TBSOTf-Promoted Versatile *N*-Formylation Using DMF at Room Temperature

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TBSOTf-Promoted Versatile *N*-Formylation Using DMF at Room Temperature

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ABSTRACT

Hydrazides and amines were *N*-formylated by DMF in the presence of *tert*-butyldimethylsilyl triflate (TBSOTf) at room temperature, in good to excellent yields.

1. Introduction

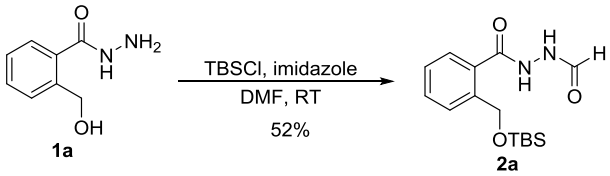
Formamide is one of the most important members of the amide family and has been used in various fields of organic chemistry. *N*,*N*-Dimethylformamide (DMF) is a widely used because it is one of the most important aprotic highly polar solvents.[1] The Vilsmeier reagent prepared from formamide serves as a powerful tool for the preparation of aromatic aldehydes.[2] The formamide moiety is found in several pharmaceutical drugs and organic catalysts.[3]

Although acid chloride and anhydride are usually employed as the acylation agents for amines, both formyl chloride and formic anhydride are too unstable to be used in formylation. Therefore, various alternative methods have been developed for formylation. The mixed anhydride of formic acid with a bulky acid is one of the most powerful formylation agents,[4] although it cannot be stored for a long time. Ethyl formate is conveniently used for the formylation of amines,[5] although heating is generally necessary, and the low boiling point of ethyl formate often limits its availability.

DMF is the most widely used formic acid derivative, which also finds application as a formylation agent.[6] Because of the low electrophilicity of DMF, heating is necessary to carry out formylation, even in the presence of an effective activation agent.[7] Formylation by DMF using excess trimethylsilyl chloride (TMSCl) or *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole or triethylamine at room temperature has been reported,[8] although this system is applicable only to secondary amines and hence finds limited application.

During the course of our research on hydrazides,[9] we investigated the silylation of **1a** with TBSCl in DMF at room ~~temperatu~~re. Unexpectedly, diacylhydrazine **2a** was obtained in 52% yield as the only isolable product (Scheme 1), indicating that even a primary amine can be formylated by the DMF-TBSCl system. Soon after this observation, it was found that the DMF-TBSOTf system is a simple and powerful *N*-formylation method that can be extended to various amines.

Scheme 1



2. Results and Discussion

To optimize the reaction conditions for the *N*-formylation, **1b** was used as a simple hydrazide. Activating agents were added to the DMF solution of **1b**, and the reactions were carried out at room temperature for 20 h. The results are summarized in Table 1.

When 1 equiv of TBSCl and imidazole were used to activate DMF, **2b** was obtained in 33% yield (entry 1). The yield increased in the absence of imidazole (entry 2). Although TBSCl has previously been used with tertiary amines to activate DMF,[8] it was found that the tertiary amine deactivated TBSCl and reduced its activation effect.[7e] No reaction occurred without TBSCl, and other typical Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$ and $SnCl_4$ gave **2b** only in poor yields (entries 3-6). Thus, other silane-based Lewis acids were examined to activate DMF. While TMSCl turned out to be a poor activator (entry 7), trimethylsilyl triflate (TMSOTf) gave **2b** in excellent yield (entry 8), and *tert*-butyldimethylsilyl triflate (TBSOTf) gave the best

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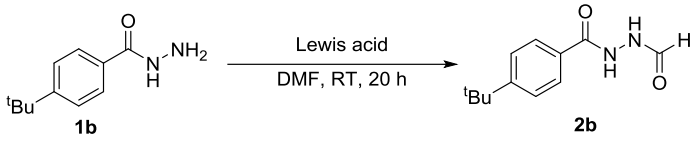
result (entry 9). The yield of **2b** was almost proportional to the amount of TBSOTf (entry 10). Therefore, we concluded that TBSOTf acts as an activator but not as a catalyst.

Table 1. Optimization of the activating agent for DMF.

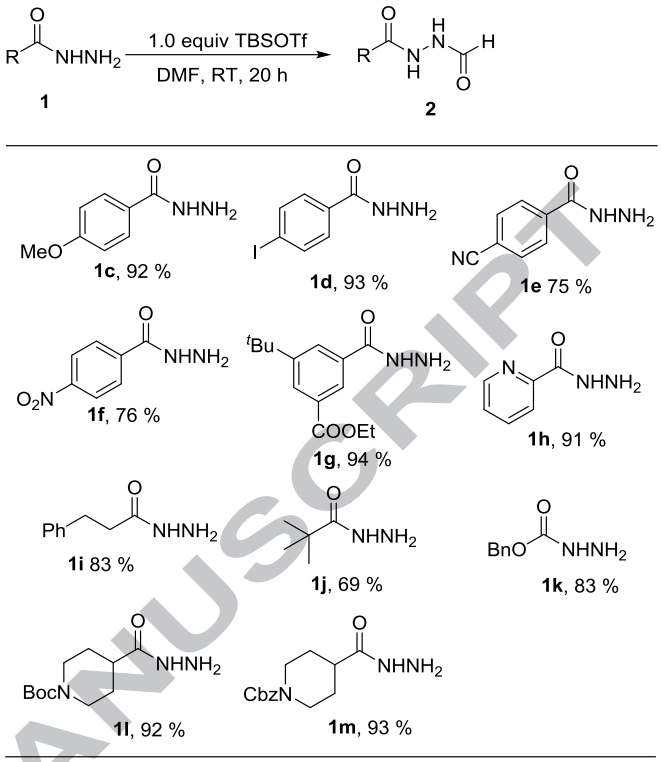


Entry	Lewis acid (equiv)	Yield (%)[a]
1	TBSCl (1.0) + imidazole (1.0)	33
2	TBSCl (1.0)	86
3	$BF_3{\cdot}OEt_2$ (1.0)	43
4	$AlCl_3$ (1.0)	0
5	$TiCl_4$ (1.0)	0
6	$SnCl_4$ (1.0)	2
7	TMSCl (1.0)	18
8	TMSOTf (1.0)	95
9	TBSOTf (1.0)	97
10	TBSOTf (0.40)	44

[a]Isolated yield.

The *N*-formylation was next carried out using various hydrazides. The results are summarized in Table 2. Both aromatic and aliphatic hydrazides, including the sterically hindered hydrazide **1j**, gave the corresponding diacylhydrazines in good to excellent yields. Carbazic acid ester **1k** was also formylated smoothly. Acid-sensitive protecting groups such as Boc and Cbz were tolerated under these reaction conditions.

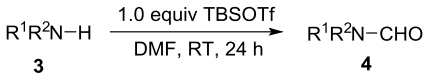
Table 2. Formylation of hydrazides.[a]

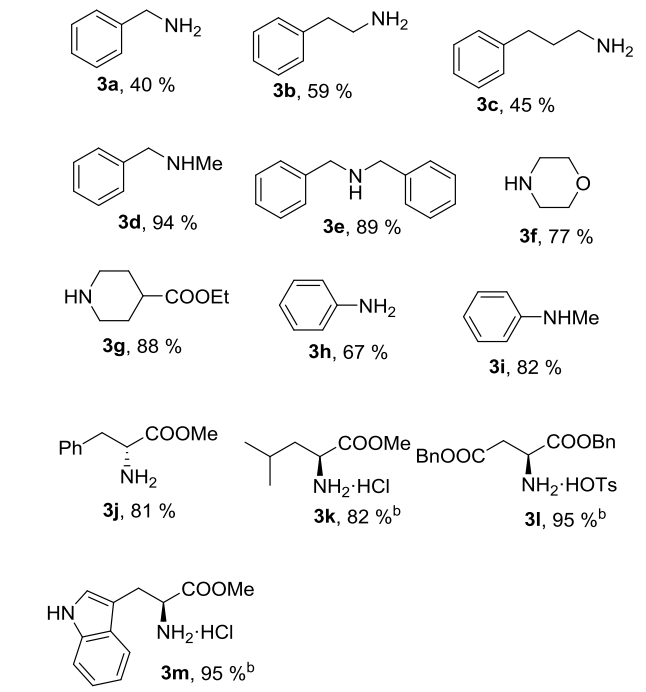


[a]Isolated yield.

Next, the DMF-TBSOTf system was applied to the formylation of amines. The results are summarized in Table 3. Primary amines gave the corresponding formamides, as opposed to previous studies, in which only a trace amount of formamide was obtained from a primary amine in the presence of a tertiary amine.[8] The yield of formamides was moderate probably because the highly basic and nucleophilic primary amine deactivated TBSOTf in the absence of a tertiary amine. When a secondary amine was used, formamide was obtained in good to excellent yield. Anilines as well as aliphatic amines were *N*-formylated. Despite the primary amino groups, amino acid derivatives gave *N*-formylated products in high yields. No formylation of the indole NH in **3m** was observed.

Table 3. Formylation of amines.[a]

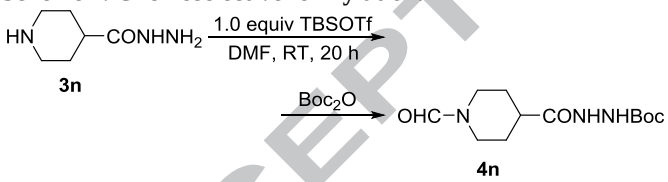




[a]Isolated yield. [b]1.0 equiv of imidazole was added to neutralize the ammonium group.

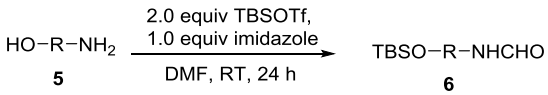
Then, a competitive reaction was carried out. When **3n** was subjected to the *N*-formylation conditions, **4n** was obtained in 56% yield after treatment with Boc_2O to protect the unreacted hydrazide (Scheme 2). No formylation of the hydrazide was observed, indicating that the amine is more reactive than the hydrazide under these reaction conditions.

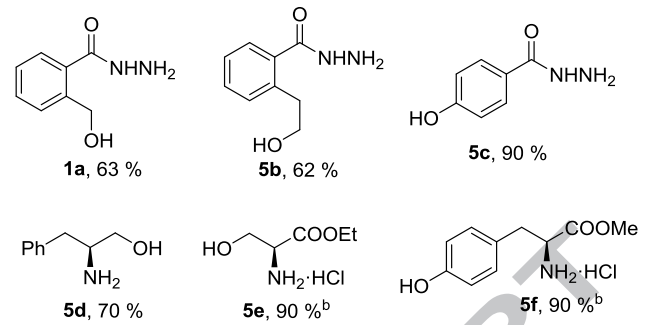
Scheme 2. Chemoselective formylation.



The chemoselectivity in the formylation of aminoalcohols was complicated because the hydroxy group was silylated by TBSOTf in the presence of the amino group. To avoid this complexity, the *N*-formylation of hydrazides and amines bearing a hydroxy group was carried out using 2.0 equiv of TBSOTf and 1.0 equiv of imidazole, so that silylative protection of the hydroxy group and formylation of the amino group occurred simultaneously. The results are summarized in Table 4. Formamide or formylated diacylhydrazine bearing a siloxy group was obtained in moderate to high yields.

Table 4. Silylative formylation of aminoalcohol.[a]

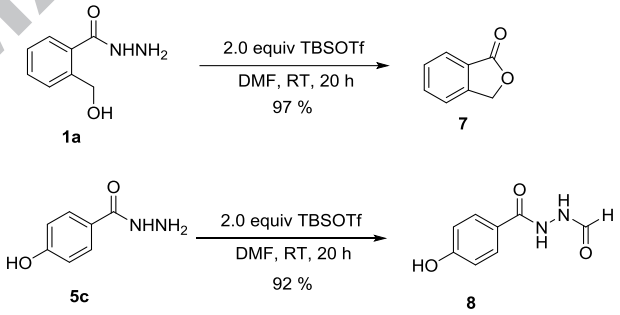




[a]Isolated yield. [b]2.0 equiv of imidazole was used.

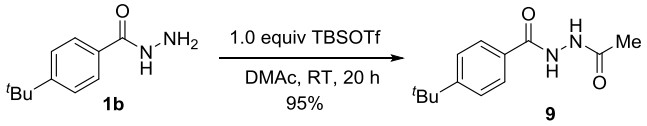
When the reaction was carried out with 2.0 equiv of TBSOTf but in the absence of imidazole, phthalide **7** was obtained from **1a** in quantitative yield, and diacylhydrazine **8** without silylation of the hydroxyl group was obtained from **5c** in 92% yield (Scheme 3). These results indicated that imidazole effectively induces silylation of the hydroxy group for *in situ* protection. In the absence of imidazole, activation of the carbonyl group in the amide or hydrazide by TBSOTf occurred. In the case of **1a**, the activated hydrazide group was attacked by the neighboring hydroxy group to induce cyclization.

Scheme 3. Activation of hydrazide without protection of the hydroxy group.



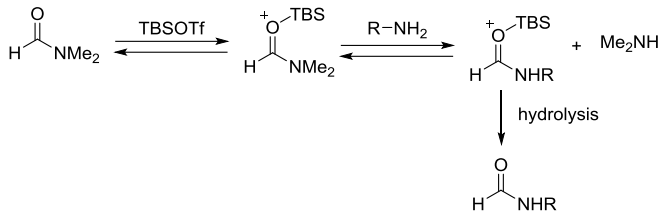
When a DMAc solution of **1b** was treated with TBSOTf, the corresponding acetylation product **9** was obtained in excellent yield (Scheme 4). Thus, TBSOTf is expected to be used as an activator for various amides.

Scheme 4. Acetylation of hydrazide.



The outstanding effect of TBSOTf can be explained by its high Lewis acidity and oxophilicity. The plausible mechanism underlying the TBSOTf-promoted formylation is illustrated in Scheme 5. Even in the presence of a nucleophilic amino group, TBSOTf can selectively silylate DMF at the highly Lewis basic amide carbonyl oxygen. The activated DMF is expected to be attacked by the amine so that an efficient amide-exchange reaction occurs. Hydrolysis of the exchange product gives formamide.

Scheme 5. Plausible mechanism of the TBSOTf-promoted formylation.



3. Conclusion

The TBSOTf-promoted *N*-formylation of hydrazides and amines using DMF as the formylation agent is demonstrated. The DMF-TBSOTf system can be used for the *N*-formylation of various amines in the absence of a tertiary amine. Because of the easy availability of DMF and TBSOTf, simple procedure, mild reaction conditions, high chemoselectivity, and broad scope for various acylation systems, the TBSOTf-promoted *trans*-amidation can emerge as one of the most effective methods for the *N*-formylation of hydrazides and amines.

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Supplementary Material

Experimental procedure and spectral data are provided in the Supplementary Material.

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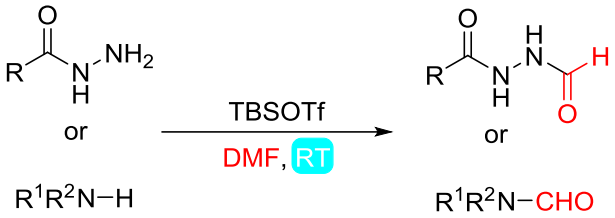
Graphical abstract



Highlights

Amines were formylated with DMF activated by TBSOTf at room temperature.

Amino group was chemoselectively formylated in the presence of hydrazide.

O-Silylative *N*-formylation of aminoalcohol occurred in high yield.