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Efficient access to 5-substituted thiazoles by a novel metallotropic rearrangement

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Abstract—A novel rearrangement process involving the migration of trimethylstannanyl or trimethylsilanyl groups around the thiazole ring provides access to either 2- or 5-metallated thiazoles by tuning the reaction conditions. The proposed mechanism, based on experimental evidence, is characterized by the catalytic role of thiazole bisadducts as metal-transfer agents.

Thiazoles are a prominent class of heterocycles with a wide range of biological properties,[1] as well as being investigated for other applications such as liquid crystals[2] and molecular diodes.[3] The interest in substituted thiazoles with reactive functionalities resides also in their synthetic potential as building blocks for natural product synthesis[4] and/or as masked aldehydes,[5] thanks to the ready conversion of the thiazole ring into the formyl group. Furthermore, synthetic thiazoles offer the opportunity to increase the structural diversity of natural thiazole substrates.

Although the Hantzsch process,[6] in which an α-halo ketone is condensed with a thioamide, has been for decades the method of choice for the synthesis of thiazoles, great attention has been recently dedicated to more flexible and rapid procedures, and particularly to that of carbon–carbon bond formation at the thiazole ring.[7] Among the literature methods, the functionalization of the desired positions with silicon or tin allows the direct insertion of the thiazole ring into greater molecular systems, via Stille coupling or substitution of the silanyl or stannanyl group by carbon electrophiles.[8] According to these considerations, our approach to the synthesis of substituted thiazoles was based on the use of 5- and 2-trimethylstannanyl-thiazole as building blocks. The regioselectivity of both the silanylation and stannanylation reactions is normally regulated by the recognized acidity of thiazole protons, H2 > H5 ≫ H4: the insertion of functional groups at the 2-position (generation of 2-trimethylsilanyl-thiazole **2a** or 2-trimethylstannanyl-thiazole **2b**) is then accomplished by the addition of 1 equiv of strong base and 1 equiv of chlorosilane or chlorostannane.[9] On the other hand, the generation of 5-trimethylsilanyl- **3a** or 5-trimethylstannanyl-thiazole **3b** requires either the metal–halogen exchange reactions of synthetically more demanding monohalogenated thiazoles[7b] or the use of a protecting group on the more reactive 2-position.[8] In the case of silanylation to **4a**, the protection can be accomplished by the same functional group, so that 2 equiv of strong base and 2 equiv of chlorosilane are required. The silanyl group can then be selectively removed from the more labile 2-position by treatment with acid (Scheme 1, i–iii).[8]

During the metallation of thiazole **1** we observed an unreported rearrangement that raised the opportunity to obtain 5-stannanyl- or 5-silanyl-thiazole **3a**,**b** from unbrominated starting materials and without protecting groups.[10] In fact, when the reactions were run with an excess of base and up to 2 equiv of metal chloride, the 2-substituted products **2a**,**b** were still obtained at low temperature and within short reaction times (Scheme 1, i), but started to interconvert to their 5-substituted analogues when longer reaction times and higher temperatures were applied (Scheme 1, iii). After overnight stirring, a 10% excess of base and chloride was sufficient

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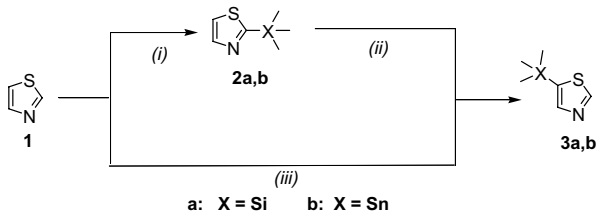


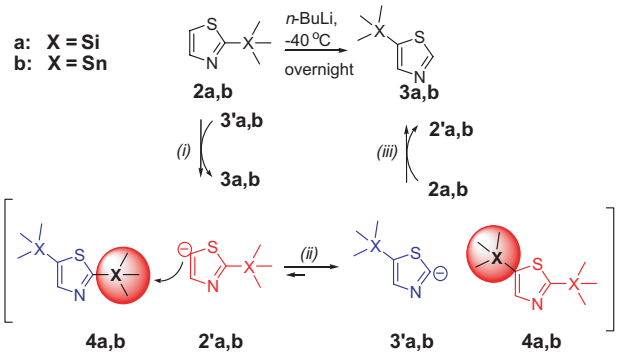
Scheme 1. Access routes to 2-functionalized (**2a**,**b**) and 5-functionalized (**3a**,**b**) thiazoles. Reagents and conditions: (i) *n*-BuLi and Me_3XCl (1 equiv), −78 °C, THF; (ii) *n*-BuLi (0.1 equiv) and Me_3XCl (0.1 equiv), −40 °C, THF; (iii) *n*-BuLi (1.1 equiv) and Me_3XCl (1.1 equiv), −40 °C, THF.

to reach a total conversion of the initial 2-substituted compounds **2a**,**b** to their 5-substituted analogues **3a**,**b**.

It is worth noticing that the rearrangement took place only if slight excesses of both base and electrophile were present, while no change in the initial product pattern was observed if any of these two reagents was less than stoichiometric. The same phenomenon was observed when a clean sample of 2-substituted thiazole was treated for 5 h at −40 °C with a catalytic amount (10%) of both electrophile and base (Scheme 1, ii).

Besides the synthetic advantages, the reaction presents some intriguing mechanistic aspects. On the basis of our experimental data, we propose for this rearrangement the mechanism illustrated in Scheme 2. The key step is the nucleophilic attack of the 2-metallated thiazole-5-anions **2′a**,**b** on the 2,5-difunctionalized thiazoles **4a**,**b**, which in turn generate the corresponding 5-metallated thiazole-2-anions **3′a**,**b**; difunctionalized thiazoles are then both consumed and created by the same nucleophilic attack. The essential thiazole bisadducts **4a**,**b** are probably formed in small amount during the metallation of thiazole, while steps i and iii of Scheme 2 are acid–base reactions. Given the catalytic amount of strong base required, it is likely that the thiazole-5-anions are also generated by deprotonation of **2a**,**b** by the thiazole 2-anions **3′a**,**b**. Such an acid/base equilibrium is possible due to the close pK_a values of H2 and H5 in thiazole.[11]

The proposed mechanism presents many similarities with the base-catalyzed halogen dance (BCHD) reaction,[12] in which a halogen substituent moves to a new position on an aromatic ring system under basic conditions. In BCHD the driving force of the rearrangement is the formation of a more stable organolithium; on heterocycles, as, for example, in the rearrangement of 2,3-dibromothiophene to 2,4-dibromothiophene,[13] the driving force is related to the different site acidities. Recently, the stannanylation of the 4- and 5-positions of the thiazole ring has been achieved by the application of the BCHD reaction to halothiazoles.[14] Following the acidity order of the thiazole protons, the migration of the halogen atom occurs from the 2-position to the thermodynamically favoured 5- or 4-positions, and is followed by the generation of the corresponding tin compounds by metal–halogen exchange and quenching with organic chlorostannane.

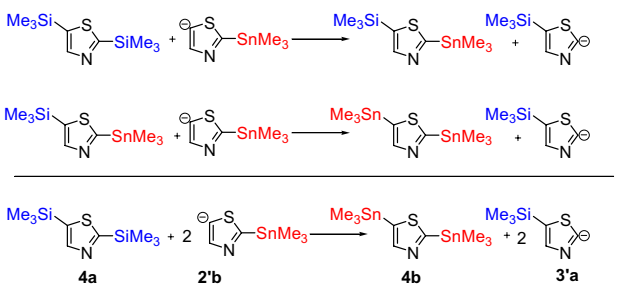


Scheme 2. Proposed mechanism for the interconversion of 2-substituted thiazoles **2a**,**b** into 5-substituted **3a**,**b**.

The catalytic role of the base and the conversion towards the conjugated bases of the stronger acids bring evident similarities of this new rearrangement with BCHD. Interestingly, also in BCHD the nucleophilic attack of an aryl anion on a hyperbrominated intermediate is the proposed key step.[12a] The apparent inconsistency of having a metal cation instead of a halogen as the migrating group is not surprising, when it is considered that BCHD occurs by the transfer of a positive halogen fragment from one carbon to another and the release of an aryl anion as leaving group.[12]

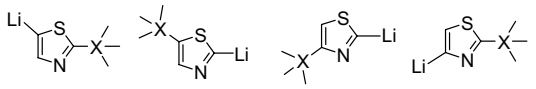
To test this hypothesis, a 5% molar of 2,5-bis-trimethylsilanyl-thiazole **4a**[8a] was added to a solution of 2-stannanylated **2b** in the presence of 10% molar excess of base. The resulting rearrangement rate was much faster than the one measured running the reaction under the same conditions without any added silanyl adduct, thus confirming the role of difunctionalized species in the reaction. Scheme 3 illustrates how disilylated **4a** may promote the rearrangement, reacting with two molecules of 2-trimethylstannanyl-thiazole-5-anion **2′b** to give the catalytic 2,5-bis-trimethylstannanyl-thiazole **4b** and two molecules of 5-trimethylsilanyl-thiazole-2-anion **3′a**.

The key steps in Schemes 2 and 3 are the nucleophilic attacks on silicon or tin by the thiazole-5-anion, which occurs selectively on the 2-position of the bisadduct; this selectivity can be explained by the already mentioned lability of the bond between the metal and the electron-poor C2 carbon, which is far more reactive than C5 and C4.[8]



Scheme 3. Catalytic effect of disilanylated species **4a** on the rearrangement of 2-trimethylstannanyl-thiazole **2b**.

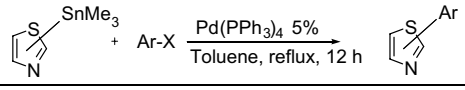
Table 1. Absolute energies of the lithiated structures **2′**, **2″**, **3′** and **5′**, optimized at the B3LYP/DGDZVP level and with bulk solvent (THF) effect (CPCM method)

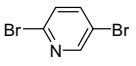
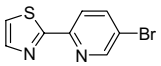
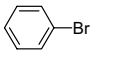
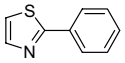
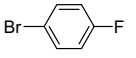
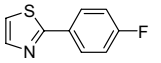
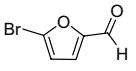
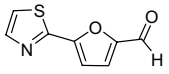
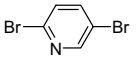
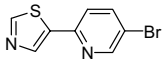
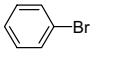
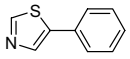
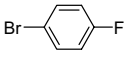
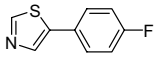
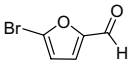
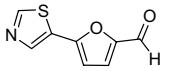


2'a,b-Li **3'a,b-Li** **5'a,b-Li** **2''a,b-Li**

Compound	Hartree	kcal mol^{-1}
2′a-Li	−984.68969811	1.47
3′a-Li	−984.69204261	0.00
5′a-Li	−984.68669349	3.36
2″a-Li	−984.67278407	12.09
2′b-Li	−6719.93771004	1.11
3′b-Li	−6719.93947337	0.00
5′b-Li	−6719.93421201	3.30
2″b-Li	−6719.92201711	10.96

Table 2. Stille coupling of stannanyl thiazoles **2b** and **3b**



	Thiazole	Halide	Product	Yield (%)
1	**2b**			60
2	**2b**			75
3	**2b**			60
4	**2b**			70
5	**3b**			60
6	**3b**			67
7	**3b**			50
8	**3b**			65

The influence of the steric hindrance of the metal migrating group on the rearrangement can be regarded as a further proof of the nucleophilic character of the reaction. In fact, no reaction was observed when we tried to perform the rearrangement with TIPS (triisopropylsilanyl) rather than with TMS (trimethylsilanyl) as leaving group on the 2-position, probably because the bulky isopropyl groups prevent the approach of the thiazole anion to the metal centre.

The exchange involves the two more acid protons of thiazole, namely H2 and H5, while H4 is unaffected. To get some insight on the regioselectivity of the rearrangement, we optimized the relevant structures at the B3LYP/DGDZVP level.[15] Since the key step of the reaction is the nucleophilic attack of the 2-anions on the bismetallated thiazoles, the computational studies were performed on the charged species rather than on the neutral ones. We have then optimized the lithium salts of the 2-, 5- and 4-substituted thiazoles **2′a**,**b-Li**, **3′a**,**b-Li** and **5′a**,**b-Li** in the presence of the THF solvent, using the conductor-like polarizable continuum model (CPCM).[16] As 2-substituted thiazoles we also considered structures **2″a**,**b-Li**, lithiated on the 4 position. The results are collected in Table 1, and are similar for the silanyl and for the stannanyl derivatives.

It can be appreciated that the 5-functionalized **3′a**,**b-Li** structures are more stable than the 2-functionalized **2′a**,**b-Li** structures. Also, of the two sets of 2-functionalized structures, **2′a**,**b-Li** and **2″a**,**b-Li**, the former one remains the more stable. This finding supports the proposed mechanism (Scheme 2), which postulates nucleophiles **2′a**,**b** as intermediates. On the other hand, the 4-functionalized **5′a**,**b-Li** structures are less stable than both the 2- and 5-functionalized isomers, and do not appear anywhere along the reaction paths.

Indeed, these computational findings explain why all our attempts to induce a migration of the silanyl or stannanyl moiety from the 2- or 5- to the 4- position were unsuccessful. In one experiment, 5-trimethylstannanyl-2-triisopropylsilanylthiazole was reacted under the same condition utilized for **3a**,**b**. We expected a rearrangement from the 5- to the 4-position, as the 2-position is ruled out by the steric hindrance of the TIPS group as mentioned before. We could only recover unrearranged starting material.

To explore the synthetic potential of the stannanyl substrates as building blocks, we tested their reactivity in Stille coupling reactions under standard conditions. The results are reported in Table 2. Both 2-trimethylstannanyl- and 5-trimethylstannanyl-thiazole reacted smoothly with both electron-poor and electron-rich aryl halides, with no appreciable difference in reactivity.

In summary, the two protocols, labelled i and iii in Scheme 1, allow the selective and quantitative functionalization of either the 2- or the 5-position of the non-substituted and non-protected thiazole ring. The proposed mechanism, based on experimental evidences, is characterized by the nucleophilic attack of the thiazole anion on the catalytic bismetallated species. Studies aimed at the extension of this reaction to other hetero cycles are presently underway in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.029.

References and notes

1. (a) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196–229; (a) Lewis, J. R. *Nat. Prod. Rep.* **1996**, *13*, 435–467.
2. Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701.
3. Ng, M.; Yu, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3598–3601.
4. (a) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R.; Boddy, C. N. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 81–84; (b) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623–4633; (c) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665–697.
5. Dondoni, A.; Marra, A. *Chem. Rev.* **2004**, *104*, 2557–2559.
6. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 942–946; (b) Wiley, R. H.; England, D. C.; Behr, L. C. In *Organic Reactions*; John Wiley, 1951; Vol. 6, pp 367–409.
7. (a) Deng, S.; Tauton, J. *Org. Lett.* **2005**, *7*, 299–301; (b) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 1363–1365; (c) Stanetty, P.; Schnurch, M.; Mereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 567–574; (d) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 8004–8005.
8. (a) Dondoni, A.; Fogagnolo, M.; Medici, A.; Negrini, E. *Synthesis* **1987**, 185–186; (b) Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N. P.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 84–87; (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pegrini, P. *J. Org. Chem.* **1988**, 1748–1761.
9. Dondoni, A.; Mastellari, A. R.; Medici, A.; Negrini, E.; Pedrini, P. *Synthesis* **1987**, 757–760.
10. A similar rearrangement, however, occurring on a thiazole ring functionalized with bromine, has been reported in: Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 9293–9296.
11. Shen, K.; Fu, Y.; Li, J. N.; Liu, L.; Guo, Q. X. *Tetrahedron* **2007**, *63*, 1568–1576.
12. (a) Bunnet, J. F.; Scorrano, G. *J. Am. Chem. Soc.* **1971**, *93*, 1190–1198; (b) Bunnet, J. F. *Acc. Chem. Res.* **1972**, *5*, 139–147.
13. (a) Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771–773; (b) Fröhlich, H.; Kalt, W. *J. Org. Chem.* **1990**, *55*, 2993–2995.
14. (a) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381–2385; (b) Stangeland, E. L.; Sammakia, T.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385–2388.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. GAUSSIAN 98, revision 5.4; Gaussian: Pittsburgh, PA, 1998.
16. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669–681.