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Trifluoroacetyl-Activated Nitrogen–Nitrogen Bond Cleavage of Hydrazines by Samarium(II) Iodide

Hui Ding and Gregory K. Friestad*

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

gregory.friestad@uvm.edu

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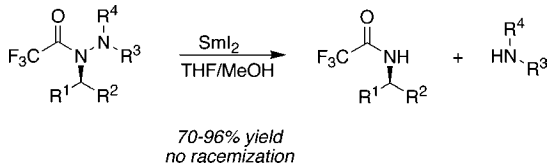
ABSTRACT



Trifluoroacetyl derivatives of hydrazines undergo clean and efficient reductive cleavage of the N–N bond with SmI_2 in the presence of MeOH. After N-trifluoroacetylation, acyl-, aryl-, and alkyl-substituted hydrazines are reductively cleaved by this method to afford trifluoroacetamides in yields ranging from 70 to 96%. These conditions accommodate alkene functionality, avoid racemization, and furnish chiral amines bearing a readily removable TFA protecting group.

Chiral α-branched amines are ubiquitous components of biologically active compounds and are versatile building blocks for medicinal chemistry and natural product synthesis. Among approaches to asymmetric amine synthesis, addition of carbon-centered radicals[1] and organometallic or hydride reagents[2] to hydrazones potentially provides straightforward access to chiral amines.[3] The advantages of hydrazones over imines include a favorable equilibrium in their formation (even in aqueous media), ease of purification and handling, and resistance to tautomerization.

We required a general method for N−N bond cleavage, compatible with alkene functionality, to facilitate access to enantiopure homoallylic amines via allylsilane addition to chiral *N*-acylhydrazones.[2b] Recently, cleavage of the N−N bond in hydrazines has been achieved by oxidation with magnesium monoperoxyphthalate.[4] More commonly, reduction has been employed, using hydrogenolysis[5] (H_2 with Pd−C, $Pd(OH)_2$, PtO_2, Pt, or Raney nickel catalysts), dissolving metal reduction,[6] hydroboration,[7] or other methods.[8] Reductive cleavage with samarium(II) iodide[9] (SmI_2), with various additives, has gained prominence in many recent studies.[10,11]

Our experimental work became focused on samarium(II) iodide because of its compatibility with alkene functionality and the operational simplicity of the experimental procedures (e.g., rapid reaction at ambient temperature and pressure). It has previously been found that an activating acyl group on one of the nitrogens may be needed to promote reaction with SmI_2 or other one-electron reductants.[6,8,10,11] Accordingly, we found dramatically different results upon direct treatment of **1a**[2b] or **2**[2b] with SmI_2 and HMPA in THF (eq 1). The free amine **1a** gave no reaction, but the corresponding *N*-benzoyl derivative **2** underwent rapid, quantitative N−N bond cleav-

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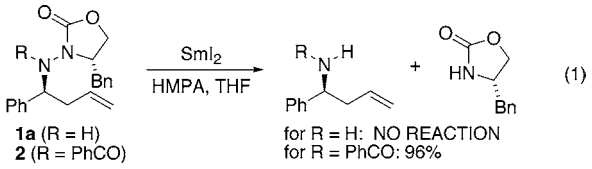
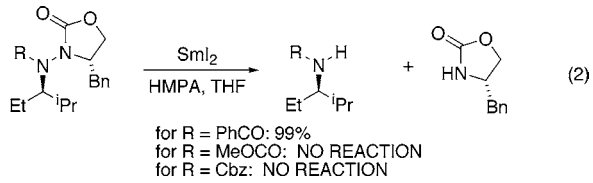
age under these conditions. Unfortunately, hydrolysis of the resulting benzamide required harsh conditions that ultimately caused decomposition. From this it was concluded that general applications in multifunctional synthetic schemes would require a more readily removable acyl activating group.



(1)

We sought an acyl group that could combine N−N bond activation with wide acceptance as a protecting group. Previously, we had attempted to exploit carbamate derivatives (eq 2, R = methoxycarbonyl or benzyloxycarbonyl) to meet these requirements.[12] However, on the same substrate for which benzoyl activation had enabled quantitative N−N cleavage, these carbamate derivatives underwent no reaction at all (eq 2), a dramatic illustration of the unusual N−N bond activation properties of the benzoyl group. This chemical behavior toward SmI_2 is consistent with activating effects previously documented by electroreductive measurements, which showed increased potentials proportional to the number of benzoyl substituents.[8a]



(2)

A key inference, suggesting an alternative to the benzoyl group, was drawn from a recent kinetic analysis of ketone reductions by SmI_2. In these elegant studies, Flowers showed that ortho fluorine substituents gave dramatically enhanced rates of reduction of aryl ketones by SmI_2.[13] A chelation model (Figure 1a) was advanced to explain the enhanced reducing power of SmI_2 under these circumstances. A similar chelated structure can be envisioned involving the trifluoroacetyl (TFA) moiety (Figure 1b). From this we were led to the hypothesis that TFA might facilitate the N−N bond cleavage process.[14] Importantly, TFA is a popular amine-

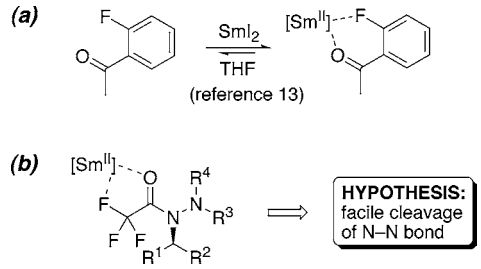


Figure 1. (a) Chelation model proposed by Flowers, and supported by rigorous analysis of activation parameters, to explain increased reduction rates of 2′-fluoroacetophenone by SmI_2. [Sm^{II}] represents samarium(II) species with undetermined ratios of iodide and THF ligands. (b) Our hypothesis: trifluoroacetyl group should facilitate reductive cleavage of the N−N bond of hydrazines.

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(14) (a) Trifluoroacetamides have been employed in N−N bond cleavage with Li/NH_3 or Al/Hg. See refs 6a and 6e. (b) Trifluoroacetyl protection has been exploited during N−O bond cleavage. However, acetamides and carbamates were also effective in these studies, in contrast to eq 2. See: Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422. Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Org. Chem.* **1999**, *64*, 4465−4476. Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755−11772.

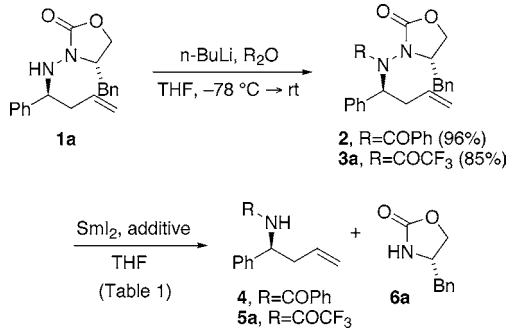
Table 1. Effect of Additives on N−N Bond Cleavage after Acylation of **1a** (Scheme 1)

entry	hydrazine	additive	products (yield, %)
1	**2**	HMPA	**4** (96), **6a** (93)
2	**2**	MeOH	**4** (94), **6a** (94)
3	**2**	none	**4** (68), **6a** (82)
4	**3a**	HMPA	**5a** (83), **6a** (47)
5	**3a**	MeOH	**5a** (95), **6a** (93)
6	**3a**	none	**5a** (67), **6a** (nd)

protecting group and is easily hydrolyzed. Here we report that N-trifluoroacetylation activates the SmI_2-mediated N−N bond cleavage process, enabling smooth conversion of a variety of trisubstituted hydrazines to TFA-protected amines.

To compare the effects of trifluoroacetyl and benzoyl groups in N−N bond activation, these two acylated compounds were prepared by lithiation of **1a**[2b] and reaction with trifluoroacetic anhydride (TFAA) or benzoic anhydride, respectively (Scheme 1). The *N*-benzoyl hydrazine **2**[2b] was exposed to SmI_2 to afford benzamide **4**[2b] in high yield, in the presence of either HMPA or MeOH as an additive. Meanwhile, the oxazolidinone **6a** was recovered in high yield in each case. When the *N*-TFA hydrazine **3a** was treated with samarium(II) iodide for 30 min at room temperature in the presence of HMPA (entry 4), the reaction gave a good yield of trifluoroacetamide **5a**.[15] Replacing HMPA with MeOH, which probably worked as a proton source, gave superior results (entry 5), particularly with respect to recovery of **6a**. In the absence of additive, however, yields decreased (entries 3 and 6[16]) due to some side reactions. Thus, optimal conditions[17] for studies of the scope of the TFA-activated N−N cleavage called for use of MeOH as an additive.

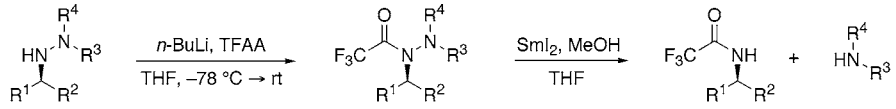
Scheme 1

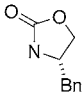


For exploration of the reaction scope, a series of hydrazines with varying substitution patterns were available from our previous studies of allylsilane additions (**1a**, **1b**)[2b] and radical additions (**1c**, **1d**)[1a,c] to *N*-acylhydrazones or prepared by $NaBH_3CN$ reduction[18] (**1e**−**h**; see Supporting Information) of the corresponding hydrazones.

Cleavage of the N−N bond of various types of hydrazines occurred with good yields (Table 2). Upon conversion to their TFA derivatives, *N*-acylhydrazines (entries 1, 2, and 4−6) were cleaved by SmI_2 to afford the corresponding trifluoroacetamides **5a**−**d**[15] or **5e**[14b] in excellent yields (91−96%), although **1c** was an exception (entry 3, 70%). Trisubstituted hydrazines bearing *N*,*N*-diaryl (**1g**) or *N*,*N*-dialkyl substitution (**1h**) also were cleaved to afford **5e** in good yields (82%) although a longer reaction time (2 h) was required. It is worth noting that the steric hindrance of α-branched hydrazines **1c** and **1d** did not impede the N−N bond cleavage.

Table 2. Examples of Trifluoroacetyl-Activated Hydrazine N−N Bond Cleavage

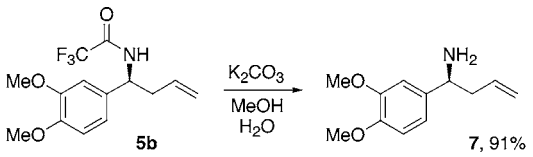


		trifluoroacetylation				N–N bond cleavage	
entry	hydrazine	R^1	R^2	NR^3R^4	**3** (% yield)	**5** (% yield)	**6** (% yield)
1	**1a**	Ph	allyl		**3a** (85)	**5a** (95)	**6a** (93)
2	**1b**	3,4-DMP[a]	allyl		**3b** (81)	**5b** (91)	**6a** (85)
3	**1c**	Et	*i*-Pr		**3c** (88)	**5c** (70)	**6a** (92)
4	**1d**	*i*-Pr	Ph		**3d** (84)	**5d** (96)	n.d.[b]
5	**1e**	Ph	H		**3e** (54)	**5e** (96)	n.d.[b]
6	**1f**	Ph	H		**3f** (72)	**5e** (93)	n.d.[b]
7	**1g**	Ph	H	NPh_2	**3g** (49)	**5e** (82)	**6g** (52)
8	**1h**	Ph	H	NBn_2	**3h** (56)	**5e** (82)	n.d.[b]

[a] 3,4-Dimethoxyphenyl. [b] Yield not determined.

Importantly, the enantiomeric purities of chiral hydrazines are unchanged by N−N bond cleavage according to the method described in Table 2. For example, trifluoroacetamides **5b** and **5d** were obtained without detectable racemization according to chiral HPLC analysis.[19]

Furthermore, as expected from ample precedent, removal of the TFA protecting group from **5b** was achieved in high yield under mild conditions (eq 3). The TFA group, with its ease of removal, effectively avoided the degradation that had been observed during hydrolysis of the related benzamide as described above (eq 1).



(3)

In summary, we have found that the trifluoroacetyl substituent enables clean and efficient reductive cleavage of the N−N bond of various hydrazines using SmI_2 in the presence of MeOH. These conditions are compatible with alkene functionality, and thus offer an important complement to hydrogenolysis or hydroboration. Furthermore, the method furnishes chiral amines that bear a convenient TFA protecting group to facilitate subsequent synthetic applications.

Acknowledgment. We thank NIH (RO1-GM67187) and Vermont NSF EPSCoR for generous support.

Supporting Information Available: Characterization data for **1b**, **1e**, **1f**, **5a**−**d**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Structures of new compounds **1b**, **1e**, **1f**, **5a**−**d**, and **7** are consistent with combustion analyses and spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) provided in Supporting Information.

(16) In addition to the lower yield of **5a**, oxazolidinone **6a** was contaminated in this case by a complex mixture of byproducts. Complete consumption of starting material occurred.

(17) (a) **Representative Experimental Procedure.** To a solution of **1b** (79 mg, 0.206 mmol) in THF (2.0 mL) under N_2 at −78 °C was added *n*-BuLi (1.6 M in hexanes, 140 μL, 0.224 mmol) at −78 °C. After 40 min, trifluoroacetic anhydride (50 μL, 0.353 mmol) was added at −78 °C. The mixture was allowed to warm to ambient termperature overnight. Concentration and flash chromatography (4:1 hexanes/ethyl acetate) gave **3b** (80 mg, 81%) as a pale yellow oil. To a solution of **3b** (48 mg, 0.1 mmol) in MeOH (0.2 mL) under N_2 was added SmI_2 (2.6 mL, 0.3 M in THF) dropwise. After 30 min, the dark blue solution was opened to air, and the color changed to yellow. Concentration and flash chromatography gave **5b** (27.5 mg, 91%) and **6a** (15 mg, 85%). (b) The concentration of SmI_2 was assumed on the basis of the preparation; the actual concentration is likely somewhat lower. Use of a freshly titrated SmI_2 solution (0.10 M) showed that a 3:1 molar ratio of SmI_2:**3d** was sufficient to achieve complete conversion (93% yield).

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(19) Compound **5b** was enantiomerically pure as judged by HPLC comparison with a racemic sample (see Supporting Information). A nonracemic sample of **1d** (50.4% ee), prepared according to a procedure reported in ref 2b, gave **5d** of the same enantiomeric purity.