Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8609-8612, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01977-6

Synthesis of Brominated Compounds. A Convenient Molybdenum- Catalyzed Procedure Inspired by the Mode of Action of Haloperoxidases.

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Abstract: A two-phase ($CHCl_3$ / H_2O) procedure for the synthesis of halogenated compounds has recently been developed. Such procedure mimics the mode of action of the enzymes haloperoxidases which contain vanadium in their active center. We have investigated the possibility to substitute vanadium with molybdenum. The molybdenum-based reactions show some advantages over the vanadium-based ones. In fact reaction times are shorter and overall yields are larger, under similar experimental conditions, both in the reaction with double bonds as well as with aromatic rings. Moreover, with double bonds, the molybdenum catalyzed process preferentially yields bromohydrins which are valuable synthetic intermediates. On the other hand, the molybdenum-catalyzed reactions show peculiar mechanistic features which deserve further investigation.
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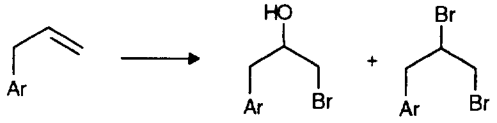
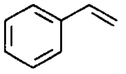
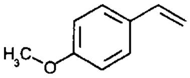
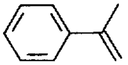
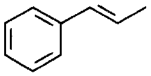
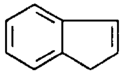
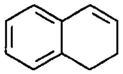
Haloperoxidases are enzymes which catalyze the halogenation of organic compounds.[1-3] Their mode of action is currently under active investigation.[4-11] Some general features have already been established. The enzymes contain vanadium(V) in their active center. Thus, in the presence of hydrogen peroxide, a peroxovanadium species is formed which is a much stronger oxidant than hydrogen peroxide.[12,13] This peroxo-complex oxidizes X^- (Cl^- or Br^-) to an intermediate whose nature is still poorly understood.[14] The intermediate reacts with appropriate organic substrates, *i.e.* olefins and aromatic compounds, yielding halogen containing derivatives, *e.g.* halocompounds or halohydrins.[2,4] In spite of the fact that the intermediate might decompose the oxidant by reacting with a second molecule of hydrogen peroxide, the chemoselectivity of the enzyme-catalyzed reactions is very large.[14] Accordingly, the yields of halogenated products, based on hydrogen peroxide consumed, are also very high.[3] This led us to suggest that the formation of the intermediate and the halogenation reactions occur in two different compartments of the enzymatic system.[9-11] In particular, the former process should take place into a hydrophilic portion of the enzyme whereas the latter reaction should occur into a lipophilic one.[9-11] Along this line we developed a biphasic procedure aimed at mimicking the mode of action of the enzymes.[9-11] In our system hydrogen peroxide, NH_4VO_3 and KBr are dissolved into the aqueous phase in which both the formation of the peroxovanadium complex and the oxidation of Br^- take place. The intermediate thus formed is transferred, under stirring, into the organic phase in which the reaction with the substrate occurs. The high yields of bromine-containing derivatives provided support to our mechanistic proposal on the mode of action of bromoperoxidases.[9-11] At the same time, they were also of synthetic significance in the light of the advantages of such a procedure compared with the traditional bromination and bromohydrin formation methods.[15]

The success of the procedure outlined above is related to the strong oxidizing power of the peroxovanadium formed.[12,13] Therefore, we decided to investigate the behavior of other metals which are also capable of forming peroxocomplexes.[12,13,16-18] In this paper we report results concerning the catalysis by molybdenum(VI) in the reaction with double bonds, Table 1, and with aromatic compounds, Table 2. Molybdenum(VI) is known to react with hydrogen peroxide in acidic aqueous media forming oxo-diperoxo complexes[12,18] which are usually more reactive than the vanadium analogous.[12] For comparison purposes the Tables include also some data obtained with vanadium(V) under identical conditions.

Table 1: Reaction of various olefins (0.4 mmoles) with H_2O_2 (0.4 mmoles) and KBr (0.5 mmoles), catalyzed by Na_2MoO_4 or NH_4VO_3 (0.2 mmoles) in a two-phase system (20 mL H_2O/20 ml $CHCl_3$) under stirring (1000 rpm) at 25°C.



A **B**

#	*Substrate*	*Catalyst*	*Time, hours*	*Substrate conversion*[a] *%*	*A:B*[b]
1		Mo(VI)	4	84	94 : 6
			24	97	95 : 5
2	"	V(V)	4	53	92 : 8
			72	66	94 : 6
3		Mo(VI)	4	76	91 : 9
			24	88	90 : 10
4		Mo(VI)	4	80	89 : 11
			24	99	88 : 12
5		Mo(VI)	4	85	94 : 6
			24	99	95 : 5
6		Mo(VI)	4	79	84 : 16
			24	97	94 : 6
7		Mo(VI)	4	77	47 : 53
			24	90	61 : 39
8		Mo(VI)	4	75	73 : 27
			24	91	68 : 32
9	"	V(V)	4	42	47: 53
			24	51	54 : 46
			120	61	57 : 43

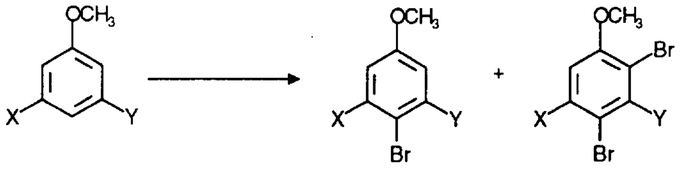
a) since no products other than A and B are detected, this is also the chemical yield of the reaction; in the reactions with molybdenum catalyst the almost quantitative consumption of the peroxide is observed in 2 hours. b) the identity of the products has been confirmed by comparison of their MS and ^{1}H-NMR spectra with authentic samples.

The data show that molybdenum can indeed substitute vanadium in the two series of reactions examined. In fact the reaction times are shorter and the overall yields are larger. It may be noted that, when a competition between the formation of a dibromoderivative and of a bromohydrin is possible, the Mo(VI) catalyzed system compared with the vanadium one appears to favor the formation of the latter compound, as shown by the data of Table 1 (entries 1-4 and in particular, 8 and 9).

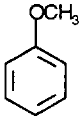
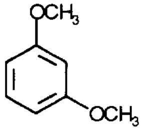
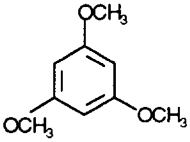
Worthy of note is that the process may operate under catalytic conditions. In fact after consumption of H_2O_2 the reaction starts again by further addition of H_2O_2. In the case of styrene, further addition of 0.4 mmoles of H_2O_2 and 0.5 mmoles of KBr affords, in 24 hours, 99% yield of products with an A:B ratio of 88:12 (0.8 mmol of styrene used).

The synthetic significance of our results may be illustrated by looking at the results of the reaction of indene, entry 6, which provides 91% yield of the corresponding bromohydrin. A literature recommended procedure for such a transformation which utilizes N-bromosuccinimide in DMSO in the presence of water, at temperature below -20°C under nitrogen, gives 72% yield of the bromohydrin.[15]

Table 2: Reaction of aromatic substrates (0.4 mmoles) with H_2O_2 (0.4 mmoles) and KBr (0.5 mmoles), catalyzed by Na_2MoO_4 or NH_4VO_3 (0.2 mmoles) in a two-phase system (20 mL H_2O pH 1.1 / 20 ml $CHCl_3$) under stirring (1000 rpm) at 25°C.



C **D**

#	*Substrate*	*Catalyst*	*Time, hours*	*yield^a %*	*C:D^b*
1		Mo(VI)	4	56	100:0
			24	68	100:0
2	"	V(V)	4	35	100:0
			72	48	100:0
3		Mo(VI)	4	65	76:24
			24	82	75:25
4	"	V(V)	4	35	85:15
			72	47	84:16
5		Mo(VI)	4	65	75:25
			24	69	72:28
6	"	V(V)	4	41	69:31
			72	49	67:33

a) see note a Table 1. b) see note b Table 1.

Some features of the present system, which may also have mechanistic significance, are worthy of mention. Thus, it is observed that hydrogen peroxide is consumed in two hours, well before the completion of the halogenation reaction. This is in line with the strong oxidizing power of peroxomolybdenum complexes suggesting at the same time that one or more intermediates, including bromine, accumulate in the system. Moreover, experiments carried out in the absence of the substrate show that the reddish color of the organic phase fades with time so that in 12 hours a colorless solution is observed. We have also directly tested that in aqueous solutions containing bromine and Mo(VI) a rapid disappearance of the halogen takes place. This does not occur with vanadium.[9] Therefore, the molybdenum-based reactions might be less efficient than the vanadium-catalyzed ones with particulary unreactive substrates. As an example, under the conditions adopted here, benzene does not react.

Finally the different selectivity exhibited by molybdenum compared with vanadium, as far as the ratio dibromoderivative-bromohydrin is concerned, suggests that the intermediates present in solution are somehow reminiscent of the peroxocomplex from which they have been formed. This agrees with the suggestion, supported also by *ab initio* calculations,[11] that a hypobromite-like metal complex may be involved.

Acknowledgments

Financial support from MURST and "Progetto Strategico Tecnologie Chimiche Innovative of CNR" is gratefully acknowledged. Thanks are due to Ms. Fabiola Salamon for preliminary experiments.

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(*Received in UK* 22 *July* 1996; *accepted* 26 *September* 1996)