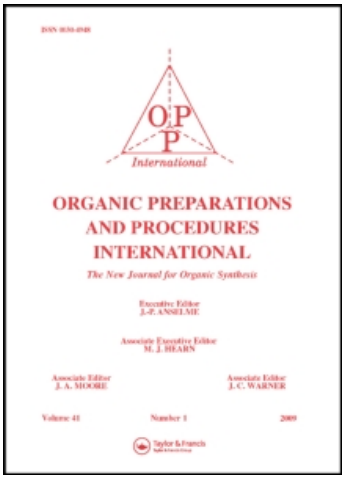

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HYDROXYLAMINE-O-SULPHONIC ACID. ITS USE IN ORGANIC SYNTHESIS. A REVIEW

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HYDROXYLAMINE-O-SULPHONIC ACID. ITS USE IN ORGANIC SYNTHESIS.

A REVIEW

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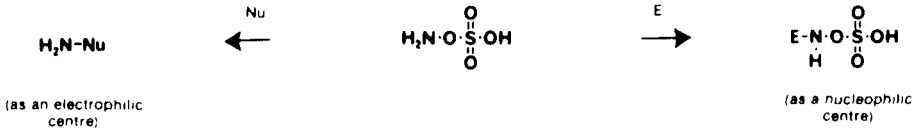
INTRODUCTION

Hydroxylamine-O-sulphonic acid, NH_2OSO_3H, is a synthetically interesting molecule because of the ability of the nitrogen atom to behave as either a nucleophile or electrophile according to circumstances.



It is not surprising therefore to find that the compound is able to participate in a wide variety of reactions and indeed, a close examination of the literature reveals that there are many examples of the use of hydroxylamine-O-sulphonic acid in organic synthesis. What is surprising however is that this information has not previously been collated to any degree[1] especially as there has been a steady stream of publications concerning its use since the late 1950's.

This present review article seeks to redress this situation and provide the reader with a detailed summary of the uses of hydroxylamine-O-sulphonic acid. The article presents to a wider audience a more comprehensive account of the synthetic uses of hydroxylamine-O-sulphonic acid which were discussed in a short review written by the author for a commercial publication.[2]

Hydroxylamine-O-sulphonic acid (abbreviated to HOSA from now on)[3] has been known since the early part of this century. The standard preparative method is by reaction of hydroxylamine sulphate with 30% fuming

sulphuric acid as described by Matsuguma and Audrieth.[4] The compound has also been prepared by reacting hydroxylamine sulphate with chlorosulphonic acid[5] or by bubbling gaseous hydrogen azide through fuming sulphuric acid.[6] A simplified preparation from hydroxylamine sulphate and 60% oleum has more recently been described by Schimitz et al.[7] and recently a Japanese patent[8] has claimed an efficient process for making HOSA by reacting hydroxylamine or its inorganic acid salt with fuming sulphuric acid in the presence of ammonium or sodium sulphate or gypsum.

Preparation of Hydroxylamine-O-sulphonic Acid[7]. - 60% Oleum (300 cm^3) is added dropwise over 1 hr to hydroxylamine sulphate (250 g), the reaction mixture being stirred and moisture being excluded (EXOTHERMIC REACTION). After further stirring for 1 hr the thick paste is left overnight and then 'sucked dry' as rapidly as possible on a glass sinter and the crude acid added to ether (600 cm^3), cooled in ice (EXOTHERMIC REACTION - FIRE HAZARD). The temperature of the mixture is not allowed to exceed 20°. Filtration and subsequent washing with ether (400 cm^3) gives 99% pure hydroxylamine-O-sulphonic acid (240-260 g) which is dried under vacuum over P_2O_5 and stored over P_2O_5.

HOSA in the pure form is normally a white microcrystalline solid (although long needles are sometimes observed), melting with decomposition at 210-211°. It is hygroscopic in nature but is stable for long periods of time if stored in a moisture-free atmosphere. However, aqueous solutions of the material are unstable, decomposing slowly below 25° but rapidly above this temperature. It is thus important to use freshly prepared solutions in reactions. The decomposition is markedly affected by pH and by the presence of traces of copper ion.[4] Decomposition in acidic media yields hydroxylammonium and hydrogen sulphate ions while in alkaline solution the products are nitrogen, ammonia and sulphate ions.

HOSA is a monobasic acid with an ionisation constant of approximately $1,3 \times 10^{-2}$ in cold aqueous solution. In addition to being soluble in water,

it dissolves in methanol but is only slightly soluble in ethanol. It is insoluble in chloroform, diethyl ether and carbon tetrachloride. Infrared studies[9] indicate the presence of NH_2, NH_3^+, OH, $SO_4^=$ and SO_3^- groups and it is believed that the compound is an equilibrium mixture of $NH_2.O.SO_3H$ and the zwitterionic form, $\overset{+}{N}H_3\text{-}O\text{-}SO_3^-$.

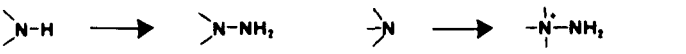
HOSA reacts quantitatively with potassium iodide to liberate iodine and can be analysed by dissolving a sample in water and treating it with a solution of potassium iodide in 2N sulphuric acid. After five minutes the solution is titrated with sodium thiosulphate using starch as indicator, the solution being boiled towards the end of the titration to ensure complete liberation of the iodine.

The amino group in HOSA, as we have seen can behave either as an electrophile or nucleophile and as might be anticipated, the electrophilic nature is generally evident under basic conditions and the nucleophilic character observed under essentially neutral or acidic conditions. Many of the reactions of HOSA are however mechanistically far from simple and can, for example, proceed via free radical pathways. Some reactions require the presence of co-reagents. HOSA may serve as an in situ source of other chemical entities, for instance diimide, which then undergo reaction (diimide will reduce double bonds). Examples of all these reactions will be presented.

I. AMINATION

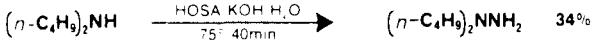
Amination reactions are illustrative of electrophilic attack by the amino group of HOSA. Indeed, probably the best known use for HOSA is for amination on nitrogen. Amination both at carbon and at sulphur are also important reactions of HOSA and amination on phosphorus is possible with the reagent.

1. At Nitrogen

a. Preparation of Mono- and Disubstituted Hydrazines and Trisubstituted Hydrazinium Salts 

Monosubstituted hydrazines may be prepared in yields of the order of 50% by treatment of a primary amine with HOSA in aqueous solution in the presence of base.[5,10-13]

In a similar fashion, 1,1-disubstituted hydrazines may be obtained from secondary amines.[11,12]

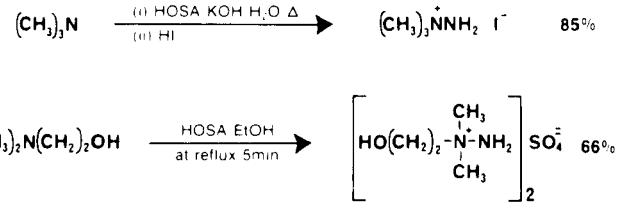


An alternative procedure[14] for preparing mono- or disubstituted hydrazines is to use an aqueous solution of the amine and a ketone or the corresponding Schiff's base as described below. The main advantage of the method is that it avoids the use of a considerable excess of amine to suppress further reaction of the hydrazine products. The reaction involves formation of a diaziridine (vide infra). Its merits are further discussed by Ohme and Zubeck.[14]

Preparation of Monosubstituted Hydrazines[13]. - Cyclohexanone (98.15 g, 1 mol) and the alkylamine (3-6 mol) are dissolved in water (800-1000 cm^3) and HOSA is added portionwise over 1 hr at 0-10°. Stirring is maintained for a further 1 hr at 10° and the solution then extracted with toluene (3 x 500 cm^3). Excess alkylamine is removed from the toluene phase by shaking several times with ice-cold 10% oxalic acid solution. The yield of intermediate diaziridine is determined by iodometric titration. (An aliquot of the toluene extract is treated with a solution of potassium iodide in 2N sulphuric acid. Ethanol is added until the solution is homogeneous and this is then titrated with sodium thiosulphate solution (0.1N) - starch as indicator; 1 mmol of diaziridine is equivalent to 20 cm^3 0.1N sodium thiosulphate). Aqueous oxalic acid (20%) is then added to the

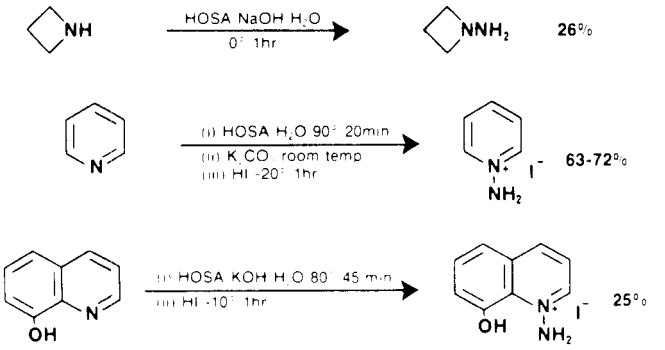
toluene extract (1.05 mol of oxalic acid per 1 mol of diaziridine) and the mixture heated under reflux until the toluene phase no longer liberates iodine from acid KI solution (about 2 hrs). The aqueous phase is separated, filtered through decolorizing charcoal and concentrated on a rotary evaporator. The precipitated crystals of alkylhydrazine oxalate are recrystallized from 80-90% ethanol. Yield 50-70%.

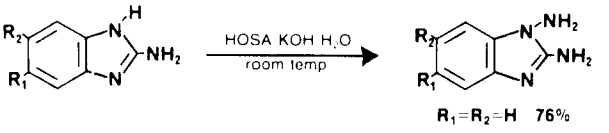
Treatment of tertiary amines with HOSA under basic conditions in aqueous or alcoholic media gives rise to 1,1,1-trisubstituted hydrazinium salts.[11,12,15,16]



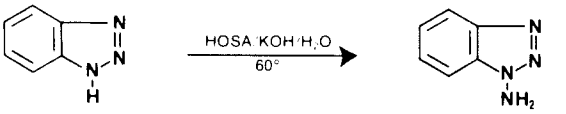
b. Amination at Nitrogen of Nitrogen Heterocycles

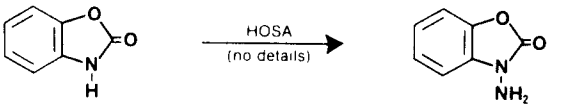
Many nitrogen heterocycles have been aminated on nitrogen using HOSA. These include azetidine,[17] benzimidazole,[18,19] benzoxazole,[20] indole,[18,21] purine,[18,22] pyrazine,[23] pyridazine,[23] pyridine,[11,12] pyrimidine,[16] quinoline,[11,12] tetrazole,[24] triazine,[25,26] and triazole[26,27] ring systems.

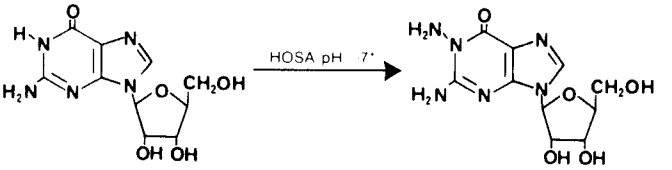




$R_1=R_2=H$ 76%

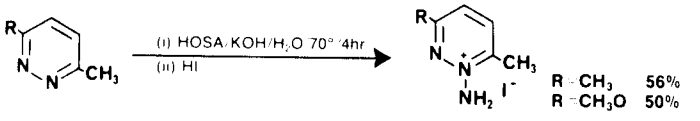




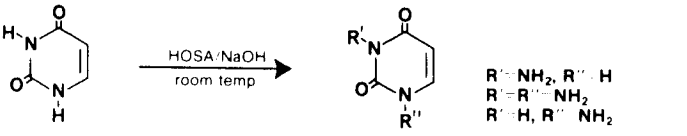


*Note pH 2-4 gives C-8 amination

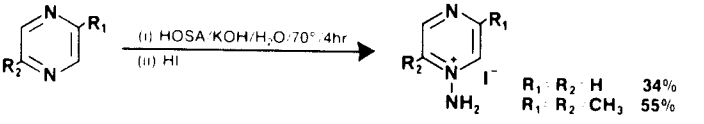
almost quantitative



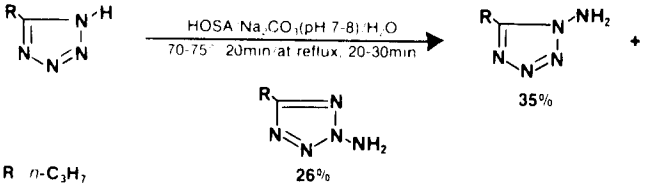
R = CH_3 56%
R = CH_3O 50%



R' = NH_2, R'' = H
R' = R'' = NH_2
R' = H, R'' = NH_2



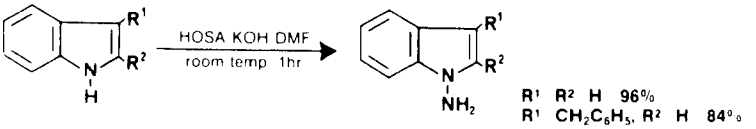
R_1 = R_2 = H 34%
R_1 = R_2 = CH_3 55%



35%

R = n-C_3H_7

26%



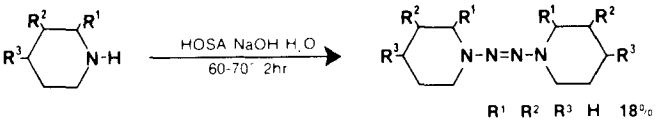
R^1 R^2 = H 96%
R^1 = $CH_2C_6H_5$, R^2 = H 84%

In the case of the pyrimidine ring system ring opening and rearrangement reactions can also occur.[23] An example of this is given later in the review. For 1-aminoindole,[21] the 1-aminopyridinium cation[11,12] and 1,2-diaminobenzimidazole[19] in particular, the reaction with HOSA is of significant preparative value since it can provide a more direct route to the compounds in question (indole, benzimidazole) or simply fails with other reagents (pyridine). A typical procedure is illustrated below.

Preparation of 1-Aminopyridinium Iodide[12]. - Pyridine (24 g, 0.3 mol) is added to a solution of HOSA (11.3 g, 0.1 mol) in water (64 cm^3) and the mixture heated on a steam bath for 20 min. After cooling to room temperature, potassium carbonate (13.8 g, 0.1 mol) is then added and the water and excess pyridine removed on a rotary evaporator. The residue is treated with ethanol (120 cm^3) and the insoluble potassium sulphate filtered. To the remaining solution is added 57% hydroiodic acid (22 g, 0.1 mol) and the solution chilled to -20° for 1 hr. The solid that separates is filtered and recrystallized from ethanol to give 1-aminopyridinium iodide as nearly white crystals (63-72%), mp. 160-162°.

c. Preparation of 2-Tetrazenes 

Pipecolines and piperidine in aqueous solution react with HOSA in the presence of base to give 1,1,4,4-tetrasubstituted-2-tetrazenes.[28] Oxidation of the initially formed hydrazines would appear to be the probable course of the reaction.

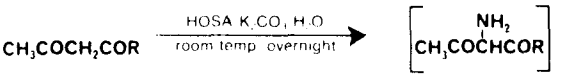


2. At Carbon

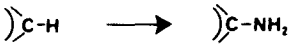
a. Aliphatic Carbon 

HOSA will C-aminate active methylene compounds. For instance methyl

acetoacetate will react with HOSA in 10% aqueous potassium carbonate to give methyl α-aminoacetoacetate which further reacts with a molecule of methyl acetoacetate to give 2,4-dimethyl-3,5-dicarbomethoxypyrrole (vide infra).[29]

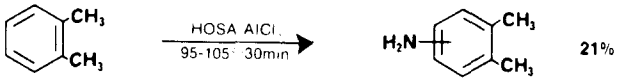


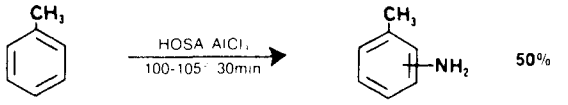
The amination of an α-lithiated carboxylic acid by HOSA in a very low yield is also observed.[30]

b. Aromatic Carbon 

Although three different methods have been described for the direct amination of an aromatic ring using HOSA, unfortunately in none is the yield of product particularly high.

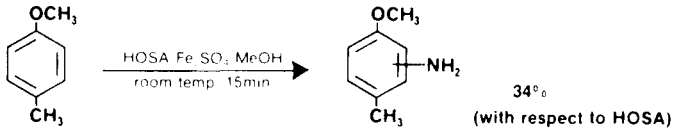
The first method, which has been fairly extensively investigated by Keller[31] and Kovacic[32] employs aluminium chloride to catalyse the reaction between HOSA and the aromatic substrate. The precise aminating species is not known. There are a number of points of disagreement between the work of the two authors and the interested reader is referred to the original papers.[31,32]



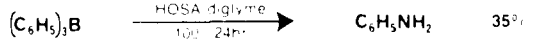


The second method, developed by Minisci and his co-workers,[33] is a homolytic amination procedure. The use of ferrous ion in conjunction with HOSA produces a redox system in which a protonated amino radical is generated. In the presence of an aromatic substrate amination of the ring

by this species takes place. Yields of 10-40% of monoaminated product are observed (quantitative, in many cases, with respect to the amount of aromatic starting material actually consumed). In some of these reactions some degree of regiospecifity is observed.

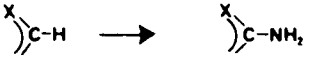


The third method[34], is based on Brown's procedure[35] for the conversion of alkenes to aliphatic amines via the organoborane derivative (see III. 1). Triphenylborane reacts with HOSA in diglyme at 100° to give aniline. Triphenylborane is prepared from phenylmagnesium bromide and boron trifluoride. The reaction differs from that of trialkylboranes in that only one of the phenyl groups is utilised, as opposed to two of the three alkyl groups in the reaction of trialkylboranes. By this method, the potential yield from a given aromatic halide is thus limited.



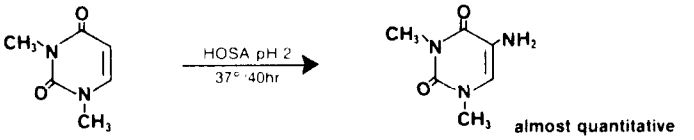
Preparation of 2- and 4-Methoxyaniline[33]. - A saturated methanolic solution of ferrous sulphate heptahydrate (13.90 g, 0.05 mol) is added with stirring over 15 min. to a solution of anisole (21.62 g, 0.2 mol) and HOSA (5.65 g, 0.05 mol) in methanol (100 cm^3). The majority of the methanol is then removed and the residue poured into water. Unreacted anisole is extracted with ether and the aqueous solution basified with NaOH. Extraction of the alkaline solution with ether gives 2- and 4-methoxyaniline (ratio 1:2) in 38% yield based on the HOSA used. (The yield based on reacted anisole is quantitative).

c. In Heterocycles

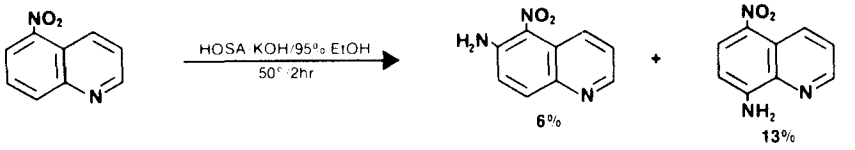


A number of different heterocyclic systems will react with HOSA to

give C-aminated products. For example, 1,3-dimethyluracil undergoes C-amination at pH 2 to give 1,3-dimethyl-5-aminouracil in almost quantitative yield.[36]

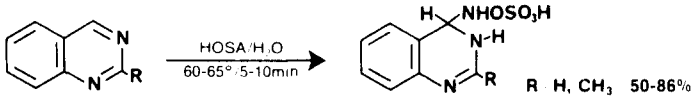


Guanosine is aminated at position-8 at pH 2-4[22] (contrast the behaviour at pH > 7) while 5-nitroquinoline is aminated at the 6- and 8-positions under basic conditions[37] [contrast the behaviour of 8-hydroxyquinoline (p. 278) where N-amination is observed]. Direct replacement of the nitro group at the 5-position by $-NH_2$ is also observed.[37]



Thus it can be seen that both conditions of pH and also the nature of substituents present in the ring can determine whether C- or N-amination occurs.

An indication as to the possible mechanism of some of these C-amination reactions is given from the behaviour of quinazolines, unsubstituted in the 4-position. These derivatives react with HOSA over 5-10 minutes, at 60-65°, to give N-(3,4-dihydro-4-quinazolinyl)hydroxylamine-O-sulphonic acids which can be isolated in good yield.[38]



If treatment with HOSA is prolonged (4 hr, 70°), the major product is 4-aminoquinazoline, with no dihydro-compound found. Hence it seems likely that the mechanism of substitution of the amino-group is one of addition of HOSA across the 3,4-position of the heteroaromatic ring followed by

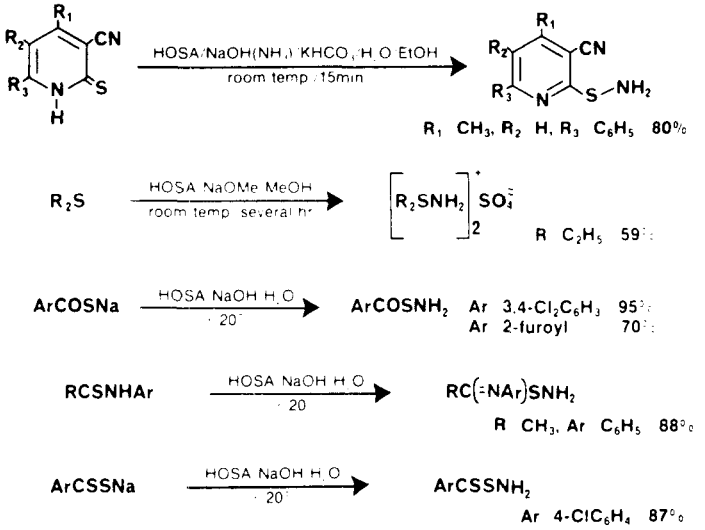
rearomatization by elimination of sulphuric acid. It is interesting to note that benzimidazoles and ortho-disubstituted benzenes are also products of the reaction with the prolonged reaction time.[38]

Preparation of 1,3-Dimethyl-5-aminouracil[36]. - 1,3-Dimethyluracil (40.6 g, 0.29 mol) is treated with HOSA (128.9 g, 1.14 mol) at 37° for 40 hrs in aqueous buffered sodium phosphate (pH 2). The solution is then made alkaline and extracted with chloroform. Removal of the chloroform gives 1,3-dimethyl-5-aminouracil in almost quantitative yield.

3. At Sulphur

Preparation of Hydrosulphamines and Hydrosulphonium Salts

Amination of organo sulphur compounds in a variety of environments is possible using HOSA. Thus thiols(ones),[39] thioacids,[40] thioamides,[40,41] dithioacids and dithioethers[42] all can be aminated with the reagent. The yields of hydrosulphamines and hydrosulphonium salts are in general good and as with most HOSA transformations, the experimental procedure is easy. The amination of sulphur is illustrated below.

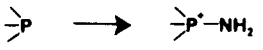


The reaction gives rise to important products; sulphilamines ($R_2\overset{+}{S}-\bar{N}-H$), for example, are useful intermediates in the preparation of isoxazoles.[43]

Preparation of S-Aroyl, S-Thioaroyl- and S-(N-Phenylamino) Hydrosulphamines[40].- A ca. 30% solution of sodium hydroxylamine-O-sulphonate (prepared from equal amounts of HOSA and NaOH) is added slowly below 20° to a stirred ca. 15% solution of the sodium salt of the thioacid, dithioacid or thioamide until no further precipitation occurs. The product is collected, dried and recrystallized. The S-thioaroyl and S-(N-phenylimino)hydrosulphamines are unstable and have to be stored at -78°. Yields are generally 70-95%.

4. At Phosphorus

Preparation of Triphenylphosphiminium Hydrogen Sulphate



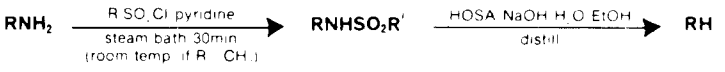
Triphenylphosphine reacts with HOSA in methanol over 5 min. at room temperature to give triphenylphosphiminium hydrogen sulphate in 69% yield.[44]

II. DEAMINATION

In what may seem a strange dichotomy, HOSA is also able to effect deamination. Reductive deamination is a term which has been used to describe the net replacement of an amino group by hydrogen. Two methods for converting $RNH_2 \rightarrow RH$ using HOSA have been reported: an indirect, but nonetheless effective method via the sulphonamide and a direct route which has appeared recently in the literature. What has made the latter method even more significant is its extension to the conversion $RNH_2 \rightarrow RD$ or RT using labelled HOSA, thus giving a route to compounds specifically labelled at one site.

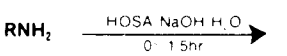
In the first method,[45] treatment of a primary alphatic or aromatic

amine with an aliphatic or aromatic sulphonyl chloride (typically methane- benzene- or p-toluenesulphonyl chloride) gives the sulphonamide which is dissolved in base and reacted with HOSA and the reaction mixture distilled to obtain the alkane or arene.



R $C_6H_5CH_2$, R C_6H_5 85%
R n-C_6H_{13}, R 4-$CH_3C_6H_4$ 90%

The intermediacy of the sulphonamide is not required for the transformation as has been shown by Doldouras and Kollonitsch[46] who have described the direct replacement of organic primary amino groups by hydrogen. In their method a primary amine is reacted with 2-3 molar equivalents of HOSA in the presence of sodium hydroxide, at 0°, to produce the deaminated product. The yields are generally of the order of 50% or more. The authors claim that the reaction is applicable to a variety of structural types, including amines containing other functionalities, and have coined the name "hydrodeamination" for the process.



R $(CH_2)_5CO_2H$ 55%
R 2-$CO_2HC_6H_4$ 72%

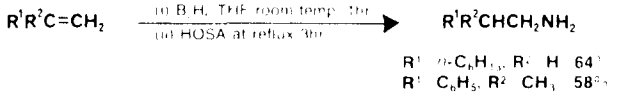
A monosubstituted diimide (RN=NH) is proposed as an intermediate in the suggested reaction pathways of both transformations, which then breaks down to give RH and nitrogen.

Preparation of Caproic Acid[46]. - HOSA (4.52 g, 0.038 mol) is added to 6-aminocaproic acid (2.62 g, 0.02 mol) in aqueous 2.5M NaOH (40 cm^3) and the mixture stirred in an ice bath. After 35 min, an additional quantity of HOSA (2.26 g, 0.019 mol) is added and stirring is continued until gas evolution virtually ceases. Acidification with sulphuric acid, extraction with ether, and distillation of the extract gives caproic acid (1.22 g, 55%).

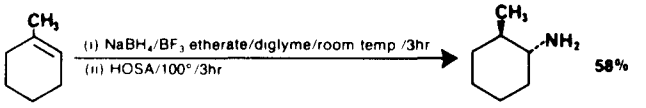
III. OTHER NET DISPLACEMENT REACTIONS

1. Replacement of -B< by $-NH_2$

Organoboranes react readily with HOSA to form the corresponding amines. This reaction forms the basis of a procedure developed by Brown[35] for the simple one-step conversion of alkenes into primary amines. The organoborane is prepared *in situ* from the alkene either by the addition of diborane to the alkene in tetrahydrofuran or by the addition of boron trifluoride etherate to the alkene and sodium borohydride in diglyme. HOSA is then added and the reaction mixture heated under reflux.



The method is applicable to a wide variety of alkenes and can be exploited successfully for the conversion of relatively hindered alkenes[47] by conducting the reaction in diglyme (second method above) in which HOSA is soluble, rather than in tetrahydrofuran as in the standard procedure.[35]

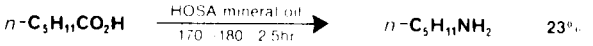


The reaction is highly stereospecific as is demonstrated in the conversion of norbornene and α-pinene to the isomerically pure *exo*-norbornylamine and isopinocampheylamine, respectively.[47] Occasionally a rearranged amination product is observed.[48]

Preparation of *cis*-Myrtanylamine[35]. - A 1.8M solution of diborane in tetrahydrofuran (9.2 cm^3) is added, under nitrogen to β-pinene (6.8 g, 0.05 mol) in tetrahydrofuran (8 cm^3). To the resultant solution is added HOSA (4.16 g, 0.036 mol) and the reaction mixture heated under reflux for 3 hrs. Acidification (dil. HCl) and extraction with ether to remove non basic materials, followed by basification (NaOH) of the aqueous phase and reextraction with ether gives the amine (4.05 g, 53% after distillation), bp. 60-61°/2 mm.

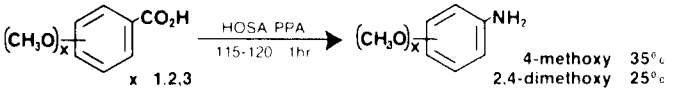
2. Replacement of $-CO_2H$ by $-NH_2$

Numerous attempts have been made[49,50] to prepare amines in high yield by the reaction of carboxylic acids or their derivatives with HOSA. So far, the yields have been low (ca. 20-30%) and clearly the conditions for the reaction still need to be optimized. Bachman and Goldmacher[49] found that the best yield for the conversion of caproic acid or its anhydride to n-amylamine using HOSA was obtained by heating equimolar amounts of the two components in mineral oil at 160-180° until gas evolution ceased.



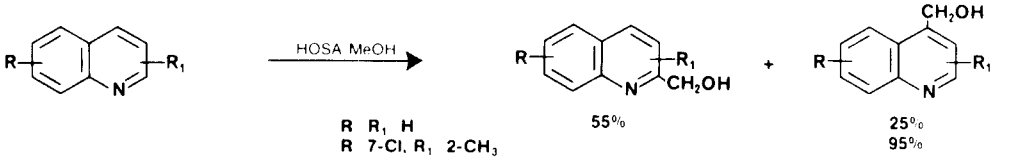
In a study comparing hydroxylamine hydrochloride, hydroxylamine sulphate and HOSA as aminating agents, Dhareshwar and Hosangadi[50] used polyphosphoric acid as the reaction medium and found that for the conversion of methoxybenzoic acids to aniline derivatives, yields of up to 35% could be obtained using a 2:1 ratio of PPA:HOSA at 115-120° for 1 hr.

It seems that the mechanism of the conversion of the carboxylic acid to the corresponding amine involves, in most cases, formation of a hydroxyamic acid intermediate and its subsequent conversion to an amine by the Lossen rearrangement, with loss of carbon dioxide.



3. Replacement of Hydrogen by $-CH_2OH$

It has been found that quinolines can be hydroxymethylated in the 2- and/or 4-position using HOSA in methanol.[51]



This chance discovery arose out of a solubility problem encountered

when trying to aminate the nitrogen atom of some quinolines using the standard HOSA procedure. As these quinolines were insoluble in the aqueous medium, the reaction solvent was changed to methanol, whereupon it was discovered that hydroxymethylation of the ring took place during reaction instead of the desired amination.

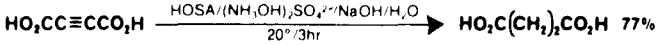
The reaction has been found to be general for quinolines substituted in the carbocylic ring and having either a 2- or 4-position (or both) vacant. The authors[51] consider that the substitution is most probably radical in nature, the attacking species being $\cdot CH_2OH$.

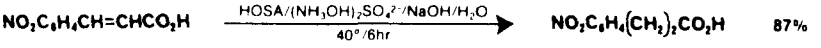
IV. ADDITION TO MULTIPLE BONDS

1. Addition of Hydrogen

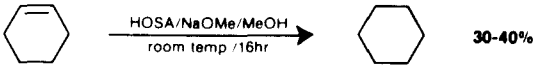
a. Carbon-carbon Bonds

HOSA can reduce multiple bonds. The active species for the reduction is diimide which is generated *in situ* from HOSA, or HOSA and a co-reagent, by the action of base. For instance, α,β-unsaturated carboxylic acids are reduced to fully saturated acids if a solution of the acid, HOSA and hydroxylamine sulphate in water is treated with concentrated sodium hydroxide.[52]



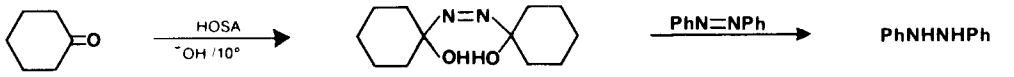


Appel and Büchner[53] give examples of the reduction of both conjugated and non-conjugated C-C multiple bonds using HOSA alone. The yields however seem to be lower as compared with using the joint reagents.



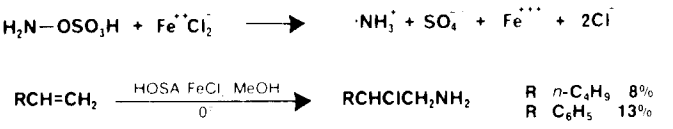
b. Hetero Multiple Bonds

In a fashion similar to that described for C-C multiple bonds, HOSA will reduce hetero multiple bonds. Thus treatment of HOSA with cyclohexanone in alkaline solution at 10° gives 1,1-dihydroxyazocyclohexane, an unstable substance, which, if allowed to decompose at room temperature (which it does rapidly by way of diimide) in the presence of quinone or of azobenzene, yields hydroquinone and hydroazobenzene respectively.[54]



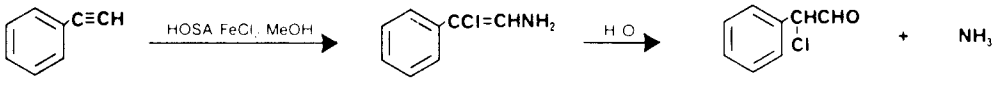
2. Addition of $ClNH_2$

The previously mentioned metal salt redox system of Minisci (I.2b Amination at an aromatic carbon atom, second procedure) provides a medium for the radical amination of unsaturated carbon compounds. If HOSA is decomposed by $FeCl_2$ in the presence of an alkene, the elements NH_2 and Cl are added across the double bond.[55,56]



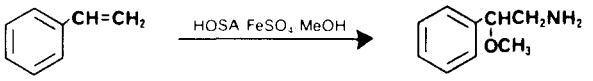
It seems that the amino group attaches itself to the least substituted carbon atom. The reaction is not stereospecific and the yields from a preparative point of view[56] tend to be on the low side.

Phenylacetylene with $FeCl_2$ and HOSA yields α-chlorophenylacetaldehyde by hydrolysis of the corresponding intermediate enamine.[55]



3. Addition of CH_3ONH_2

If the redox system described above instead comprises HOSA/$FeSO_4$ in methanol the alkene adds the elements NH_2 and CH_3O to give an amino ether.[56] Again free radical processes are involved.



4. Addition of N_3NH_2

The presence of sodium azide in 3. above leads to the formation of an azido amine.[56]

V. ADDITION-ELIMINATION REACTIONS

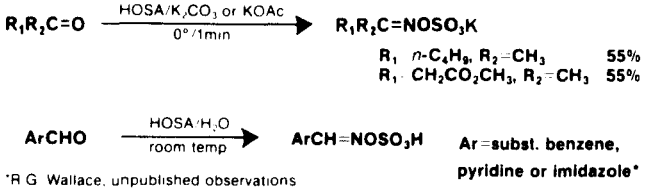
1. Carbonyl compounds

HOSA undergoes a variety of reactions with carbonyl compounds ranging from the aliphatic transformations described below through to heterocyclic ring formation reactions described a little later (see VII. 1a and 1b). Indeed the versatility in the manipulation of the carbonyl function using HOSA is quite remarkable.

The reactions discussed in this section are illustrative of nucleophilic attack by the amino group of HOSA.

a. Formation of Oxime Sulphonates $\rangle C{=}O \longrightarrow \rangle C{=}N\text{-}OSO_3X$

Aldehydes and ketones react readily with HOSA in aqueous solution to give oxime-O-sulphonic acids and salts.[57,58] These derivatives can be prepared in good yield and many of the oxime-O-sulphonic acids and salts are stable when pure and easily crystallized (for instance potassium ketoxime-O-sulphonates and pyridine carboxaldoxime-O-sulphonic acids).

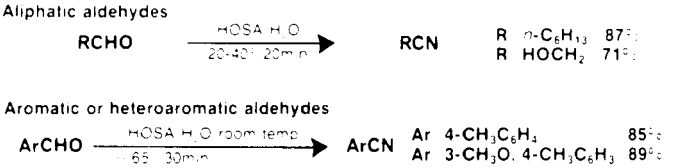


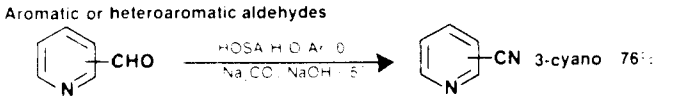
This condensation reaction constitutes a common first step in a number of related and synthetically very useful transformations.

Preparation of Potassium Ketoxime-O-Sulphonates[57]. - Potassium carbonate or acetate (0.1 mol) in concentrated aqueous solution is added to an aqueous (or sometimes methanolic) solution of HOSA (11.3 g, 0.1 mol) and the ketone (0.1 mol) in an ice-bath. After about 1 min. (when the reagents have reacted as evidenced by the formation of a homogeneous solution), the side of the reaction vessel is scratched to induce crystallization. The crystals are collected and washed with water and/or methanol and subsequently with ether or benzene. For those salts which are appreciably soluble in water, the contaminating potassium sulphate is first removed by filtration from highly supersaturated alcoholic solutions of the salts. The salts are recrystallized from water or ethanol (yields 40-67%).

b. Formation of Nitriles **—CHO ⟶ —CN**

With aldehydes if the treatment with HOSA is prolonged and carried out at room temperature or above or if the reaction medium is made strongly basic, a nitrile is formed.[38,58] This is an extremely useful reaction. The precise conditions required to bring about the elimination of sulphuric acid from the intermediate oxime-O-sulphonate vary. Those derived from aliphatic aldehydes apparently spontaneously eliminate H_2SO_4 at room temperature.[58] Heating at around 65-70°[38,58] is required or treatment with sodium hydroxide[58] at room temperature in the case of aromatic oximino intermediates. Formylpyridines and formylpyrroles are successively treated at 0° with HOSA and then with sodium hydroxide to yield the corresponding nitriles.[58] In the case of certain imidazoles, aqueous ammonia is used to generate the nitrile from the intermediate oxime-O-sulphonate.[59,60]



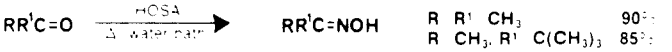


Preparation of Aliphatic Nitriles[58].- To a vigorously stirred suspension of the aldehyde (0.01-0.02 mol) in water (5 cm^3) is added a solution of HOSA (generally 1.2 molar equiv.) in water (5-10 cm^3). An exothermic reaction often ensues. The temperature of the reaction mixture is maintained at around 30° (20-40°) for 20 min. and the product extracted with dichloromethane or ether as appropriate. Concentration and (generally) distillation gives the nitrile in yields usually > 70%.

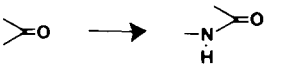
Preparation of Aromatic Nitriles[58].- The method is as described above except that when the reaction mixture has become homogeneous after formation of the oxime-O-sulphonate, it is heated at 65° for 0.5 hr. or treated with 2N NaOH (20 cm^3). The nitrile, generally a solid, crystallizes out on refrigeration and is purified by recrystallization or sublimation. For easily oxidised aldehydes, the reaction is carried out under an inert atmosphere. The yields are usually > 75%.

c. Formation of Oximes $\quad >C=O \longrightarrow >C=N\text{-}OH$

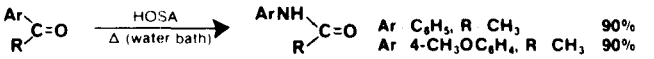
Again, as with aldehydes, reaction of a ketone with HOSA at elevated temperatures, gives a product different from that obtained in the cold. Indeed aliphatic ketones react exothermally when warmed with HOSA in a water bath to give the corresponding oxime in very good yield.[62] The method has the advantage over the standard oxime preparation procedure employing hydroxylamine hydrochloride in that no adjustment in pH of the reaction medium is required to facilitate reaction, indeed a solvent is not necessary, the ketone and HOSA simply being mixed together. The reaction is accompanied by the loss of nitrogen.



Preparation of Aliphatic Oximes[62]. - Equimolar amounts of the ketone and HOSA are mixed in a large test-tube and warmed (if necessary) in a water bath until reaction commences (evolution of nitrogen). If the reaction is vigorous, the tube is cooled to prevent overheating. When reaction is complete the product is partitioned between water and ether. The ethereal layer is washed (water, sodium bicarbonate, water until neutral), dried (magnesium sulphate) and the ether removed to give the oxime which can be crystallized if desired (yields 60-90%).

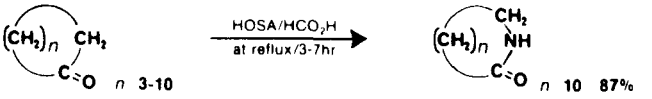
d. Formation of Amides (Beckmann rearrangement) 

Under the conditions described above aryl alkyl ketones yield N-aryl aliphatic amides, again in good yields.[62]



Diaryl ketones do not react under these conditions according to Sherk et al.[62] but Ho[63] has since reported the formation of amides in tetrahydrofuran. The mechanisms of these rearrangements are thought to be of the Schmidt and Beckmann type.[62,63] However, the precise details have not been resolved.

Quite recently Olah and Fung[64] have reported an improved one-step conversion of alicyclic ketones into their corresponding lactams using HOSA, thus further extending the scope of this synthetic transformation. In this method[64] an alicyclic ketone and HOSA are heated together under reflux in 95-97% formic acid to give the lactam in high yield.



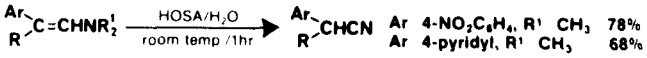
Benzophenone, under similar conditions gives benzanilide in 68% yield.[64]

Preparation of Lactams[64]. - To a magnetically stirred solution of the acyclic ketone (0.01 mol) in 95-97% formic acid (10 cm^3) is added dropwise a solution of HOSA (1.7 g, 0.015 mol) in 95-97% formic acid (5 cm^3) at room temperature over 10 min. The mixture is then heated under reflux for

3-7 hrs. After cooling, the reaction mixture is quenched with ice/water, neutralized with 5% NaOH solution and extracted with chloroform (4 x 30 cm^3). Drying (sodium sulphate) and concentration of the combined chloroform extracts gives the crude reaction product which is either distilled or crystallized as appropriate (yields 60-90%).

2. Enamines. Formation of Nitriles $\rangle CH(NR_2) \longrightarrow \rangle CH \cdot CN$

In an intriguing reaction Biere and Russe[65] have reported the conversion of enamines to nitriles in good yields using HOSA under aqueous conditions. Their method[65] consists simply of stirring the enamine and excess HOSA together in aqueous solution at room temperature to obtain the nitrile. Details of specific syntheses, together with information on permitted variations in conditions have been given recently in a patent.[66]

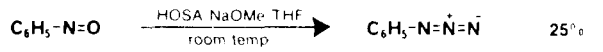


The reaction is analogous to the conversion of aldehydes to nitriles using HOSA and, indeed, the enamine can be looked upon as a synthon of the aldehyde; however, though enamines can be obtained from aldehydes, they are also readily accessible from other active methylene compounds, particularly, as was pointed out by the authors, those of the type shown above. Thus the HOSA procedure provides a means for the relatively simple 2-step replacement of a hydrogen atom by cyanide in certain active methylene compounds. An example of the procedure is given below.

Preparation of 5-Nitroindane-1-carbonitrile[66]. - To a solution of HOSA (0.85 g, 0.0075 mol) in water (15 cm^3) is added 1-dimethylaminomethylene-5-nitroindane (0.66 g, 0.003 mol) and the mixture stirred for 2 hrs at room temperature. The resultant crystals are collected and washed with water. Recrystallization from ethanol gives 5-nitroindane-1-carbonitrile (0.51 g, 90%), mp. 117°.

3. Nitroso Compounds Formation of Azides $-N=O \longrightarrow -N=\dot{N}=\bar{N}$

HOSA reacts with nitrosobenzene in tetrahydrofuran in the presence of sodium methoxide to give phenyl azide[67] (cf. Forster reaction below).

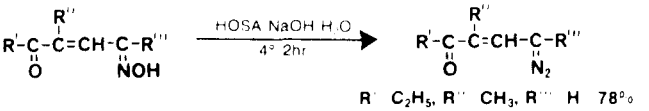


The first step of the reaction may be viewed as a condensation of the nitroso group with HOSA to give the salt of the mixed anhydride ($Ph-N=N-OSO_3^-$) of benzenediazoic acid and of sulphuric acid which subsequently gives the azide via a diazonium ion ($Ph-N=\overset{+}{N}$) or diazotate ion ($Ph-N=N-O^-$) pathway.[67]

VI. MISCELLANEOUS TRANSFORMATIONS

1. Forster reaction

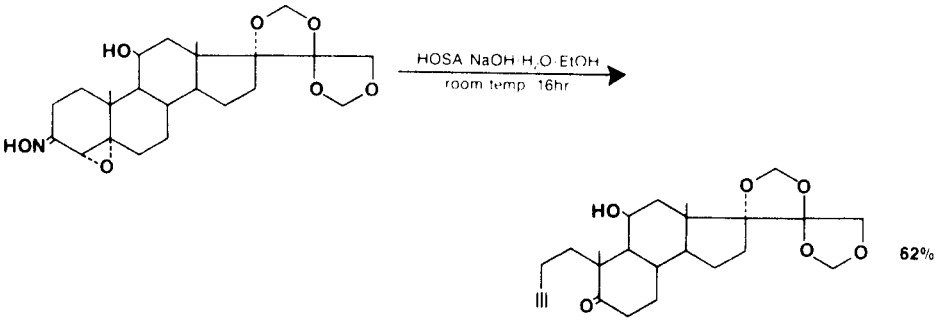
The base-catalysed conversion of α-ketoximes into α-diazoketones by means of chloramine, known as the Forster reaction,[68] has been shown by Meinwald et al.[69] to be a general reaction of oximes which can be effected using HOSA as well as chloramine. Thus it has been found that oximes react with HOSA in aqueous base to give diazo compounds.[69] Fluorenone oxime gives diazofluorene in 60% yield and benzophenone oxime, diphenyldiazomethane in 30% yield. More recently the reaction has been applied successfully to the preparation of fully conjugated α,β-unsaturated 1,4-diazoketones.[70]



Preparation of Diazo Compounds[70]. - The oxime (0.01 mol) is dissolved in 1N NaOH solution (50 cm^3) and HOSA (4.52 g, 0.04 mol) added with stirring at 4°. The diazo compound which separates is collected after 2 hrs and washed with water. The product is taken up in dichloromethane and dried over calcium chloride. In the case of oils, the reaction mixture is extracted with dichloromethane and the dichloromethane extracts washed

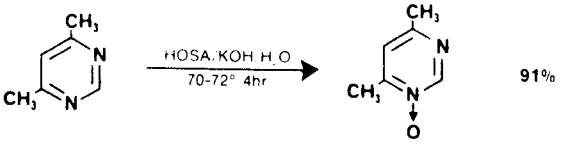
(water) and dried. Further purification can be effected by filtering a dichloromethane solution of the diazo compound through Al_2O_3-III.

A sagacious extension of Meinwald's modification[69] of the Forster reaction (viz. the conversion of oximes to diazo compounds), has been applied to the field of steroidal chemistry by Wieland, Kaufmann and Eschenmoser[71] who showed that it is possible to convert an α,β-oxido oxime into an alkynone using HOSA. A further example of this facile conversion and a discussion of the mechanism of the reaction is given in a later paper.[72]



2. N-Oxide Formation

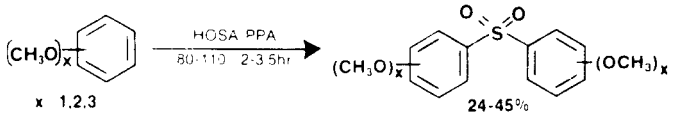
As has already been seen, the anticipated reaction of HOSA with N-heterocyclic compounds is one of N- or possibly C-amination. Anomalous reactions, however, do sometimes occur (vide infra). In particular, it is found that certain 4-substituted pyrimidines[23] and condensed pyrimidines (quinazolines)[38] give N-oxides on treatment with HOSA. For example, 4,6-dimethylpyrimidine, with the potassium salt of HOSA in aqueous methanol over 4 hrs at 70-72°, gives, 4,6-dimethylpyrimidine-1-oxide.[23]



The mechanism proposed for the reaction involves addition of HOSA to the pyrimidine ring, at the 2-position, followed by ring opening and then recyclization and finally, loss of sulphur trioxide and ammonia.[23]

3. Sulphone Formation

Generally the reactions of HOSA lead to the incorporation of the HOSA nitrogen in one guise or another in the final product. In the only instance so far described (oxime-O-sulphonate formation), sulphur is incorporated and remains attached to the nitrogen of the original HOSA. Unique among the reactions of HOSA however, is its behaviour with aromatic ethers in the presence of polyphosphoric acid. Dhareshwar and Hosangadi[73] have found that aromatic ethers react with HOSA (2:1 molar ratio) in polyphosphoric acid at 80-110° over 2-3.5 hrs to give diaryl sulphones.



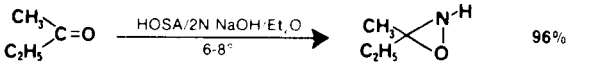
It is suggested that HOSA is cleaved to give H_2SO_4 which reacts further to give rise to the sulphone.

VII. FORMATION OF HETEROCYCLES

1. Cyclizations

a. Oxaziridines

Oxaziridines are produced by the reaction of aliphatic ketones[74,75] or benzaldehyde[76] with HOSA in 2N NaOH solution at 6-8°. 3-Ethyl-3-methyl-oxaziridine, for instance, is obtained in 96% yield from 2-butanone.[74]



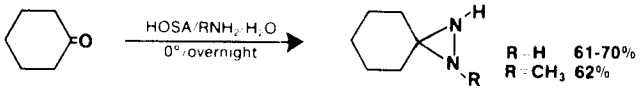
N-Unsubstituted oxaziridines are generally stable only at very low temperature. A more stable product can be obtained by acylating the unsubstitued oxaziridine in situ.[76]

Preparation of Oxaziridines[75]. - The carbonyl compound (0.2 mol), ether (or dichloromethane) (350 cm^3) and 2N NaOH solution (100 cm^3) are mixed and cooled in ice. To the mixture is added in one portion an ice-cold solution of HOSA (23 g, 0.2 mol) in water (200 cm^3) and 2N NaOH (100 cm^3) with stirring. Stirring is maintained for 8-10 min. and then the organic layer is separated. The solution of the oxaziridine in ether or dichloromethane can be dried over calcium chloride. (Yields, estimated by titration, normally 10-50%).

b. Diaziridines

Although oxaziridines were discovered several years before the diaziridines, the method for preparing them using HOSA was an extension of extensive work of Schmitz[77,78] on the preparation of the nitrogen analogues, diaziridines.

Diaziridines are formed by the reaction of HOSA with ketone/ammonia mixtures, Schiff's bases or a mixture of a carbonyl compound and a primary amine. Typical procedures are described below.



The process is remarkable in the smoothness of formation of the C-N-N three-membered ring and the general applicability of the synthesis.

The synthesis of both simple[79] and complex diaziridines such as those with steroidal[80] and multifused[81] ring structures have been described. Schmitz notes in his review[77] that by 1964, fifty or so diaziridines had been prepared by the HOSA method. The diaziridines may easily be oxidised to diazirines.

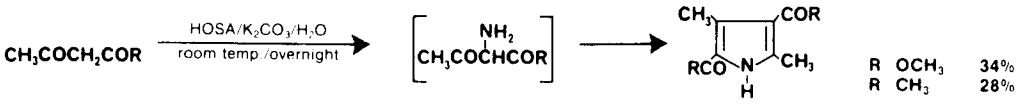
Preparation of 3,3-Pentamethylenediaziridine[82]. - A mixture of cyclohexanone (147 g, 1.5 mol) and 15N aqueous amminia (400 cm^3, 6 mol) are stirred and cooled to 0°. The temperature of the solution is maintained between 0-10° while HOSA (114 g, 1 mol) is added in 1 g portions over 1 hr. The reaction mixture is then stirred for a further 1 hr at 0° and then left at -15°

overnight. The precipitated solid is collected and washed with 50 cm^3 portions of ice-cold, ether, toluene and finally ether to give 110-115 g of 70-90% pure product. The product is divided into two portions, each of which is boiled briefly with a 50 cm^3 portion of toluene and the solutions decanted from salt residues and cooled to 0° for 2 hrs. The solids obtained are collected and washed with ice-cold petroleum ether to give 3,3-pentamethylenediaziridine (68-78 g, 61-70%) of 96-100% purity, mp. 104-107°. Ammonia can be replaced by a primary amine and cyclohexanone by other ketones in the procedure.

Preparation of 1,2-Diaziridino-1,2,3,4-Tetrahydroisoquinoline[81]. - HOSA (18.8 g, 0.17 mol) is added portionwise with stirring to 4N methanolic ammonia (84 cm^3) at -20°. To this is added dropwise a solution of 3,4-dihydroisoquinoline (2.0 g, 0.15 mol) in methanol (60 cm^3). The reaction mixture is stirred for 1 hr in the cold and then allowed to warm to room temperature over 3 hrs. The salt is removed and the filtrate evaporated to dryness in vacuo. The residue is dissolved in a little water and extracted several times with ether. The combined etheral extracts are dried with potassium carbonate. Filtration and evaporation of the ether gives a solid which can be crystallized from ethanol to give a 38% yield of 1,2-diaziridino-1,2,3,4-tetrahydroisoquinoline of 99% purity, mp. 98-99°. The product can be further purified by high vacuum sublimation.

c. Pyrroles

A simple one-step method for the preparation of tetrasubstituted pyrroles has been described by Tamura et al.[29] In their method, a β-diketo compound is treated with HOSA in aqueous potassium carbonate solution overnight to give a symmetrically substituted pyrrole.



The process uses two molecules of diketo compound which are incorporated in the final product.

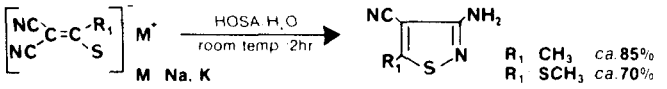
Preparation of 2,4-Dimethyl-3,5-Dicarbethoxypyrrole[29]. - HOSA (0.9 g, 0.008 mol) is added to a suspension of ethyl acetoacetate (2 g, 0.015 mol)

in 10% aqueous potassium carbonate (48 cm^3) and the reaction mixture is stirred at room temperature overnight. The precipitated crystals are collected, washed with water and dried to give almost pure 2,4-dimethyl-3,5-dicarbethoxypyrrole (30%), mp. 134-135°. Similarly prepared from appropriate starting materials are the methoxy and methyl analogues shown in the equation above.

3-Pyrroline is produced in low yield when HOSA is treated with sodium methoxide in methanol in the presence of 1,3-butadiene.[83] The 1,4-addition of nitrene ($\overline{N}H$) to the diene is invoked in this reaction.

d. Isothiazoles

3-Aminoisothiazoles are formed when dicyanothioalkene salts react with HOSA in aqueous solution.[84,85]

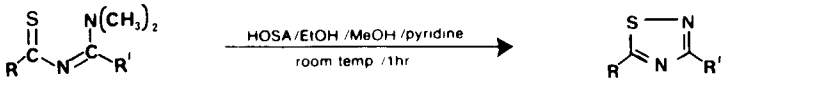


Dicyanothioalkene salts can easily be prepared by the thioacylation of malononitrile by esters of dithiocarboxylic, thionocarboxylic, xanthic or trithiocarbonic acids at room temperature (yields over 70%). The yields of crude 3-aminoisothiazoles are generally good but isolation of the pure isothioazole may in some cases prove tedious. Monocyanothioalkene salts give only very low yields of aminoisothiazoles.

Preparation of 5-Substituted 3-Aminoisothiazolo-4-Carbonitriles[85]. - HOSA (1.13 g, 0.01 mol) is dissolved in water (10 cm^3) and neutralized with potassium bicarbonate (1.5 g, 0.015 mol). To this solution is added the sodium or potassium salt of an appropriate 2-substituted-1,1-dicyano-2-mercaptoethene (0.01 mol) in water (10 cm^3). The 5-substituted-3-amino-isothiazolo-4-carbonitrile begins to separate immediately and is collected after 2 hrs (crude yields 50-80%) and purified either by recrystallization (ethanol) or sublimation.

e. Thiadiazoles

1,2,4-Thiadiazoles can be prepared in excellent yield by treatment of N'-(thioaroyl)-N,N-dimethylamidines with HOSA in a mixture of absolute ethanol and methanol at room temperature in the presence of pyridine.[86]



R= Ar, R'=H or CH_3

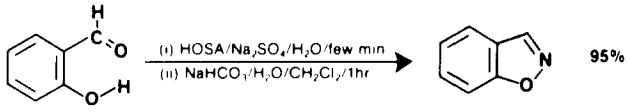
R C_6H_5, R' CH_3 91%
R pyridyl, R' H 86%

The method, recently reported in the literature, provides a route to the hitherto inaccessible 5-monosubstituted-1,2,4-thiadiazoles.

Preparation of 5-Substituted and 3,5-Disubstituted-1,2,4-thiadiazoles[86]. - To a solution or suspension of the N'-(thioaroyl)-N,N-dimethylamidine (0.02 mol) in a mixture of pyridine (3.2 cm^3, 0.04 mol) and absolute ethanol (50 cm^3) at room temperature is added rapidly a solution of HSOA (2.48 g, 0.022 mol) in absolute methanol (30 cm^3). The reaction mixture is stirred for 1 hr and the volatile components removed under reduced pressure at room temperature. The residue is taken up in dichloromethane (200 cm^3) and the dichloromethane solution washed successively with water (50 cm^3), 0.1N NaOH solution (50 cm^3) and finally water (50 cm^3) and then dried over sodium sulphate. Concentration and distillation or crystallization as appropriate gives the 1,2,4-thiadiazole (yields 84-91%).

f. Benzisoxazoles

HOSA can bring about the ring closure of o-hydroxybenzaldehydes to give benzisoxazoles.[87,88]



95%

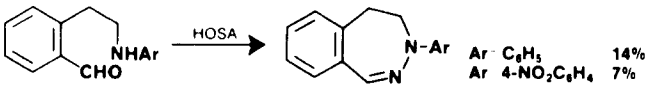
The reaction, originally described by Kemp and Woodward,[87] was found to be suitable for the large scale preparation of benzisoxazole in high yield. In this method,[87] salicylaldehyde is combined with HOSA in water and subsequently treated with sodium bicarbonate at room temperature to give the product in 95% yield. Eleven years later, a similar preparation

was reported by Suwiński,[88] who seems to have been unaware of the former authors' work.

Preparation of Benzisoxazole[87]. - HOSA (250 g, 2.2 mol) and salicylaldehyde (230 g, 1.88 mol) are reacted together in water (800 cm^3) in the presence of sodium sulphate (20 g). After a few minutes vigorous stirring, the aldehyde dissolves and a few crystals of the sodium salt of the oxime sulphonate separate. Water (400 cm^3) and dichloromethane (400 cm^3) are then added and the mixture vigorously stirred and cooled in an ice-bath as sodium bicarbonate (340 g, 4.0 mol) is added in small portions. During the reaction water is added as needed (to a total of 300 cm^3) to reduce the viscosity of the suspension. When the addition is complete, the reaction mixture is stirred for 1 hr at room temperature or until the crystals of oxime sulphonate salt have disappeared. The two phases are separated and the aqueous phase returned to the reaction flask along with dichloromethane (80 cm^3) and sodium bicarbonate (30 g). The mixture is stirred for 2 hrs at room temperature and the phases again separated. The aqueous phase is extracted with dichloromethane (5 x 30 cm^3) and the combined dichloromethane extracts (totalling 630 cm^3) dried ($MgSO_4$), filtered and concentrated. Distillation of the residual liquid in vacuo gives benzisoxazole (212 g, 95%) bp. 35-38°/2 mm.

g. Benzodihydro-[1,2]-diazepines

Benzodihydro-[1,2]-diazepines can be prepared from δ-amino aromatic aldehydes using HOSA although the yields tend to be low.[89]



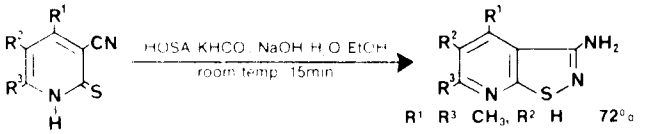
The major product of the reaction of δ-amino aromatic aldehydes with HOSA is the aromatic nitrile (vide supra). Nonetheless, if the nucleophilicity of the nitrogen atom of the aniline function is increased, the yield of diazepine improves (see equation). If mesitylsulphonyl-hydroxylamine is used in place of HOSA, yields of up to 76% can be achieved.

Interestingly, the mechanism proposed for the reaction involves the

formation of a quaternary 1,2-diaziridino-1,2,3,4-tetrahydroisoquinoline which subsequently undergoes ring expansion to give the diazepine; an additional benzodiazepine ring synthesis, which is a direct ring expansion of a preformed starting material, is described later.

h. Isothiazolopyridines

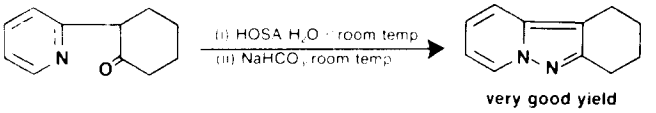
In a method related to the synthesis of isothiazoles described above, Gerald et al.[39] have reported the preparation of 3-aminoisothiazolo-[5,4-b]-pyridines starting from 3-cyanopyridine-2-thiones. The cyclization takes place on treatment with HOSA in the presence of base. The yields in this reaction are good.

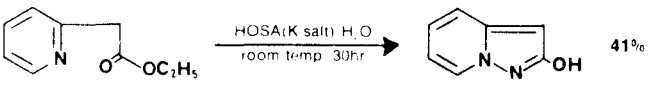


Preparation of 3-Aminoisothiazolo-[5,4-b]-pyridines.[39] - To a solution of the appropriate 3-cyanopyridine-2-thione (0.01 mol) in 4% aqueous or ethanolic sodium hydroxide (20 cm^3) is added with stirring a solution of HOSA (1.2 g, 0.01 mol) in water (20 cm^3) which has previously been neutralized with potassium bicarbonate. After 15-20 min. the reaction mixture is either diluted with water and the product collected or it is acidified with hydrochloric acid and the resultant product collected and washed with a little ethanol. The isothiazolopyridine is recrystallized from benzene or ethanol (yields 50-75%).

i. Pyrazolopyridines

2-Substituted pyridines in which the 2-substituent contains a β-carbonyl functionality undergo ring closure in the presence of HOSA at the ring nitrogen to give pyrazolo-[1,5-a]-pyridines.[88,90] Examples where the β-carbonyl functionality is a ketone or an ester have been reported.



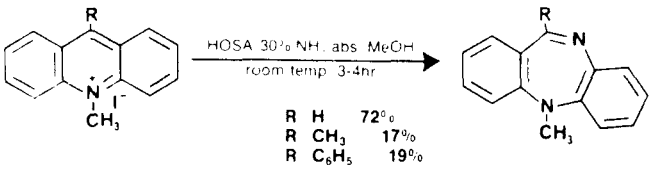


The reaction of the ester function is particularly interesting - the authors[90] of the paper state that the cyclization reaction occurs via N-imination.

Preparation of 2-Hydroxypyrazolo-[1,5-a]-pyridine[90]. - Ethyl 2-pyridylacetate (3 g, 0.018 mol) and HOSA (0.6 g, 0.005 mol) are stirred together in water (3 cm^3) for 30 hours and the mixture then extracted with dichloromethane. The aqueous layer is made alkaline (pH 9) with 10% sodium carbonate solution and extracted with dichloromethane. The combined dichloromethane extracts are dried ($MgSO_4$), filtered and concentrated. The residual oil is shaken with ether/10% sodium carbonate solution. The ethereal layer which contains unreacted ethyl 2-pyridylacetate is discarded. The aqueous phase is adjusted to pH 5 with acetic acid to precipitate the product (brown powder). Recrystallization from benzene/hexane gives 2-hydroxy-pyrazolo-[1,5-a]-pyridine (0.36 g, 41% based on starting material consumed), mp. 127-128°.

2. Ring Expansion to Dibenzo-[1,4]-diazepines

N-Methylacridinium derivatives when treated with HOSA in absolute methanol containing 30% ammonia for 3-4 hrs at room temperature undergo an expansion of the heterocyclic ring to give 5-methyldibenzo-[b,e]-(1,4)-diazepines.[91]

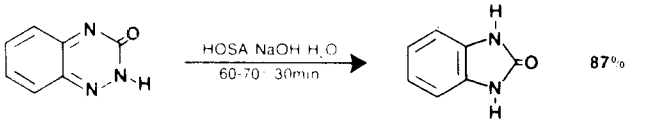


The first step in this reaction is considered to be nucleophilic attack by the nitrogen of HOSA on the 9-position of the ring which is followed by formation of a fused aziridine ring, culminating with ring expansion to give the product. The yields for this reaction are variable.

3. Ring Contractions

a. Imidazolin-2-ones and their Benzo Derivatives

Treatment of 1,2,4-triazin-3-ones with HOSA in aqueous alkali at around 70° results in a contraction of the heterocyclic ring, to yield imidazolin-2-ones.[92] N-Aminotriazinones are proposed as intermediates in the reaction.

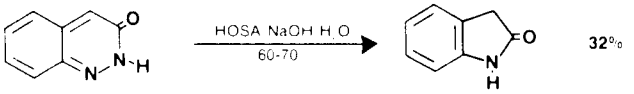


5,6-Diphenyl-1,2,4-triazin-3-one gives 4,5-diphenylimidazolin-2-one (68%), 1,2,4-benzotriazin-3-one gives benzimidazolin-2-one (87%) and phenanthro-[9,10-e]-[1,2,4]-triazin-3-one (requiring aqueous/ethanolic NaOH) gives 1,3-dihydrophenanthro-[9,10-d]-imidazol-2-one (74%).[92]

Preparation of Benzimidazolin-2-one[92]. - 1,2,4-Benzotriazin-3(2H)-one (0.44 g, 0.003 mol) is dissolved in water (25 cm^3) containing sodium hydroxide (0.72 g, 0.018 mol). HOSA (2 g, 0.018 mol) is added over 30 min. to the stirred solution at 60-70° and more sodium hydroxide is added as required to maintain an alkaline pH. The mixture is then cooled and extracted with chloroform. Evaporation followed by crystallization of the residue from water gives benzimidazolin-2-one (0.35 g, 87%), mp. 310-311° (dec.)

b. Oxindole

Cinnolin-3-one reacts with HOSA in the presence of sodium hydroxide at 60-70° to give oxindole in 32% yield.[92]



CONCLUSION

The reader will have appreciated from the foregoing paragraphs the

vast range of reactions of HOSA, which span a whole spectrum of synthetic organic chemistry. Only when these are brought together can the importance of the compound as a synthetic reagent be appreciated. As was mentioned in the opening paragraph, what makes HOSA such an interesting compound is its ability to function as both a nucleophile and electrophile depending on conditions. The fact that in addition to reacting directly with substrates, HOSA can also act as an in situ source of other chemical entities, makes it one of the most versatile of the modern chemical reagents available to the synthetic organic chemist.

It would be incorrect to imagine that the syntheses described in this article constitute the total synthetic possibilities for the use of HOSA. Indeed, it is probably true that much of the potential of HOSA is yet to be realised. There is clearly scope for improvement in some of the syntheses described and for the further application of HOSA to organic transformations. Undoubtedly it has a role to play in new heterocyclic syntheses.

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REFERENCES

*On secondment from the Cancer Research Campaign's Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex. HA6 2RN. Present address: Department of Physical Sciences, Trent Polytechnic, Clifton Lane, Nottingham, NG11 8NS, GREAT BRITAIN.

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60. The reactions of nitroimidazole carboxaldehydes in particular are interesting since slight variations in the reaction conditions can lead to different, or additional, products. For instance in the conversion of 1-methyl-2-nitroimidazole-5-carboxaldehyde to 1-methyl-2-nitroimidazole-5-carbonitrile, if solid sodium carbonate is added after 15 min. to the reaction mixture (see preparations) at 55° (final pH 6.4), on work-up, the major product obtained is the oxime with little of the nitrile.[59] If instead the reaction mixture is

maintained at 30-38° for 45 min. and then 6N NaOH (6 x molar quantity of HOSA and aldehyde used) added, the sole product is the amide.[59] In order to obtain the nitrile exclusively from the intermediate oxime-O-sulphonic acid, aqueous ammonia has to be used in place of the sodium carbonate or sodium hydroxide.[59] 1-(2-Acetoxyethyl)-5-nitro-imidazole-2-carboxaldehyde gives a mixture of the carboxamidoxime and the nitrile after treatment with HOSA (room temperature and then at 65°) and neutralization of the reaction mixture with sodium carbonate.[61]

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