Selective reductive cleavage of 2-(phenylthio)pyrimidines for efficient synthesis of 2-(*H*)pyrimidines

Yujin Oh, Jihong Lee, Hyunik Shin, Jeong-Hun Sohn

PII: S0040-4039(19)30641-0
DOI: https://doi.org/10.1016/j.tetlet.2019.07.002
Reference: TETL 50911

To appear in: *Tetrahedron Letters*

Received Date: 25 April 2019
Revised Date: 30 June 2019
Accepted Date: 2 July 2019

Please cite this article as: Oh, Y., Lee, J., Shin, H., Sohn, J-H., Selective reductive cleavage of 2-(phenylthio)pyrimidines for efficient synthesis of 2-(*H*)pyrimidines, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.07.002

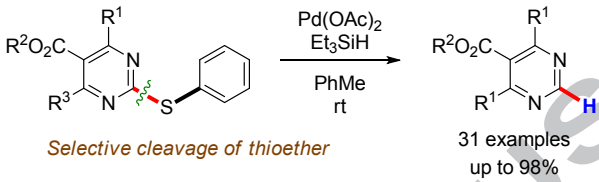
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Selective reductive cleavage of 2-(phenylthio)pyrimidines for efficient synthesis of 2-(*H*)pyrimidines

Leave this area blank for abstract info.

Yujin Oh[a], Jihong Lee[a], Hyunik Shin[b] and Jeong-Hun Sohn[a,*]



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Selective reductive cleavage of 2-(phenylthio)pyrimidines for efficient synthesis of 2-(*H*)pyrimidines

Yujin Oh[a], Jihong Lee[a], Hyunik Shin[b] and Jeong-Hun Sohn[a,*]

[a] *Department of Chemistry, College of Natural Sciences, Chungnam National University, Dajeon 305-706, Korea*
[b] *Yonsung Fine Chemicals R&D Center, 602 Innoplex 2, 306 Sinwon-ro, Yeongtong-gu, Suwon 443-380 Korea*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-(*H*)pyrimidine
reductive cleavage
2-(arylthio)pyrimidine
selective reduction
decarboxylative coupling

ABSTRACT

A reaction method is described for selective reductive cleavage of 2-(phenylthio)pyrimidines using $Pd(OAc)_2$ and Et_3SiH to produce 2-(*H*)pyrimidines. The reaction proceeds efficiently with a wide range of 2-(phenylthio)pyrimidines. Considering the ready availability of 2-(arylthio)pyrimidines derived from oxidative C–S cross coupling of 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs), this method unambiguously provides a shortcut to the preparation of 2-(*H*)pyrimidines with unprecedented diversity.

Compounds containing the pyrimidine structure have attracted much attention from organic and medicinal chemists due to their biological profile.[1] They exhibit antimicrobial, antiviral, anticancer, antimycobacterial, anti-inflammatory, antihypertensive, and antidiabetic activities, and inhibitory activity in the case of xanthin oxidase for treating gout.[2] Notably, the 2-(*H*)pyrimidine motif has been incorporated into several commercial tyrosine kinase inhibitor drugs, such as Ruxolitinib, Tofacitinib, and Baricitinib, and antifungal drugs such as Voriconazole (Figure 1)[3].

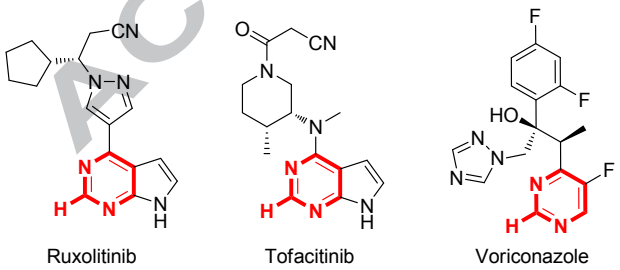
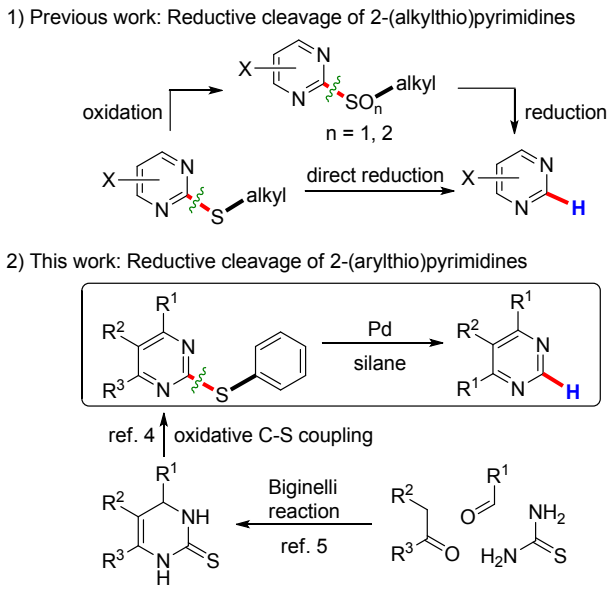


Figure 1. Examples of pharmacologically important 2-(*H*)pyrimidines

Notwithstanding their pharmacological importance, where they act as a binding fragments of biological targets, synthetic strategies toward 2-(*H*)pyrimidines bearing diverse substituents at the C4–C6 positions are limited in scope and generality. We report herein the synthesis of 2-(*H*)pyrimidines by selective reductive cleavage of 2-(arylthio)pyrimidines using a Pd catalyst and a silane. Previously, we reported one-step synthesis of 2-(arylthio)pyrimidines from 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) and aryl iodides, which likely proceeded via C–S cross-coupling with concomitant oxidation.[4] Since DHPM compounds can be easily prepared by the Biginelli three-component reaction with aldehyde, β-ketoester, and thiourea to provide various substituents at the C4–C6 positions,[5] we expected that selective reductive cleavage of a thioether could provide 2-(*H*)pyrimidines bearing various substituents at these positions (Scheme 1).

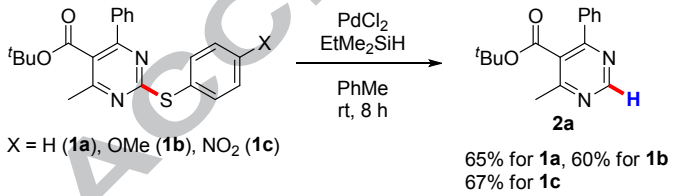


Scheme 1. Strategy for general synthesis of 2-(*H*)pyrimidines

There are several methods for reductive cleavage of (hetero)aryl sulfides, most of which follow two general routes. First, direct reduction of the C−S bond of a (hetero)aryl sulfide using Raney nickel as the most common reagent is well known.[6] This reaction also uses other reducing agents including Raney copper,[7] $NiCl_2$-$NaBH_4$,[8] NiCRA-NiCRAL,[9] Zn-HCl,[10] Zn-AcOH-Ac_2O,[11] Red-Al,[12] Al-$HgCl_2$,[13] and Pd/C-hydrazine.[14] However, many of these reductants suffer from low functional group tolerance and use stoichiometric quantities of metal reagents. A two-step sequence serves as a second approach: oxidation of the sulfide to the corresponding sulfoxide or sulfone, followed by reduction.[15] This route obviously cannot be used in the presence of oxidation-labile functional groups and needs an additional step.

For the single-step route, the catalytic hydrogenation using Pd/C or $Pd(OH)_2$/C with H_2 was utilized but is limited to the substrates free of functional groups that can be reduced under the conditions.[16] Recently, Graham et al. reported a catalytic reducing system using Pd/C-silane, which exhibited high substrate scope and functional group tolerance.[17] Martin et al.[18] and Nakada et al.[19] also reported the catalytic reductive cleavage of (hetero)aryl sulfides using $Ni(COD)_2$-silane and $PdCl_2$-silane, respectively. To our best knowledge, reductive cleavage of the thioether was only accomplished with alkylthiopyrimidines which requires two-step reaction sequence from DHPMs including alkylation of sulfur followed by oxidation.[20] Thus, we decided to investigate unreported reductive cleavage of 2-(arylthio)pyrimidines prepared in a single-step from DHPMs, which could afford a fast access to the 2-(*H*)pyrimidines with enhanced diversity at C4-C6 positions.[21]

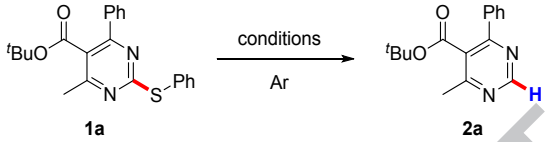
We initiated our study with the reaction of phenyl (**1a**), *p*-methoxyphenyl (**1b**) and *p*-nitrophenylthioethers (**1c**) to investigate the electronic effect of the leaving group on C−S bond cleavage. When the reactions of **1a**−**c** in the presence of $PdCl_2$ (10 mol%) and $EtMe_2SiH$ (3 equiv.) were carried out in toluene (0.15 M) at room temperature for 8 h under Ar, we obtained the desired product, **2a**, in 60−67% yields (Scheme 2). The similar yields led us to further optimization with **1a** because iodobenzene is less expensive than 1-iodo-4-methoxybenzene and 1-iodo-4-nitrobenzene, which are used in the synthesis of **1a**−**c** via oxidative C−S cross-coupling with the corresponding DHPM.



Scheme 2. Initial studies

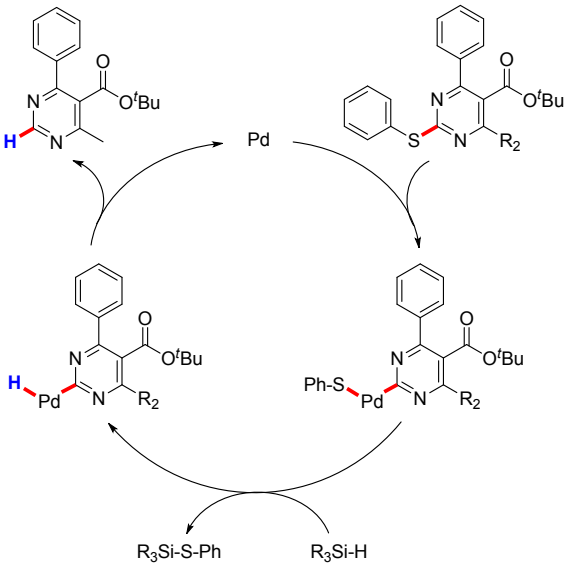
We investigated alternative Pd sources for further optimization studies: $Pd(OAc)_2$, which provided **2a** in 87% yield, was superior to $PdCl_2$ and other Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ (entries 1−3, Table 1). With respect to silanes, Et_3SiH gave the desired product in 96% yield and was better than other silanes, such as $EtMe_2SiH$, $MePh_2SiH$, and Ph_3SiH (entries 4−6). Among the solvents examined in our studies, the highest efficacy was found for toluene (entries 4 and 7−10). Higher temperature, i.e., 40, 70, 100, and 140 °C, did not significantly improve the reaction yield (entries 11−18). Thus, we decided to examine the scope of the substrate at room temperature. A tentative mechanism for the selectivity of the reaction is likely oxidative addition of Pd into the pyrimidine C−S bond (Scheme 3).[22]

Table 1. Optimization of the reductive cleavage[a,b]



Entry	[Pd]	Silane	Solvent	T (°C)	Yield(%)
1	$Pd(OAc)_2$	$EtMe_2SiH$	PhMe	rt	87
2	$Pd(PPh_3)_4$	$EtMe_2SiH$	PhMe	rt	11
3	$Pd_2(dba)_3$	$EtMe_2SiH$	PhMe	rt	36
4	$Pd(OAc)_2$	Et_3SiH	PhMe	rt	96
5	$Pd(OAc)_2$	$MePh_2SiH$	PhMe	rt	90
6	$Pd(OAc)_2$	Ph_3SiH	PhMe	rt	89
7	$Pd(OAc)_2$	Et_3SiH	DMF	rt	92
8	$Pd(OAc)_2$	Et_3SiH	THF	rt	82
9	$Pd(OAc)_2$	Et_3SiH	CH_3CN	rt	88
10	$Pd(OAc)_2$	Et_3SiH	xylene	rt	93
11	$Pd(OAc)_2$	Et_3SiH	PhMe	40	96
12	$Pd(OAc)_2$	Et_3SiH	DMF	40	95
13	$Pd(OAc)_2$	Et_3SiH	xylene	40	92
14	$Pd(OAc)_2$	Et_3SiH	PhMe	70	97
15	$Pd(OAc)_2$	Et_3SiH	DMF	70	95
16	$Pd(OAc)_2$	Et_3SiH	xylene	70	88
17	$Pd(OAc)_2$	Et_3SiH	PhMe	100	96
18	$Pd(OAc)_2$	Et_3SiH	PhMe	140	97

[a]Reaction conditions: substrate **1** (0.15 mmol), silane (0.45 mmol), Pd catalyst (10 mol%), and solvent (1 mL) for 8 h under Ar. [b]Isolated yields.

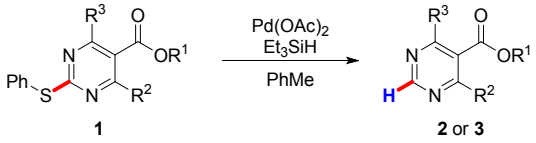


Scheme 3. Plausible reaction mechanism

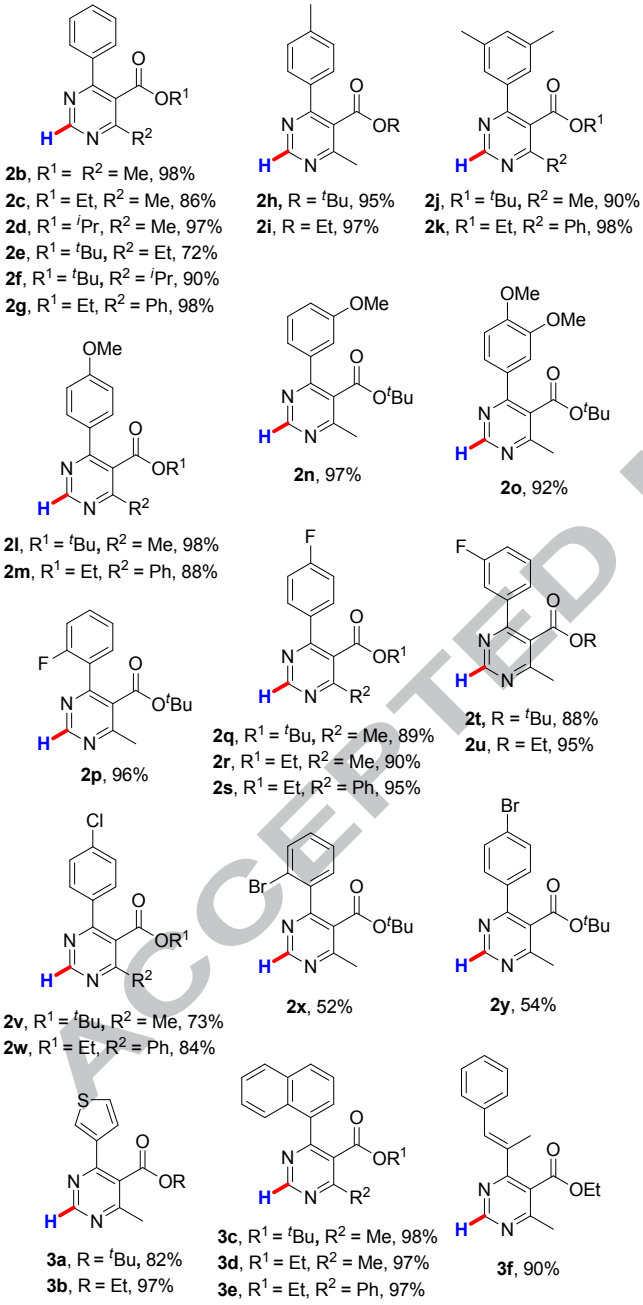
Optimal reaction conditions were used with diverse 2-(phenylthio)pyrimidines **1** to explore the substrate scope. First, we tested the reaction with substrates by varying the R^1 group of the alkoxycarbonyl to give the desired products **2b**−**d** in good yields (86−98%) for methyl-, ethyl-, and *i*-propyl esters. With

respect to R^2 at the C6 position, ethyl, isopropyl, and phenyl groups were examined instead of the methyl group and provided the corresponding products **2e–g** in 82–98% yields, showing no significant steric effect of R^2 in the formation of the products.

Table 2. Reaction scope[a,b]



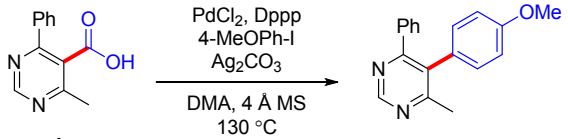
1 **2** or **3**



[a]Reaction conditions: substrate **1** (0.15 mmol), Et_3SiH (0.45 mmol), $Pd(OAc)_2$ (10 mol%), and PhMe (1 mL) at room temperature for 8 h under Ar. [b]Isolated yields.

To investigate the substituent effect of the C4 position, the reactions of thioether substrates possessing aryl groups with electron-donating and -withdrawing substituents, heteroaryl, bicyclic and alkenyl groups at the C4 position were investigated. The substrates containing 4-methyl and 3,5-dimethyl groups on C4 aryl provided corresponding products **2h–k** in high yields. No significant dependence of the yield of the corresponding products (**2l–o**, 88–98%) on the position or number of methoxy groups was observed. In the case of halides, fluoride on C4 aryl exhibited good results, as did its regioisomers (**2p–u**, 88–96%). However, other halides, i.e., Cl and Br, gave lower yields (**2v** and **2w**, 73–84% for Cl; and **2x** and **2y**, 52–54% for Br), which might be due to competitive oxidative addition of palladium species to the carbon–halide bond. The reaction of substrates possessing heteroarene and bicyclic groups at the C4 position, such as thiophenyl and naphthyl, produced **3a** and **3b** (92–97%) and **3c–e** (97–98%), respectively, in good yields. Furthermore, the reaction method was compatible with a substrate containing an alkenyl group at C4, providing **3f** in 90% yield. This substrate was not suitable for the previous methods using single-step reductive cleavage of thioethers.[17] Overall, considering the ready availability of 2-(arylthio)pyrimidines derived from oxidative C–S cross coupling of DHMPs, this method readily and unambiguously provides access to 2-(*H*)pyrimidines substituted diversely at the C4–C6 positions.[23]

For greater diversification of the substituent at the C5 position, we attempted the decarboxylative C–C cross-coupling reaction. After hydrolysis of ester **2a**, the corresponding acid **4** was reacted with 1-iodo-4-methoxybenzene in the presence of $PdCl_2$, Dppp, Ag_2CO_3 and 4 Å molecular sieves in DMA under Ar at 130 °C; the desired product, **5**, was obtained in 52% yield (Scheme 4). The reaction sequence of selective reductive cleavage of 2-(phenylthio)pyrimidine after the Biginelli reaction and oxidative C–S cross-coupling, followed by decarboxylative C–C cross-coupling could be used for highly efficient synthesis of diversely substituted 2-(*H*)pyrimidines.



4 **5**, 52%

Scheme 3. Decarboxylative arylation at C5 of **2a**

In summary, we developed selective reductive cleavage of 2-(phenylthio)pyrimidines using $Pd(OAc)_2$ and Et_3SiH to produce 2-(*H*)pyrimidines, a privileged scaffold. The reaction proceeded well with a wide range of 2-(phenylthio)pyrimidines bearing diverse substituents at the C4–C6 positions. Due to our previous one-step synthesis of 2-(phenylthio)pyrimidines from DHPMs prepared by the Biginelli three-component reaction,[4] the present reaction method secures a shortcut to diverse 2-(*H*)pyrimidines. Additionally, decarboxylative C–C cross-coupling of the acid generated by hydrolysis could provide further functionalization at the C5 position.Acknowledgments

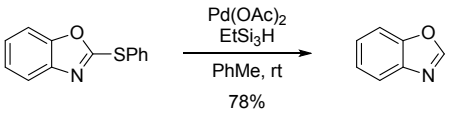
Acknowledgments

This work was supported by the NRF grant (NRF-2017R1A2B2003614) and the research fund of Chungnam National University.

References and notes

1. (a) Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289-318; (b) Lagoja, M.; *Chem. Biodivers.* **2005**, *2*, 1-50.

2. (a) Abdellatif, K. R. A.; Bakr, R. B.; *Bioorg. Chem.* **2018**, *78*, 341-357; (b) Kleemann, A.; Engel, J.; eds. *Pharmaceutical Substances: Synthesis, Patents, Applications,* Thieme: Stuttgart, Germany 2001.
3. (a) Singh, P. K.; Singh, H.; Silakari, O. *Biochim. Biophys. Acta, Rev. Cancer* **2016**, *1866*, 128-140; (b) Burmester, G. R.; Bijlsma, J. W.; Cutolo, M.; McInnes, I. B. *Nat. Rev. Rheumatol.* **2017**, *13*, 443-448; (c) Scott, L. J.; Simpson, D. *Drugs* **2007**, *67*, 269-298.
4. (a) Lee, O. S.; Lee, H.; Kim, H.; Shin, H.; Sohn, J. –H. *Tetrahedron* **2015**, *71*, 2936-2944; (b) Lee, O. K.; Kim, H.; Lee H.-S.; Shin, H.; Sohn, J.-H.; *B. Kor. Chem. Soc.* **2016**, *37*, 242-245.
5. (a) Singh, K.; Singh, K. *Adv. Heterocycl. Chem.* **2012**, *105*, 223-308; (b) Suresh, H. P.; Sandhu, J. S. *ARKIVOC* **2012**, 66-133; (c) Wan, J. -P.; Liu, Y. *Synthesis* **2010**, *40*, 3943-3953; (d) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879-888.
6. For selected recent references, see: (a) Gandin, V.; Ferrarese, A.; Dalla Via, M.; Marzano, C.; Chilin, A.; Marzaro, G. *Sci. Rep.* **2015**, *5*, 16750; (b) Park, E. J.; Ahn, Y. G.; Jung, S. H.; Bang, H. J.; Kim, M.; Hong, D. J.; Kim, J.; Suh, K. H.; Kim, Y. J.; Kim, D.; Kim, E. Y.; Lee, K.; Min, K. H. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 4271-4275; (c) Wixe, T.; Wallentin, C. -J.; Johnson, M. T.; Fristrup, P.; Lidin, S.; Waernmark, K. *Chem. Eur. J.* **2013**, *19*, 14963-14969; (d) Mattson, M. N.; Neitzel, M. L.; Quincy, D. A.; Semko, C. M.; Garofalo, A. W.; Keim, P. S.; Konradi, A. W.; Pleiss, M. A.; Sham, H. L.; Brigham, E. F. B.; Goldbach, E. G.; Zhang, H. B.; Sauer, J.-M.; Basi, G. S. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 2148-2150; (e) Scribner, A.; Moore, J. A.; Ouvry, G.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T.; *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1517-1521; (f) Guery, S.; Floersheim, P.; Kaupmann, K.; Froestl, W.; *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6206-6211; (g) Liverton, N. J.; Bednar, R. A.; Bednar, B.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Cunningham, M.; DiLella, A. G.; Gaul, S. L.; Libby, B. E.; Lyle, E. A.; Lynch, J. J.; McCauley, J. A.; Mosser, S. D.; Nguyen, K. T.; Stump, G. L.; Sun, H.; Wang, H.; Yergey, J.; Koblan, K. S. *J. Med. Chem.* **2007**, *50*, 807-819; (h) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 347-350; i) Laxer, A.; Major, D. T.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem*. **2001**, *66*, 5463-5481.
7. Pfleiderer, W.; *Tetrahedron* **1988**, *44*, 3373-3378.
8. (a) Zumbrunn, A.; *Synthesis* **1998**, 1357-1361; (b) Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron* **2006**, *62*, 10182-10192.
9. Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem*. **1989**, *54*, 4848-4853.
10. Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Ponticello, G. S.; Atkinson, J. G.; Wasson, B. K.; Sweet, C. S.; Scriabine, A. *J. Med. Chem*. **1980**, *23*, 65-70.
11. Yamazaki, C.; Arima, H.; Udagawa, S.; *J. Heterocycl. Chem*. **1996**, *33*, 41-44.
12. (a) Choshi, T.; Tonari, A.; Yoshioka, H.; Harada, K.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1993**, *58*, 7952-7954; (b) Yoshioka, H.; Matsuya, Y.; Choshi, T.; Sugino, E.; Hibino, S.; *Chem. Pharm. Bull.* **1996**, *44*, 709-714.
13. Sugimoto, T.; Nishioka, N.; Murata, S.; Matsuura, S. *Heterocycles* **1987**, *26*, 2091-2092.
14. Niwas, S.; Chand, P.; Pathak, V. P.; Montgomery, J. A. *J. Med. Chem.* **1994**, *37*, 2477-2480.
15. (a) Yamaguchi, H.; Ishikawa, F. *Chem. Pharm. Bull.* **1982**, *30*, 326-332; (b) Ueno, Y.; Kojima, A.; Okawara, M. *Chem. Lett.* **1984**, 2125-2128; (c) Kawasaki, A. M.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem*. **1990**, *33*, 3170-3176; (d) Liu, C.; Wrobleski, S. T.; Lin, J.; Ahmed, G.; Metzger, A.; Wityak, J.; Gillooly, K. M.; Shuster, D. J.; McIntyre, K. W.; Pitt, S.; Shen, D. R.; Zhang, R. F.; Zhang, H.; Doweyko, A. M.; Diller, D.; Henderson, I.; Barrish, J. C.; Dodd, J. H.; Schieven, G. L.; Leftheris, K. *J. Med. Chem*. **2005**, *48*, 6261-6270; (e) Seto, S.; Asano, J. *Bioorg. Med. Chem*. **2007**, *15*, 5083-5089; (f) Kikelj, V.; Grosjean, S.; Meslin, J. -C.; Julienne, K.; Deniaud, D. *Synthesis* **2010**, 2811-2813; (g) Williams, D. R.; Fu, L. *Synlett* **2010**, 1641-1646; (h) Calter, M. A.; Li, N. *Org. Lett.* **2011**, *13*, 3686-3689.
16. Vignaroli, G.; Mencarelli, M.; Sementa, D.; Crespan, E.; Kissova, M.; Maga, G.; Schenone, S.; Radi, M.; Botta, M. *ACS Comb. Sci*. **2014**, *16*, 168-175.
17. Graham, T. H.; Liu, W.; Shen, D. -M. *Org. Lett.* **2011**, *13*, 6232-6235.
18. Barbero, N.; Martin, R. *Org. Lett.* **2012**, *14*, 796-799.
19. Matsumura, T.; Niwa, T.; Nakada, M. *Tetrahedron Lett.* **2012**, *53*, 4313-4316.
20. Phan, N. H. T.; Sohn, J. -H.; *Tetrahedron* **2014**, *70*, 7929-7935**.**
21. Other routes to 2-(*H*)pyrimidines from DHPMs were reported by Shin et al.[a] and Wang and Quan et al.[b] (a) Kim, S. S.; Choi, B. S.; Lee, J. H.; Lee, K. K.; Lee, T. H.; Kim, Y. H. Shin, H. *Synlett* **2009**, 599-602; (b) Yang, T. –Y.; Wang, X. –C.; Quan, Z. –J. *Synlett* **2017**, *28*, 847-850.
22. When the reactions using less than three equivalents of Et_3SiH were performed, yields of the desired product was reduced. Under the optimal reaction conditions, by-product Et_3SiSPh was obtained in 60% yield.
23. Our reaction method was also compatible with 2-(Phenylthio)benzoxazole, providing benzoxazole in 78% yield.



Supplementary Material

Detailed experimental procedures, and ^{1}H and ^{13}C NMR spectra of all new compounds.

Highlights

- Synthesis of 2-(H)pyrimidines
- Novel selective reduction of 2-(phenylthio)pyrimidines
- High functionalization
- Wide substrate scope