities for further transformations. Halides in the 2-, 4-, and 5-position can be used as aryl donors in cross-coupling reactions. Alternatively, Br and I in the 4- and 5-position can undergo metal–halogen exchange reactions for the subsequent introduction of electrophiles. Chlorine in a 2-position is readily attacked by nucleophiles as already reported (Scheme 3). Finally, the electrophiles introduced to the 5-position can also be further manipulated. Such applications are currently under investigation in our laboratories (Figure 1).

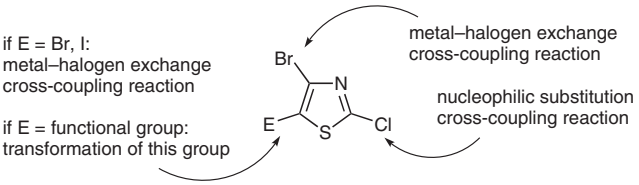


Figure 1 Further synthetic possibilities

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References and Notes

(1) (a) Takayama, H.; Kato, K.; Kimura, M.; Akita, H. *Heterocycles* **2007**, *71*, 75. (b) Altmann, K.-H.; Pfeiffer, B.; Arseniyadis, S.; Pratt, B. A.; Nicolaou, K. C. *ChemMedChem* **2007**, *2*, 396. (c) Müller, H. M.; Delgado, O.; Bach, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4771. (d) Delgado, O.; Heckmann, G.; Müller, H. M.; Bach, T. *J. Org. Chem.* **2006**, *71*, 4599. (e) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (f) de Souza, M. *J. Sulfur Chem.* **2005**, *26*, 429. (g) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644. (h) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196.

(2) (a) Dunkel, R.; Elbe, H.-L.; Greul, J. N.; Hartmann, B.; Gayer, H.; Seitz, T.; Wachendorff-Neumann, U.; Dahmen, P.; Kuck, K.-H. WO 2006061215, **2006**; *Chem. Abstr.* **2006**, *145*, 62881. (b) Murakami, H.; Takii, S.; Mizuno, M. JP 200466855, **2005**; *Chem. Abstr.* **2005**, *143*, 306303. (c) Mueller, U.; Eberle, M.; Pillonel, C.; Lutz, W.; Stanetty, P. WO 2003029249, **2003**; *Chem. Abstr.* **2003**, *138*, 304297. (d) Doemling, A.; Kolb, J. DE 10134478, **2003**; *Chem. Abstr.* **2003**, *138*, 137301.

(3) *Five-Membered Hetarenes with One Chalcogen and One Additional Heteroatom*, In *Science of Synthesis*, Vol. 11; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, **2002**, 627.

(4) (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 942. (b) Prakash, R.; Kumar, A.; Aggarwal, R.; Prakash, O.; Singh, S. P. *Synth. Commun.* **2007**, *37*, 2501. (c) Egan, R. S.; Tadanier, J.; Garmaise, D. L.; Gaunce, A. P. *J. Org. Chem.* **1968**, *33*, 4422. (d) Babadjamian, A.; Metzger, J.; Chanon, M. *J. Heterocycl. Chem.* **1975**, *12*, 643.

(5) (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245; and references cited therein. (b) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283; and references cited therein. (c) Stanetty, P.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2006**, *71*, 3754. (d) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 1363. (e) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2003**, *5*, 2911.

(6) (a) Athmani, S.; Bruce, A.; Iddon, B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 215. (b) Dondoni, A.; Mastellari, A. R.; Medici, A.; Negrini, E.; Pedrini, P. *Synthesis* **1986**, 757. (c) Herkes, F. E.; Blazer, T. A. *J. Heterocycl. Chem.* **1976**, *13*, 1297. (d) Reynaud, P.; Robba, M.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1962**, 1735.

(7) (a) Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046. (b) Nora de Souza, M. V. *Curr. Org. Chem.* **2007**, *11*, 637. (c) Duan, X.-F.; Zhang, Z.-B. *Heterocycles* **2005**, *65*, 2005. (d) Fröhlich, J. *Prog. Heterocycl. Chem.* **1994**, *6*, 1. (e) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139.

(8) Boga, C.; Del Vecchio, E.; Forlani, L.; Todesco, P. E. *J. Organomet. Chem.* **2000**, *601*, 233.

(9) **General Procedure for the HD Reaction and Quenching with Electrophiles to Compounds 2a–h:**
To a solution of 5-bromo-2-chlorothiazole (**1**, 199 mg, 1 mmol, 1 equiv) in anhydrous THF under argon atmosphere a freshly prepared solution of LDA (1.2 equiv) in anhydrous THF was added at –80 °C and the mixture stirred at that temperature until TLC analysis showed complete HD reaction (15–20 min). Then the corresponding electrophile (1.5 equiv) was added at –80 °C and the reaction was allowed to warm to r.t. The reaction mixture was poured into 2 N HCl and the aqueous phase was extracted with Et_2O. The organic layer was washed with 2 N HCl (2×), H_2O (2×) and brine (2×), dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified either by column chromatography or by Kugelrohr distillation.

(10) **4-Bromo-2-chloro-5-iodothiazole (2d)**
Light yellow solid (76%); mp 60–61 °C; bp 150 °C (2 mbar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.9 (s, C5), 132.6 (s, C4), 156.3 (s, C2).

(11) **4-Bromo-2-chlorothiazole-5-carbaldehyde (2g)**
Light yellow crystals (56%); mp 83–84 °C; bp 100 °C (0.35 mbar). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.88 (s, 1 H, CHO). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.1 (s), 134.9 (s), 160.1 (s, C2), 181.9 (d, CHO).