Generation of Dimethyl Sulfoxide Coordinated Thermally Stable Halogen Cation Pools for C-H Halogenation

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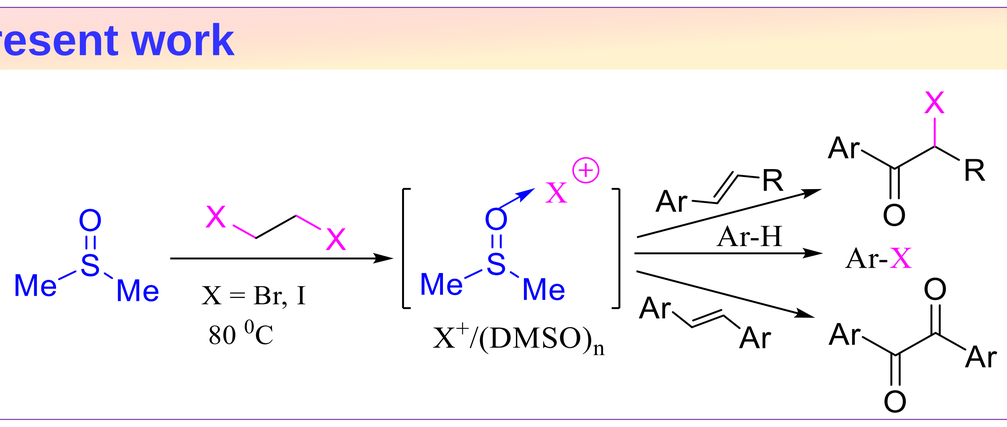
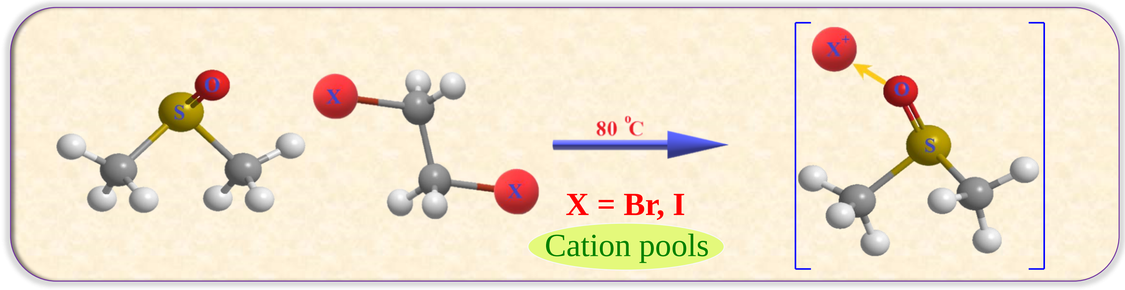
Adv. Synth. Catal. **2022**, *364*, 1031

Abstract:

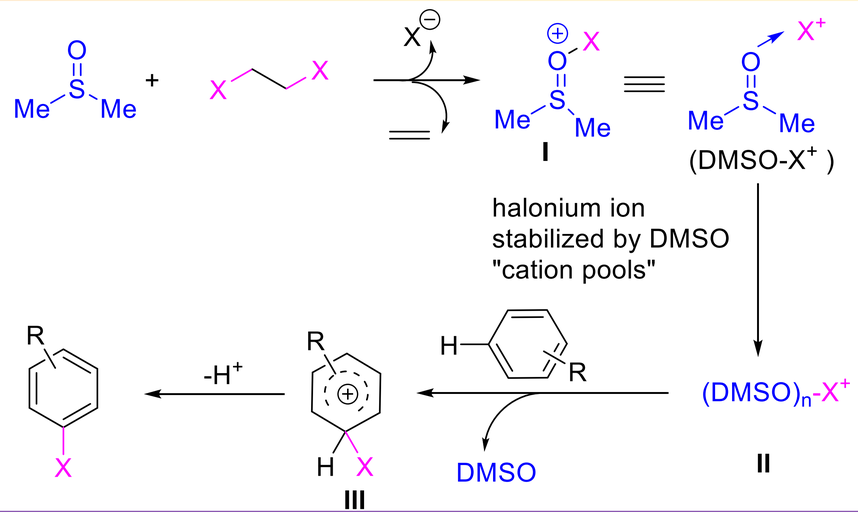
A method to generate halogen cation pools from the reaction of 1,2-dihaloethanes (hal= Br, I) and dimethyl sulfoxide (DMSO) for C-H halogenation of arenes and heteroarenes was reported. The initial reaction of DMSO and 1,2-dihaloethane generates the sulfur ylide, which undergoes pyrolytic elimination of ethylene by affording halonium ions. These ions were accumulated and stabilized by DMSO through coordination by forming halogen cation pools for the halogenation reaction. This protocol was selective for electrophilic monohalogenation of arenes at room temperature; however, polyhalogenated products were formed by raising the reaction temperature. Late-stage halogenation of heteroarenes and some commonly marketed drugs signifies the synthetic utility of this protocol in pharmaceutical chemistry. Unlike the classical methods, the in-situ generated electrophilic bromonium ion was further exploited for the direct synthesis of α-diketones from the alkenes under base-free conditions.

Present work

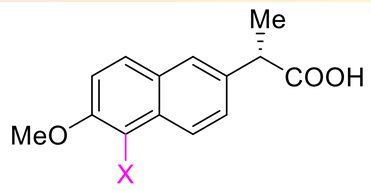




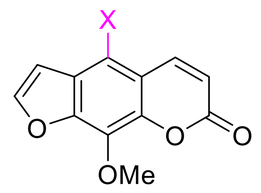
Our hypothesis



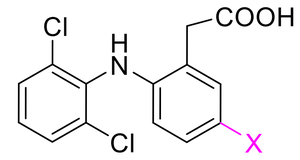
Mono-halogenation of some selected drugs



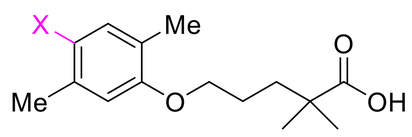
Br-naproxen (90 %)
I-naproxen (71 %)



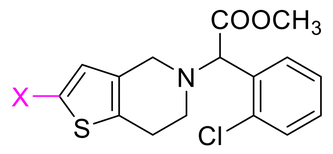
Br-xanthotoxin (72 %)
I-xanthotoxin (60 %)



Br-dichlofenac (87 %)
I-dichlofenac (75 %)

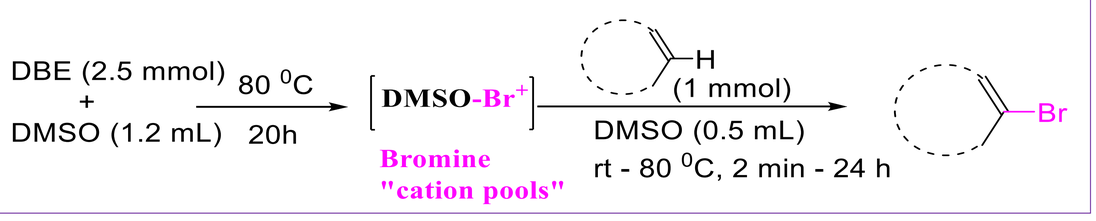


Br-gemfibrozil (83 %)
I-gemfibrozil (74 %)

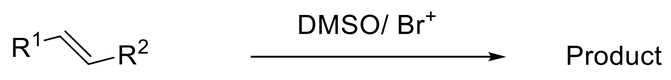


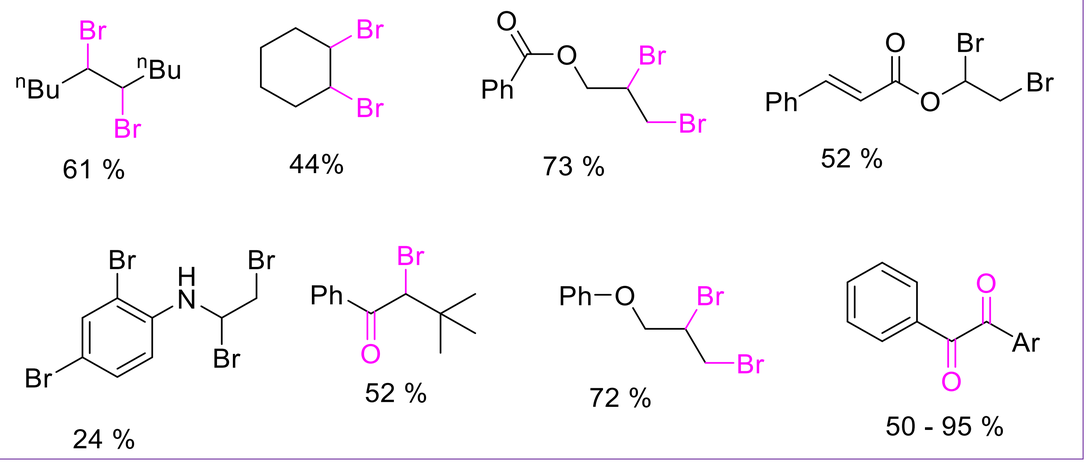
Br-clopidogrel (41 %)
I-clopidogrel (0 %, decomposition)

DBE/DMSO mediated C-H bromination

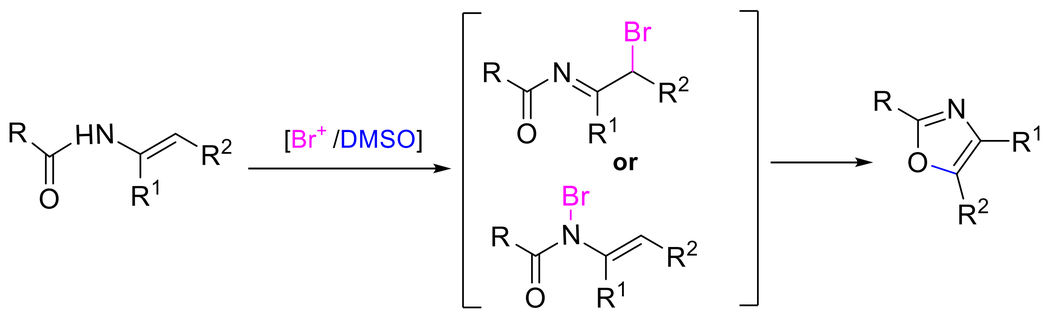


Reaction of olefin with bromine cation pools





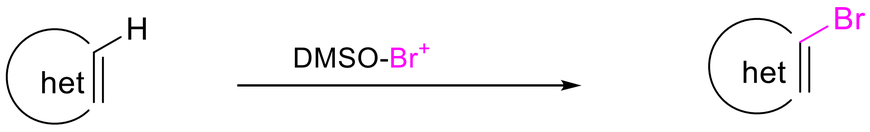
Metal-free synthesis of oxazoles from enamides



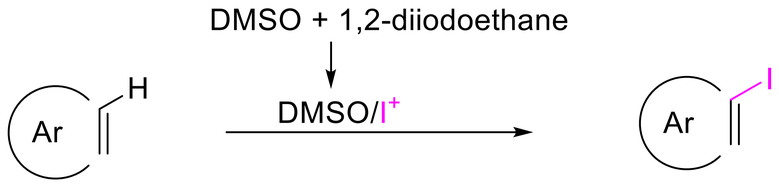
Conclusions

- ❑ Exploited the combination of dihaloethane (hal= Br, I)and DMSO as a precursor for generating thermally stable halogen cation pools (DMSO-X^+).
- ❑ Using this preformed bromonium ion enamides proceeds intramolecular annulation to afford oxazoles.
- ❑ This protocol is also efficient to produce dibromoalkane from alkyl olefin and α-diketone from diaryl alkenes.
- ❑ The mild reaction conditionsand operational simplicity allow the late-stage bromination and iodination of biologically potent heterocycles and drug candidates.
- ❑ 132 Substrates.

Bromination of heteroarenes



1,2-diiodoethane mediated iodination



References

P.G. Dalai, K. Palit, N. Panda, *Adv. Synth. Catal*. **2022**, *364*, 1031.

Acknowledgements

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