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Comparison of Amine Additives Most Effective in the New Methyltrioxorhenium-Catalyzed Epoxidation Process

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Abstract: Three different heterocyclic amine additives, pyridine, 3-cyanopyridine and pyrazole are compared in the methyltrioxorhenium (MTO) catalyzed epoxidation of olefins using aqueous hydrogen peroxide. © 1999 Elsevier Science Ltd. All rights reserved.

Methyltrioxorhenium, following the Herrmann group's discovery of its remarkable catalytic properties, has emerged as a useful catalyst for a number of organic transformations, especially epoxidations [1]. Olefins are efficiently transformed into their corresponding epoxides using MTO as catalyst and aqueous hydrogen peroxide as terminal oxidant. However, due to the Lewis acidic nature of the rhenium center in the catalyst, the original process only produces epoxides which are uncommonly resistant to ring-opening. We subsequently discovered that the addition of pyridines within a certain window of concentration both protected the epoxide products and enhanced catalyst activity [2], provided that other key reaction variables were also changed. Herrmann *et. al.* have since found that pyrazole can be an excellent replacement for pyridine and/or 3-cyanopyridine in the ligand-enhanced epoxidation process [3] [4]. In order to evaluate the efficiency and scope of these three ligand-variations, we compare them here using a small group of representative olefins.

Styrene-type olefins are fairly unreactive. The resulting longer reaction times required, only exacerbate the often serious side-reactions initiated by ring opening of the sensitive benzylic epoxide products. As shown in the Figure, styrene reaches full conversion after 5 h using either a mixture of 3-cyanopyridine and pyridine (6 mol% each) or pure pyrazole (12 mol%) as additive [note that this result contradicts the experiments in reference 3 which claim that pyrazole is the additive of choice for epoxidation of styrene]. In the reaction where pyridine (12 mol%) is the only additive, full conversion is never reached, presumably due to competition from catalyst decomposition into perrhenate (ReO_4^-) and methanol.

MTO is known to be stable at acidic pH but unstable in basic media. Comparing the *p*Ka values of the additives used in this study, pyridine is the most basic (pyridine = 5.4; 3-cyanopyridine = 1.9; pyrazole = 2.5), and the basicity of the additive seems to affect the rate of catalyst decomposition, a factor which is most noticeable with unreactive olefins.

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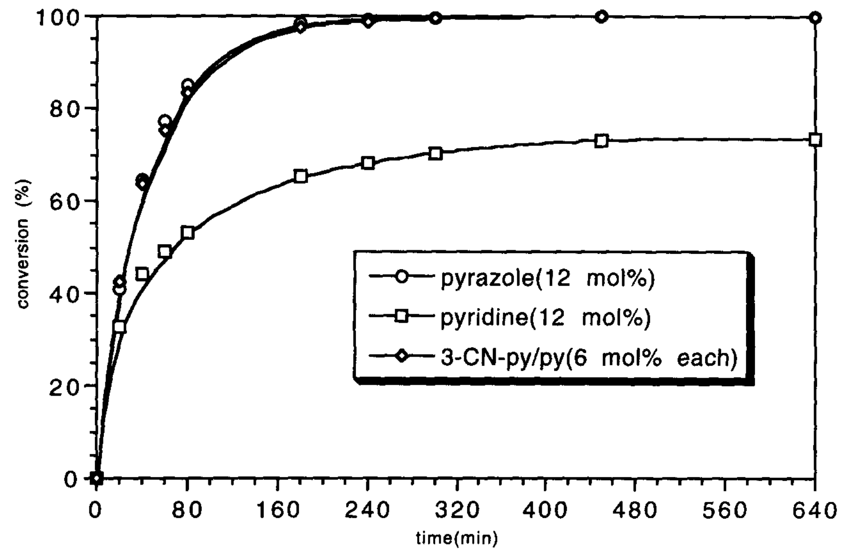
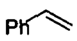
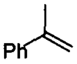
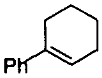
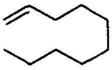
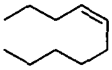
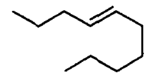
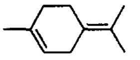


Figure. Conversion of styrene in the MTO (0.5 mol%) catalyzed epoxidation reaction with 30% aqueous hydrogen peroxide (2 eq) in the presence of pyrazole (12 mol%), pyridine (12 mol%) and 3-cyanopyridine/pyridine (6 mol% of each), respectively. These experiments sought to duplicate those reported in the recent communication by Herrmann et al [3]. However, in our hands, the time/conversion plots are virtually superimposable for the additives pyrazole (O) or 3-cyanopyridine/pyridine (◊).

As shown in the Table, using either pyrazole or the 3-cyanopyridine/pyridine mixture as additive produces styrene oxide in high yield. However, for α-methylstyrene pyrazole is the clear choice since with pyridine or the mixture of pyridine and 3-cyanopyridine as additive a substantial amount of diol is formed. The more substituted styrene derivative (entry 3) resulted in full conversion and high yield under all of the conditions. Monosubstituted olefins are known to be slow to epoxidize, but 1-decene (entry 4) gave full conversion and high yields employing either 3-cyanopyridine (10 mol%) or pyrazole (12 mol%). High yields of *cis*-4,5-epoxydecane (entry 5) were obtained using either pyridine or pyrazole as additive. The *trans* analog was fully converted in a short time using only 2 mol% 3-cyanopyridine [5] or pyrazole (12 mol%). While α-terpinolene (entry 7) was fully converted to the bis-epoxide using pyridine as additive, the use of 3-cyanopyridine or pyrazole gave only low conversion and practically no bis-epoxide was formed.

We hope the trends noted above will aid in the selection of the "best" heterocyclic amine additive (or additive mixture) to try first with a new olefin. However, the results in entry 7 for bis-epoxidation of α-terpinolene are surprising, since the other results in the Table lead to the expectation that epoxidation of α-terpinolene, with pyrazole as the additive will proceed readily. Nevertheless, our predictive abilities for this new heterocyclic amine-assisted epoxidation method are steadily improving. The process should find numerous uses due to its unique ability to deliver acid sensitive epoxides in good yields.

Table: Epoxidations of alkenes with aqueous hydrogen peroxide catalyzed by methyltrioxorhenium and three different amine additives[a].

		Pyridine			3-Cyanopyridine			Pyrazole		
Entry	Olefin	Conv.[b] (%)	Yield[c] (%)	Time (h)	Conv.[b] (%)	Yield[c] (%)	Time (h)	Conv.[b] (%)	Yield[c] (%)	Time (h)
1		70	58	5	>99[d]	96	5	>99	96	5
2		>99	53	5	>99[d]	74	1.5	>99	93	1.5
3		>99	98	1	>99[d]	96	1	>99	95	1
4		61	60	14	>99[e]	99	14	>99	99	14
5		>99	99	1	63	60	2	>99	99	1
6		98	98	4	>99[f]	99	2	>99	99	2
7[g]		>99	99[h]	2	43	26[i]	2	59	50[j]	2

a) Reaction conditions: Olefin (10 mmol), MTO (0.5 mol%), additive (12 mol% unless otherwise noted), 30% aqueous hydrogen peroxide (20 mmol); olefin concentration 2 M (CH_2Cl_2). See reference 6 for specific experimental details. b) Conversion determined by GC with internal standard. c) Yields determined by GC with internal standard. d) 3-cyanopyridine (6 mol%) and pyridine (6 mol%). e) 3-cyanopyridine (10 mol%). f) 3-cyanopyridine (2 mol%). g) MTO (1 mol%), additive (24 mol%), 50% aqueous hydrogen peroxide (40 mmol). h) bis-epoxide, *cis:trans* 4:1. i) mono-epoxide, no bis-epoxide detected. j) mono-epoxide, 3% bis-epoxide.

It is because pyrazole is so effective with α-methyl styrene that one predicts an excellent outcome with α-terpinolene (both olefins give very acid-sensitive epoxides). In retrospect, the substantially lower basicity of pyrazole (pyridine is ca. 1000 times more basic) makes it hard to understand why it is more effective than pyridine in the α-methyl styrene case. While the much weaker buffering effect of pyrazole may contribute to its ineffectiveness for producing some acid-sensitive epoxides, this can not be the whole story. Other, as yet unknown factors must be in play here.

To conclude, pyrazole is an effective additive for most olefins and, especially for some, but not all (eg., entry 7, Table), acid sensitive epoxides. Thus, in most cases, the addition of either pyridine (12 mol%) or pyrazole (12 mol%) will result in the same outcome; pyridine, however, is generally preferred since it is much less expensive and is found in every chemistry laboratory. Olefins of lower reactivity (terminal and *trans* di-substituted) can be efficiently converted to their corresponding epoxides using either 3-cyanopyridine (for *trans*-disubstituted only 2 mol% is required) or pyrazole as additives.

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[2] a) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189. b) Copéret, C.; Adolfsson, H.; Sharpless, K. B. *Chem. Commun.* **1997**, *16*, 1565.

[3] Herrmann, W. A.; Kratzer, R. M.; Ding, H.; Thiel, W. R.; Glas, H. *J. Organomet. Chem.* **1998**, *555*, 293.

[4] Epoxidations using pyrazoles in place of pyridines are also described in the Scripps Research Institute U.S. Patent Application Serial# 08/842,732.

[5] A full paper on the use of the 3-cyanopyridine additive in MTO-catalyzed epoxidations is in preparation

[6] General experimental procedure described for 1-phenylcyclohexene: 1-Phenylcyclohexene (7.9 g, 50 mmol) is dissolved in CH_2Cl_2 (16 mL; olefin concentration = 2M) and pyridine (0.48 mL, 475 mg, 6 mmol) and MTO (62 mg, 0.25 mmol) is added [for the other heterocyclic additives in the Table the amounts is as follows; 3-cyanopyridine (312 mg, 3 mmol) and pyridine (0.24 mL, 238 mg, 3 mmol); pyrazole (408 mg, 6 mmol)]. The reaction flask is placed in a water bath (24 °C) and 30% aqueous hydrogen peroxide (10 mL, 100 mmol) is added. The reaction mixture is vigorously stirred for 1h, then placed in an ice bath and a catalytic amount of MnO_2 (ca 5 mg) is added. When no more oxygen gas evolution is observed the phases are separated and the aqueous layer is washed with CH_2Cl_2 (3 x 25 mL). The combined organic phases are dried with Na_2SO_4 (s) and the solvent is removed under reduced pressure. The crude epoxide is purified by vacuum distillation to yield 7.58 g (87%).