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TMS·OTf-Catalyzed α-bromination of carbonyl compounds by *N*-bromosuccinimide

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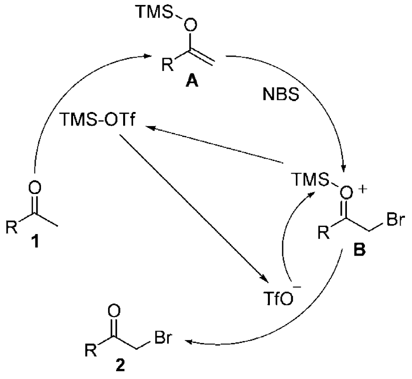
Abstract—Various carbonyl compounds undergo α-bromination reaction under a mild and practical condition utilizing *N*-bromosuccinimide (NBS), catalyzed by trimethylsilyl trifluoromethanesulfonate (TMS·OTf). This method is also effective for the side-chain bromination of heteroaromatic carbonyl compounds without the ring brominations.

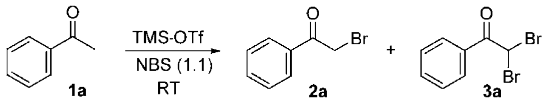
The α-bromination of carbonyl compounds[1] is the first step of introducing a heteroatom,[2] generating a stabilized carbon radical or carbanion,[3] and providing conjugation to the carbonyl groups.[4] Various α-bromination protocols of carbonyl compounds[5] have been developed including the basic method using Br_2.[6] The unfriendly and dangerous nature of bromine, however, urged on to invent milder conditions making use of manageable reagents such as *N*-bromosuccinimide (NBS).[7] The two-step sequence utilizing NBS through the formation of silyl enol ethers[8] is an efficient and valuable α-bromination method of carbonyl compounds under a mild and neutral condition considering the fact that enolization is the rate determining step in the electrophilic halogenation reactions.

We envisioned that this reaction would be very useful if the reaction proceeded by a catalytic use of the silicon reagent, which would make it a single-step process. The catalytic cycle may be completed by the utilization of trimethylsilyl trifluoromethanesulfonate (TMS·OTf) as delineated in Scheme 1. TMS·OTf is reactive enough that the silyl enol ether **A** from the carbonyl compound **1** can be readily formed without adding a base. Electrophilic addition of bromonium ion to **A** produces the intermediary oxocarbenium species **B**, which then reacts with the triflate ion that was liberated in the formation of **A** to regenerate TMS·OTf as well as to give rise to the α-bromination product **2**. This scenario has proven to be successful for various carbonyl compounds including those containing a heteroaromatic ring, in which the ring bromination was usually the major problem.[9] Details of our study on the α-bromination of carbonyl compounds are disclosed in this letter.



Scheme 1. The catalytic cycle of TMS·OTf in the bromination of carbonyl compounds by *N*-bromosuccinimide.

The optimization of the reaction condition for the TMS·OTf-catalyzed α-bromination of carbonyl compounds by NBS has been studied for acetophenone (**1a**) as a model case (Scheme 2 and Table 1). The desired



Scheme 2. The TMS·OTf-catalyzed bromination of acetophenone (**1a**) by NBS.

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Table 1. The TMS·OTf-catalyzed bromination of acetophenone by NBS

Entry	TMS·OTf (mol %)	Solvent	Time (h)	Ratio (**2a**:**3a**:**1a**)	Yield **2a** (%)
1	5	Et_2O	3.5	58:1:41	64[a]
2	5	DMF	3.5	4:0:96	6[a]
3	5	CH_2Cl_2	3.5	58:7:35	59[a]
4	5	THF	3.5	38:0:62	39[a]
5	5	MeCN	3.5	76:3:21	82[a]
6	5	MeCN	24	92:3:5	85[b]
7	30	MeCN	3.5[c]	90:6:4	85[b]

[a] Calculated yield of **2a** based on the ratio by ^1H NMR (±3%) from the crude product.

[b] Calculated yield of **2a** based on the ratio by ^1H NMR (±3%) after SiO_2 column chromatography.

[c] A solution of NBS in MeCN was slowly added via dropper.

Table 2. The TMS·OTf-catalyzed bromination of various acetyl compounds by NBS

Entry	1	R	TMS·OTf (mol %)	Time (h)	Ratio (**2**:**3**:**1**)	Yield **2** (%)[a]
1	**b**	4-MeO–Ph	5	24	89:7:4	87
2	**c**	4-Cl–Ph	5	24	90:4:6	89
3	**d**	4-F–Ph	5	24	47:1:52	47
4			30	24[b]	88:4:8	84
5	**e**	4-NO_2–Ph	5	24	32:2:66	32
6			30	24[b]	84:3:13	82
7	**f**	2-Naphthyl	5	24	62:1:37	57
8			30	24[b]	88:4:8	86
9	**g**	*t*-Butyl	5	24	88:12:0	73
10			5	5	94:6:0	79
11	**h**	2-Furanyl	5	24[b]	70:14:16	68
12			30	24[b]	75:21:4	66
13			30[c]	24[b]	89:5:6	84
14	**i**	3-Thiophenyl	5	24[b]	63:2:19	59[d]
15			30	24[b]	86:6:8	80

[a] Calculated yield of **2** based on the ratio by ^1H NMR (±3%) after SiO_2 column chromatography.

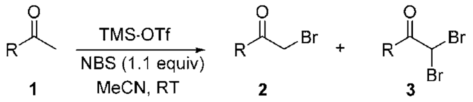
[b] A solution of NBS in MeCN was slowly added via a dropper for 2 h.

[c] Triisopropylsilyl trifluoromethanesulfonate (TIPS·OTf) was used.

[d] Bromination products on the thiophene ring were also obtained, and the total yield of the ring brominations was calculated to be 15%.

mono-bromination product **2a** was accompanied by the di-bromination product **3a** along with the unreacted starting material **1a**, which were inseparable by the SiO_2 column chromatography. It was reasonable to obtain the di-bromination product considering the above reaction mechanism especially for the acetyl compounds that were not sterically congested. We calculated the ratio of **2a**:**3a**:**1a** by the comparison of the calibrated area of the peaks corresponding to the α-protons of the carbonyl groups in the ^1H NMR spectra. It seemed that a polar medium was required to facilitate the formation of the silyl enol ether from **1a** by TMS·OTf. However, most of **1a** was recovered unreacted in DMF presumably because TMS·OTf reacted preferentially with the solvent (entry 2). Even though 30 mol % TMS·OTf accelerated the reaction to be completed within 3.5 h, 5 mol % TMS·OTf was sufficed to give the comparable yield in 24 h (entries 6 and 7). The best result was obtained using 5 mol % TMS·OTf in MeCN at rt for 24 h, in which the yield of **2a** was calculated to be 85% from a 92:3:5 mixture of **2a**:**3a**:**1a** (entry 6).[10]

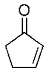
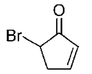
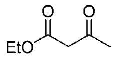
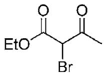
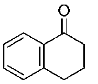
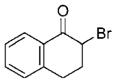
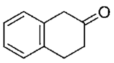
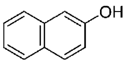
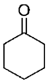
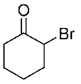
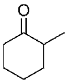
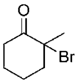
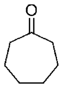
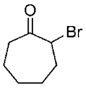
The generality of the TMS·OTf-catalyzed α-bromination utilizing NBS has been tested for diverse acetyl compounds under the above optimized condition (Scheme 3 and Table 2). The *p*-substituted acetophenone derivatives **1b–e** have been studied to check the electronic effects of the substituents on the α-bromination of the acetyl group. Comparable yields and ratios of the α-bromination products to those of the model case were obtained for 4-MeO- and 4-Cl-substituted acetophenones **1b** and **1c** under the above condition (entries 1 and 2). However, the α-bromination reaction, presumably the formation of the silyl enol ethers, was sluggish for acetophenones with electron withdrawing *p*-substituents such as F and NO_2 (entries 3 and 5), in which 30 mol % TMS·OTf was required to improve the yields to the level of the model case (entries 4 and 6). The α-bromination of 2-acetylnaphthalene (**1f**) was also slow such that 30 mol % TMS·OTf was utilized (entries 7 and 8), whilst an appreciable amount of the di-bromination product **3g** was obtained for pinacolone (**1g**) even under the condition of using 5 mol % TMS·OTf in 24 h (entry 9). The yield of the mono-bromination product **2g** was increased by reducing the reaction time to 5 h (entry 10).



Scheme 3. The TMS·OTf-catalyzed bromination of various acetyl compounds by NBS.

The α-bromination of the acetyl compounds containing a heteroaromatic ring without the ring brominations is a challenging task. The TMS·OTf-catalyzed α-bromination of the acetyl group by NBS has been studied for 2-acetylfuran (**1h**) and 3-acetylthiophene (**1i**). The ring bromination product was not observed in any cases for **1h**. A significant amount of the di-bromination product **3h** was obtained even with 5 mol % of the catalyst (entry 11). The amounts of **3h** as well as the mono-bromination product **2h** were increased a little with 30 mol % of the catalyst (entry 12). The best result was obtained with 30 mol % triisopropylsilyl trifluoromethanesulfonate (TIPS·OTf), in which the bulky catalyst minimized the formation of the di-bromination product **3h** (entry 13). The ring brominations (15% calculated yield) have been observed for 3-acetylthiophene (**1i**) when 5 mol % TMS·OTf was used (entry 14). The ring bromination products were, however, eliminated as the rate of the α-bromination was increased with 30 mol % TMS·OTf, thereby producing **2i** in 80% calculated yield from an 86:6:8 mixture of **2i**:**3i**:**1i** (entry 15). Whenever 30 mol % of the catalyst or the acetyl compound containing a heteroaromatic ring was used, a solution of NBS in MeCN was added slowly for 2 h to minimize the side reactions such as the di-bromination or the bromination on the heteroaromatic ring.

Table 3. The TMS·OTf (5 mol %)-catalyzed bromination of carbonyl compounds **1** by NBS

Entry	1		Time (h)	2	Yield (%)
1	**j**		4		93[a]
2	**k**		3.5		82[a]
3	**l**		24		87[a]
4	**m**		10 min		91[a]
5	**n**		4		66[b,c]
6	**o**		2		63[b,d]
7	**p**		1		72[b,e]

[a] Purified yields after SiO_2 column chromatography.

[b] Calculated yield of **2** based on the ratio by ^1H NMR (±3%) after SiO_2 column chromatography.

[c] 2,6-Dibromocyclohexanone was also obtained, and the yield was calculated to be 14%.

[d] 2,6-Dibromo-2-methylcyclohexane was also obtained, and the yield was calculated to be 13% yield.

[e] 2,7-Dibromocycloheptanone was also obtained, and the yield was calculated to be 12%.

We then applied the TMS·OTf-catalyzed α-bromination reaction using NBS to various carbonyl compounds, and the reaction time and the yield were summarized in Table 3. The above standard condition of 5 mol % TMS·OTf with 1.1 equiv of NBS in MeCN at rt was utilized in these reactions. Mono-bromination products were selectively obtained in high yields for 2-cyclopenten-1-one (**1j**), ethyl acetoacetate (**1k**), and α-tetralone (**1l**). The reaction of β-tetralone (**1m**) was very fast to give rise to the aromatic 2-naphthol (**2m**) within 10 min in 91% yield after dehydrobromination and enolization. The reactions of cycloalkanones **1n**–**p** consistently produced an appreciable amount of the inseparable α,α′-di-bromination products (12–14% yields) along with the desired mono-bromination products in 63–72% yields. The major α-bromination at the more-substituted carbon of 2-methylcyclohexanone (**1o**), indicated that the thermodynamically more stable silyl enol ether was formed.

In conclusion, we have developed an efficient and practical α-bromination method of various carbonyl compounds by the catalytic use of TMS·OTf with NBS in MeCN. Our method is especially valuable for the α-bromination of carbonyl compounds containing a heteroaromatic ring without the ring brominations.

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10. The representative experimental procedure for **2a**: To a stirred solution of **1a** (120 mg, 1.0 mmol) and NBS (196 mg, 1.1 mmol) in MeCN (6 mL) was added TMS·OTf (12 mg, 0.05 mmol). The mixture was stirred at rt for 24 h, diluted with ether, washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give a 92:3:5 mixture of **2a**:**3a**:**1a** (184 mg total). The yield of **2a** was calculated to be 85%.