Hydroxylamine-*O*-sulfonic acid — a versatile synthetic reagent

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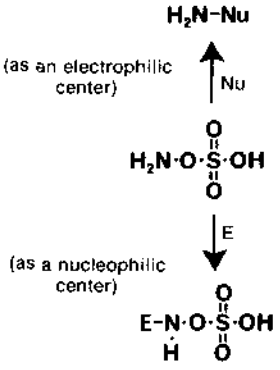
Synopsis

Hydroxylamine-*O*-sulfonic acid (HOSA) has only recently become widely commercially available despite the fact that it has proved to be a valuable synthetic reagent in preparative organic chemistry. Unfortunately, however, information regarding the use of HOSA in organic synthesis has remained scattered in the literature, and it is to focus attention on the versatility and potential of this reagent that this information has been brought together now in the form of a short review article.

Important among the areas of application of HOSA are amination and reductive deamination reactions, nitrile and oxime formation, and the preparation of amides and diazo compounds. These and other reactions, including the use of HOSA for the synthesis of heterocycles such as oxaziridines, diaziridines, pyrroles, isothiazoles, benzisoxazoles, benzodiazepines, isothiazolo- and pyrazolopyridines, and imidazolinones and related derivatives are discussed in the review. Many of these preparations can be carried out in high yield.

Hydroxylamine-*O*-sulfonic acid, $NH_2 \cdot OSO_3H$ (abbreviated to HOSA in this article) has become in recent years commercially available. Although much fruitful chemistry has been carried out using HOSA, to this author's knowledge, there has been no systematic review in English* of its use as a synthetic reagent. It is a chemically interesting compound because of the ability of the nitrogen center to act in the role of both nucleophile and electrophile, dependent on circumstances, and thus it has proved to be a reagent of great synthetic versatility.



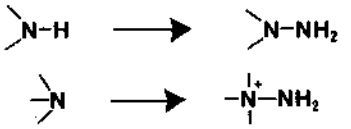
Besides being directly involved in reactions, it may serve as an *in situ* source of other chemical entities (*e.g.*, imene) which then undergo reaction with a given substrate. Reference will be made from time to time to these various modes of reaction. The uses of HOSA as a reagent are organized below according to the different synthetic transformations that it can bring about.

Probably by far the most well known and explored reactions of HOSA are amination reactions, illustrating electrophilic attack by HOSA, with amination on nitrogen being the most important, although a significant number of aminations on both carbon and sulfur have been reported. Amination on phosphorus also occurs.

AMINATION

(a) At a nitrogen atom

(i) Preparation of mono- and disubstituted hydrazines and trisubstituted hydrazinium salts



Monosubstituted hydrazines can 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 (eq. 1).[2-5] Similarly, secondary amines react to give 1,1-disubstituted hydrazines (eq. 2).[4,5]

An alternative route for mono- or disubstituted hydrazines uses an aqueous solution of the amine and a ketone, or the

*For a short review in Japanese see ref. 1.

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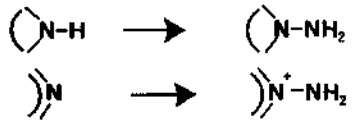
corresponding Schiff's base, instead of the amine alone and involves diaziridine ring formation (*vide infra*) which avoids the use of a considerable excess of amine to suppress further reaction of the hydrazine product and has additional advantages (for a discussion see reference 6 and references cited therein).

1,1,1-Trisubstituted hydrazinium salts are formed when tertiary amines are treated with HOSA under basic conditions in aqueous or alcoholic media (eqs. 3,4).[4,5,7]

(ii) Masked hydrazines - amination on the nitrogen heteroatom of nitrogen heterocycles



Many nitrogen heterocycles can be aminated on nitrogen using HOSA. These include azetidine,[8] pyridine,[4,5] quinoline,[4,5] pyridazine,[9] pyrimidine,[7] pyrazine,[9] tetrazole,[10] indole,[11,12] benzimidazole,[12,13] triazine,[14] benzoxazole,[15] and purine[12,16] ring systems (eqs. 5-16). (The pyrimidine ring system, however, will often undergo ring opening and rearrangement reactions as alternative reaction pathways:[9] a specific example of this is given under miscellaneous reactions.) Here, as in the synthesis of the simple hydrazines, the nitrogen of the HOSA acts as an electrophilic center in the reaction.

In the case of the 1-aminopyridinium cation,[4,5] 1-aminoindole,[11] and 1,2-diaminobenzimidazole[13] especially, the method constitutes an important preparative procedure since the reaction either fails with other reagents (pyridine) or the HOSA synthesis provides a more straightforward route to the compounds in question (indole, benzimidazole). 1-Aminobenzotriazole[14] forms a convenient benzyne precursor.

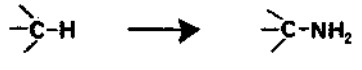
(iii) Preparation of 2-tetrazenes

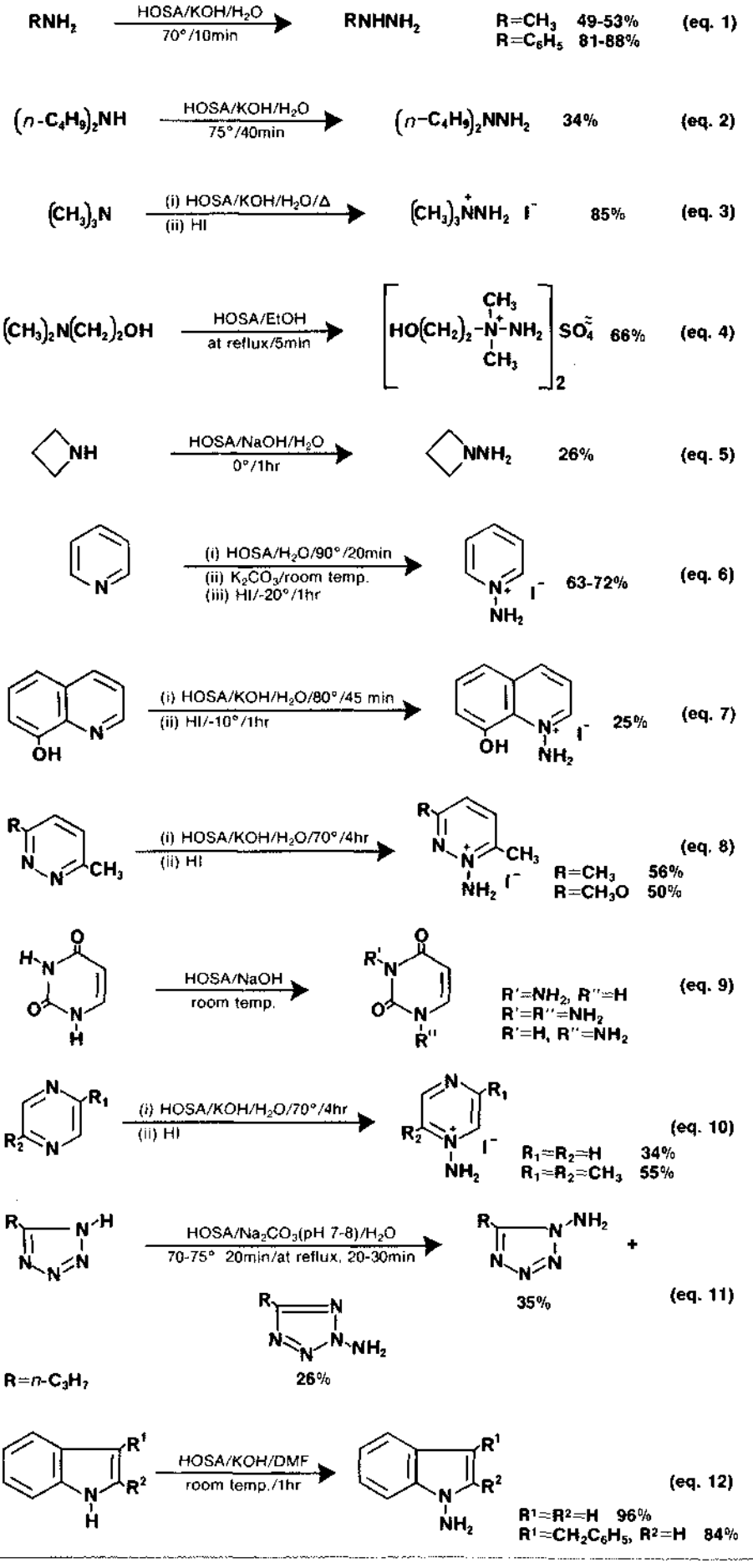
Piperidine and pipercolines react with HOSA in aqueous solution, in the presence of sodium hydroxide, to give 1,1,4,4-tetrasubstituted 2-tetrazenes (eq. 17).[17] Presumably, the simple hydrazine is initially formed and is subsequently oxidized to the tetrazene.

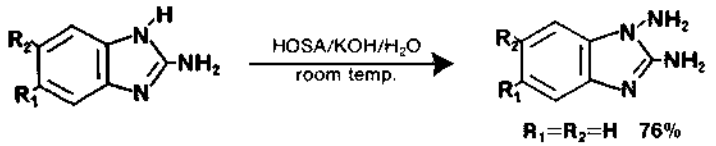
(b) At a carbon atom

HOSA will aminate on aliphatic, aromatic and heterocyclic carbon atoms under a variety of conditions.

(i) Aliphatic carbon

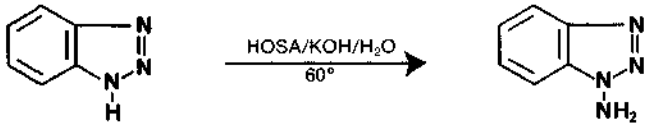




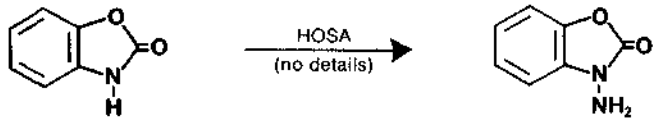


$R_1=R_2=H$ 76%

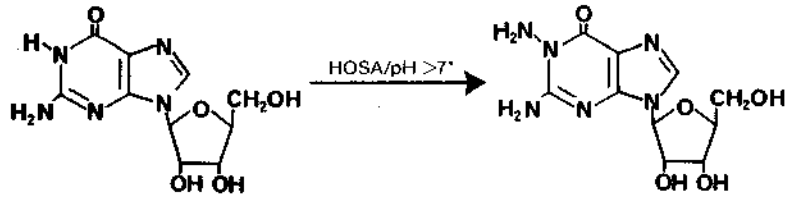
(eq. 13)



(eq. 14)



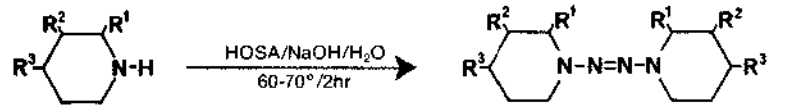
(eq. 15)



almost quantitative

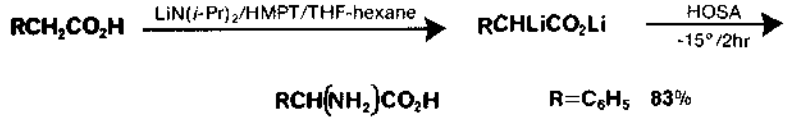
(eq. 16)

*Note: pH 2-4 gives C-8 amination



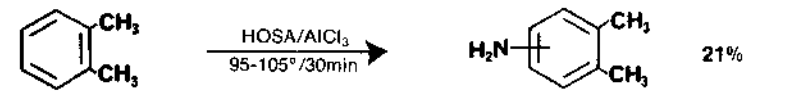
$R^1=R^2=R^3=H$ 18%

(eq. 17)



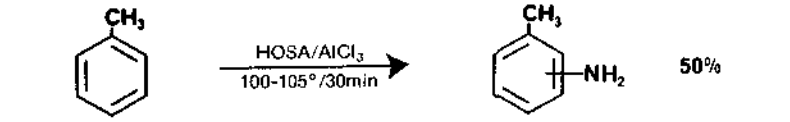
$R=C_6H_5$ 83%

(eq. 18)



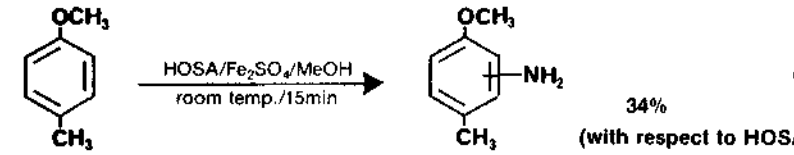
21%

(eq. 19)



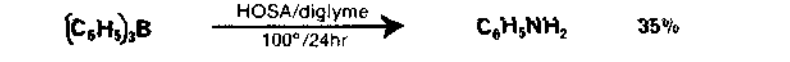
50%

(eq. 20)



34%
(with respect to HOSA)

(eq. 21)



35%

(eq. 22)

One of the most successful of these procedures is the elegant one-step synthesis of α-amino acids from carboxylic acids. The acid is lithiated in a mixed solvent system and afterwards treated with HOSA (eq. 18)[18] to give the α-amino acid. HOSA will also aminate active methylene compounds as is demonstrated in the synthesis of substituted pyrroles[19] from β-keto esters and β-diketones.

(ii) Aromatic carbon

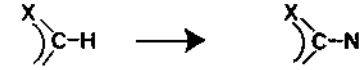
Two main methods have been employed to bring about direct amination in aromatic systems using HOSA. In both cases the yields tend to be on the low side.

The first employs aluminum chloride as a catalyst and has been fairly extensively investigated by Keller[20] and Kovacic.[21] There appears to be a number of points of variance between the work of the two authors. The precise aminating species is not known. Examples from both authors' work are given below (eqs. 19,20).[20,21]

The second method is a homolytic amination procedure developed by Minisci and his co-workers,[22] whereby what is thought to be a protonated amino radical is generated in a redox system (H_2N-$\cdot OSO_3H$/Fe^{++}) at room temperature and this then attacks an aromatic substrate. Yields of between 10 and 40% of monoaminated product are reported (eq. 21). (In many instances the yields are quantitative with respect to the aromatic substrate actually consumed.) In certain cases the reaction shows a degree of stereospecificity.

A third method,[23] from the very recent literature, is based on H.C. Brown's procedure for the conversion of alkenes *via* the organoborane to aliphatic amines (*vide infra*). If an aryl organoborane is substituted for the alkyl borane in the reaction (the paper gives triphenylborane as an example — prepared from phenylmagnesium bromide and boron trifluoride) an arylamine is produced (eq. 22). The disadvantage of the method is that, unlike trialkyl boranes, which utilize two of the three alkyl groups in amine formation, triphenylborane uses only one phenyl group and thus the overall yield with regard to amination on the aromatic ring is not high.

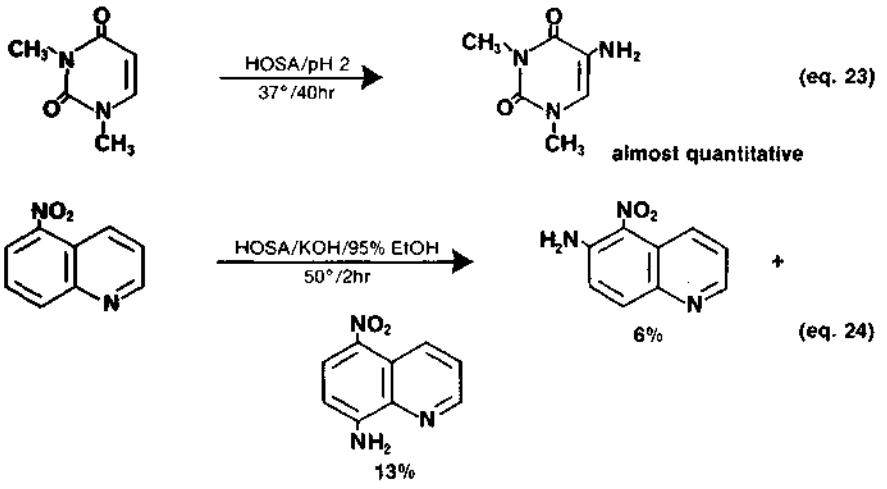
(iii) Heterocyclic carbon



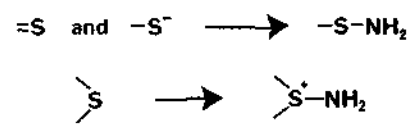
Certain heterocycles will react with HOSA to give a C-substituted amino derivative. For instance, 1,3-dimethyl-

uracil reacts with HOSA at pH 2 over 40 hours to give the C-amino product in almost quantitative yield (eq. 23).[24] Guanosine (eq. 16) aminates at the 8-position[16] at pH 2-4 (70°) and 5-nitroquinoline (*cf.* 8-hydroxyquinoline) aminates at the 6- and 8-positions under basic conditions (eq. 24).[25]

That the mechanism of some of these reactions may be one of addition followed by elimination is suggested by the fact that quinazolines, unsubstituted in the 4-position, react with HOSA at 60-65° over 5-10 minutes to give *N*-(3,4-dihydro-4-quinazolinyl)hydroxylamine-*O*-sulfonic acids, which can be isolated in good yield (eq. 25).[26] However, prolonged treatment with HOSA (70°, 4 hours) gives principally the 4-aminoquinazoline and no dihydro compound. (Interestingly, benzimidazoles and *ortho*-disubstituted benzenes are also products of the reaction under these conditions).[25]



(c) At a sulfur atom



Amination of sulfur in a variety of organic situations can be carried out using HOSA. Thus thiols(ones),[27] thioacids,[28] thioamides,[28,29] dithioacids[28] and thioethers[30] undergo amination to give the corresponding hydrosulfamines and hydrosulfonium salts (eqs. 26-30). The yields for the reactions are generally good and, as with most HOSA transformations, the experimental procedure is relatively simple.

Sulfilimines, in particular, have proved to be very useful intermediates in organic synthesis.[31]

(d) At a phosphorus atom

Triphenylphosphine, when treated with HOSA in methanol, gives triphenylphosphiminium hydrogen sulfate (eq. 31) in 69% yield.[32]

REDUCTIVE DEAMINATION

Two methods of bringing about the transformation $RNH_2 \rightarrow RH$ using HOSA are available: an indirect method *via* the sulfonamide[33] and a direct route[34] which has appeared in the literature only recently.

Reductive deamination refers to the transformation of an amine to a product of lower oxidation level (in the sense proposed by Robinson) and involves the net replacement of an amino group by hydrogen.

In the indirect route,[33] a primary aliphatic or aromatic amine is treated with sulfonyl chloride (typically benzene-, *p*-toluene- or methanesulfonyl chloride) in dry pyridine and the mixture warmed on a steam bath. The sulfonamide, which is isolated, is dissolved in NaOH and then treated with HOSA and the reaction mixture distilled to give the alkane or arene. Yields of product are usually high (eq. 32).

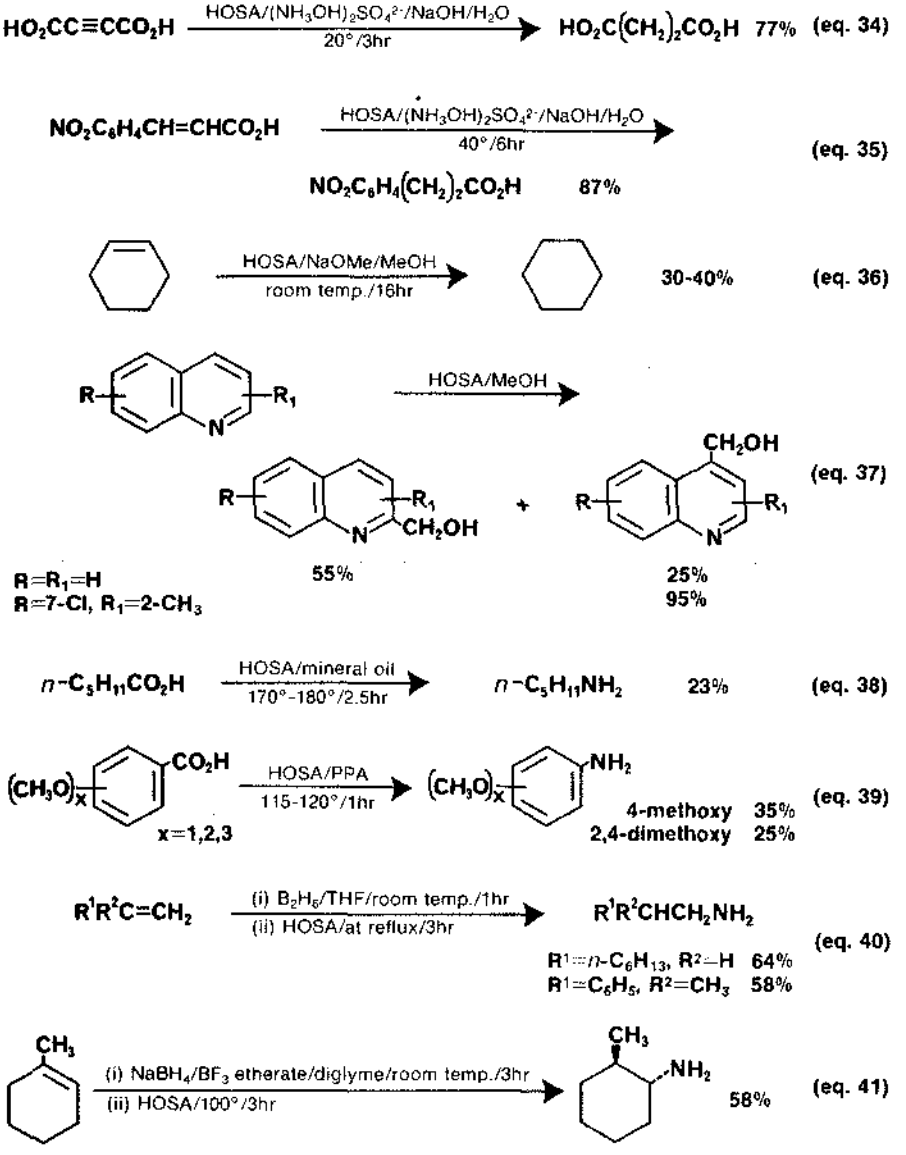
Doldouras and Kollonitsch[34] have shown that there is no need to proceed *via* the sulfonamide, since the primary amine will react directly with 2-3 molar equivalents of HOSA, in the presence of

base, at 0°, to give the deaminated product in yields in excess of 50% (eq. 33). The authors have shown that the reaction works for a variety of structural types including amines containing other functionalities, and claim that it is a selective and general method. They have coined the name 'hydrodeamination' for the process and furthermore have illustrated how it may be extended to the conversions $RNH_2 \rightarrow RD$ and RT.

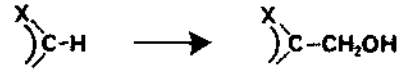
In both methods a common monosubstituted diimide (RN=NH) is proposed as an intermediate (their mode of formation differing) which readily decomposes to RH and nitrogen.

REDUCTION

HOSA alone, or in conjunction with other reagents, provides under basic conditions a source of diimide which will reduce double bonds. Thus, HOSA with cyclohexanone 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 hydrazobenzene respectively.[35] HOSA and hydroxylamine sulfate together form an *in situ* source of diimide capable of selectively hydrogenating conjugated multiple bonds (eqs. 34, 35).[36] Using HOSA alone, Appel and Büchner[37] give examples of the reduction of both conjugated and nonconjugated multiple bonds but the yields tend to be lower (eq. 36).



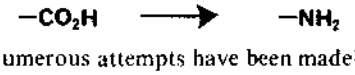
HYDROXYMETHYLATION



Quinolines can be hydroxymethylated in the 2- and/or 4-position using HOSA in methanol (eq. 37).[38] The discovery arose when a desired amination on nitrogen using the standard HOSA method could not be achieved owing to insolubility of some quinolines in the aqueous medium and, as a result, the solvent was changed to methanol. The reaction has been found to be general for quinolines substituted in the carbocyclic ring and having either a 2- or 4-position (or both) vacant.

FUNCTIONAL GROUP TRANSFORMATIONS:

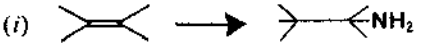
Loss of carbon



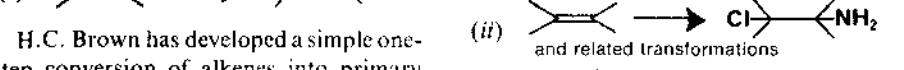
Numerous attempts have been made[39,40] to prepare amines in high yield by the reaction of carboxylic acids or their derivatives with HOSA. The best results to date have been yields of the order of 20-30% and have been obtained by heating the acid (or its anhydride) with HOSA in mineral oil at 160-180° (eq. 38)[39] or polyphosphoric acid at 115-125° (eq. 39).[40] However, the conditions for this transformation clearly still need to be optimized.

Addition to double bonds

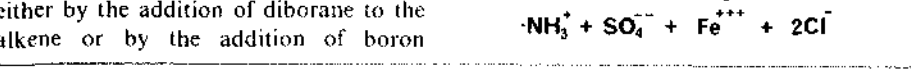
Alkenes

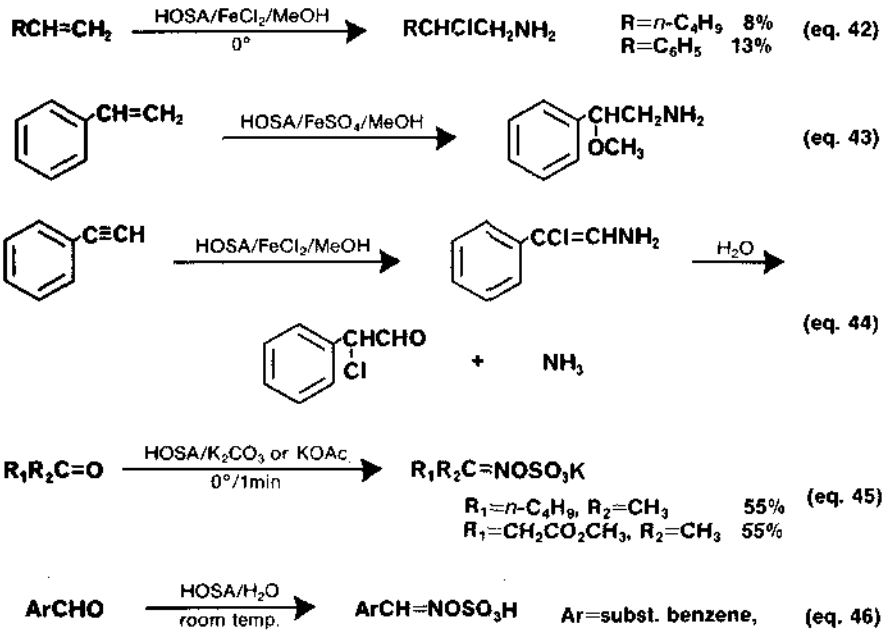


H.C. Brown has developed a simple one-step conversion of alkenes into primary amines *via* the corresponding organoborane using HOSA (eq. 40).[41] The method is applicable to a wide variety of alkenes, and in a later paper,[42] he has shown that it can be applied to relatively hindered alkenes with equal success by conducting the reaction in diglyme, in which HOSA is soluble, rather than in tetrahydrofuran as in the earlier work (eq. 41). In both cases the organoborane is prepared *in situ* — either by the addition of diborane to the alkene or by the addition of boron trifluoride etherate to the alkene and sodium borohydride in diglyme. 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.[42] Occasionally a rearranged amination product is observed.[43]



In a related but mechanistically quite different process, the metal salt redox system of Minisci (*cf.* amination on aromatic carbon — method two) is used to bring about the addition of the elements NH_2 and Cl across a double bond.[44,45] The addition occurs when HOSA is decomposed by $FeCl_2$ in the presence of the alkene:





*R.G. Wallace, unpublished observations.

Examples are given in eq. 42. It would appear that the amino group attaches itself to the least-substituted carbon atom. The addition differs from the organoborane method in not being stereospecific.

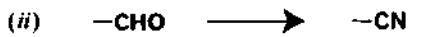
If addition is carried out in methanolic solution with $FeSO_4$ instead of $FeCl_2$, an amino ether is produced (eq. 43)[44] and if sodium azide is also present an azido amine is formed.[45]

Phenylacetylene with $FeCl_2$ yields α-chlorophenylacetaldehyde by hydrolysis of the corresponding intermediate enamine (eq. 44).[44]

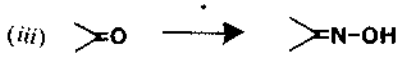
Carbonyl compounds

Both ketones and aldehydes react with HOSA to give oxime-*O*-sulfonic acids and salts (eqs. 45, 46).[46,47] In the case of ketones and some aldehydes, these derivatives can be isolated and are well defined, reasonably stable, crystallizable solids. They can be prepared in good yield and undergo a variety of further reactions. This transformation illustrates the alternative role of the HOSA nitrogen as nucleophile.

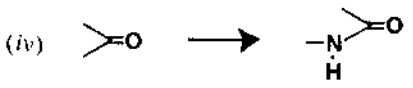
The condensation reaction to give the oxime-*O*-sulfonic acid or salt forms a common first stage in a number of related and synthetically very useful transformations.



Aldehydes, in aqueous solution/suspension, can be smoothly converted in high yield into nitriles (of the same carbon number) with *HOSA*.[36,47] The precise conditions depend on the nature of the aldehyde (details are given in eqs. 47-49), the important factor being for them to be sufficiently rigorous to bring about the elimination of sulfuric acid from the intermediate oxime-*O*-sulfonate.



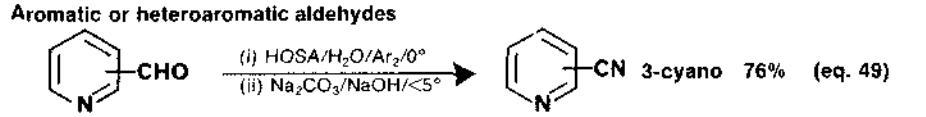
Aliphatic ketones react exothermically when warmed together with HOSA in a water bath to give the corresponding oxime in very good yield (eq. 50).[48] The reaction is accompanied by the loss of nitrogen.

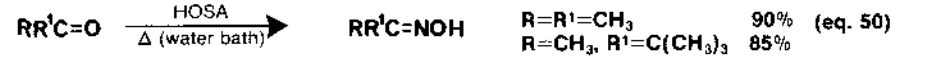


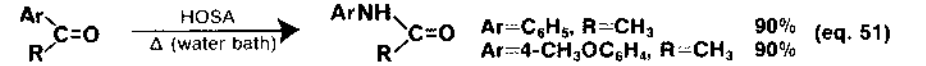
Aliphatic aldehydes

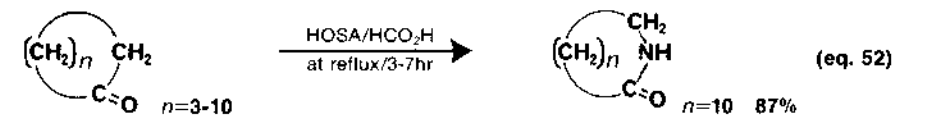
Aromatic or heteroaromatic aldehydes

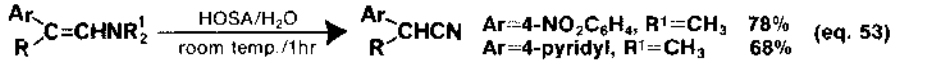
Aromatic or heteroaromatic aldehydes









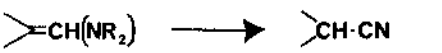


Aryl alkyl ketones, under the above conditions (eq. 51), yield N-aryl aliphatic amides, again in good yields.[48]

According to Sherk *et al.*,[48] diaryl ketones do not react under these conditions, but Ho[49] has reported the formation of amides in tetrahydrofuran. Schmidt- and Beckmann-type mechanisms are proposed for these rearrangement reactions, the precise details of which have not been resolved.[48,49]

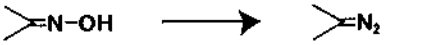
In a very recent extension of this synthetic transformation, Olah and Fung[50] have shown that alicyclic ketones can be converted to their corresponding lactams, in high yield, by heating the ketone and HOSA under reflux in formic acid for several hours (eq. 52). Benzophenone, under similar conditons, gives benzanilide in 68% yield.[50]

Enamines



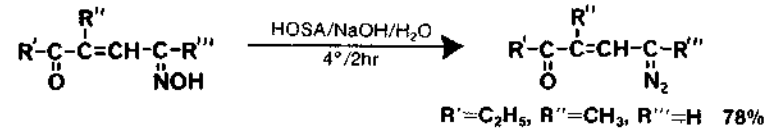
An additional nitrile synthesis using HOSA has recently been reported.[51] This time the precursor is an enamine. The method is extremely useful since enamines can be prepared readily from a variety of active methylene compounds and ketones. The enamine and HOSA are stirred together for 1 hour at room temperature, whereby the nitrile is obtained in good yield (eq. 53).

Forster reaction



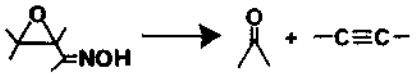
Oximes react with HOSA in aqueous base to give diazo compounds.[52] Thus,

fluorenone oxime gives diazofluorene in 60% yield and benzophenone oxime gives diphenyldiazomethane (30%). The reaction also works well for fully conjugated α,β-unsaturated 1,4-ketoximes (eq. 54).[53]

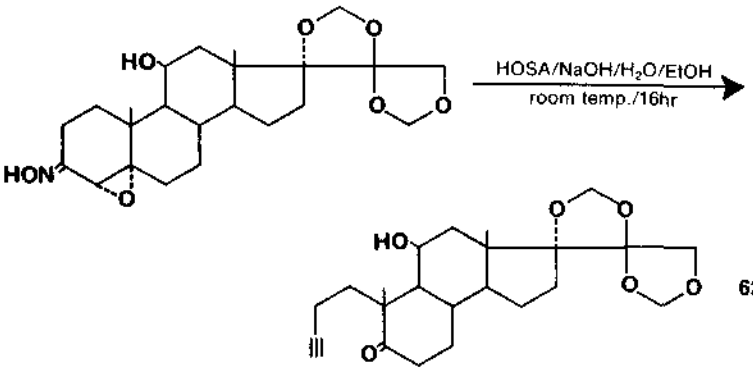


(eq. 54)

Fragmentation reactions

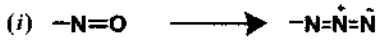


In a sagacious extension of the diazo functionality formation reaction just described, Wieland, Kaufmann and Eschenmoser[54] have demonstrated in the field of steroidal chemistry the facile conversion of an α,β-oxido oxime to an alkynone (eq. 55). A further example and a discussion of the mechanism of the reaction is given in a later paper.[55]



(eq. 55)

Miscellaneous

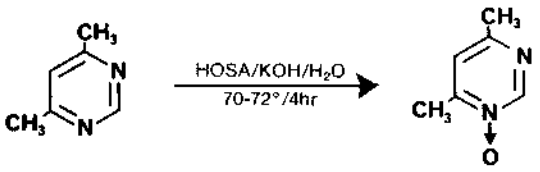


Nitrosobenzene will react with HOSA in tetrahydrofuran in the presence of base to give phenyl azide (*cf.* Forster reaction) (eq. 56).[56]

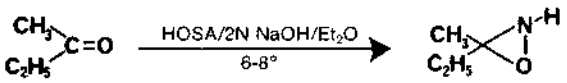
(eq. 56)

(ii) N-Oxide formation

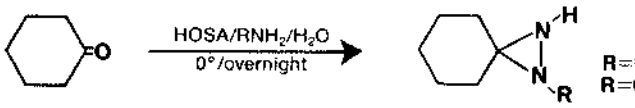
Certain 4-substituted pyrimidines[9] and condensed pyrimidines (quinazolines)[26] react with HOSA to give N-oxides. For example, 4,6-dimethylpyrimidine, with the potassium salt of HOSA in aqueous methanol over 4 hours at 70°-72°, gives 4,6-dimethylpyrimidine-1-oxide (eq. 57).[9] A mechanism involving addition of HOSA, followed by ring opening and then recyclization and, finally, loss of sulfur trioxide and ammonia is proposed for the reaction.[9]



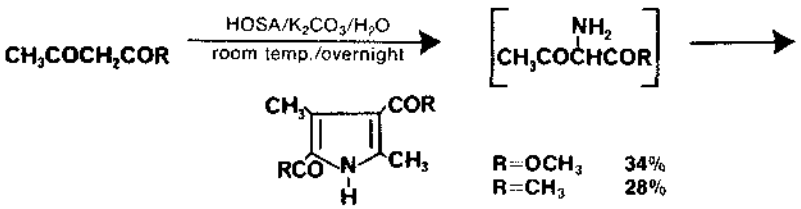
(eq. 57)



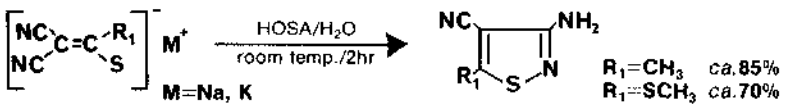
(eq. 58)



(eq. 59)



(eq. 60)



(eq. 61)

HETEROCYCLE FORMATION

(a) Cyclization reactions

Oxaziridines

The oxaziridine ring system can be prepared by the reaction of HOSA with an aliphatic ketone[57,58] or benzaldehyde[59] in 2*N* NaOH at 6-8°. Thus, 3-ethyl-3-methyloxaziridine is obtained in 96% yield (eq. 58)[57] from 2-butanone. The oxaziridine is stable only at very low temperature. More stable oxaziridines are generally obtained by acylating the unsubstituted oxaziridine *in situ*.[59]

Diaziridines

Related to the preparation of oxaziridines and probably another of the most widely explored areas of HOSA chemistry has been the synthesis of diaziridines. Both simple[60] and complex diaziridines such as those with steroidal[61] and multifused[62] ring structures have been described. Principal references are given in reviews by Schmitz[63,64] who notes that by 1964, fifty or so diaziridines had been prepared by the HOSA method.

The diaziridine is formed by reaction of HOSA with ketone/ammonia mixtures, Schiff's bases or a mixture of a carbonyl compound and a primary amine. A typical synthetic procedure, described in *Organic Syntheses*,[65] is illustrated in eq. 59. The diaziridines may easily be oxidized to diazirines.

The pyrrole system

Tamura *et al.*[19] have described a simple one-step method for the preparation of tetrasubstituted pyrroles. A β-diketo compound is treated with HOSA in aqueous potassium carbonate solution overnight to give a symmetrically substituted pyrrole (yields 28-34%, eq. 60). Pyrroline is formed in low yield when HOSA is treated with NaOMe in methanol in the presence of 1,3-butadiene.[66] The 1,4-addition of imene ($\overline{\text{N}}$H) to the diene is invoked in this reaction.

Isothiazoles

Dicyanothioalkene salts* (eq. 61, these

*The yields from monocyano compounds are very low.

can easily be prepared in yields of over 70% by the thioacylation of malononitrile by esters of dithiocarboxylic, thionocarboxylic, xanthic or trithiocarbonic acids at room temperature) react with HOSA in aqueous solution to give 3-aminoisothiazoles.[67,68] The yield of crude reaction product is generally good but isolation of the pure isothiazole may in some cases present technical difficulties.

Benzisoxazoles

Kemp and Woodward[69] have described how benzisoxazole can be prepared in 95% yield when salicylaldehyde is combined with HOSA in water, followed by treatment with sodium bicarbonate for 1 hour at room temperature (eq. 62). A similar preparation was reported eleven years after the publication of Kemp and Woodward's paper, by Suwiński,[70] who seems to have been unaware of the former authors' work. The reaction involves nucleophilic attack by the HOSA nitrogen. The preparation of Kemp and Woodward is suited to large-scale reaction.

Benzodihydro-[1,2]-diazepines

δ-Amino aromatic aldehydes (see eq. 63) can be cyclized in low yield using HOSA to give diazepines.[71] The major product of the reaction, however, is the aromatic nitrile (*vide ante*). The yields of diazepines, nevertheless, can be increased by increasing the nucleophilicity of the nitrogen atom of the aniline function (see eq. 63) and/or by employing mesitylsulfonylhydroxylamine in place of HOSA in the reaction (yields up to 76%).

The proposed mechanism for the cyclization involves a ring expansion step; an additional benzodiazepine ring synthesis, which is a direct ring expansion of a preformed starting material, is described a little later.

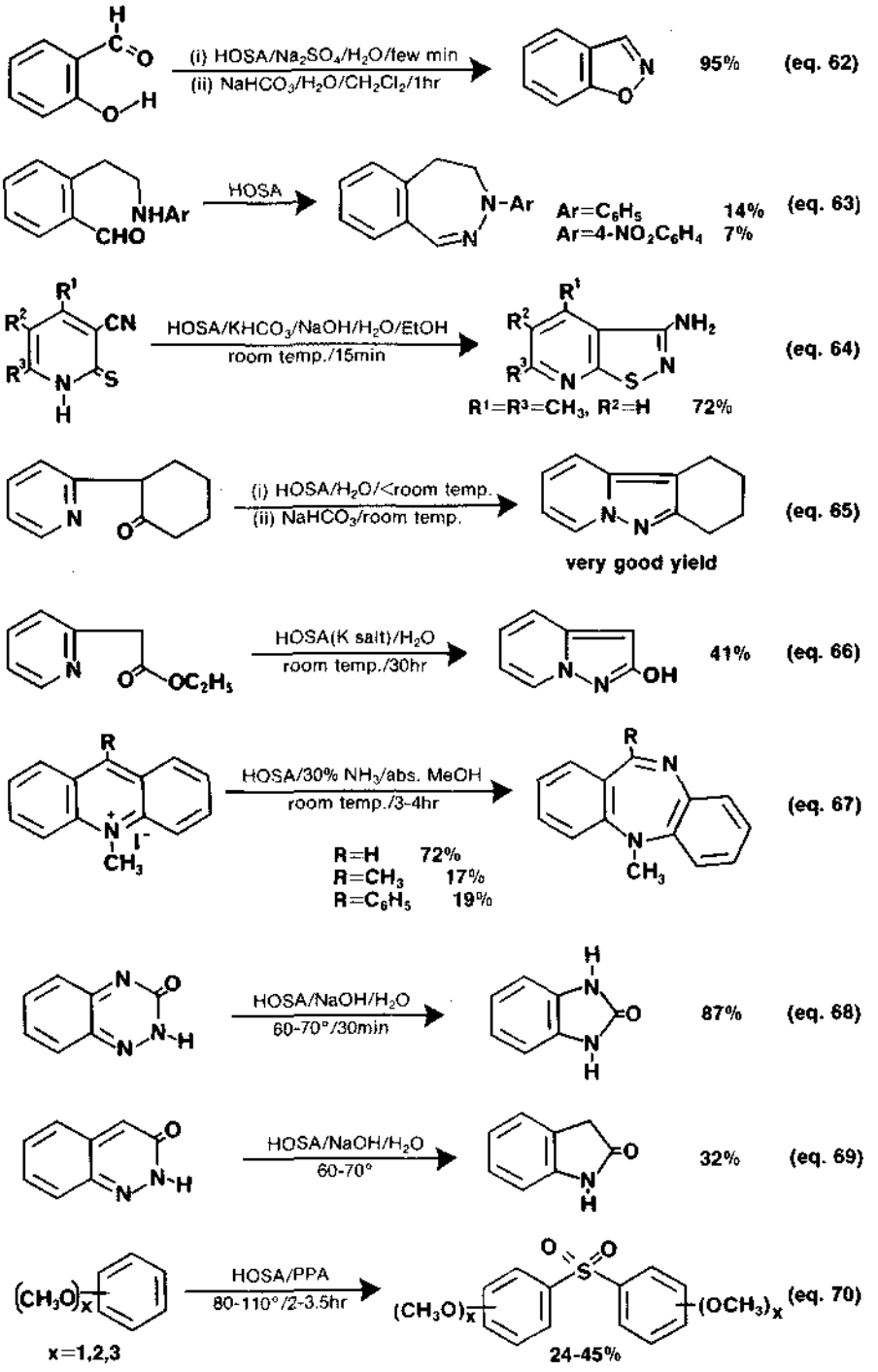
Isothiazolopyridines

In an extension of the isothiazole synthesis described above, 3-cyanopyridine-2-thiones are found to cyclize on treatment with HOSA in the presence of base to give 3-aminoisothiazolo[5,4-*b*]pyridines (eq. 64).[27] The yields in this reaction are good.

Pyrazolopyridines

Pyridines with a β-carbonyl functionality in the 2-position undergo ring closure with HOSA to give pyrazolo[1,5-*a*]-pyridines (eqs. 65,66)[70,72] in good yield. The reaction would seem to occur by electrophilic attack of the HOSA on the carbonyl function to give a derived oxime-*O*-sulfonate, with subsequent electrophilic attack of the oxime nitrogen on the nitrogen of the pyridine ring.

(b) Ring expansion



Dibenzo-[1,4]-diazepines

Treatment of *N*-methylacridinium derivatives with HOSA in absolute methanol containing 30% ammonia for 3-4 hours at room temperature results in an expansion of the heterocyclic ring. The resulting 5-methyldibenzo[*b,e*]-(1,4)-diazepines[73] are obtained in variable yield (eq. 67).

(c) Ring contraction

Imidazolin-2-ones and their benzo derivatives

1,2,4-Triazin-3-ones, when treated with HOSA in aqueous alkali at 70°, undergo a ring contraction reaction to give imidazolin-2-ones in high yield.[74] Thus, 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%, eq. 68) 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%). *N*-Aminotriazines are considered to be intermediates in these ring contractions.

Oxindole

Cinnolin-3-one, under similar conditions to those above, reacts with HOSA

to give oxindole in 32% yield (eq. 69).[74]

MISCELLANEOUS

Most of the preceding reactions described have involved the incorporation of the nitrogen of the HOSA in the reaction product. One reaction which differs from all of these is that between aromatic ethers and HOSA in polyphosphoric acid. Here, sulfur is incorporated and the product is a diaryl sulfone (eq. 70).[75] It is suggested that HOSA is cleaved to give H_2SO_4 and it is further reaction of this that gives rise to the sulfone.

CONCLUSIONS

HOSA has proved to be a reagent of diverse synthetic utility, its multifarious uses having been amply illustrated in the foregoing paragraphs. Such versatility is a consequence of the inherent ability of HOSA to act as both a nucleophile and electrophile and also to provide an *in situ* source of other chemical entities, factors referred to at the beginning of this article. These properties have led to its exploitation in such a variety of situations.

Clearly there is scope for its application in further organic transformations, and in particular, it must have a further part to play in new heterocyclic syntheses.

ACKNOWLEDGMENT

I wish to thank the Cancer Research Campaign for financial support.

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About the Author

Dr. Wallace is a research scientist working for the Cancer Research Campaign. He obtained his B.Sc. degree from Southampton University in 1968 and subsequently carried out his Ph.D. research at the School of Pharmacy, Portsmouth Polytechnic. His main interests lie in the area of heterocyclic chemistry and in particular he is concerned with the synthesis of hypoxic cell radiosensitizers for use in cancer therapy. He holds a Visiting Research Fellowship at Brunel University.

Aldrich offers HOSA and many of the reagents cited by Dr. Wallace:

"Please Bother Us."

by Aldrich Boys.

Last year, Professor G.R. Wyatt of the Department of Biology at Queen's University wrote to me suggesting that we make 7-ethoxy-6-methoxy-2,2-dimethylchromene (Ethoxy-Precocene). "The substance has activity as a 'precocene' or specific cytotoxic agent for the corpus allatum of insects, which stops the production of the juvenile hormone and thus brings about precocious metamorphosis and prevents reproductive maturation. . . . we have found it to be highly effective in the 'chemical allatectomy' of African migratory locusts. We find that 1 mg applied to newly emerged adult female locusts completely blocks reproductive maturation, including the juvenile hormone-dependent synthesis of yolk protein, which is a central subject of our research."

Ethoxy-Precocene seems a very exciting compound, related to the anti-juvenile hormones Precocene I and II, which we have been making for some time. And so we made it.

It was no bother at all, just a pleasure to be able to help.