ORGANIC
LETTERS

2000
Vol. 2, No. 18
2877−2880

Unexpected Reactivity of Imidazo[2,1-*b*]thiazolines with Organometallic Reagents

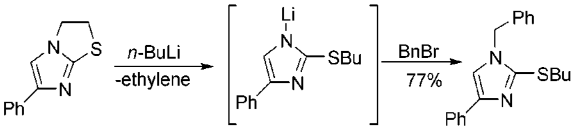
Joseph Sisko,* Andrew J. Kassick, and Steven B. Shetzline

SmithKline Beecham Pharmaceuticals, Synthetic Chemistry Department,
709 Swedeland Road, PO Box 1539, King of Prussia, Pennsylvania 19406

joe_sisko-1@sbphrd.com

Received July 7, 2000

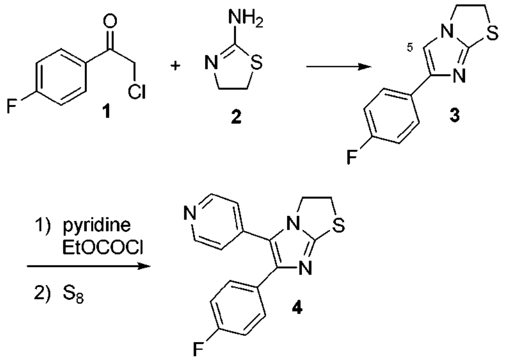
ABSTRACT



The reaction of imidazo[2,1-*b*]thiazolines with various organometallic reagents is described. Nucleophilic attack of organolithium reagents on sulfur occurs with extrusion of ethylene to produce 2-thioalkyl- or 2-thioarylimidazoles. The outcome with Grignard reagents, however, is less predictable, with some reagents adding at sulfur and others reacting at C-2 or not at all.

In 1988, a report from this department described a novel Comins-type addition of an imidazo[2,1-*b*]thiazoline (**3**) to an acylpyridinium salt as a key step in the process to prepare the antiinflammatory agent SK&F 86002 (**4**, Scheme 1).[1] In the intervening years, a number of 1,4,5-trisubstituted imidazoles have been proposed as development candidates for the treatment of rheumatoid arthritis and other chronic inflammatory diseases.[2] As part of this program, imidazo[2,1-*b*]thiazolines such as **3** were evaluated as potential intermediates for the synthesis of these imidazoles due to their structural similarity, reactivity at C-5, and ready accessibility from α-halo ketones (**1**) and 2-aminothiazoline (**2**). The purpose of this paper is to disclose the unexpected reactivity of imidazo[2,1-b]thiazolines such as **3** with organolithium and Grignard reagents.

Scheme 1



The nucleophilic character of imidazo[2,1-*b*]thiazolines at C-5 (imidazole numbering) has been well documented in the literature.[1,3] Despite this, the C-5-lithiated derivative of **3** was expected to be a more versatile intermediate for our plans

---

(1) Lantos, I.; Gombatz, K.; McGuire, M.; Pridgen, L.; Remich, J.; Shilcrat, S. *J. Org. Chem.* **1988**, *53*, 4223.

(2) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529. Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111.

(3) (a) Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Andreani, F.; Gehret, J.-C. *Pharm. Acta Helv.* **1996**, *71*, 247. (b) Andreani, A.; Rambaldi, M.; Bonazzi, D. *Farmaco Ed. Sci.* **1980**, *35*, 573. (c) Isomura, Y.; Ito, N.; Sakamoto, S.; Homma, H.; Abe, T.; Kubo, K. *Chem. Pharm. Bull.* **1983**, *31*, 3179.

(4) (a) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918. (b) Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Anderson, R. J. *J. Org. Chem.* **1998**, *63*, 9850. (c) Shapiro, G.; Marzi, M. *Tetrahedron Lett.* **1993**, *34*, 3401. (d) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899. (e) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

10.1021/ol006302n CCC: $19.00

and became the focus of our attention. Although direct lithiation of imidazo[2,1-*b*]thiazolines has not been described in the literature, several groups have reported that imidazoles resembling **3** can be lithiated with *n*-BuLi at C-5 directly (Figure 1, **A** and **B**)[4a−c] or via metal−halogen exchange (Figure 1, **C**),[4d] while other systems are metalated on the carbon adjacent to sulfur (Figure 1, **D**).[4e]

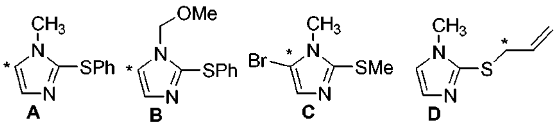
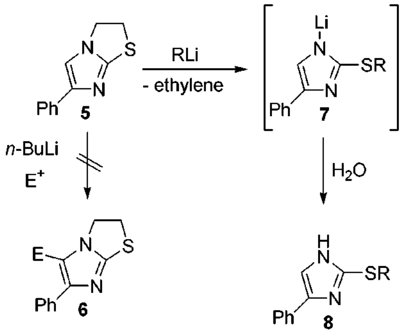


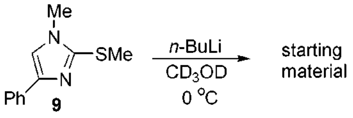
Figure 1. Imidazoles that have been lithiated with *n*-BuLi. The * indicates the site of lithiation.

Sequential exposure of a THF solution of **5** to 2 equiv of *n*-BuLi and an electrophile (DMF) at 0 °C, however, produced none of the expected product **6** (Scheme 2). To our surprise, the 2,4-disubstituted imidazole **8a** was identified as the sole product and was isolated in 84% yield. This product is believed to arise from direct addition of the butyl group at sulfur[5] followed by elimination of ethylene to produce imidazole **8** after aqueous workup. The process is apparantly driven by the relief of ring strain since **9**, the acyclic analogue of **5**, returned only unlabeled starting material after treatment with *n*-BuLi and CD_3OD under otherwise identical reaction conditions (Scheme 3).

Scheme 2



Scheme 3



The purity and high yield of the crude product (**8**), as well as the novelty of this transformation as a convenient imidazole synthesis, compelled us to investigate this reaction further. Table 1 summarizes the results of exposing **5** to various organolithium reagents (2 equiv).[6]

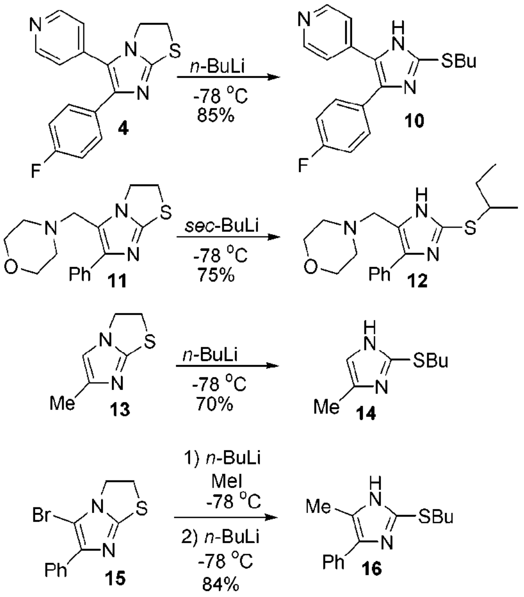
Table 1. Reaction of 5 with Various Organolithium Reagents (2 Equiv)

entry	RLi	T (°C)	product	yield (%)
1	*n*-BuLi	−78	**8a**	84
2	*s*-BuLi	−78	**8b**	82
3	*t*-BuLi	−78	**8c**	79
4	PhLi	0	**8d**	60
5	MeLi	−78	**8e**	70
6	Vinyl-Li	−78	**8f**	83

In general, the reactions proceeded smoothly at −78 °C in THF even with bulky nucleophiles, such as *t*-BuLi, and were complete in 30−60 min. Only PhLi required higher temperatures (0 °C) for complete reaction. Less reactive organolithiums, such as lithium acetylides, $LiCH_2P(O)(OMe)_2$, and $LiCH_2CN$, failed to add to **5**, returning only the starting material.

In addition to the parent system **5**, several other imidazo[2,1-*b*]thiazolines were successfully converted to 2-thioimidazoles using this methodology (Scheme 4). Allowing the disubstituted substrate **4** to react with 2 equiv of *n*-BuLi at −78 °C delivered imidazole **10** in 85% isolated yield. Likewise, compound **11** (which is readily available from **5**)[4c] reacted with *s*-BuLi (2 equiv) to deliver **12** in good yield. Replacing the C-4 aryl substituent with a methyl group (**13**)

Scheme 4



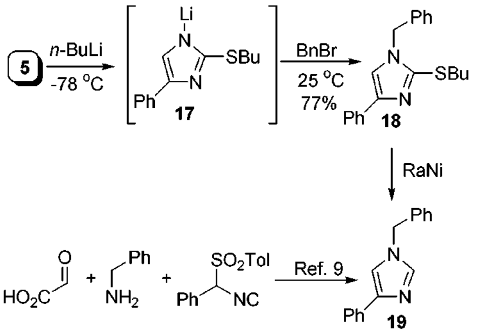
---

(5) Bordwell, F. G.; Andersen, H. M.; Pitt, B. M. *J. Am. Chem. Soc.* **1954**, *76*, 1082. Mase, T.; Murase, K.; *Heterocycles* **1987**, *26*, 3159. Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992.

was also tolerated, providing **14** in 70% yield after reaction with 2 equiv of *n*-BuLi. The reaction of bromide **15**[4a,c] took a slightly different course. In this case, lithium−halogen exchange with *n*-BuLi (1 equiv) occurred faster than addition at sulfur.[4d,7] After trapping the resultant lithiate with MeI, however, *n*-BuLi (2 equiv) cleanly added at sulfur to yield **16** in 84% yield.

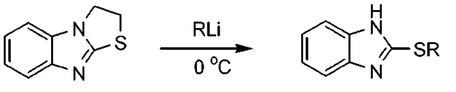
The availability of 2-thioalkyl- or 2-thioarylimidazoles with alternate substitution patterns was also explored using this new protocol. For instance, trapping intermediates such as **7** with an electrophile should give rise to 1,2,4-trisubstituted imidazoles.[8] Thus, addition of *n*-BuLi (2 equiv) to **5** produced intermediate **17**, which was trapped with benzyl bromide to give **18** in 77% isolated yield (Scheme 5). The regiochemistry of the alkylation was confirmed after Raney nickel desulfurization of **18** gave a compound with NMR spectra identical to those for imidazole **19**, which was prepared independently.[9]

Scheme 5



In addition to imidazole substrates, the reactivity of the corresponding benzimidazole substrates with organolithium reagents was also examined in this study (Scheme 6).

Scheme 6



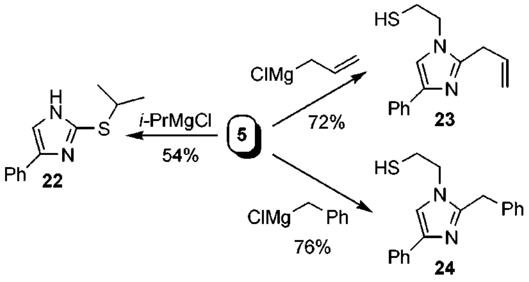
20

21 a, R = Ph, 72%
21 b, R = *sec*-Bu, 75%

Addition of either PhLi or *s*-BuLi (2 equiv) at 0 °C to **20**, itself readily prepared from 2-benzimidazolethiol,[10] produced **21a** (72%) and **21b** (75%), respectively.

The addition of Grignard reagents to **5** was also examined. Adding *i*-PrMgCl (2 equiv) to a THF solution of **5** produced the isopropyl adduct **22** in 54% isolated yield (Scheme 7).

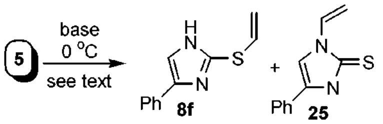
Scheme 7



However, switching to allylmagnesium chloride and benzylmagnesium chloride (2 equiv) gave **23** and **24**, respectively, in which the Grignard added to C-2 of the imidazole nucleus and ejected the ethanethiol moiety.[11,12] Unfortunately, we found no reaction conditions which could induce other alkyl or aryl Grignard reagents to add to **5**, regardless of the choice of solvent, reaction temperature, magnesium counterion, or choice of catalyst.[13]

Returning to our original goal, we attempted to access the C-5 lithiated intermediateby treating **5** with lithium amide bases (Scheme 8). Adding LDA to a THF solution of **5**,

Scheme 8



however, gave a mixture of **8f** and **25** in a 1:1 mixture, presumably from deprotonation adjacent to either sulfur or nitrogen followed by *β*-elimination. Using a less hindered base such as lithium pyrrolidide, however, produced the *N*-vinyl compound **25** as the sole product.

In summary, we have observed that imidazo[2,1-*b*]-thiazolines react with organolithium reagents at sulfur to deliver 2-thioalkyl- and 2-thioarylimidazoles in high yield. This process constitutes a versatile and expedient synthesis of polysubstituted imidazoles prepared ultimately from

---

(6) Typical procedure: A solution of **5** (0.29 g, 1.44 mmol) in THF was cooled to −78 °C and MeLi (1.5 M, 1.9 mL, 2.88 mmol) was added. After 1 h, the mixture was diluted with H_2O and EtOAc and the organic layer was concentrated to dryness. After silica gel chromatography, the product **8e** was obtained as a white solid (0.19 g, 70%): mp = 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.23 (1H, s), 7.67 (2H, d, $J = 7.7$ Hz), 7.33 (3H, m), 7.22 (1H, m), 2.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 139.6, 132.3, 128.7, 127.1, 124.8, 118.0, 17.2; MS (ESP) 191 (M + 1).

(7) Pridgen, L. N.; Shilcrat, S.; Lantos, I.; McGuire, M. Private communication.

(8) Dodson, R. M. *J. Am. Chem. Soc*. **1950**, *72*, 1478.

(9) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem*. **2000**, *65*, 1516.

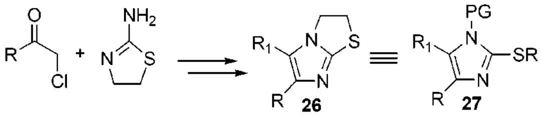
(10) Suri, O. P.; Khajuria, R. K.; Saxena, D. B.; Rawat, N. S.; Atal, C. K. *J. Heterocycl. Chem*. **1983**, *20*, 813.

(11) We are unaware of other examples of nucleophilic displacement of 2-thioalkyl or 2-thioaryl groups of imidazoles. Jones, however, has reported a similar process with 2-phenylthio-2-imidazolines. See: Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett*. **1990**, *31*, 1767.

(12) For a similar process with 2-thioalkylbenzothiazoles, see: Katritzky, A. R.; Kuzmierkiewcz, W.; Aurrecoechea, J. M. *J. Org. Chem*. **1987**, *52*, 844.

(13) Pridgen, L. N.; Killmer, L. B. *J. Org. Chem*. **1981**, *46*, 5402. Pridgen, L. N. *Synthesis* **1984**, 1047.

Scheme 9



α-halo ketones and 2-aminothiazoline (Scheme 9). In this context, the imidazo[2,1-*b*]thiazoline intermediates (**26**) function as synthons for the N-1 protected, 2-thio-imidazole **27**. While most Grignard reagents are unreactive toward these same substrates, *i*-PrMgCl reacts at sulfur while benzyl and allyl Grignard reagents react at C-2. Finally, treatment of **5** with amide bases leads to the *S*-vinyl or *N*-vinyl derivatives **8f** and **25**, respectively.

Acknowledgment. We thank Dr. P. Grant Spoors for numerous helpful discussions and Dr. Alan J. Freyer for NMR assistance to confirm the structure of **25**. A.J.K. thanks SmithKline Beecham for financial support.

OL006302N