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A Chlorinating Reagent: *N*-chloro-*N*-methoxybenzene Sulfonamide

Xiaoqiu Pu,[a] Qingwei Li,[a] Zehai Lu,[a] and Xianjin Yang*[ab]

Dedication ((optional))

Abstract: A structurally simple and reactive chlorinating reagent, *N*-chloro-*N*-methoxybenzenesulfonamide, was conveniently and economically prepared in high yield. 1,3-Diketones, β-keto esters, benzoyl trifluoroacetones, phenols, anisoles, heteroarenes and aromatic amines were chlorinated with it, obtaining chlorinated products in good to high yields.

Chlorine exists widely in many pharmaceutical and pesticide molecules and it can greatly improve the activity of medicaments,[1] such as Thiamphenicol, Pyoluteorin, AZD3463, etc.[2] (Figure 1). Hence, the economical, convenient and rapid protocols of introduction halogen atom into organic molecules have been a hot topic.

A large array of chlorinating reagents have been successfully developed. For examples, N-chlorosuccinimide (NCS)[3] and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH)[4] have high stability and

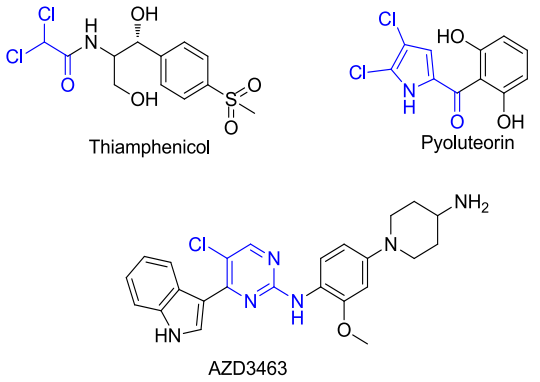
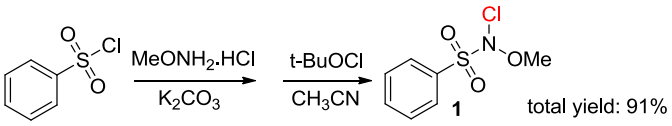


Figure 1. Classical chlorine-containing medicines

provide mild operating conditions. However, the reactivity of these conventional chlorination reagents are not satisfactory and the scope of substrates are limited. SO_2Cl_2,[5] Cl_2,[6] PhSeCl,[7] $SbCl_5$,[8] and *t*-BuOCl[9] have satisfactory reaction reactivity, but their high toxicity, poor regioselectivity, heat and light sensitivity stinted their practice application.

In our group, the reagents contained nitrogen-halogen bond have been studied for many years and some worthy outcomes have been achieved.[10] Very recently, an efficient chlorinating reagent, *N*-chloro-*N*-fluorobenzenesulfonylamide (CFBSA), has been developed in our group.[11] Dong's group reported 1-chloro-1,2-benziodoxol-3-one, an age-old reagent, which exhibited high reactivity and broad substrates scope.[12] However, using Selectfluor and 2-iodobenzoic acid respectively as raw materials is uneconomical in the preparation of CFBSA and 1-chloro-1,2-benziodoxol-3-one. Therefore, developing more convenient and economical chlorinating reagents is still a sustained topic in synthetic chemistry.

Scheme 1. Preparation of *N*-chloro-*N*-methoxybenzene sulfonamide (CMOBSA)



Thus, we would like to report a novel chlorinating reagent, *N*-chloro-*N*-methoxybenzene sulfonamide (CMOBSA, **1**), which was prepared in high yield from cheap starting material benzenesulfonyl chloride by a simple two-step synthetic process (Scheme 1). The detailed process was described as follows: Firstly, benzenesulfonyl chloride was reacted with methoxylamine hydrochloride in CH_3CN in the presence of K_2CO_3 at room temperature; and then, *t*-BuOCl was added to the reaction system, obtaining CMOBSA with a overall isolated yield of 91%. CMOBSA is able to the chlorination not only of 1,3-diketones, β-keto esters, phenols, heteroarenes and aromatic amines, but also the chlorination of benzoyl trifluoroacetones.

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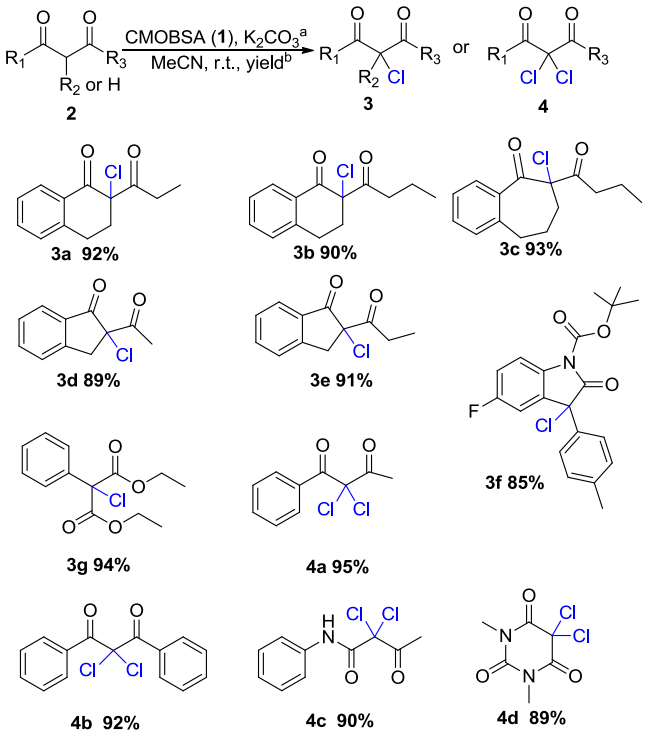
Results and discussion

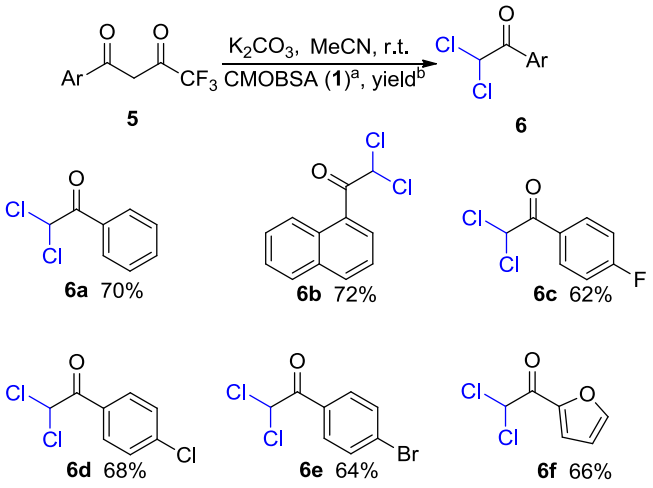
CMOBSA is a colorless liquid at ambient temperature. The stability of CMOBSA was first examined. The TLC-monitoring experiment confirmed that no decomposition occurred upon exposing it to air for several weeks. TGA experimental analysis for *N*-chloro-*N*-methoxybenzene sulfonamide exhibited sufficient thermal stability until it was heated to 162 °C. With good stability in hand, then we began to study its chlorination activity as follows.

Table 1 Chlorination of Carbonyl Compounds with CMOBSA



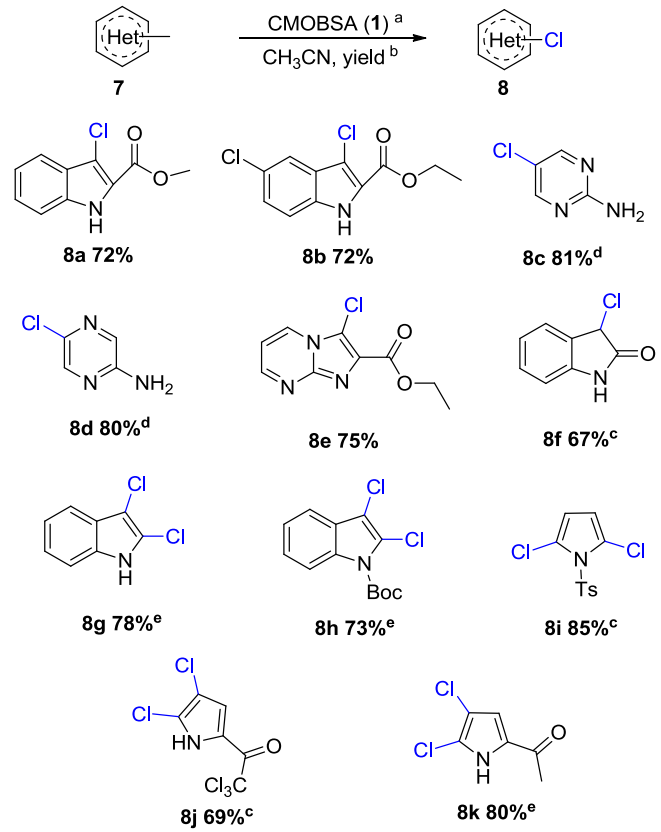
The reaction conditions are as follows: [a] Carbonyl compound **2** (1.0 equiv), CMOBSA (1.2 equiv) and K_2CO_3 (1.2 equiv) for the formation of compounds **3a**-**3f**, [b] CMOBSA (2.4 equiv) and K_2CO_3 (2.4 equiv) for the formation of compounds **4a**-**4d**, CH_3CN (3 mL), r.t., overnight.

Table 2 Chlorination of Benzoyl Trifluoroacetones with CMOBSA



The reaction conditions are as follows: [a] Benzoyl trifluoroacetones (1.0 equiv), CMOBSA (2.4 equiv) and K_2CO_3 (2.4 equiv) for the formation of compounds **6**, CH_3CN (3 mL), r.t., overnight. [b] Isolated yields based on compounds **5**.

Table 3 Chlorination of Heterocycles with CMOBSA

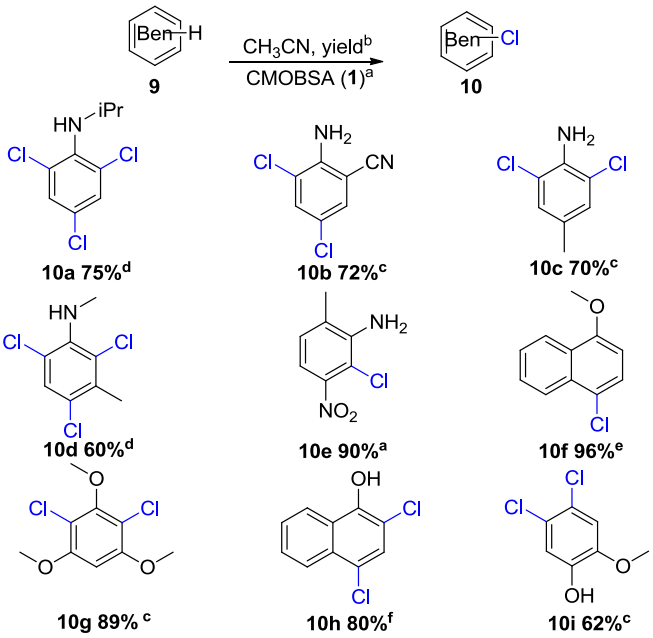


The reaction conditions are as follows: [a]Heterocycle compounds **7**(1.0 equiv), CMOBSA (1.2 equiv), r.t., CH_3CN (3 mL), 5h; [c]CMOBSA (2.4 equiv). CH_3CN (3 mL), r.t., overnight. [d]CMOBSA (1.2 equiv), CH_3CN (3 mL), 50°C, 5h. [d]CMOBSA (1.2 equiv), CH_3CN (3 mL), r.t., overnight. [e]CMOBSA (2.4 equiv), CH_3CN (3 mL), 50°C, overnight.[b] Isolated yields based on compounds **7**.

In our initial study, we found that by treatment of 2-propionyl-3,4-dihydronaphthalen-1(2*H*)-one (**2a**) with 1.2 equiv of chlorination reagent (CMOBSA) in CH_3CN (3 mL) at room temperature for 12h, 2-chloro-2-propionyl-3,4-dihydronaphthalen-1(2H)-one (**3a**) was obtained in 92% isolated yield. Under appropriate reaction conditions, yields of chlorinated products were all above 85% (Table 2, **3a-3g, 4a-4d**). Monochlorination products (**3a-3g**) were generated in excellent yields from the corresponding one-active-site substrates, while dichlorination products (**4a-4d**) were separated in much high yields in the presence of 2.4 equivalents of base and 2.4 equivalents of CMOBSA. The above results preliminarily express the good chlorination reactivity of CMOBSA.

α,*α*-Dichloroketones[13] are key intermediates in the synthesis of unsaturated acids, ynols, and heterocycles and *α*,*α*-dichloroketones also plays a significant role in cyclopropanation reactions.[14] Additionally, the *gem*-dichloromethyl group (-$CHCl_2$) is an important substructure in pharmaceuticals.[15] Occasionally, by the reaction of benzoyl trifluoroacetones with CMOBSA using K_2CO_3 as base, *α*,*α*-dichloroacetophenone (**6a**) instead of the corresponding dichloro benzoyl was obtained in 70% yield (Table 2). Substrates with electron-withdrawing group such as F, Cl and Br on the benzene ring resulted in acceptable yields (**6c-6e**). Furthermore, trifluorodione containing furanyl and nathranyl afforded similar results (**6b, 6f**). It supplied a route to selectively synthesize *α*,*α*-dichloroketones, avoiding the formation of monochloro or trichloro ketones. Trifluoroacetyl group might be attributed to the decomposition of *β*,*β*-dichloro substitution intermediates under base conditions.[16]

Table 4 Chlorination of Aromatics with CMOBSA



The reaction conditions are as follows: [a] Aromatics compounds **9** (1.2 equiv), CMOBSA (1.2 equiv), CH_3CN (3 mL), r.t., 1h. [C] CMOBSA (2.4 equiv), CH_3CN (3 mL), r.t., 1h. [d] CMOBSA (3.6 equiv), CH_3CN (3 mL), r.t., 5 min. [e] CMOBSA (1.2 equiv), CH_3CN (3 mL), 0°C, 3h. [f] CMOBSA (2.4 equiv), CH_3CN (3 mL), 0°C, 3h. [b] Isolated yields based on compounds **9**.

Indole, pyrimidine, pyrazine, pyrrole and other heterocycles were chlorinated in good yields. And the results are shown in Table 3. When 1.2 equiv of CMOBSA was used, the reaction showed good regioselectivity, and monochlorinated products (**8a, 8b, 8e)** were obtained in **72%, 72%, 75%** respectively at room temperature. Pyrimidin-2-amine, pyrazin-2-amine, indolin-2-one were also chlorinated, providing **8c, 8d, 8f** at 50 °C in acceptable yields. For N-Ts-protected pyrrole, 2,5-dichlorinated product **8i** was afforded in 85% yield with 2.4 equiv of CMOBSA. Indol and *N*-Boc-indol gave 2,3-dichlorinated products with acceptable yields (**8g, 8h**). 1-(4,5-Dichloro-1*H*-pyrrol-2-yl)one (**8k**) was synthesized by using 2.4 equiv of CMOBSA, which acted as precursor for the synthesis of Pyoluteorin. [17]

Aniline, phenol, anisole can also be chlorinated in moderate to good yields by CMOBSA under mild reaction conditions (Table 4, **10a-10i**). With electron-donating (methyl) and electron-withdrawing (cyano and nitro) as substituent, anilines produced corresponding products (**10a-10e**) with good yields. To our delight, 1-methoxynaphthalene was easily regioselectively transformed into the 4-chlorinated product (**10f**) in 96% yield.[18] 1,3,5-trimethoxybenzene, naphthalen-1-ol, 2-methoxyphenol were also chlorinated under mild conditions with satisfactory yields in **89%**,**80%** and **62%**, respectively.

Conclusions

In this work, *N*-chloro-*N*-methoxybenzene sulfonamide, a new chlorinating reagent was conveniently and economically prepared in high yield. It has properties of high reactivity, easy availability, wide substrate range and stable storage. It is also of more economic value in relation to other chlorinating reagents, such as CFBSA and 1-chloro-1,2-benziodoxol-3-one. 1,3-Diketones, *β*-keto esters, benzoyl trifluoroacetones, phenols, anisoles, heteroarenes and aromatic amines could be chloridized by this reagent. Furthermore, the dichlorination of benzoyl trifluoroacetones with CMOBSA and the subsequent removal of trifluoroacetyl supplied a way to selectively synthesize *α*,*α*-dichloroketones, avoiding the formation of monochloro or trichloro ketones. The application of this chlorinating reagent in other transformations is actively underway.

Acknowledgements

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Keywords: CMOBSA • chlorination • economic • stability • *a*,*a*-dichlorketones

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Layout 1:

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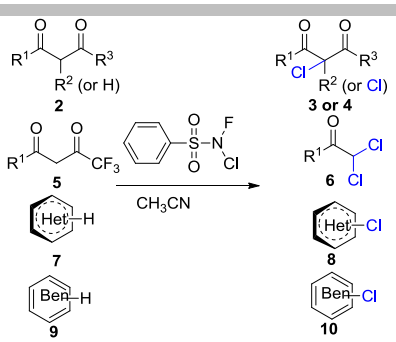
1,3-Diketones, *β*-keto esters, benzoyl trifluoroacetones, phenols, anisoles, heteroarenes and aromatic amines were chlorinated by a novel chlorinating reagent, N-chloro-N-methoxy-benzenesulfonamide, in good to high yields.



R^1, R^2, R^3 = H, alkyl, acyl; 37 examples; 60-96% yield; mild conditions

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Page No. – Page No.

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