Oxybromination of Ethynylbenzene Catalysed by Molybdenum Complexes in Organic Solvent and in Ionic Liquids

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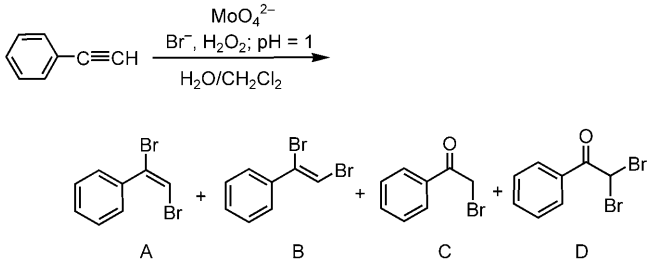
Abstract: The molybdenum(VI)-catalysed oxybromination of ethynylbenzene was performed with hydrogen peroxide as oxidant and potassium bromide as source of bromine, in a two-phase water/solvent system, where solvent was either dichloromethane or an ionic liquid. The selectivity was toward 1,2-dibromostyrene when performed in water/dichloromethane. In ionic liquids better yields and shorter reaction times were obtained that, together with the complete ethynylbenzene conversion and the preferred formation of α,α-dibromoacetophenone, make the reaction synthetically useful.

Keywords: alkynes; green chemistry; ionic liquids; molybdenum(VI); oxybromination

Alkynes have accompanied organic chemistry from the very beginning and are still an important class, because they can be used as building blocks for complex molecules or transformed into different functional groups, taking advantage of similarities and differences with the reactivity of alkenes.[1] Among the alkene reactions, the oxybromination by vanadium(V) complexes could be performed with cheap and non-toxic reagents, such as hydrogen peroxide and KBr.[2–4] The reaction was carried out in a two-phase system, water-CH_2Cl_2, with the oxybromination reagents dissolved in water and the substrate dissolved in the organic solvent. It is characterized by a good overall yield and a good selectivity toward the formation of the synthetically valuable bromohydrin.



Scheme 1. Mo(VI)-catalysed oxybromination of ethynylbenzene with hydrogen peroxide and KBr in water/halogenated solvent.

Subsequently, reactivity and selectivity were improved by using environmental benign ionic liquids (ILs), instead of the molecular solvent.[5]

In view of these results, it seemed desirable to investigate whether the oxybromination reaction in these systems could be extended to alkynes. We report here the results obtained on reacting ethynylbenzene with H_2O_2/KBr. Since bromination of this alkyne is expected to be more difficult than that of styrene,[6] the more reactive Mo(VI) species[7] was used as catalyst.

The oxybromination reaction of ethynylbenzene was carried out at room temperature in a two-phase system H_2O/CH_2Cl_2. The reaction output (Scheme 1) was quantified by GC analyses, with dodecane as internal standard and the results are reported in Table 1. They are the average of at least three independent runs. Chloroform was also used as organic solvent. The conversion of ethynylbenzene and yields were determined independently and were in good agreement for the reaction in dichloromethane, where 1,2-dibromostyrene (*cis*+

Table 1. Mo(VI)-catalysed oxybromination of ethynylbenzene with hydrogen peroxide and KBr in water/halogenated solvent.

Entry	Solvent	[PhC≡CH] [M]	[MoO_4^-], [M]	[KBr] [M]	[H_2O_2] [M]	Time [h][a]	Conversion [%]	Relative yield[b]	Absolute yield[c]	Selectivity A : B : C : D
1	CH_2Cl_2	0.01	0.005	0.05	0.01	18	50	84%	42%	20 : 56 : 20 : 4
2	CH_2Cl_2	0.02	0.01	0.025	0.02	18	50	94%	47%	11 : 31 : 7 : 51
3	$CHCl_3$	0.02	0.01	0.025	0.02	18	50	64%	32%	11 : 25 : 15 : 49

[a] Time necessary for the oxidant to be consumed.
[b] Relative to the consumed substrate.
[c] Relative to the initial concentration of alkyne.

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Table 2. Mo(VI)-catalysed oxybromination of ethynylbenzene with hydrogen peroxide and KBr in water/ionic liquids.

Entry	Solvent	[PhC≡CH] [M]	[MoO_4^-] [M]	[KBr] [M]	[H_2O_2] [M]	Time [h][a]	Conversion [%]	Relative yield[c]	Absolute yield[d]	Selectivity A : B : C : D
1	bmim Tf_2N[b]	0.02	0.01	0.10	0.02	2	50	64%	32%	3 : 8 : 43 : 46
2	bmim Tf_2N	0.04	0.02	0.05	0.04	4	40	80%	32%	4 : 6 : 24 : 66
3	bmim PF_6	0.02	0.01	0.10	0.02	2	55	96%	53%	0 : 7 : 19 : 74
4	bmim PF_6	0.04	0.02	0.05	0.04	2	50	92%	46%	2 : 4 : 16 : 78
5	bmim PF_6	0.04	0.02	0.10	0.04	2	60	95%	57%	2 : 7 : 38 : 53

[a] Time necessary for the oxidant to be consumed.
[b] $Tf_2N = (CF_3SO_2)_2N$.
[c] Relative to the consumed substrate.
[d] Relative to the initial concentration of alkyne.

Table 3. Oxybromination of ethynylbenzene with hydrogen peroxide added batchwise and KBr in H_2O/bmim PF_6.

Entry	[PhC≡CH] [M]	Catalyst	[Catalyst] [M]	[KBr] [M]	[H_2O_2][a] [M]	Conversion [%]	Absolute yield[b]	Selectivity A : B : C : D
1	0.02	MoO_4^-	0.01	0.1	0.04	100	88%	6 : 9 : 10 : 75
2	0.02	VO_3^-	0.02	0.1	0.04	100	70%	13 : 15 : 9 : 63

[a] Added in two portions.
[b] Relative to the initial concentration of alkyne.

trans mixture) was the main product and the overall yield was around 50%. In chloroform, the amount of ethynylbenzene that disappeared was higher than that transformed into brominated products, probably due to side reactions. At the same time, a parallel decomposition of H_2O_2 can occur upon prolonged contact with Mo(VI), as it was observed with V(V) species.[4,8] Initial reaction conditions were chosen in order to favour the formation of molecular bromine (entry 1) or to disfavour it (entry 2). As can be seen from inspection of Table 1, an increase of the alkyne/Br^- ratio from 0.2 to 0.8 – consequently diminishing the reagent that gives dibromo derivatives – shifted the selectivity toward α,α-dibromoacetophenone. This result indicates that bromoalkenes and bromo ketones are formed by different routes. If we compare the reactions in dichloromethane and chloroform, other conditions being equal, selectivities are comparable, although the yield is somewhat lower in chloroform than in CH_2Cl_2 (entries 2 and 3).

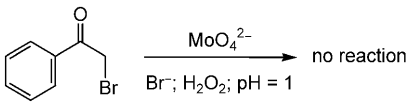
The reaction was then performed in water/ionic liquids, in order to verify whether it was possible to replace the halogenated solvent with a more sustainable one. Hydrophobic ILs with the 1-butyl-3-methylimidazolium [$bmim^+$] cation were used, with different anions, i.e., hexafluorophosphate, [PF_6^-], and bis(trifluoromethanesulfonyl)imide, [$(CF_3SO_2)_2N^-$].[9] The results are collected in Table 2.

A number of interesting aspects emerged. First, the reaction performed in water/ILs was faster than that in molecular solvents. The reduced reaction times, especially in bmim PF_6, had the positive side effect that almost all the consumed ethynylbenzene was converted into the reaction products. Second, yields were comparable, but the selectivity was definitely shifted toward the dibromo ketone (Table 2).

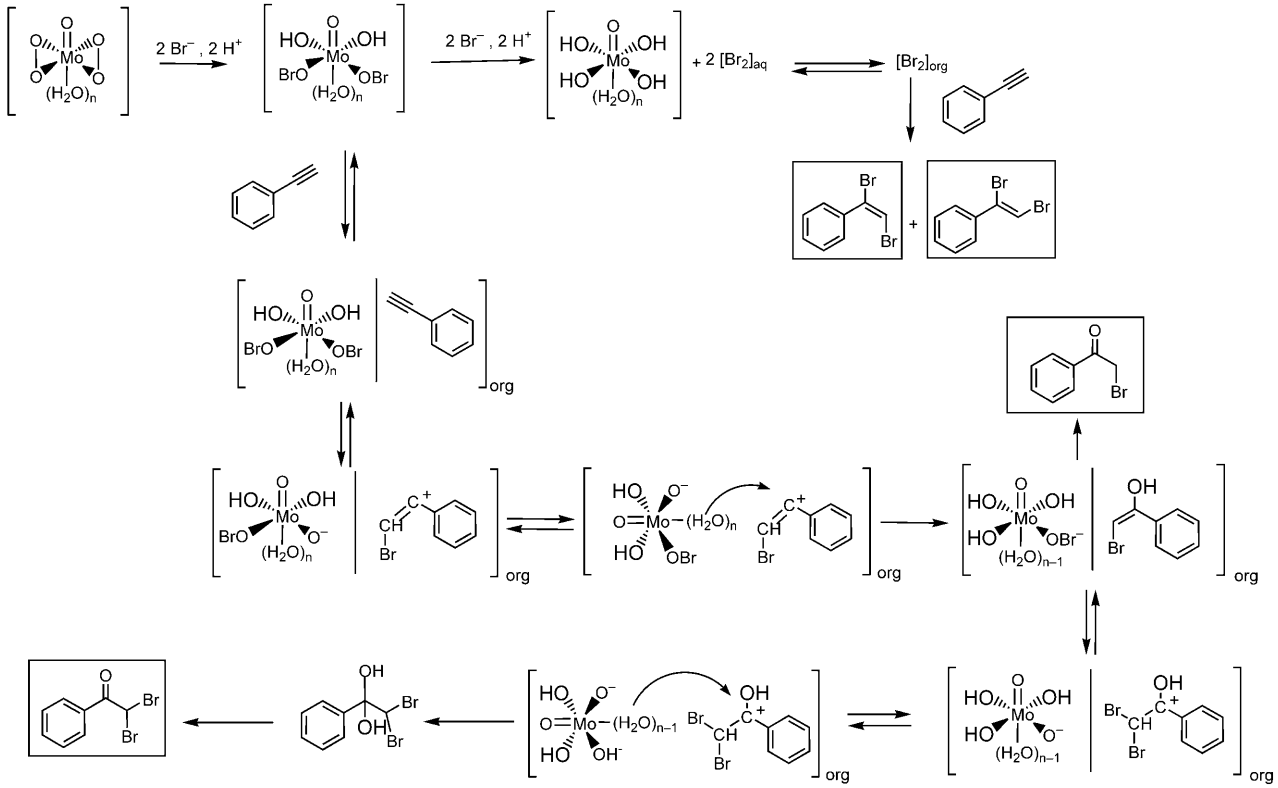
This is an important result, because α,α-dibromoacetophenone is important per se, having antibacterial, fungicidal and algicidal properties, as evidenced by a number of patents.[10] Moreover, it is a valuable intermediate for further transformations, for example, to α-haloenolates[11] or biologically active heterocyclic compounds.[12] The synthesis of α,α-dihaloacetophenones still needs improvement and new procedures were recently reported.[12,13]

In order to improve the yield, experiments were carried out by adding H_2O_2 in two portions, in order to keep its decomposition at a minimum. As can be seen from Table 3, yield rose up to 88%, while selectivity remained the same (entry 1). The reaction was repeated with the same procedure, i.e., batchwise addition of H_2O_2, using V(V) as catalyst. As expected, yields were lower (Table 3, entry 2), although still good, with a similar product distribution.

In order to understand how α,α-dibromoacetophenone formed, a blank experiment was performed, starting from α-bromoacetophenone [Eq. (1)]. Under the same conditions, no reaction was observed. Therefore, the formation of the dibromo derivative must occur after the first addition to the triple bond, before the bromoenol transforms into α-bromo ketone.



(1)



Scheme 2. Reaction pathways of the Mo(VI)-catalyzed oxybromination of ethynylbenzene.

The pathways of ethynylbenzene oxybromination are represented in Scheme 2, in analogy to what was found in alkene oxybromination.[5] for which reactive species were experimentally detected.[14]

This mechanistic scheme is in agreement with the experimental results. In fact, the sharp decrease of 1,2-dibromostyrene on going from dichloromethane to bmimPF_6 can be ascribed to different distribution of molecular bromine between the two phases. In the ionic liquid, a more polar medium,[15] where the functionalisation of the substrate is likely to occur,[5] the Br_2 concentration is expected to be lower than in dichloromethane. Moreover, the very nature of the IL may help in keeping the reactive species within the organized solvent cage, thus rendering the reaction faster.

In conclusion, the oxybromination reaction by H_2O_2/KBr was successfully applied to an alkyne. The catalysis by Mo(VI) was more effective than that by V(V). The conversion of ethynylbenzene could be made almost quantitative, just by adding H_2O_2 in portions. Finally, the selectivity could be diverted from the 1,2-dibromoalkene to the synthetically useful dibromo ketone, by changing the solvent from dichloromethane to ionic liquid.

Work is in progress to extend the reaction to other alkynes and to elucidate factors affecting the mechanism. However, it is already possible to say that in H_2O/IL, provided that H_2O_2 is added batchwise, the method compares favourably with previously reported synthesis of α,α-dibromoacetophenone.[16] The system made of Mo(VI)/KBr/H_2O_2 is a mild, efficient and sustainable catalyst for alkynes as well as for alkenes.

Experimental Section

General Methods

GC analyses were carried out with a Varian CP 3900 instrument, equipped with a 30 m × 0.25 mm SPB 35 capillary column, coated with 0.25 μm methylsilicone. A Bruker AM400 spectrometer was used to obtain ^{1}H NMR spectra, as $CDCl_3$ solutions, with tetramethylsilane as the internal standard. Mass spectra were obtained with a GC-MS Shimadzu CP 6000 instrument. IR spectra were recorded with a Perkin-Elmer 983 spectrophotometer, using an NaCl cell and CCl_4 as the solvent.

Preparation of Ionic Liquids

The synthesis of ILs used in this work consisted in two steps. The first was a quaternisation reaction between an alkyl-substituted imidazole and an alkyl bromide, to obtain a solid precursor. The second one was a metathesis reaction in which the bromide ion is exchanged by an appropriate anion able to give a liquid product at room temperature. Both these processes

were executed following literature procedures.[17–21] Characterization of ionic liquids was made by ^{1}H NMR and their identity was confirmed by comparison with literature data,[22] where available.

Determination of Response Factors

1,2-Dibromostyrene (*cis* + *trans*) was prepared in 22% yield by reacting 3 mmol ethynylbenzene in 30 mL CH_2Cl_2 with 6 mmol KBr and 1.2 mmol $KBrO_3$ in 30 mL water, with the pH adjusted at 1.0 ($HClO_4$), until the reddish-brown colour disappeared.

α-Bromoacetophenone is a commercial grade reagent. α,α-Dibromoacetophenone was isolated by column chromatography from the crude reaction product (silica gel; eluent: 40–70 °C petroleum ether containing 5% diethyl ether); IR: $\nu_{CO} = 1750\ cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 8.1$ (broad s, 5H, Ph), 6.55 (s, 1H, $CHBr_2$).

Four solutions in $CHCl_3$, containing a known concentration of decane (0.01 M) as the internal standard, were prepared for each compound (ethynylbenzene, 1,2-dibromostyrene, α-bromoacetophenone, α,α-dibromoacetophenone), with concentrations in the range 0.002 to 0.02 M). The solutions were injected in the gas-chromatograph at least three times each and the average ratios (area of compound/area of standard) were plotted against the concentration ratios. The slope of the straight line obtained with a linear regression calculation gave the response factor for the examined compound.

Oxybromination of Ethynylbenzene

In water-organic solvent: In a typical experiment, 1 mmol KBr and 0.4 mmol $(NH_4)_2(MoO_4)$ were dissolved in 40 mL H_2O and the pH adjusted at 1.0 with $HClO_4$. 0.8 mmol ethynylbenzene were dissolved in 40 mL CH_2Cl_2. The two solutions were mixed in an Erlenmeyer flask, stirred at 1000 rpm, and 0.8 mmol hydrogen peroxide added. The reaction was stopped as soon as the yellow colour of diperoxomolybdenum disappeared. The residue from the organic layer, separated and evaporated, was examined by GC. The product identification was made by comparison with authentic samples.

In water-ionic liquids. 1 mmol KBr and 0.1 mmol $(NH_4)_2(MoO_4)$ were dissolved in 10 mL H_2O and the pH adjusted at 1.0 with $HClO_4$. 1 mL of this solution was added in a Schlenk tube containing 0.02 mmol ethynylbenzene dissolved in 1 mL IL. The resulting mixture was stirred at 1000 rpm and 0.02 mmol H_2O_2 added. At the end of the reaction (disappearance of yellow colour), 100μL of the ionic liquid solution were taken and diluted in 1 mL $CHCl_3$, 0.01 M in dodecane. The solution was examined by GC.

Acknowledgements

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