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Development and Novel Applications of Halogenating Agents

Abstract

Organic halides are one of the most extensively utilized compounds for synthetic intermediates and useful final products in various areas such as pharmaceuticals, agrochemicals, fine chemicals, materials, polymers, among others. To meet these demands, many halogenating agents have been developed.[1-2] However, these reagents still suffer from lower efficiency or selectivity, difficult handling, stability issues, or limited substrate scope. In this context, our laboratory has developed more concentrated and bench-stable halogenating agents, stable complexes formed between 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and HF, HCl and HBr molecules, which proved to be superior to the conventional halogenating agents. [3-5]

With the objective of exploring other applications of HCl.DMPU beyond chlorination, we developed a HCl·DMPU-assisted one-pot conversion of aldehydes to nitriles. This method exhibited broad substrate scope with high yields for the aromatic, aliphatic, and allylic aldehydes incorporating various functional groups.[6]

Trifluoromethylthiolation (-SCF_3) and trifluoromethylselenolation (-$SeCF_3$) of organic compounds have been sought by medicinal chemists because their incorporation into drug candidates may lead to improved pharmacokinetics, eventually leading to enhanced therapeutic effects. In this regard, transition metal catalyzed trifluoromethylthiolation (-SCF_3) and trifluoromethylselenolation (-$SeCF_3$) of organic halides have received much attention. But the contemporary existing methods suffer from harsh reaction conditions and limited substrate scope. We addressed this issue by employing $AgSCF_3$ and [(NMe_4)($SeCF_3$)] in combination with commercially available gold catalyst [(MeDalphos) AuCl] on a diverse array of aromatic, alkenyl and alkynyl halides and obtained the corresponding trifluoromethylthio and trifluoromethylseleno derivatives in good to excellent yields. [7]

Another crucial member of the organo-halogen family is the trifluoromethyl (CF_3) group, which has garnered significant attention due to its unique properties, particularly in pharmaceutical and agrochemical areas. This interest has guided the development of various trifluoromethylating reagents to introduce a trifluoromethyl (CF_3) group to an organic molecule. Umemoto reagents are among the most widely used electrophilic trifluoromethylating agents.

Moreover, recently developed Umemoto reagents II[8] & III[9] can be synthesized in a one-pot method and are more powerful than their predecessors I and II. However, costly production of III and the restricted commercial availability due to patent protections are some of the challenges associated with these reagents. In this regard, we have developed an affordable, easy-to-handle and bench-stable trifluoromethylating agent that is more powerful than Umemoto reagent II. The broad reactivity of this reagent towards various nucleophiles was demonstrated.

We also designed and attempted to synthesize dithiadication electrophilic trifluoromethylating agents endowed with two transferable trifluoromethyl groups. However, our efforts to date have not produced satisfactory results.

References

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