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A facile reduction of 2-aminopyrimidines with triethylsilane and trifluoroacetic acid

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Abstract—2-Aminopyrimidines were facilely reduced to 2-amino-dihydro- or 2-amino-tetrahydropyrimidines with triethylsilane and trifluroacetic acid in high yields. By controlling the equivalents of reducing reagents and temperature, selective reduction could also be achieved for some substrates.
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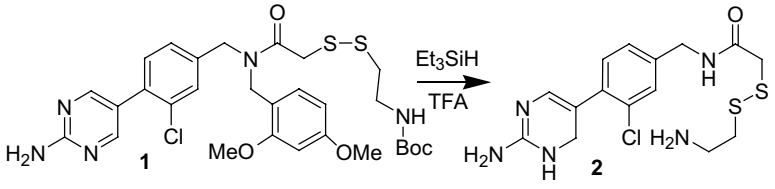
2-Amino-3,4,5,6-tetrahydro- and 2-amino-3,4-dihydropyrimidines have been used extensively in biologically important molecules against a variety of targets.[1,2] 2-Aminotetrahydropyrimidines are usually synthesized by displacing the methylmercapto- group from tetrahydro-2-methylmercaptopyrimidines[1] or hydrogenation of 2-aminopyrimidines.[3] While these methods provide an efficient synthesis of the target molecules, they suffer from multi-step preparation of the reagents or potential chemical selectivity problems. Only one method has been reported for the preparation of 2-aminodihydropyrimidines.[4] During the development of Tethering[SM,5] we needed to generate disulfide (S–S) linked 2-aminopyrimidines, as well as 2-amino-dihydro- and tetrahydropyrimidines. We encountered difficulties in the syntheses of these classes of compounds, due primarily to the presence of the disulfide bond. To our surprise, during the concurrent removal of protecting groups 2,4-dimethoxybenzyl and *tert*-butylcarboxylate (Boc) of compound **1**[6] with trifluoroacetic acid (TFA) in the presence of triethylsilane, 2-aminodihydropyrimidine **2** was obtained exclusively in quantitative yield (Eq. 1).[7] Although triethylsilane in TFA has been used extensively as a reducing reagent,[8] to our knowledge this is the first application of reagents to the pyrimidine ring reduction.



(1)

With the serendipitous discovery, the reaction conditions were examined as shown in Table 1. It was found that the reduction of **3** to corresponding 2-aminodihydropyrimidine **4** could be carried out at lower temperature with equal efficiency (entry 1). Further reduction of **4** to 2-aminotetrahydropyrimidine **5** was not observed after 10 h (entry 2). However, when the reaction was run in refluxing TFA, **4** was slowly converted to **5**. Heating the reaction in a pressure vessel at 90 °C for 24 h gave **5** as the major product (entries 3 and 4). It was discovered that the reduction of **3** to **4** could be carried out in dichloromethane with as few as 2.5 equiv of triethylsilane and 5 equiv of TFA at room temperature (entry 5). However, the amounts of triethylsilane and TFA

Keywords: Reduction; Pyrimidine; Triethylsilane; Guanidine.
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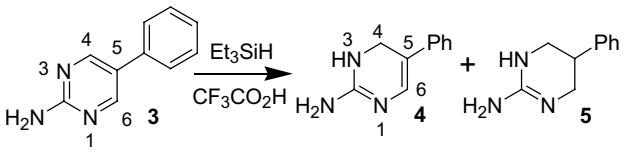
Table 1. Survey of reaction conditions[a]



Entry	Et_3SiH (eq)	Solvent	T (°C)	Time	Result[b]
1	10	TFA	−20	10 min	**4** (100%)
2	10	TFA	25	10 h	**4** (100%)
3	10	TFA	75	48 h	**4**:**5** (1:1)[c]
4	10 × 2[d]	TFA	90	24 h	**4**:**5** (15:85, 91%)[c]
5	2.5[e]	DCM	25	2 h	**5** (100%)

[a] The reactions were run with 86 mg (0.50 mmol) **3** in the given solvent (2 mL).
[b] Isolated yield given in parentheses.
[c] The products **4** and **5** are not separable, ratios are based on NMR and LC-MS.
[d] Et_3SiH (10 equiv) was added at the beginning and after 12 h.
[e] TFA (5 equiv) was used.

could not be further reduced even though the reaction theoretically requires only 1 equiv of triethylsilane.

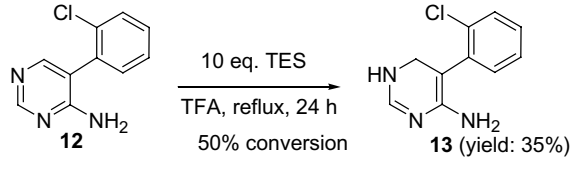
This facile reduction is widely applicable, as shown in Table 2. Substitutions on the amino nitrogen do not impact the reduction (entries 1–6), which proceeds rapidly even when the amine is substituted by an aryl or sulphonyl group. However, reduction of unsubstituted 2-aminopyrimidines yields 2-aminotetrahydropyrimidines (entries 3–5). In these cases, attempts to stop the reduction at the dihydropyrimidine stage failed,[9] possibly due to the lack of conjugative stabilization of the corresponding 2-aminodihydropyrimidine as seen in **2** and **4**. Interestingly, 2-amino-5-bromopyrimidine is reduced cleanly to the corresponding dihydropyrimidine (entry 6).

When 4-arylvinyl-2-aminopyrimidine is reduced by triethylsilane in TFA (entry 7A), 4-arylethyl-2-aminotetrahydropyrimidine is obtained. However, when the reaction is subjected to milder conditions (entry 7B), the product from an apparent reduction of the olefin moiety was obtained cleanly. The structure of this product was unequivocally established by proton NMR and mass spectra. Reduction of 4-aryl-2-aminopyrimidine to 4-aryl-2-aminotetrahydropyrimidine occurred readily (entry 8). However, attempts to obtain corresponding 2-aminodihydropyrimidines from C4-substituted 2-aminopyrimidines were not successful.

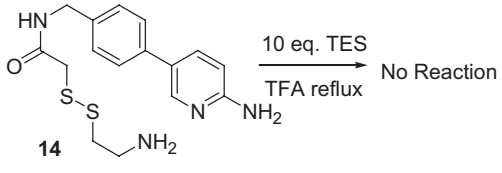
Reduction of the pyrimidine ring can be more facile than reduction of the ketone functionality, as evidenced by the formation of 2-amino-dihydropyrimidine **7** from 5-acetyl-4-methyl-2-aminopyrimidine **6** (Table 2, entry 9B; also see Scheme 1). The fully reduced product **11** is obtained after **6** is subjected to the reduction conditions for 24 h. LC-MS monitoring of the reaction did not reveal the presence of potential intermediates **8**, **9** and/or **10** over the course of the reaction. The mechanism of this particular reduction is proposed in Scheme 1, and the observed results could be explained by different reaction rates for each step.

Reduction of 4,6-disubstituted-2-aminopyrimidine (entries 10 and 11) is much slower, and only about 50% conversions to the corresponding tetrahydropyrimidines are achieved after the reactions were refluxed for 24 h in TFA. The intermediate dihydropyrimidines were not obtained in these cases. The sluggish reduction could be rationalized by the increased difficulty in hydride delivery from triethylsilane because of the steric hindrance (see first step in Scheme 1). It was also found that the reduction failed when 2-aminopyrimidine rings were further substituted with amine, hydroxy, or alkoxy functionality at the C4 position (entries 12–14).

Conversion of 4-aminopyrimidine **12** to product **13** was observed when it was subjected to similar reduction conditions, but the reaction is much slower than the reduction of 2-aminopyrimidines (Eq. 2). 2-Aminopyridine **14** remained unchanged even after refluxing in TFA for 3 days (Eq. 3). Interestingly, the reduction of pyrimidine **15** to dihydropyrimidine **16** is facile (Eq. 4), and the scope and limitation of this and other related reactions are under investigation and will be reported in the future.

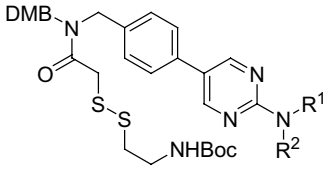
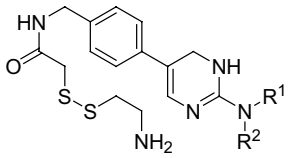
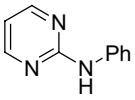
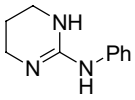
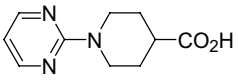
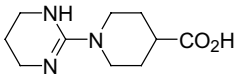
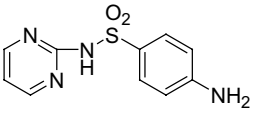
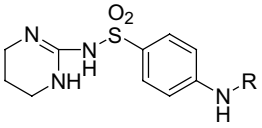
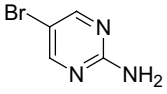
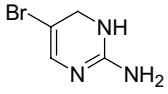
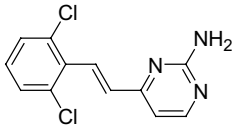
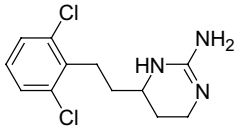
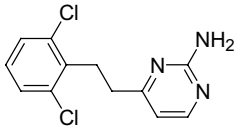
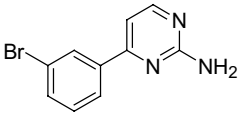
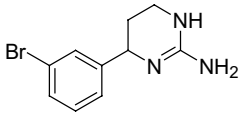
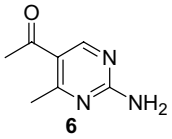
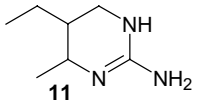
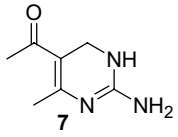
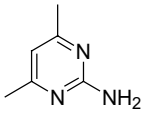
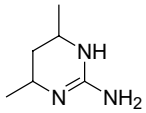


(2)



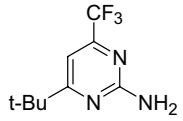
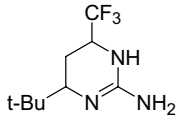
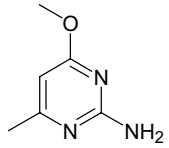
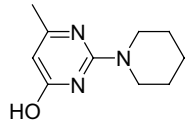
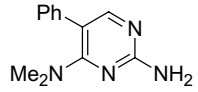
(3)

Table 2. Reduction of 2-aminopyrimidines

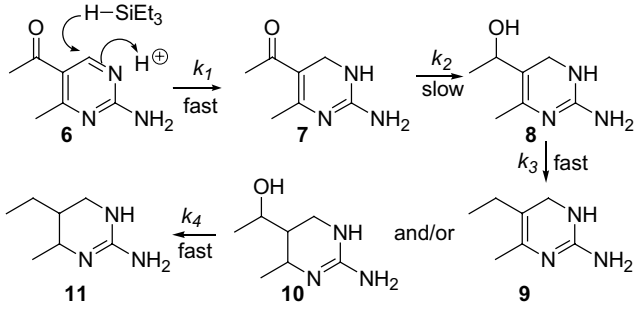
Entry	SM (structure)	Conditions[a]	Product	Yield[b]
1[c]		A, 25 °C, 4 h		61% ($R^1 = H$, $R^2 = Me$)
2[c]		A, 25 °C, 4 h		68% ($R^1 = R^2 = Me$)
3		A, 25 °C, 5 h		58%
4		A, 25 °C, 5 h		78%
5		A, 25 °C, 0.5 h		25% (R = H) 50% (R = $COCF_3$)
6		A, 25 °C, 10 min		90%
7A		A, 25 °C, 0.5 h		81%
7B		B, 25 °C, 2 h		67%
8		A, 25 °C, 2 h		73%
9A	 **6**	A, 25 °C, 24 h	 **11**	65%
9B		A, 0 °C, 30 min	 **7**	81%[d]
10		A, 75 °C, 24 h		50%[e]

(*continued on next page*)

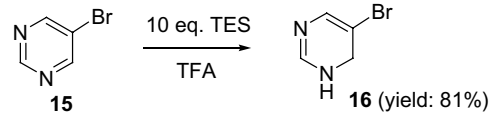
Table 2 (*continued*)

Entry	SM (structure)	Conditions[a]	Product	Yield[b]
11		A, 75 °C, 24 h		30%[f]
12		A, 75 °C, 24 h	NR	
13		A, 75 °C, 24 h	NR	
14		A, 75 °C, 24 h	NR	

[a] Conditions **A**: 2-Aminopyrimidine (0.5 mmol), Et_3SiH (5 mmol) in TFA (2 mL); **B**: 2-aminopyrimidine (0.5 mmol), Et_3SiH (1.5 mmol) and TFA (2.5 mmol) in DCM.
[b] Isolated yield (as a TFA salt).
[c] DMB is 2,6-dimethoxybenzyl.
[d] Inseparable mixture with compound **11** (ratio of **7**:**11**, 15:1).
[e] Recovered starting material 30%.
[f] Recovered starting material 50%.



Scheme 1.



(4)

In conclusion, we have demonstrated the facile reduction of 2-aminopyrimidines to yield partially or fully reduced cyclic guanidines. With the easy access of 2-aminopyrimidines via commercial sources or synthesis, this methodology provides an efficient entry to 2-amino-3,4-dihydro- or 2-amino-3,4,5,6-tetrahydropyrimidines. This reaction could find many useful applications considering the importance of guanidine derivatives in modern medicinal chemistry.

1. General procedures

(1) To a solution of a 2-aminopyrimidine (1 mmol) in TFA (3 mL) was added Et_3SiH (10 mmol). Upon completion, the reaction was concentrated in vacuum and the residue was rinsed with ether and dried to give the desired product in quantitative yield as a TFA salt. Alternatively, the residue after ether rinse was loaded on a reversed phase (C18) silica gel column, and eluted with 0–50% acetonitrile in water to give the desired product as a TFA salt. (2) Mild reduction condition: same as (1) except the reaction is run with Et_3SiH (2.5–3 mmol) and TFA (5 mmol) in dichloromethane (3 mL).

Acknowledgements

The authors thank Mr. Stuart Lam, Thomas Webb and Alex Shi for their expertise in the analysis and purification of complex reaction mixtures. The authors also thank Dr. Matthew Williams for helpful discussions.

References and notes

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Siev, D. V.; Araldi, G.-L.; Cui, J. J.; Ho, J.; Reddy, K. M.; Mamedova, L.; Vu, P. H.; Lee, K.-S. S.; Minami, N. K.; Gibson, T. S.; Anderson, S. M.; Bradbury, A. E.; Nolan, T. G.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1203; (c) Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Forsynthe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41.

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3. Duggan, M. E.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Perkins, J. T.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. A.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736.
4. 2-Amino-3,4-dihydropyrimidines are prepared by Michael addition of guanidine and subsequent condensation, see Reference 2 and (a) Kahsima, C.; Shimizu, M.; Omote, Y. *J. Heterocycl. Chem.* **1989**, *26*, 251; (b) Vargo, L.; Nagy, T.; Kovesdi, I.; Benet-Buchholz, J.; Dorman, G.; Uerge, L.; Darvas, F. *Tetrahedron* **2003**, *59*, 655.
5. Tethering^{SM} is a service mark of Sunesis Pharmaceuticals Inc. for its fragment-based drug discovery.
6. Pyrimidines **1**, **3** starting pyrimidines in Table 2 (entries 1 and 2) are synthesized by Suzuki coupling from the corresponding 2-amino-5-bromo(or chloro)pyrimidines. Pyridine **14** was synthesized in a similar manner.
7. The intended 2-amino-pyrimidine derivative was obtained at 40–60% yield if anisole is used instead of triethylsilane in TFA, or by using 4.0 M HCl in dioxane.
8. Triethylsilane as reducing reagent, (a) a review: Fry, J. L. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; Wiley-VCH: Chichester, 1999; p 479; (b) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652; (c) Olivo, H. F.; Colby, D. A.; Hemenway, M. S. *J. Org. Chem.* **1999**, *64*, 4966.
9. Monitoring the reactions with LC-MS revealed that 2-aminodihydropyrimidines always appeared concurrently with significant amounts of starting material and further reduced 2-aminotetrahydropyrimidines.