# Selective Synthesis of Oximes with Primary Aliphatic Amines and Hydrogen Peroxide in the Presence of Catalytic Quantities of Titanium Silicalite Molecular Sieves

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Primary aliphatic amines with α-hydrogen atoms are oxidized in the presence of hydrogen peroxide as oxidant and catalytic quantities of titanium silicalite molecular sieves to give the corresponding oximes as the main products; the latter are formed with good substrate selectivity and peroxide efficiency. Since the substrate dimensions allow an intracrystalline reaction, by-products, which become significant for larger substrates, are determined by steric constraints in the intracrystalline voids rather than by reaction of electrophilic oxygen with carbon of increased nucleophilicity.

The oxidation pathways of primary amines having α-hydrogen atoms with the help of mono oxygen donors are well-established.[1-6] In this respect, peroxotungstophosphate,[2] dimethyldioxirane,[3] salts of tungstic, molybdic and vanadic acids,[4] sodium perborate,[6] and hydrogen peroxide in acetic acid[5] have been proposed. A general reaction scheme (Scheme 1) based on these observations[1,2,5] indicates consecutive

$$H_2O_2 + R^1R^2CHNH_2 \xrightarrow{[O]} R^1R^2CHNHOH\cdot$$
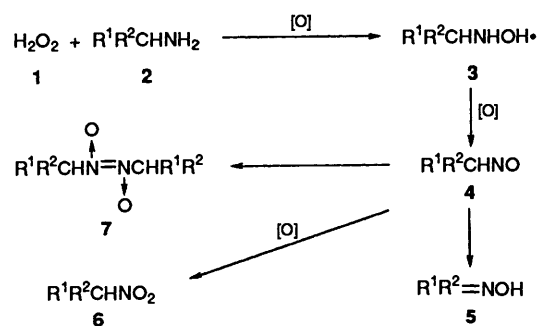
Scheme 1 General reaction network for the oxidation of primary aliphatic amines with α-hydrogen atoms 2 in presence of mono oxygen atom donors 1: alkyl hydroxy amines 3 and, alkyl nitroso compounds 4 are intermediates; alkyl oximes 5, alkyl nitro compounds 6 and alkyl nitroso dimers 7 are the reaction products

formation of alkylhydroxylamines 3 and alkylnitroso compounds 4 as intermediates. The ultimate oxidation products are the oxime 5, and nitroso dimer 7, while traces of the nitro compounds 6 are always observed.

Titanium silicalite molecular sieves (TS-1 and TS-2), exhibit unique catalytic properties in various reactions with H_2O_2 as oxidant,[7] such as the hydroxylation of phenol, the ammoximation of carbonyl compounds, the epoxidation of olefins, the oxyfunctionalisation of alkanes and the sulfoxidation of thioethers. Recently, Tonti et al.[8] reported that the oxidation of secondary amines into the corresponding hydroxylamines is possible with the same system. For all these, reaction conditions can be selected so as to achieve high selectivities on a substrate as well as on a peroxide basis.

In the present work, it is reported that selective oxidation of primary amines having α-hydrogen atoms is possible with H_2O_2 in presence of catalytic quantities of titanium silicalite (TS-1 or TS-2). The constrained environment of the 10-membered ring zeolite suppresses the formation of the bulky nitroso dimer 7, and catalyzes the selective formation of the oximes 5. From the synthetic point of view, all substrates that can enter the intracrystalline voids of the zeolite are oxidized to oximes

with high selectivity on a substrate as well as on a peroxide basis.

The results obtained in the oxidation of various primary amines with α-hydrogen atoms are summarized in Table 1. The data obtained with TS-2 are, within a few percent, identical with those reported in the Table. In the absence of any catalyst the conversion is small and occurs only with low peroxide efficiency.

For n-alkylamines, the major product is the corresponding oxime. The activity, oxime selectivity and peroxide efficiency gradually decreases when the alkyl chain length increases, pointing to the presence of shape selective effects. The by-products formed are zeolite-specific and are an a posteriori verification for the occurrence of the intermediates 3 and 4 (Scheme 1). Indeed, aliphatic azo compounds 8 are the major by-products which tautomerize into the corresponding hydrazones 9 (Scheme 2). Evidently, azo compounds are formed upon

$$R^1R^2CHNH_2 \xrightarrow{[O]} R^1R^2CHNHOH \xrightarrow{[O]} R^1R^2CHNO$$
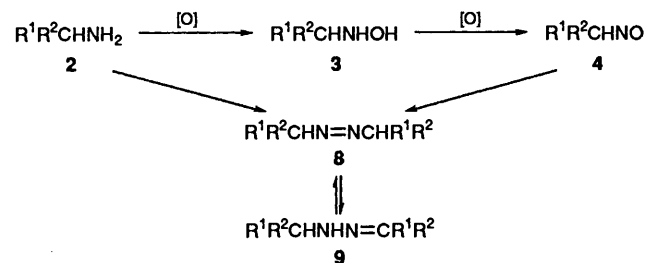
Scheme 2 Zeolite-specific by-products formed upon oxidation of primary aliphatic amines with α-hydrogen atoms 2: alkyl azo compounds 8 and isomeric hydrazones 9

condensation of the amine substrate 2 with an alkyl nitroso intermediate 4. With cyclohexylamine, which most probably does not enter the catalyst pores, low activity and selectivity is found. The position of benzylamine is intermediate between that of the alkylamines and of cyclohexylamine.

Methanol and tert-butyl alcohol are suitable inert solvents for the reactions. In presence of acetone, the amines are first converted into large quantities of the corresponding N,N'-dimethyl imines 10, which are then epoxidized into the corresponding oxaziridines 11 (Scheme 3).

$$RNH_2 + Me_2CO \xrightarrow{-H_2O} RN=CMe_2 \xrightarrow{[O]} RN-CMe_2$$
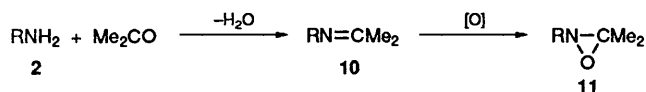
Scheme 3 Formation of imines 10 and oxaziridines 11 upon oxidation of aliphatic primary amines in presence of acetone as solvent

Table 1 Oxidation of primary amines over TS-1 with methanol as a solvent[a]

Substrate	Catalyst	Conv'n (%)[b]	Oxime selectivity (%)	H_2O_2 efficiency (%)[c]
$MeNH_2$	TS-1	40	88	90
$MeNH_2$	None	3	0	0
$PrNH_2$	TS-1	32	73	86
$PrNH_2$	None	3	0	0
Pr^iNH_2	TS-1	38	77	88
Pr^iNH_2	None	4	0	0
Pr^iNH_2[d]	TS-1	29	74	85
Pr^iNH_2[d]	None	8	19	4
Pr^iNH_2[d]	TS-2	31	84	90
$C_6H_{11}NH_2$[e]	TS-1	3	33	8
$C_6H_{11}NH_2$[e]	None	5	8	2
$C_6H_{11}NH_2$[d,e]	TS-1	3	32	8
$C_6H_{11}NH_2$[d,e]	None	10	0	0
$PhCH_2NH_2$	TS-1	20	82	55
$PhCH_2NH_2$	None	23	21	4

[a] Reaction conditions: catalyst wt. = 0.75 g; amine (mmol) = 69; hydrogen peroxide (mol) = 35; amount of solvent = 25 cm³; duration of run (h) = 1; reaction temp. (K) = 338. [b] GC conversion. [c] (mol of oxime formed/mol of hydrogen peroxide fed) × 100. [d] tert-Butyl alcohol as a solvent. [e] Duration of run 3 h.

Upon the basis that upon interaction of hydrogen peroxide with titanium silicalite a surface peroxo or hydroperoxo species is formed,[9] mechanistically the reaction may be visualized as follows. The active oxotitanium inserts an oxygen atom into the amine giving an alkylhydroxylamine. The latter is then further oxidized to an unstable alkyl dihydroxy amine, which upon dehydration gives the corresponding nitroso alkane. The latter then rearranges via a prototropic shift,[10] giving the corresponding oxime. Since the electrophilic oxidation occurs in a constrained environment, the expected increase in activity of the longer chains is more than compensated for by diffusional restrictions in the zeolite pores. Olefin and alkane oxidation data on TS-1 have been rationalized as well by an electrophilic series perturbed by steric constraints.[11]

Detailed studies on the oxidation of other primary and secondary amines are in progress to establish the generality of this concept.

Experimental

TS-1 and TS-2 catalysts were prepared according to established procedures.[12] Reactions were carried out batchwise in a 100-cm³ round-bottom flask with continuous stirring. The flask contained the catalyst (0.75 g), amine (69 mmol) and a suitable solvent (25 cm³), while aqueous hydrogen peroxide (35 mmol) was added dropwise with a syringe as soon as the reaction temperature (338 K) was reached. Products were analyzed by capillary gas chromatography (50 m CPSil5B column from Chrompack with 0.32 mm internal diameter). Product identification was established by GCMS.

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