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A Quick, Mild and Efficient Bromination Using CFBSA/KBr System

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Bromination is a fundamental transformation in organic chemistry and brominated compounds as building blocks are of paramount importance in organic synthesis. In our study, we have developed an efficient method of bromination by using CFBSA/KBr system at room temperature in short reaction time. Notably, this approach has been proven applicable to a range of substrates including 1,3-diketones and β-keto esters, phenols, aromatic amines and heteroarenes with good to excellent yields.

The general importance of halogenation reactions in organic chemistry[1] and, in particular, the role of bromination[2] in the synthesis of organic intermediates or antitumor, antibacterial and antiviral compounds have consequently captured great interest from synthetic and medicinal chemists.[3] Aryl bromides are highly important intermediates in the synthesis of agrochemicals and functional materials through cross-coupling reactions.[4] The development of modern coupling reactions,[5] such as Tamao-Kumada, Suzuki-Miyaura, Migita-Kosugi-Stille, Negishi, Hiyama-Hatanaka, Sonogashira, and Mizorogi–Heck reactions, has greatly increased the demand for brominated aromatics as starting materials. Therefore, developing efficient methodologies for the synthesis of brominated compounds is highly desirable.

Traditional methods of bromination usually involve the use of elemental bromine under harsh reaction conditions,[6] and require careful control of the addition rate and temperature to avoid undesirable side reactions. Due to its toxic nature, the use of elemental bromine is troublesome and environmentally hazardous. Therefore, new bromination protocols have been developed. Some reagents reported for this transformation include organic ammonium tribromides (OATB),[7] copper(II) bromide,[8] N-Bromosuccinimide (NBS),[9] and 2,4,4,6-Tetrabromo-3-n-pentadecyl-2,5-cyclohexadienone (TBPCO),[10] Bromodimethylsulfonium bromide (BDMS),[11] Sodium monobromoisocyanurate (SMBI)[12]. Another method involves using the bromide generated in situ from the oxidation of bromide ions. The combinations of oxidants and bromides such as H_2O_2-HBr,[13a] H_2O_2-V_2O_5-NH_4Br,[13b] H_2O_2-NH_4VO_3-KBr (a sustainable two-phase procedure for toluene oxidative bromination),[13c] TBHP-HBr,[13d] oxone/NaBr,[14a] oxone/HBr,[14b] cerium(IV) ammonium nitrate (CAN)/KBr,[15a] CAN/LiBr,[15b] Selectfluor/KBr[16] and $NaBrO_3$-NaBr[17] have been employed in these bromination reactions. Recently, Jiao and co-workers reported an efficient and practical system for inexpensive bromination and iodination of arenes as well as heteroarenes by using readily available dimethyl sulfoxide (DMSO) and HX (X = Br, I) reagents.[18] Despite the variety of reagents available for bromination, the completeness and quickness under mild condition continue to be problematic. In this communication, we reported a quick, mild and effective bromination protocol for 1,3-diketones, *β*-keto esters, aromatic amine, phenols and heteroaromatic compounds by using KBr and CFBSA developed in our laboratory.[19]

CFBSA, *N*-chloro-*N*-fluorobenzenesulfonylamide, is a novel chlorinating reagent, which has special characteristics such as simple structure, high reactivity, easy availability, wide substrate range and stable storage. And it can be easily prepared from the Chloramine B (one normal industrial disinfectant) by the reaction with Selectfluor. Inspired by this reagent, we attempted to prepare a compound structurally similar with CFBSA, *N*-bromo-*N*-fluorobenzenesulfonamide, as a brominating reagent. So we use Bromamine-B[20] to react with Selectfluor and, as expected, a new compound was monitored through TLC. However, we didn't get pure compound during the aftertreatment. We suspected that the side product tertiary amine originated from Selectfluor will deteriorate *N*-bromo-*N*-fluorobenzenesulfonamide. Hence, KBr instead of Bromamine-B as bromo sources was used to react with CFBSA in DCM (Scheme 1). Appreciatively, CFBSA were completely converted after 12h and an orange-red oil substance was got through extraction from water and vacuum distillation. To the best of our knowledge, the ^{19}F NMR chemical shift of CFBSA at 17.72 *ppm* and the above substance was detected at 8.53 *ppm*. Thus, combined with ^{1}H NMR and ^{13}C NMR data we can confirm this

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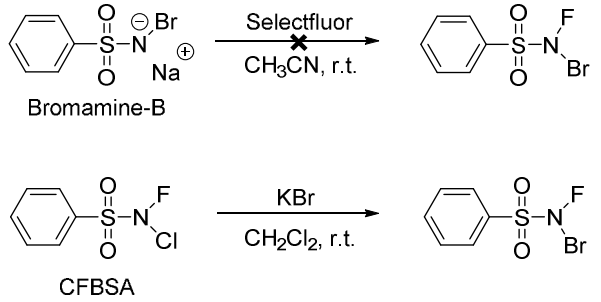
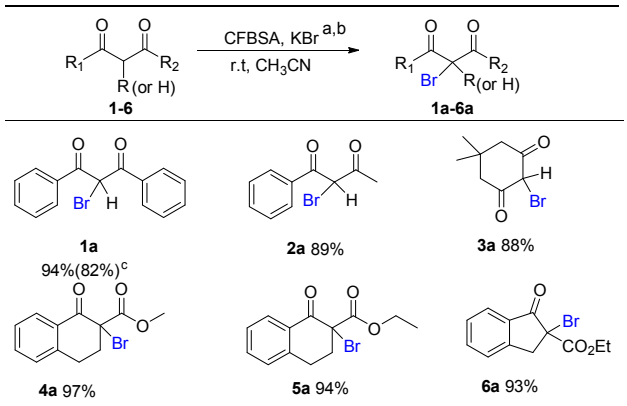
orange-red oil is *N*-bromo-*N*-fluorobenzenesulfonamide. However, *N*-bromo-*N*-fluorobenzenesulfonamide was found to be easily decomposed when we intended to take it as brominating reagent into reaction application. In this case, we projected to employ the combined CFBSA/KBr system as brominating reagent in the reaction.

Scheme 1 The synthetic strategy of N-bromo-N-fluorobenzenesulfonamide



Considering the low polarity of CH_2Cl_2 and long reaction time, we changed the reaction solvent into CH_3CN and found that CFBSA was completely converted into *N*-bromo-*N*-fluorobenzenesulfonamide in 10 minutes. Subsequently, to test the bromination efficiency of this way, 1,3-diphenylpropane-1,3-dione (**1**) was added into the reaction mixture. After 5 minutes, the starting material was transformed completely and the corresponding mono-bromide (**1a**) was isolated in 94% yield. This process was also applicable to other 1,3-diketones or *β*-keto esters and the results are presented in Table 1. Other unsubstituted 1,3-diketones (**2** and **3**) were *α*-monobrominated to afford products (**2a** and **3a**) in good yields. And *α*-brominated *β*-keto esters (**4a**, **5a** and **6a**) were also got in excellent yields. It is notable that these mild reactions were accomplished with high yields in quite short time.

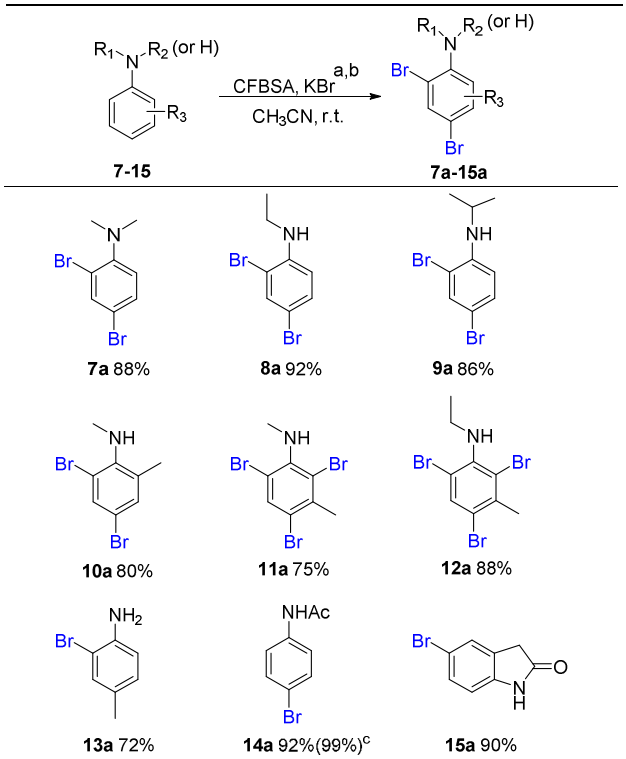
Table 1 The Bromination of 1,3-diketones and β-keto esters



[a] Conditions: 1,3-diketones or *β*-keto esters (1 mmol), CFBSA (1.2 equiv.) and KBr (1.5 equiv.) , CH_3CN (8 mL), r.t., 15 min. [b] Isolated yields based on starting materials. [c] conditions: H_2O_2/HBr, H_2O, r.t., reaction time :9h, Ref 13a.

Next, we are interested in expanding substrates to aromatic amines. Our results are presented in Table 2, and it is clear that this procedure is general, quick and efficient. The bromination of *N*-alkylanilines took place at the *ortho* position and *para* position because the latter high reactivity leads to the difficulty of selective monobromination. For *para*-methylaniline, monobromonation occurred with the formation of **13a** in 72% yields. With 2.2 equiv. CFBSA/KBr as brominating reagent, dibrominated products (**7a**-**10a**) were got in 80-92% yields. For *N*-alkyl-3-methylanilines (**11**, **12**), tribrominated products (**11a**, **12a**) were formed in 88% and 75% yields respectively with 3.2 equiv. CFBSA/KBr as bromo source. Furthermore, this method can be extended to the bromination of *N*-acyl aromatic amine like *N*-phenylacetamide (**26**) and indolin-2-one (**27**), mono-bromination occurred at the para position with 92% and 90% yields, respectively.

Table 2 The Bromination of Aromatic Amines.



[a] Conditions: aromatic amines (1.0 equiv.), CFBSA (2.2 equiv. for the formation of compounds **7a**, **8a**, **9a**, **10a**; 3.2 equiv. for the formation of compounds **11a**, **12a**; 1.2 equiv. for the formation of compounds **13a**, **14a**, **15a**), KBr (2.5 equiv. for the formation of

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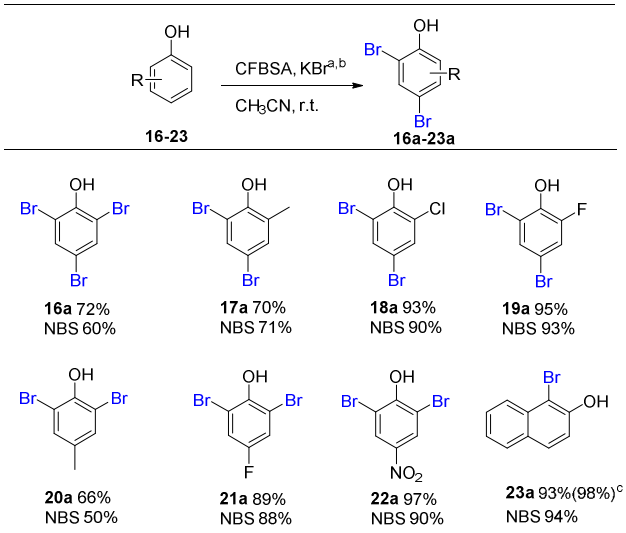
compounds **7a**, **8a**, **9a**, **10a**; 3.5 equiv. for the formation of compounds **11a**, **12a**; 1.5 equiv. for the formation of compounds **13a**, **14a**, **15a**), CH_3CN (8 mL), room temperature, 20 min. [b] Isolated yields based on starting materials. [c] conditions: CAN/LiBr, CH_3CN, r.t., reaction time: 7h, Ref 15b.

Similarly, we investigated the substrate scope for phenols. As illustrated in Table 3, bromination of phenol (**16**) proceeded with clean and quick conversion with the generation of tribromophenol (**16a**) in 72% yield. When *ortho*-cresol (**17**), *ortho*-chlorophenol (**18**), *ortho*-fluorophenol (**19**), *para*-cresol (**20**), *para*-fluorophenol (**21**) and *para*-nitrophenol (**22**) were employed to react with 2.4 equiv. CFBSA/KBr, the corresponding dibrominated products (**17a**-**22a**) were obtained in good yields (77–91%). It is obvious that the introduction of electron-withdrawing groups on the aromatic ring substantially increased the yields of bromination, which is different from the results using traditional brominating reagents.[21] The fused ring phenolic compound *β*-naphthol (**23**) afforded the expected 2-bromo-*β*-naphthol (**23a**) with 93% yield. The substituent on the phenols had a vital and cooperative effect on the regioselectivity of the bromination reactions. Our current procedure provided a mild and effective alternative to the synthesis of multisubstituted bromophenols. The attempted monobromination of the above phenol substrates **16**-**22** failed because the reaction tended to give a mixture of products.

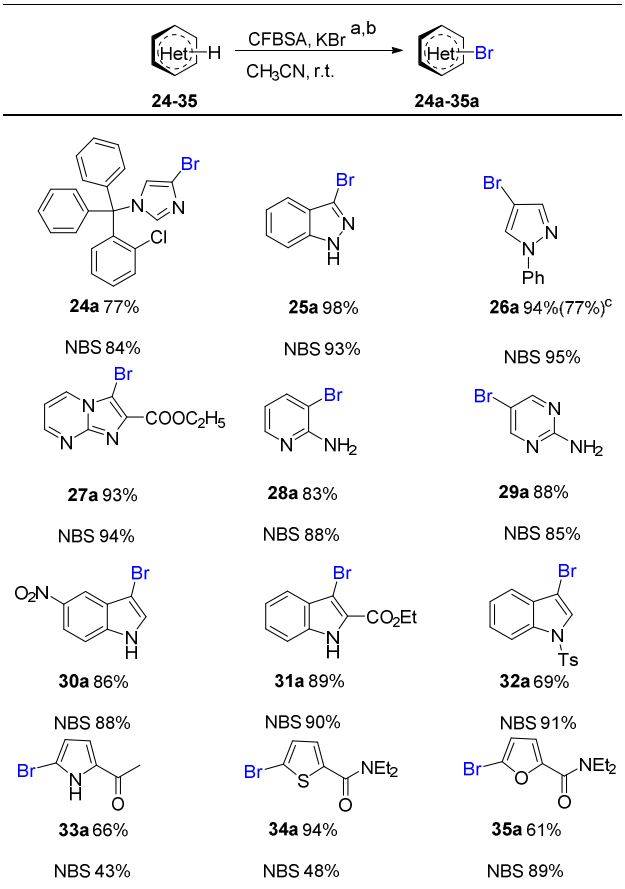
Table 3. The Bromination of Phenols



[a] Conditions: phenols（1.0 equiv.）, CFBSA (2.2 equiv. for the formation of compounds **17a**, **18a**, **19a**, **20a**, **21a**, **22a**; 3.2 equiv. for the formation of compounds 16a; 1.2 equiv. for the formation of compounds 23a), KBr (2.5 equiv. for the formation of compounds **17a**, **18a**, **19a**, **20a**, **21a**, **22a**; 3.5 equiv. for the formation of compounds **16a**; 1.5 equiv. for the formation of compounds **23a**), CH_3CN (8 mL), room temperature, 20 min. [b] Isolated yields based on starting materials. [c] conditions: TBPCO, Et_2O, r.t., reaction time: 0.5h, Ref 10.

To further demonstrate the versatility of our present methodology, the bromination of various heterocyclic aromatics including imidazole (**24**), pyrazoles (**25**, **26**), indoles (**30**-**32**), pyrrole (**33**) and other heterocycles (**27**, **28**, **29**, **34**, **35**) were scrutinized under the present conditions. As shown in Table 4, varieties of heterocycles were successfully brominated in good to excellent yields, demonstrating the high efficiency and functional group tolerance of this approach. Brominated indole compounds (**30a**-**32a**) were obtained in excellent yields within 15 min. It is noteworthy that the oxidative bromination of indole compounds without the protecting group on the nitrogen atom could not be achieved using other oxidants such as Selectfluor.[16] Some of the products were used in pharmaceutical chemistry,[22] for example, compound **25a** is a versatile and important building block to access CDK7 inhibitors.[23] Other heteroarenes including pyrazoles (**25**, **26**), imidazo[1,2-a]pyrimidine (**27**) pyrrole (**28**), pyrimidine (**29**), thiophene (**34**) and furan (**35**) could all be regioselectively brominated in good yields.

Table 4 The Bromination of Heteroarenes



[a] Conditions: heterocycles (1.0 equiv.), CFBSA (1.2 equiv.), KBr (1.5 equiv.), CH_3CN (8 mL), room temperature, 15 min. [b] Isolated yields

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based on starting materials. [c] conditions: DMSO/HBr, EtOAc, 60°C. reaction time: 5h, Ref 18.

Conclusions

In summary, a quick, mild and efficient oxidative bromination by using CFBSA/KBr system has been developed. It was successfully applied into four different types of compounds including 1,3-diketones and *β*-keto esters, aromatic amines, phenols and heteroarenes. This methodology of bromination could be efficiently accomplished in quite short time at room temperature, and also shows good group tolerance and broad substrate scopes.

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