ORGANIC LETTERS

2011
Vol. 13, No. 23
6232–6235

A Method for the Reductive Scission of Heterocyclic Thioethers

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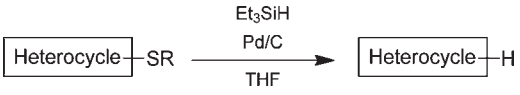
Received October 5, 2011

ABSTRACT



A mild, chemoselective, and generally high-yielding method for the reductive scission of heterocyclic thioethers is described. Suitable heterocycles have a thioether substituent at the 2-position relative to a ring heteroatom. The convenient and straightforward method is demonstrated with reactants which are not compatible with the standard Raney nickel conditions such as sulfides, sulfones, and thiophenes. In addition, benzyl esters, benzyl amides, and benzyl carbamates are tolerated by the reductive reaction conditions.

Heterocyclic thioethers are a common structural motif found in pharmaceuticals and other biologically active molecules.[1] Heterocycles with the thioether substituent at the 2-position relative to a ring heteroatom are also important intermediates in organic synthesis. Many transformations are based on the displacement of the sulfur atom through nucleophilic *ipso*-substitution[2] and cross-coupling reactions.[3,4] The unique reactivity often allows heterocyclic thioethers to be carried through a synthetic sequence and then activated under specific conditions.

The reductive scission of heterocyclic thioethers to directly afford the parent heterocycles under mild and chemoselective conditions can be a challenging transformation. A recent medicinal chemistry campaign required the late-stage reduction of a penultimate 2-(methylthio)pyrimidine intermediate to access the 2-(*H*)pyrimidine. The presence of cross-reactive functional groups in the advanced intermediate inspired a re-evaluation of heterocyclic thioether reductions. The analogy with thioester reductions in the context of the pioneering studies of Fukuyama and co-workers[5] provided the fundamental rationale for the development of a mild and chemoselective method to remove thioether substituents from a variety of heterocycles.

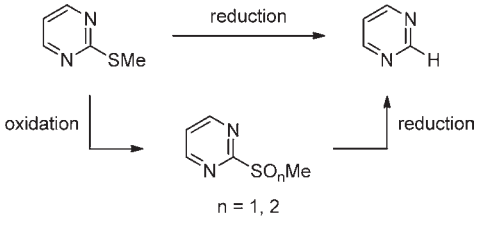


Figure 1. Common routes for the reductive scission of heterocyclic thioethers.

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10.1021/ol2026813
Published on Web 11/08/2011

Several methods are known for the reductive scission of heterocyclic thioethers and follow two general routes (Figure 1). One route involves the single-step reductive scission to directly afford the parent heterocycle. Raney nickel has become the most common reagent for the single-step reduction.[6] Less common reagents include 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 hydrazine-Pd/C.[14] These methods can suffer from low yields and poor chemoselectivity. In addition, the use of stoichiometric quantities of metal can complicate purification and presents waste disposal and safety issues. A second common route involves a two-step process: oxidation to the sulfoxide or sulfone followed by reduction.[15] Chemoselectivity can be a major issue in the presence of functional groups which are readily oxidized, and the oxidation−reduction route also suffers from inferior redox[16] and step economy.[17]

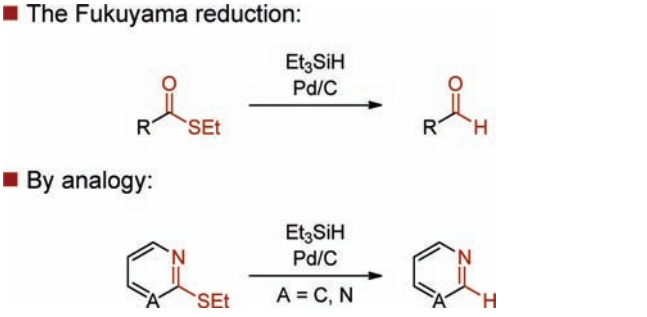

Figure 2. Analogy between thioesters and heterocyclic thioethers.

While designing an efficient method for the reductive scission of heterocyclic thioethers, the analogy with acyclic systems was considered (Figure 2). The reduction of thioesters using triethylsilane and palladium on carbon was first introduced by Fukuyama and later modified by others.[5,18] The mild reaction conditions and chemoselectivity of the Fukuyama reduction have been demonstrated on complex and chemically sensitive systems.[19] For the present study, the principal insight was the recognition that heterocyclic compounds often retain the reactivity of the carbonyl compounds from which they are often derived.[20] An additional precedent was the work of Castle and co-workers which demonstrated the use of triethylsilane and Lindlar catalyst to reductively cleave 4-(methylthio)pyridones.[21] A tangential precedent was the reductive scission of a thiomethylborondipyrromethene with triethylsilane, $Pd_2(dba)_3$, tri(furan-2-yl)phosphine, and copper 2-thienylcarboxylate (CuTC) in THF at 55 °C; however, an alternative mechanism was suggested because the standard Fukuyama conditions were not effective and CuTC was required.[22] Based on these prior works, a general method was developed for the mild and selective removal of thioether substituents from heterocycles.

Initial studies focused on 2-(alkylthio)pyrimidines because of the frequent occurrence of this motif and because of the requirements of the current medicinal chemistry campaign. The scope of the method was evaluated with a variety of 2-(alkylthio)pyrimidines (Table 1). Methyl (**1a**), ethyl (**1b**), and benzyl (**1c**) thioethers were removed in 89−93% yields. Similarly substituted aminopyrimidine **1d** and hydroxypyrimidine **1e** afforded the corresponding products in 86% and 73% yields, respectively. A variety of phenyl substitutions (**1f**−**i**) as well as trifluoromethyl substitution (**1j**) also afforded products. *N*-Benzyl-substituted pyrimidines (**1i**−**m**) were tolerated by the reductive reaction conditions and provided the corresponding products in 67−96% yields. Substrates **1a**−**d** and **1i**−**l**, with exchangeable protons, were readily *N*-silylated under the reaction conditions and thus required a mild acid or fluoride-mediated workup. For substrates **1a**−**c**, the stability of the *N*-triethylsilyl adduct (R^2 = $NHSiEt_3$) allowed for purification by chromatography on silica gel. The *N*-methyl-*N*-benzylaminopyrimidine **1m** afforded a lower yield compared to **1l**; however, this appears to be a consequence of both the substitution on the pyrimidine ring (**1p** vs **1n**, **1o**) and the substitution on the exocyclic nitrogen (**1m**, **1p** vs **1l**, **1t**, **1u**). Functional groups which are susceptible to hydrogenation or hydrogenolysis were also evaluated. A trisubstituted olefin (**1q**) gave a 7:1 mixture of the desired tetrahydropyridine (**2q**) to the saturated piperidine in a combined 89% yield. A benzyloxycarbonyl-protected amine (**1r**) was stable to the reaction conditions. A variety of sulfur-containing functional groups,

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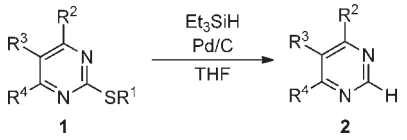
Table 1. Reductive Scission of 2-(Alkylthio)pyrimidines[a]



1 2

thioether	R^1	R^2	R^3	R^4	yield (%) in **2**[b]
1a	Me	NH_2	CO_2Et	H	89[c]
1b	Et	NH_2	CO_2Et	H	93
1c	Bn	NH_2	CO_2Et	H	91
1d	Et	NH_2	H	Me	86[d]
1e[e]	Me	OH	H	Me	73
1f	Me	Ph	H	Me	97
1g	Me	Ph	H	Ph	98
1h	Me	H	Ph	H	85
1i	Me	NHBn	H	Ph	83
1j	Me	NHBn	H	CF_3	96
1k[e,f]	Me	NHBn	H	NHBn	96[d]
1l[g]	Me	NHBn	H	H	94
1m	Me	NMeBn	H	H	67
1n	Me		H	Ph	92
1o	Me		H	Me	96
1p	Me		H	H	61
1q	Me		H	Me	89[h]
1r[g]	Me		H	Me	92
1s[e,i]	Me		H	Me	87
1t[f,j]	Me		H	H	92
1u	Me		H	H	91

[a] Reaction conditions: Et_3SiH (3 equiv), 10% Pd/C (2 mol %), THF (0.5−1 M), 0 °C to rt. [b] Yield was determined after purification by column chromatography on silica gel. [c] Without an acidic workup, the triethylsilyl adduct (R^2 = $NHSiEt_3$) was obtained in 90% yield. [d] Purified by trituration. [e] 5 mol % Pd/C. [f] Solvent was *N*,*N*-dimethylacetamide. [g] 1 mol % Pd/C. [h] 7:1 mixture of **2q**/saturated piperidine. [i] Reaction temperature was 60 °C. [j] Purified by reversed-phase liquid chromatography, isolated as the trifluoroacetate salt.

including a sulfide (**1s**), a sulfone (**1t**), and a thiophene (**1u**), which would not be tolerated by the standard Raney nickel conditions, afforded the desired products in 87−92% yields. *N*,*N*-Dimethylacetamide was used as the reaction solvent for reactants **1k** and **1t**, because of their minimal solubility in THF.[23]

4-(Alkylthio)pyrimidines were also readily cleaved (Table 2). 2,4-Bis(ethylthio)-6-phenylpyrimidine (**3b**) afforded 6-phenylpyrimidine (**4b**) in 88% yield. The cyclopropylaminopyrimidine **3f** demonstrated that cyclopropanes were stable to the reductive reaction conditions. In accordance with the known reactivity of pyrimidines, the reactions with 4-(alkylthio)pyrimidines in Table 2 generally had faster rates than the 2-(alkylthio)pyrimidines in Table 1.[24]

(23) The standard solvents for the reduction of thioesters, as described by Fukuyama, are acetone and dichloromethane. Kimura and Seki later described accelerated reaction rates with tetrahydrofuran (ref 18). In addition to these solvents, *N*,*N*-dimethylacetamide and acetonitrile are apposite solvents for the present transformation.

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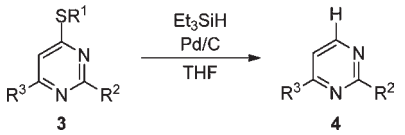
Table 2. Reductive Scission of 4-(Alkylthio)pyrimidines[a]

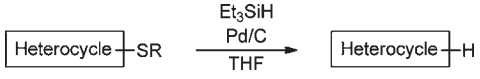


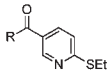
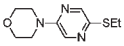
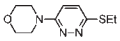
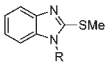
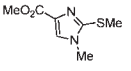
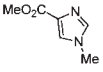
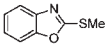
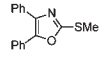
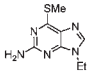
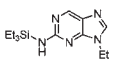
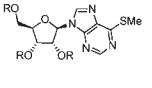
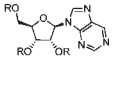
3 4

thioether	R^1	R^2	R^3	yield (%) in **4**[b]
3a	Me		H	95
3b	Et	EtS	Ph	88, R^2=H
3c	Et	Me	NHBn	97
3d	Et	Me		98
3e	Et	H		89
3f	Et	Me		97
3g	Et	MeO	Ph	98

[a] Reaction conditions: Et_3SiH (3 equiv), 10% Pd/C (2 mol %), THF (0.5−1 M), 0 °C to rt. [b] Yield was determined after purification by column chromatography on silica gel.

Table 3. Scope of the Reductive Scission Reaction[a]



thioether, R		product	yield (%)[b]
5a, R=NHBn **5b**, R=OBn			92 82
6			92
7			30
8a, R=H **8b**, R=Me **8c**, R=Bn[c]			99 98 87
9			98
10			67
11[d]			88
12a, R=H **12b**, R=Bn			90 89
13			95
14a, R=Ac **14b**, R=H[e]			94 (R=Ac) 88 (R=$SiEt_3$)

[a] Reaction conditions: Et_3SiH (3 equiv), 10% Pd/C (2 mol %), THF (0.5−1 M), 0 °C to rt. [b] Yield was determined after purification by column chromatography on silica gel. [c] Reaction temperature was 0 °C; benzimidazole (11%) was also isolated. [d] Reaction temperature was 60 °C. [e] 6 equiv of Et_3SiH.

The scope of the method was expanded to include additional heterocycles (Table 3). Pyridines **5a** and **5b** provided the nicotinic acid derivatives in 92 and 82% yields, respectively. Notably, benzyl amides and esters were relatively stable to the reaction conditions. While pyrazine **6** gave the desired product in 92% yield, pyridazine **7** afforded a complex mixture from which 30% of the desired product was obtained. 2-(Methylthio)benzimidazoles **8a** and **8b** as well as 2-(methylthio)imidazole **9** gave the corresponding products in nearly quantitative yields. The reaction of **8c**, however, was complicated by hydrogenolysis of the benzyl group. Strict control of the reaction temperature at 0 °C minimized the undesired hydrogenolysis and afforded *N*-benzylbenzimidazole in 87% yield. Benzoxazole **10** and oxazole **11** provided the desired products in 67% and 88% yields, respectively. Purine thioethers **12**–**14** were also compatible with the reaction conditions and afforded the desired products in 88–95% yields. 2-Aminopurine **13** and nucleoside **14b** were silylated under the reaction conditions, and this allowed for purification by chromatography on silica gel.

Many of the substrates in Tables 1–3 provided the products in nearly quantitative yields. Pyrimidine **3d** was selected as a substrate to better understand the mass balance of the transformation (Scheme 1). Careful purification of the crude reaction mixture by column chromatography afforded the 4-triethylsilyl adduct **15** in 1.7% yield and **4d** in 98% yield. The formation of **15** suggests that an alternative pathway in the catalytic cycle was operating. Specifically, reductive elimination from a triethylsilylpalladium intermediate rather than from a hydridopalladium intermediate would afford **15**.[25]

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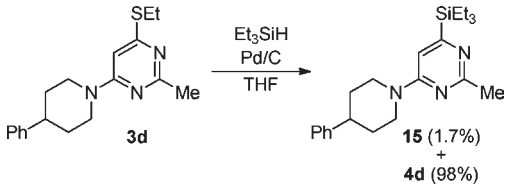
Scheme 1. Formation of a Triethylsilyl Adduct



In summary, a method for the mild and chemoselective single-step reductive scission of heterocyclic thioethers using triethylsilane and Pd/C was developed.[26] Thioethers at the 2-position relative to the ring heteroatom are sufficiently activated to participate in palladium catalysis. As a result, the method is suitable for a variety of heterocyclic systems. The chemoselectivity of the reaction allows for functional groups which are not compatible with Raney nickel reductions as well as functional groups which are susceptible to hydrogenolysis or hydrogenation. The method is convenient and straightforward to implement and generally affords the products in high yields and purity.

Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) General procedure: A 21 mm × 72 mm vial with a PTFE/silicone septa and a nitrogen-bubbler line was charged with 10% Pd/C (dry powder, 35.5 mg), THF (3 mL), and 4-methyl-2-(methylthio)-6-(4-phenylpiperidin-1-yl)pyrimidine (**1o**) (500 mg, 1.67 mmol). The vial was placed in a 0 °C bath, treated with triethylsilane (800 μL, 5.01 mmol), and stirred at 0 °C for 30 min and then at rt for 4.5 h. The crude mixture was filtered through a 45 μM PTFE syringe filter, and the filtrate was concentrated to an oil. Purification by chromatography on silica gel (20 to 100% ethyl acetate/ heptane then 0 to 10% methanol/ethyl acetate) afforded 4-methyl-6-(4-phenylpiperidin-1-yl)pyrimidine (**2o**) (406.7 mg, 1.605 mmol, 96% yield) as a colorless solid. The reactions generally exhibit an induction period of 5 to 30 min as indicated by the initiation of gas release (i.e., bubbling) from the reaction mixture.