<http://www.diva-portal.org>

Preprint

This is the submitted version of a paper published in *European Journal of Organic Chemistry*.

Citation for the original published paper (version of record):

Söderström, M., Zamaratski, E., Odell, L R. [Year unknown!]
Thiomethylation, Nitro Reduction and Tandem Reduction/SMe Insertion of Nitrogen
Heterocycles Using $\text{BF}_3 \cdot \text{SMe}_2$
European Journal of Organic Chemistry

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-383868>

Thiomethylation

Thiomethylation, Nitro Reduction and Tandem Reduction/SMe Insertion of Nitrogen Heterocycles Using $\text{BF}_3 \cdot \text{SMe}_2$

Marcus Söderström,^[a] Edouard Zamaratski,^[a] and Luke R. Odell^{*[a]}

Abstract: Herein, a general, solvent free and straightforward thiomethylation of electron deficient heterocycles using $\text{BF}_3 \cdot \text{SMe}_2$ as a dual thiomethyl source and Lewis acidic activator is presented. A range of heterocycles including pyrimidine, pyrazine, pyridazine, thiazole and purine derivatives were successfully substituted using this method. An unexpected reductive property of $\text{BF}_3 \cdot \text{SMe}_2$

towards nitropyridines was also discovered including an intriguing tandem reduction/SMe insertion process in certain substrates. Notable features of the present work include its convenience and use of a non-malodorous reagent while the discovery of novel chemical transformations using $\text{BF}_3 \cdot \text{SMe}_2$ provides fundamental new insights into the reactivity of this commonly employed reagent.

Introduction

Drug scaffolds containing sulfur are commonplace in medicine, and as a consequence have an important role in medicinal chemistry.¹ Examples of common structures found in medicinal chemistry are the sulfonamides (sumatriptan, valdecoxib), thioether (ticagrelor, azathioprine, axitinib), sulfoxide (lanzoprasole, omeprazole) and sulfone (dorzolamid, tipranavir) moiety. Amongst these, compounds containing thiomethyl derivatives are highly prevalent and include thioridazine, sulindac and florfenicol. As a result, significant effort has been invested into developing synthetic methods for the preparation of these compounds. The classical method for installing a thioether moiety on an electron deficient aromatic substrate is via an $\text{S}_{\text{N}}\text{Ar}$ using thiolate salts as the nucleophile.^{2–9} Although thiolate salts are good nucleophiles, these types of reagents suffer from a range of drawbacks including volatility, instability, toxicity, and strong, unpleasant odors.^{10–13} Disulfides can also be used for the thiomethylation of aryl halides using nickel catalysts and zinc^{14–19} (Scheme 1a) or aryl diazonium salts²⁰ and boronic acids²¹ (Scheme 1c) under radical conditions although they are also known to be highly odorous. Recently, DMSO has emerged as an attractive thiomethyl source for the functionalization of a range of substrates^{22–28} (scheme 1a and b) however, these reactions require high temperatures as well as the use of stoichiometric amounts of copper salts.

In response to these limitations, the transition metal-free thiomethylation of aryl halides using DMSO¹⁰ or S-methylisothioure²⁹ (Scheme 1d) has been described. In these reactions, base-mediated formation of dimethylsulfide or methylsulfide in situ followed by a $\text{S}_{\text{N}}\text{Ar}$ on the halide substrates led to the thiomethyl ether products. Thus, the development of cheap, convenient and metal-free methods for the installation of a thiomethyl ether group remains a topic of considerable interest.

Herein, we present a method for the thiomethylation of heterocycles using $\text{BF}_3 \cdot \text{SMe}_2$ as a dual Lewis acid activator^{30–32} and nucleophilic SMe source (Scheme 1e and f). Importantly, this method is solvent and base-free and requires the addition of only one reagent, making the process highly convenient. In addition, novel nitro reduction and cascade nitro reduction/thiomethylation processes have also been discovered showcasing $\text{BF}_3 \cdot \text{SMe}_2$ as a surprisingly diverse reagent with uses far beyond its standard role as a demethylation^{33–37} and debenzylolation^{37,38} agent.

[a] M. Söderström, E. Zamaratski, L. R. Odell
Department of Medicinal Chemistry, Uppsala University
Uppsala, Biomedical Center, P. O. Box 574
SE-751 23 Uppsala, Sweden
E-mail: luke.odell@ilk.uu.se
Homepage: www.ilk.uu.se

Supporting information for this article is given via a link at the end of the document.

Previous Work

This Work

Scheme 1. Previous work on the thiomethylation of a range of substrates and the present work exploring the reactivity of BF₃·SMe₂.

Results and Discussion

This work was initiated when a serendipitous thiomethylation of 2-chloro-4-methoxypyrimidine (1a) to afford 4-methoxy-2-(methylthio)-pyrimidine (A) was observed during an attempted iodination reaction in one of our medicinal chemistry programs (Scheme 2). As there was no other sulfur source present in the reaction, it was proposed that DMSO was the source of the SMe group with the product being formed by the reduction of DMSO to DMS in acidic conditions, followed by a S_NAr reaction with DMS.

Scheme 2. Initial observation on the thiomethylation of 1 using DMSO.

It was envisaged that DMSO could serve as an alternative reagent to current metal-free thiomethylation methods, with the advantages of being non-expensive, easy to use and readily available. Initial attempts to optimize this reaction were unsuccessful as the in situ reduction of DMSO to DMS resulted only in low yields, required exhaustive work up and displayed substrate compatibility problems. Attention therefore turned to the boron trifluoride-dimethyl sulfide complex (BF₃·SMe₂), as this would provide DMS without any prerequisites of reduction, as well as providing a Lewis acid activator. Compared to thiolate salts and sulfides this reagent is non-hygroscopic, non-malodorous and easily dosed due to it being a liquid at room temperature.

Initial experiments were conducted in DCM, and 4 equivalents of BF₃·SMe₂ was found to provide full conversion of 2-chloropyrimidine (1b) after heating at 60 °C for 16h. While scouting for suitable reaction conditions, it was observed that chlorinated solvents tended to react with the reagent at elevated temperatures (DCM, DCE or CHCl₃). To avoid any unwanted interaction with solvent, solvent free conditions were explored and this appeared to be a rather attractive strategy given that the reagent is a non-viscous liquid. Pleasingly, the solvent-free conditions also resulted in full conversion of 1b and even when the amount of BF₃·SMe₂ was reduced to 2 equivalents, the desired product 2b was isolated in 80% yield (Table 1).

Table 1. Scope of the thiomethylation reaction.

2a, 83% X = Cl	2b, 80 % ^[a] X = Cl	2c, 57 % X = Br
2d, 71 % X = Br	2e, 44% ^[a] X = Cl	2f, 92 % X = Cl
2g, 85 % X = Cl	2g', 31 % ^[b] X = Cl	2h, 86 % ^[c] X = Cl
2i, 80 % X = Br	2j, 15 % ^[d] X = Br	2k, 93 % X = Cl
2l, 55 % X = Cl	2m, 88 % X = Cl	

Isolated yields. [a] isolated as HCl salt. [b] 1.1 equiv $\text{BF}_3 \cdot \text{SMe}_2$. [c] 36h reaction time. [d] 72h reaction time

Next the scope and limitations of the $\text{BF}_3 \cdot \text{SMe}_2$ mediated thiomethylation reactions was explored using a range of heteroaryl halides (Table 1). 2-Bromopyrazine (1c), 3-bromopyridazine (1d) and 4-bromoquinazoline (1f) were all found to be productive substrates and the desired products were isolated in moderate to excellent yields. 4,6-Dichloropyrimidine (1g) was readily di-substituted using an excess of $\text{BF}_3 \cdot \text{SMe}_2$ while the use of 1 equivalent afforded both mono-substituted 2-chloro-4 (methylthio)pyrimidine (2g') and di-substituted 2g in 31% and 33% yield, respectively. The introduction of a phenyl substituent was well tolerated (2h) as was the presence of a highly electron-releasing primary amino-group

(1i). Interestingly, the later reaction was highly selective for substitution at the 5-position and this is most likely due to coordination by the *ortho*- NH_2 group. This is consistent with the lower reactivity exhibited by 5-bromopyrazine-2-amine (1j) where an extended reaction time led to only a modest yield of the thiomethylated product. 6-Chloro-7H-purine (1k) was also successfully transformed into the desired product in 93% yield and the presence of an amino-group (1l) was again well tolerated and 2-(thiomethyl)-7H-purin-6-amine was isolated in 55% yield. Finally, 2-chlorobenzo[d]thiazole (1m) was efficiently thiomethylated to afford 2m in 88% yield.

Further exploration of the scope and limitations revealed a preference for heterocycles containing two or more heteroatoms with at least one of these being capable of mesomeric activation of the halide leaving group. Accordingly, the reaction of 2-chloropyridine (1n) and 5-bromopyrimidine (1o) afforded only unreacted starting material. Compared to previously reported transition metal-free reactions, the present method allows the selective functionalization of these widely employed and medically important ring systems.

Based on the results above, the reaction is believed to proceed through a $\text{S}_{\text{N}}\text{Ar}$ process, with boron trifluoride as Lewis acid activator to facilitate the nucleophilic attack of the relatively weak nucleophile SMe_2 (Scheme 3). The crucial role of BF_3 is supported by a control reaction on 1b using only SMe_2 , which resulted in the formation of only trace amounts of 2b even after heating at 60 °C for 16 hrs. Thus, substrate or thermal mediated liberation of SMe_2 followed by BF_3 capture by the nitrogen heterocycle affords the activated electrophilic complex 3. Subsequent nucleophilic attack by SMe_2 and demethylation leads to the BF_3 complex 4. Finally, workup with a suitable protic solvent (MeOH) affords the thiomethylated product 2b.

Scheme 3. Plausible mechanism for thiomethylation using $\text{BF}_3 \cdot \text{SMe}_2$

In an attempt to extend the method to more electron-deficient pyridine derivatives, we next turned our attention to nitro group bearing substrates. To this end, 2-chloro-5-nitropyridine (5a) was treated with $\text{BF}_3 \cdot \text{SMe}_2$ using the conditions outlined in Table 1. This led to the unexpected formation of 2-chloro-5-aminopyridine (6a)

arising from reduction of the nitro group and 6-chloro-2-(methylthio)pyridin-3-amine (7a) via a nitro reduction and C-S bond formation cascade (Tables 2 and 3). To the best of our knowledge, neither of these reactions utilizing $\text{BF}_3 \cdot \text{SMe}_2$ have been previously reported and, in the latter case, the nitro group reduction/SMe insertion is unprecedented in the literature. Accordingly, we sought to explore these reactions further.

During our initial investigations, it was observed that full consumption of the starting material required the addition of 6 equivalents of $\text{BF}_3 \cdot \text{SMe}_2$ and the reduction/insertion product 7a was isolated in 30% yield (Table 2). The reaction time could be reduced to 1 hour without a significant erosion in yield. In both cases, the formation of 7a was accompanied by production of 2-chloro-5-aminopyridine (6a). The use of excess $\text{BF}_3 \cdot \text{SMe}_2$ under solvent free conditions led to difficulties during the reaction workup, which was overcome by the addition of a co-solvent. Under these conditions 10 equivalents of $\text{BF}_3 \cdot \text{SMe}_2$ was needed to reach full consumption of 5a and 7a was isolated in 35% yield. To investigate whether DMS or BF_3 alone could accomplish the reduction/insertion, boron trifluoride etherate and DMS were each reacted with 5a under similar conditions. In both cases, the reactions returned only unreacted starting material indicating that both components are crucial for the reaction to occur.

Table 2. Optimization of reduction and reduction/insertion reactions of 5a

entry ^[a]	solvent	T (°C)	$\text{BF}_3 \cdot \text{SMe}_2$ equiv.	t (h)	yield [%] ^[a]
1	neat	60	2	16	-/21
2	neat	60	6	16	-/30
3	neat	60	6	1	-/28
4	DCM	60	10	16	32/34
5	DCM	60	10	3	30/35
6	DCM	60	10 ^[b]	3	-
7	DCM	60	10 ^[c]	3	-

[a] Isolated yields **6a/7a**; - = not isolated [b] SMe_2 [c] $\text{BF}_3 \cdot \text{OEt}_2$.

Next, the reaction was extended to other nitro pyridine derivatives (Table 3). 2-Chloro-3-nitropyridine (5b) was also found to undergo both reduction (6b) and reduction/insertion (7b) and the two products were isolated in 51% and 21% yield respectively. Absence of the chloro-substituent was deleterious for the reduction/insertion reaction as 3-nitropyridine afforded only the reduced product 3-aminopyridine (6c) in 54% yield. The position of the nitro group

was also important for determining the reaction outcome as 5-chloro-2-nitropyridine returned only the reduced product 6d in 72% yield. In both cases, the reduction/insertion product was not observed by LCMS analysis of the crude reaction mixture. Similarly, 2-nitropyridine underwent rapid reduction under these conditions to afford a moderate yield of 2-aminopyridine (5e). Although the reduction/insertion reaction was only detected in two substrates, the regio- and chemoselective formation of the highly substituted pyridine products is noteworthy.

Table 3. Scope of the reduction/insertion reaction on nitropyridine substrates.

entry	substrate	6a-e ^[a]	7a,b ^[a]	T (h)
1	5a	6a, 30 %	7a, 35 %	3
2	5b	6b, 51 %	7b, 21 %	4
3	5c	6c, 54 %	-	4
4	5d	6d, 72 %	-	0.5
5	5e	6e, 45 %	-	0.5

[a] Isolated yield.

Finally, the scope of the reduction reaction was examined using a range of different substrates. Interestingly, the reaction was highly selective for nitropyridine substrates as various nitrobenzene derivatives (5f-5i) were found to be unreactive towards $\text{BF}_3 \cdot \text{SMe}_2$ under these conditions. Substrates with other potentially reduction sensitive functional groups (CO_2H , SO_3H , CONH_2 and CN) afforded only unreacted starting material, even after heating for 24 h indicating $\text{BF}_3 \cdot \text{SMe}_2$ is highly selective towards the reduction of nitropyridine substrates.

Figure 1. Exploring chemoselectivity – substrates found to be unreactive towards $\text{BF}_3 \cdot \text{SMe}_2$

The methoxy-bearing substrate **5o** and methyl ester **5p** both underwent rapid demethylation, which is in accordance with the known reactivity profile of $\text{BF}_3 \cdot \text{SMe}_2$ (Scheme 4).^{33–37} Notably, treatment of 3-quinolinecarboxaldehyde (**5q**) led to the formation of the thioacetal product **8c** and represents a valuable alternative to the use of methanethiol for the installation of this protecting group. More importantly, this is to the best of our knowledge, the first known example using $\text{BF}_3 \cdot \text{SMe}_2$ to prepare thioacetal derivatives.

Scheme 4. Additional substrates found to undergo demethylation and thioacetal formation using $\text{BF}_3 \cdot \text{SMe}_2$.

Mechanistically, the reduction reaction is suggested to proceed via a BF_3 -assisted nucleophilic attack on the nitro group to give intermediate **9**, which then collapses to afford nitroso species **10** and DMSO (Scheme 5, path A). An oxygen transfer mechanism is supported by NMR studies confirming the formation of DMSO in the reduction of **5d**. A second deoxygenation reaction leads to formation of a nitrene³⁹ and subsequent hydride abstraction⁴⁰ presumably from DMSO⁴¹ or excess SMe_2 and methanolic workup furnishes the aminopyridine product **6c**.

Scheme 5. Suggested mechanisms for the $\text{BF}_3 \cdot \text{SMe}_2$ mediated reduction (A) or the cascade reduction/ SMe_2 insertion (B and C) of nitropyridine derivatives.

In the thiomethyl insertion process, capture of the nitrene intermediate **11** by Me_2S produces an azasulfonium derivative^{42–46} which can undergo *ortho*-insertion and rearomatization⁴⁶ to give **12** (Scheme 5, path B). Finally, demethylation and methanolic workup leads to formation of the reduction/ SMe_2 insertion product **7a**. Alternatively, reaction of nitroso derivative **13** with SMe_2 to give intermediate **14** followed by *ortho*-insertion and rearomatization

leads to the formation of sultinium derivative 15. Similar to pathways A and B, demethylation, deoxygenation, H-abstraction and treatment with MeOH during workup furnishes the final product 7a.

Conclusions

In conclusion, the chemistry of $\text{BF}_3 \cdot \text{SMe}_2$ has been significantly enhanced to include transformations beyond its traditional role as a dealkylating reagent. During the course of this work, four novel $\text{BF}_3 \cdot \text{SMe}_2$ mediated reactions have been discovered expanding the scope and versatility of this commonly employed reagent. Firstly, a general method for the thiomethylation of halogenated electron-poor heterocycles was identified, where $\text{BF}_3 \cdot \text{SMe}_2$ acts as a dual Lewis acid activator and thiomethyl source. Importantly, the method is solvent-free, convenient and non-malodorous and allows the selective thiomethylation of heterocyclic substrates containing more than one heteroatom. Secondly, an unexpected reductive property of $\text{BF}_3 \cdot \text{SMe}_2$ was uncovered resulting in the development of novel nitropyridine reduction and reduction/insertion protocols useful for the preparation of aminopyridines or highly functionalized methylthio-substituted amino heterocycles. Finally, preliminary studies also indicate that $\text{BF}_3 \cdot \text{SMe}_2$ can be used to prepare thioacetal derivatives and further studies to explore the use of $\text{BF}_3 \cdot \text{SMe}_2$ in this, and other synthetic, transformations are ongoing in our laboratory.

Experimental Section

General methods: All reagents and solvents were of commercial quality and used without further purification. Yields are for isolated, homogenous and spectroscopically pure material. Silica gel chromatography was carried out on E. Merck silica gel (60 Å pore size, particle size 40–63 nm) column. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. The chemical shifts for ^1H NMR and ^{13}C NMR were referenced to tetramethylsilane via residual solvent signals (^1H : methanol- d_4 at 3.31 ppm, CDCl_3 at 7.26 ppm and $\text{DMSO}-d_6$ at 2.50 ppm; ^{13}C : methanol- d_4 at 49.0 ppm, CDCl_3 at 77.16 ppm and $\text{DMSO}-d_6$ at 39.52 ppm). LC/MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (50 x 3.0 mm, particle size 2.6 μm , pore size 100 Å) running at an ionization potential of 70 eV with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient (0.05% HCOOH). Accurate mass values were determined via electrospray ionization with a 7-T hybrid ion trap and a TOF detector running in positive mode.

General procedure for the substitution reaction. To an 8 ml septum-cap vial was added the substrate (0.5 mmol) and $\text{BF}_3 \cdot \text{SMe}_2$ (1 mmol). The vial was sealed and heated under stirring at 60 °C for 16–72 h. After the reaction was deemed to have reached comple-

tion the mixture was quenched with MeOH (0.2–0.5 mL), concentrated under reduced pressure and 5 ml of saturated Na_2CO_3 was added. The aqueous phase was extracted with DCM or EtOAc (3 x 20 ml) and the organic phases dried over NaSO_4 , filtered and concentrated under reduced pressure. The resulting mixture was purified by silica gel chromatography eluting with *i*-Hexane/EtOAc or MeOH/DCM.

Alternative method with HCl formation for compound 2b: To an 8 ml septum-cap vial was added 2-chloropyrimidine (57.3 mg, 0.5 mmol) and $\text{BF}_3 \cdot \text{SMe}_2$ (1 mmol). The vial was sealed and heated under stirring at 60 °C for 16 h. After cooling to room temperature the mixture was quenched with MeOH (0.2 mL), diluted with DCM (1 mL) and filtered over silica using EtOAc. To the pooled product fractions was added 4M HCl in Dioxane (0.14 mL, 1 equiv) and the mixture was stirred for 1 h. The mixture was then concentrated under reduced pressure yielding the product as a yellow solid (65 mg, 80 %).

General procedure for reduction and reduction/insertion: To a 4 ml screwcap vial was added the substrate (0.5 mmol) and 2 ml of dry DCM. $\text{BF}_3 \cdot \text{SMe}_2$ (10 equiv.) was added and the vial was sealed and heated under stirring at the 60 °C. After the reaction was deemed to have reached completion the mixture was quenched with MeOH (1 mL), concentrated under reduced pressure and 5 ml of saturated Na_2CO_3 was added. The aqueous phase was extracted with EtOAc. The organic phase was dried over NaSO_4 , filtered and concentrated under reduced pressure. The resulting mixture was purified by silica gel chromatography eluting with *i*-Hexane/EtOAc or MeOH/DCM.

2-(methylthio)pyrimidine-4-ol (2a):⁴⁷ white solid (58.8 mg, 83 %) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.47 (s, 3H), 6.08 (d, J = 5.9 Hz, 1H), 7.85 (d, J = 5.9 Hz, 1H), 12.67 (s, 1H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 12.9, 109.9, 154.2, 163.3, 162.6.

2-(methylthio)pyrimidine hydrochloride⁴⁸ (2b): yellow solid (65 mg, 80 %). ^1H NMR (400 MHz, methanol- d_4) δ 2.65 (s, 3H), 7.39 (t, J = 5.0 Hz, 1H), 8.77 (d, J = 5.0 Hz, 2H). ^{13}C NMR (101 MHz, methanol- d_4) δ 14.1, 118.2, 158.8, 171.6. HRMS calcd for $\text{C}_5\text{H}_7\text{N}_2\text{S}$, 127.0330; found, 127.0320.

2-(methylthio)pyrazine (2c):⁴⁹ white solid (36.0 mg, 57 %). ^1H NMR (400 MHz, CDCl_3) δ 2.55 (s, 3H) 8.17 (d, J = 2.7 Hz, 1H), 8.34 (dd, J = 2.7, 1.6 Hz, 1H), 8.44 (d, J = 1.3 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 12.7, 139.2, 143.6, 144.0, 157.8.

3-(methylthio)pyridazine (2d): brown solid (44.7 mg, 71 %). ^1H NMR (400 MHz, CDCl_3) δ 2.67 (s, 3H), 7.19 (dd, J = 8.7, 4.7 Hz, 1H), 7.30 (dd, J = 8.7, 1.6 Hz, 1H), 8.85 (dd, J = 4.7, 1.6 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 13.3, 125.3, 125.7, 148.0, 163.1. HRMS calcd for $\text{C}_5\text{H}_7\text{N}_2\text{S}$, 127.0330; found, 127.0328.

4-(methylthio)pyrimidine hydrochloride (2e):⁵⁰ yellow solid (35.5 mg, 44 %). ^1H NMR (400 MHz, methanol- d_4) δ 2.62 (s, 3H), 7.54 (d, J = 5.9 Hz, 1H), 8.45 (s, 1H), 8.97 (s, 1H). ^{13}C NMR (101 MHz, methanol- d_4) δ 13.0, 120.3, 152.1, 156.8, 176.6.

4-(methylthio)quinazoline (2f):⁵¹ white solid (81.3 mg, 92 %). ^1H NMR (400 MHz, CDCl_3) δ 2.65 (s, 3H), 7.49 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.89 (ddd, J = 8.4, 0.9 Hz, 1H), 8.00 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H), 8.94 (s, 1H). ^{13}C NMR (101

MHz, CDCl₃) δ 12.6, 123.8, 124.0, 127.3, 128.8, 133.6, 147.7, 153.6, 171.8.

4,6-bis(methylthio)pyrimidine (2g): white solid (73.0 mg, 85 %). ¹H NMR (400 MHz, CDCl₃) δ 2.49 (s, 6H), 6.97 (d, *J* = 1.3 Hz, 1H), 8.65 (d, *J* = 1.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 12.6, 114.3, 157.1, 168.7. HRMS Calcd for C₆H₈N₂S₂, 173.0207; found, 173.0203.

4-chloro-6-(methylthio)pyrimidine (2g'): white solid (24.6 mg, 31 %). ¹H NMR (400 MHz, CDCl₃) δ 2.56 (s, 3H), 7.20 (d, *J* = 1.1 Hz, 1H), 8.71 (d, *J* = 1.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 12.9, 118.0, 158.1, 159.3, 172.9.

3-(methylthio)-6-phenylpyridazine (2h): white solid (86.6 mg, 86 %). ¹H NMR (400 MHz, CDCl₃) δ 2.73 (s, 3H), 8.04–7.97 (m, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.52–7.38 (m, 3H), 7.33 (d, *J* = 9.0 Hz, 1H), 2.73 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 13.3, 123.0, 126.1, 126.6, 129.0, 129.8, 136.0, 155.8, 161.2. HRMS calcd for C₁₁H₁₁N₂S, 203.0643; found, 203.0650.

5-bromo-3-(methylthio)pyrazin-2-amine (2i): yellow solid (87.8 mg, 80 %). ¹H NMR (400 MHz, CDCl₃) δ 2.61 (s, 3H), 4.61 (bs, 2H), 7.78 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 13.2, 126.6, 137.9, 142.6, 150.3. HRMS calcd for C₅H₇N₃SBr, 219.9544; found, 219.9550.

5-(methylthio)pyrazin-2-amine (2j): yellow solid (10.8 mg, 15 %). ¹H NMR (400 MHz, CDCl₃) δ 2.51 (s, 3H), 4.27 (bs, 3H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 14.8, 132.1, 140.7, 143.8, 151.8. HRMS calcd for C₅H₈N₃S, 142.0439; found, 142.0442.

6-(methylthio)-7H-purine (2k): white solid (77.6 mg, 93 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.66 (s, 3H), 8.43 (s, 1H), 8.70 (s, 1H), 13.50 (bs, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 11.2, 130.3, 143.0, 149.0, 151.5, 159.1.

2-(methylthio)-7H-purin-6-amine (2l): yellow solid (50.0 mg, 55 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.44 (s, 3H), 7.18 (s, NH₂), 7.98 (s, 1H), 12.73 (bs, NH). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 13.6, 116.0, 138.1, 151.2, 155.2, 163.7. HRMS calcd for C₆H₈N₅S, 182.0500; found, 182.0504.

2-(methylthio)benzo[d]thiazole (2m): white solid (79.6 mg, 88 %). ¹H NMR (400 MHz, CDCl₃) δ 2.78 (s, 3H), 7.27 (ddd, *J* = 8.0, 7.3, 1.2 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.74 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.88 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 16.0, 121.0, 121.4, 124.1, 126.1, 135.2, 153.4, 168.1.

6-chloropyridin-3-amine (6a): light brown solid (19 mg, 30 %). ¹H NMR (400 MHz, CDCl₃) δ 3.67 (bs, 2H), 6.95 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 3.0 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 124.3, 125.0, 136.4, 140.3, 141.8.

6-chloro-2-(methylthio)pyridin-3-amine (7a): light brown solid (30 mg, 35 %). ¹H NMR (400 MHz, CDCl₃) δ 2.61 (s, 3H), 3.63 (bs, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 13.5, 120.0, 122.9, 139.0, 139.8, 144.5. HRMS calcd for C₆H₈N₂SCl, 175.0097; found, 175.0104.

2-chloropyridin-3-amine (6b): tan solid (32.5 mg, 51 %). ¹H NMR (400 MHz, CDCl₃) δ 4.06 (bs, 2H), 7.06–7.01 (m, 2H), 7.82–7.75 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 122.6, 123.5, 137.0, 138.6, 139.8.

2-chloro-6-(methylthio)pyridin-3-amine (7b): light brown solid

(18.5 mg, 21 %). ¹H NMR (400 MHz, CDCl₃) δ 2.52 (s, 3H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 14.4, 121.8, 124.2, 136.3, 136.6, 147.4. HRMS Calcd for C₆H₈N₂SCl, 175.0097; found, 175.0099.

3-aminopyridine (6c): light brown solid (25.6 mg, 54 %). ¹H NMR (400 MHz, CDCl₃) δ 3.67 (bs, 2H), 6.95 (ddd, *J* = 8.2, 2.8, 1.4 Hz, 1H), 7.05 (ddd, *J* = 8.2, 4.7, 0.8 Hz, 1H), 7.99 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.08 (dd, *J* = 2.9, 0.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 121.6, 123.8, 137.5, 140.0, 142.7.

5-chloropyridin-2-amine (6d): white solid (46.2 mg, 72 %). ¹H NMR (400 MHz, CDCl₃) δ 4.50 (bs, 2H), 6.44 (d, *J* = 8.7, 0.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 109.6, 121.0, 137.7, 146.4, 156.9.

2-aminopyridine (6e): white solid (21.1 mg, 47 %). ¹H NMR (400 MHz, CDCl₃) δ 4.39 (bs, 2H), 6.50 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.63 (ddd, *J* = 7.2, 5.1, 1.0 Hz, 1H), 7.42 (ddd, *J* = 8.3, 7.2, 1.9 Hz, 1H), 8.05 (ddd, *J* = 5.1, 1.9, 0.9 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 108.9, 114.1, 138.0, 147.9, 158.4.

6-chloropyridin-2-ol (8a): white solid (52.5 mg, 79 %). ¹H NMR (400 MHz, CDCl₃) δ 6.68 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.73 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.54 (dd, *J* = 8.5, 7.5 Hz, 1H), 12.04 (bs, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 111.8, 113.5, 142.4, 144.2, 165.1. HRMS calcd for C₅H₅NOCl, 130.0060; found, 130.0059.

nicotinic acid (8b): white solid (41.5 mg, 67 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 8.25 (dd, *J* = 7.9, 2.0 Hz, 1H), 8.77 (dd, *J* = 4.9, 1.8 Hz, 1H), 9.07 (dd, *J* = 2.2, 0.9 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 123.8, 126.8, 137.0, 150.3, 153.3, 166.4.

3-(bis(methylthio)methyl)quinoline (8c): yellow oil (48 mg, 41 %). ¹H NMR (400 MHz, CDCl₃) δ 2.13 (s, 6H), 4.99 (s, 1H), 7.54 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.81 (ddd, *J* = 8.2, 1.7, 0.8 Hz, 1H), 8.09 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 8.96 (d, *J* = 2.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 14.9, 54.1, 127.1, 127.5, 127.9, 129.3, 129.7, 132.6, 133.9, 147.7, 150.8. HRMS calcd for C₁₂H₁₄NS₂, 236.0568; found, 236.0564.

Supporting Information

Additional experimental details and copies of ¹H and ¹³C NMR spectra for all products are provided in the supporting information.

Acknowledgments

The authors would like to thank Dr. Lisa Haigh (Imperial College London, U.K.) for assistance with accurate mass determination. The research was supported by Uppsala University and the Swedish Research Council (Vetenskapsrådet 2018-05133).

Keywords: heterocycles • thiomethylation • reduction • nucleophilic substitution •

(1) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem.*

- 2016**, 16, 1200–1216.
- (2) Montanari, S.; Paradisi, C.; Scorrano, G. *J. Org. Chem.* **1991**, 56, 4274–4279.
 - (3) Cherng, Y.-J. *Tetrahedron* **2002**, 58, 4931–4935.
 - (4) Huang, L.-K.; Cherng, Y.-C.; Cheng, Y.-R.; Jang, J.-P.; Chao, Y.-L.; Cherng, Y.-J. *Tetrahedron* **2007**, 63, 5323–5327.
 - (5) Sieb, D.; Schuhen, K.; Morgen, M.; Herrmann, H.; Wadepohl, H.; Lucas, N. T.; Baker, R. W.; Enders, M. *Organometallics* **2012**, 31, 356–364.
 - (6) Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *Bioorg. Med. Chem.* **2013**, 21, 1685–1695.
 - (7) Čapková, K.; Yoneda, Y.; Dickerson, T. J.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 6463–6466.
 - (8) Johnson, N. W.; Semones, M.; Adams, J. L.; Hansbury, M.; Winkler, J. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5514–5517.
 - (9) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, 41, 1373–1384.
 - (10) Jones-Mensah, E.; Magolan, J. *Tetrahedron Lett.* **2014**, 55, 5323–5326.
 - (11) Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. *Chem. Soc. Rev.* **2010**, 39, 1355–1387.
 - (12) Zhao, W.; Xie, P.; Bian, Z.; Zhou, A.; Ge, H.; Zhang, M.; Ding, Y.; Zheng, L. *J. Org. Chem.* **2015**, 80, 9167–9175.
 - (13) Qiao, Q.; Dominique, R.; Sidduri, A.; Lou, J.; Goodnow, R. A. *Synth. Commun.* **2010**, 40, 3691–3698.
 - (14) Heidebrecht, J.; Gendy, C.; Gelfand, B. S.; Roesler, R. *Polyhedron* **2018**, 143, 138–143.
 - (15) Serrano-Becerra, J. M.; Valdés, H.; Canseco-González, D.; Gómez-Benítez, V.; Hernández-Ortega, S.; Morales-Morales, D. *Tetrahedron Lett.* **2018**, 59, 3377–3380.
 - (16) Gómez-Benítez, V.; Valdés, H.; Hernández-Ortega, S.; Manuel German-Acacio, J.; Morales-Morales, D. *Polyhedron* **2018**, 143, 144–148.
 - (17) Gómez-Benítez, V.; Baldovino-Pantaleón, O.; Herrera-Álvarez, C.; Toscano, R. A.; Morales-Morales, D. *Tetrahedron Lett.* **2006**, 47, 5059–5062.
 - (18) Taniguchi, N. *J. Org. Chem.* **2004**, 69, 6904–6906.
 - (19) Baldovino-Pantaleón, O.; Hernández-Ortega, S.; Morales-Morales, D. *Adv. Synth. Catal.* **2006**, 348, 236–242.
 - (20) Majek, M.; von Wangelin, A. J. *Chem. Commun.* **2013**, 49, 5507–5509.
 - (21) Wu, X.; Lou, J.; Yan, G. *Synlett* **2016**, 27, 2269–2273.
 - (22) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, 12, 1644–1647.
 - (23) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y.-F. *J. Org. Chem.* **2012**, 77, 4414–4419.
 - (24) Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Sreedhar, B. *Tetrahedron* **2013**, 69, 8276–8283.
 - (25) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, 80, 4116–4122.
 - (26) Ghosh, K.; Ranjit, S.; Mal, D. *Tetrahedron Lett.* **2015**, 56, 5199–5202.
 - (27) Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, 47, 5304–5306.
 - (28) Hu, L.; Wang, D.; Chen, X.; Yu, L.; Yu, Y.; Tan, Z.; Zhu, G. *Org. Biomol. Chem.* **2017**, 15, 5674–5679.
 - (29) Zhang, C.; Zhou, Y.; Huang, J.; Tu, C.; Zhou, X.; Yin, G. *Org. Biomol. Chem.* **2018**, 16, 6316–6321.
 - (30) Kessar, S. V.; Singh, P.; Singh, K. N.; Dutt, M. *J. Chem. Soc., Chem. Commun.* **1991**, 0, 570–571.
 - (31) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, 130, 2448–2449.
 - (32) Abou-Shehadeh, S.; Teasdale, M. C.; Bull, S. D.; Wade, C. E.; Williams, J. M. J. *ChemSusChem* **2015**, 8, 1083–1087.
 - (33) Xiong, R.; Zhao, J.; Gutgesell, L. M.; Wang, Y.; Lee, S.; Karumudi, B.; Zhao, H.; Lu, Y.; Tonetti, D. A.; Thatcher, G. R. J. *J. Med. Chem.* **2017**, 60, 1325–1342.
 - (34) Yamaguchi, Y.; Okada, Y.; Chiba, K. *J. Org. Chem.* **2013**, 78, 2626–2638.
 - (35) Marchais-Oberwinkler, S.; Xu, K.; Wetzel, M.; Perspicace, E.; Negri, M.; Meyer, A.; Odermatt, A.; Möller, G.; Adamski, J.; Hartmann, R. *W. J. Med. Chem.* **2013**, 56, 167–181.
 - (36) Koufaki, M.; Tsatsaroni, A.; Alexi, X.; Guerrand, H.; Zerva, S.; Alexis, M. N. *Bioorg. Med. Chem.* **2011**, 19, 4841–4850.
 - (37) Konieczny, M. T.; Maciejewski, G.; Konieczny, W. *Synthesis* **2005**, 1575–1577.
 - (38) Kawabata, F. K.; Fujita, E. *Chem. Pharm. Bull.* **1980**, 28, 3662–3664.
 - (39) Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.*, **2005**, 70, 5014–5019.
 - (40) Hwu, J. R.; Wong, F. F.; Shiao, M. J. Reduction of Aromatic Nitro Compounds to Aromatic Amines by Sodium Trimethylsilanethiolate. *J. Org. Chem.* **1992**, 57, 5254–5255.
 - (41) Eberhardt, M. K.; Colina, R. *J. Org. Chem.* **1988**, 53, 1071–1074.
 - (42) Gassman, P. G.; Gruetzmacher, G.; Smith, R. H. *Tetrahedron Lett.* **1972**, 13, 497–500.
 - (43) Gassman, P. G.; Gruetzmacher, G. D. *J. Am. Chem. Soc.* **1974**, 96, 5487–5495.
 - (44) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc. Perkin Trans. 1* **1984**, 0, 625.
 - (45) Takeuchi, H.; Hirayama, S.; Mitani, M.; *J. Chem. Soc. Perkin Trans. 1* **1988**, 0, 521.
 - (46) Takeuchi, H.; Taniguchi, T.; Masuzawa, M.; Isoda, K. *J. Chem. Soc. Perkin Trans. 2* **1998**, 0, 1743–1746.
 - (47) Grosjean, S.; Triki, S.; Meslin, J.-C.; Julienne, K.; Deniaud, D. *Tetrahedron* **2010**, 66, 9912–9924.
 - (48) Rioz-Martínez, A.; de Gonzalo, G.; Pazmiño, D. E. T.; Fraaije, M. W.; Gotor, V. *Eur. J. Org. Chem.* **2010**, 6409–6416.
 - (49) Melzig, L.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2010**, 75, 2131–2133.
 - (50) Bauer, L.; Wright, G. E.; Mikrut, B. A.; Bell, C. L. *J. Heterocycl. Chem.* **1965**, 2, 447–452.
 - (51) Alexandre, F.-R.; Berecibar, A.; Wigglesworth, R.; Besson, T. *Tetrahedron* **2003**, 59, 1413–1419.
 - (52) Ma, H.-J.; Zhang, J.-H.; Xia, X.-D.; Kang, J.; Li, J.-H. Design, *Pest Manag. Sci.* **2015**, 71, 1189–1196.
 - (53) Pospíšil, J.; Sato, H. *J. Org. Chem.* **2011**, 76, 2269–2272.
 - (54) Lee, N. R.; Bikovtseva, A. A.; Cortes-Clerget, M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2017**, 19, 6518–6521.
 - (55) Zhou, Y.; Zhou, H.; Liu, S.; Pi, D.; Shen, G. *Tetrahedron* **2017**, 73, 3898–3904.
 - (56) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. *Org. Lett.* **2017**, 19, 2809–2812.
 - (57) Gan, Z.; Hu, B.; Song, Q.; Xu, Y. *Synthesis* **2012**, 44, 1074–1078.
 - (58) Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. *Org. Lett.* **2015**, 17, 3941–3943.
 - (59) Soni, S.; Koley, S.; Singh, M. S. *Tetrahedron Lett.* **2017**, 58, 2512–2516.

WILEY-VCH

Entry for the Table of Contents**FULL PAPER**

A practical method for the thiomethylation of halogenated heterocycles, as well as a novel reduction and reduction/SMe insertion cascade of nitropyridines using the $\text{BF}_3 \cdot \text{SMe}_2$ reagent are described. The methods are convenient and the reagent offers a non-odorous means of selectively introducing the thiomethyl moiety and reducing nitropyridines.

Thiomethylation, Reduction

Marcus Söderström, Edouard Zamratski, and Luke R. Odell*

Page No. – Page No.

Thiomethylation, Nitro Reduction and Tandem Reduction/SMe Insertion of Nitrogen Heterocycles Using $\text{BF}_3 \cdot \text{SMe}_2$