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Chemoselective monobromination of alkanes promoted by unactivated MnO_2

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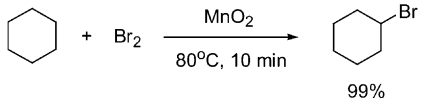
Abstract—Reaction of alkanes with bromine promoted by unactivated MnO_2 gave the corresponding alkylbromides in excellent yield with good chemoselectivity. The MnO_2 could be easily recovered and reused.

Alkanes are among the least reactive yet most abundant chemicals. Efficient functionalization of alkanes leading to the production of useful organic chemicals in an industrial scale is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge for chemists. A number of methods employing transition metal reagents have been developed for the C–H bond activation of alkanes.[1] However, these transformations, either stoichiometric or catalytic, often involve expensive metals such as Pd, Ru, Rh, Ir, or complex metal systems, and the recovery and direct reuse of catalysts are difficult.

Alkylbromides are among the most important synthetic intermediates in chemical industry. Although numerous methods have been developed for the synthesis of alkylbromides,[2] the direct bromination of alkanes is certainly the ideal way to produce alkylbromides. Various reagents have been investigated in the bromination of alkanes, including Br_2,[3] NBS,[4,5] Cl_3CSO_2Br,[6] CBr_4,[7] $Ar_2C{=}NBr$,[8] Et_4NBr,[9] $BrCCl_3$,[10] $CH_2Br_2/(SbF_5)_2$,[11] $CBr_4 2AlBr_3$,[12] Br_2/HgO.[13] Other systems involving metal ion-assisted oxidative bromination with H_2O_2 or *tert*-butylhydroperoxide as the oxidant and an inorganic bromide or $CBrCl_3$ as the bromine source were also reported.[14–19] Despite the enormous efforts already carried out, it remains desirable to develop novel bromination methods of practical value.

We report here the mild and chemoselective bromination of alkanes with Br_2 promoted by commercially available unactivated MnO_2, which can be easily recovered and reused. Thus, the mixture of cyclohexane (100 mL), bromine (10 mmol) and the commercially available unactivated MnO_2 (20 mmol) was stirred at 80 °C for 10 min, resulting in the disappearance of the bromine color. The mixture was then filtered and the filtrate was washed with water and then distilled to afford the pure product cyclohexylbromide (1.61 g) in 99% yield based on bromine (Eq. 1). The precipitate was washed with water and then air-dried to give the recovered MnO_2. Use of the recovered MnO_2 as the substitution for unactivated MnO_2 in the above reaction yielded the same result. Moreover, the titration of the combined water solution by aqueous NaOH solution indicated that quantitative amount of HBr was formed Eq. 1.



(1)

In the above reaction cyclohexane acted as both the reagent and the solvent. Increasing the concentration of bromine from 0.1 to 0.4 M led to the slight decrease of product yield (91%), probably because bromides were not very stable in the presence of MnO_2.

Other alkanes were also tested and the results are summarized in Table 1. As shown in Table 1, mono-bromination products were obtained in high yield in all the cases screened. The cyclic alkanes gave the corresponding cycloalkylbromides within 10 min (Table 1, entries 1–4). By control of the reaction temperature, good chemoselectivity could be achieved. For example, when all the CH_3, CH_2, and CH groups were present in one

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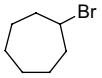
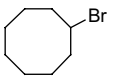
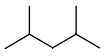
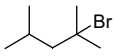
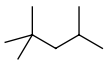
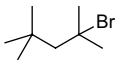
Table 1. Bromination of hydrocarbons with Br_2/MnO_2

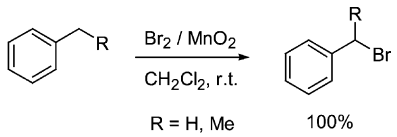
Entry	Substrate[a]	Temp (°C)	Time (min)	Product	Yield[b] (%)
1		50[c]	10		97
2		80[c]	10		99
3		80	10		97
4		80	10		97
5		10	100		100
6		10	90		100
7[d]	n-C_5H_{12}	36[c]	60	$C_3H_7CHBrCH_3$ $(C_2H_5)_2CHBr$	79 20
8[d]	n-C_6H_{14}	60	20	$C_4H_9CHBrCH_3$ $C_3H_7CHBrC_2H_5$ $C_5H_{11}CHBrCH_3$	62 36 48
9[d]	n-C_7H_{16}	60	20	$C_4H_9CHBrC_2H_5$ $(C_3H_7)_2CHBr$	32 20
10	$PhCH_3$	0	60	$PhCH_2Br$	100
11	PhC_2H_5	0	60	$PhCHBrCH_3$	100

[a] Reaction condition: Br_2 (10 mmol) and MnO_2 (20 mmol) in an alkane (100 mL).
[b] Isolated yield based on Br_2.
[c] Refluxing temperature.
[d] The product ratio was determined by ^1H NMR.

molecule (Table 1, entries 5 and 6), the bromination occurred exclusively at the tertiary carbon. For linear alkanes (Table 1, entries 7–9), only the internal carbons were brominated furnishing a mixture of regioisomers, while no bromination could be detected at the terminal methyl carbon. On the other hand, toluene having an active methyl group was converted to benzyl bromide even at 0 °C (Table 1, entry 10).

The unactivated MnO_2 played a crucial role in the bromination reactions. This could be illustrated by the following experiments with cyclohexane as the substrate. Without the presence of MnO_2, no bromination occurred. When 50 mol % of MnO_2 was employed, the reaction was incomplete and the color of bromine persisted after refluxing for 8 h. After the usual work-up, cyclohexyl-bromide was isolated in 55% yield. With equimolar amount of MnO_2, the reaction was complete within 10 min to afford the product in 98% yield. Use of freshly prepared activated MnO_2[20] as the substitution for unactivated MnO_2 showed almost no difference. The requirement for the stoichiometric amount of MnO_2 might be attributed to the formation of HBr in the bromination process. Once an alkylbromide molecule was formed, an HBr molecule was released simultaneously, which consumed one MnO_2 molecule presumably by the formation of unreactive MnO(OH)Br. Work-up with water regenerated MnO_2. Based on this assumption, we added an excess amount of water to the reaction system containing only 50 mol % of MnO_2. The color of bromine faded away in 1.5 h. However, the reaction time was longer and the product yield was lowered. With the ready availability and easy recovery and direct reuse of MnO_2, two equivalents of MnO_2 were adopted to ensure the fast and complete bromination. It should be mentioned that the direct photolysis of cyclohexane with bromine afforded the mixture of cyclohexylbromide (35%) and trans-1,2-dibromocyclo-hexane (13%), as reported by Shaw et al.[3]

We also tested some other substrates in the bromination with Br_2/MnO_2. Benzene, dichloromethane and 1,2-dichloroethane were unreactive toward MnO_2/Br_2 at room temperature. This phenomenon allows them to be utilized as the solvents in the bromination of hydrocarbons having activated C–H bonds. For example, treatment of toluene or ethylbenzene (2 equiv) with Br_2 (1 equiv) and MnO_2 (2 equiv) in CH_2Cl_2 (0.5 M) at room temperature for 10 min led to the quantitative formation of the expected product (Eq. 2).



(2)

Although no detailed study has been carried out to elucidate the reaction mechanism, it is plausible that the bromination is a hydrogen atom abstraction process

involving bromine radicals.[21] The following evidences support our hypothesis: (1) The relative reactivities of CH_n groups are parallel with their C–H bond dissociation energies. (2) The product ratio (~1.7) in the case of hexane is close to that (1.5) in the photobromination with Br_2 in trifluoroacetic acid,[22] indicating that the bromine radical might be involved in the reaction. (3) The bromination is tolerant to water. (4) Benzene is inert toward Br_2/MnO_2 at room temperature.

We also screened other metal oxides in the bromination of cyclohexane. Among those tested, CuO and Fe_2O_3 showed no activity at all. NiO_2 gave moderate yield (50%) of bromination product along with *trans*-1,2-dibromocyclohexane in 6% yield. $Mn(OAc)_3$ and pyridinium chlorochromate (PCC) led to the formation of cyclohexylbromide in good yield as MnO_2. However, the recovery and reuse of the catalysts are not feasible.

In conclusion, we have demonstrated the mild and chemoselective bromination of hydrocarbons with Br_2 and unactivated MnO_2. The great advantage of this method is that the MnO_2 can be easily recovered and reused without further activation. This method is efficient, economic, environmentally friendly, and therefore practical. Further investigation on the scope and limitation of the MnO_2/Br_2 system is currently in progress.

Acknowledgements

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