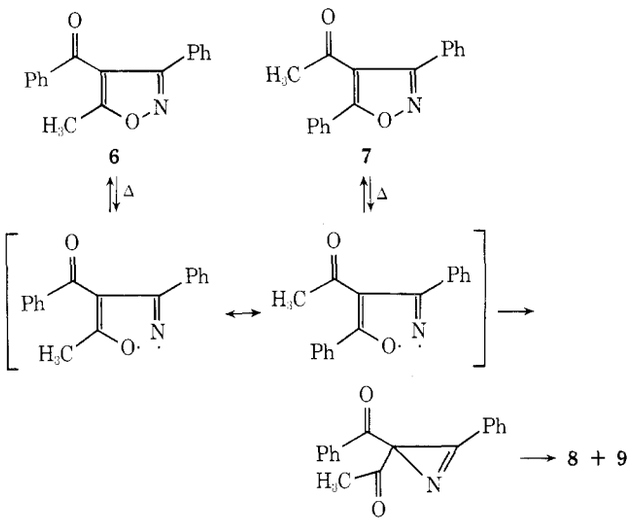
lytic cleavage of the relatively weak O–N bond of the isoxazole ring to form an acyclic intermediate which can either recyclize to generate rearranged isoxazole or close to



give a 3,3-diacyl-2-phenyl-2*H*-azirine (**10**) intermediate. The second step, **10** → **8** + **9**, most likely involves C–C bond rupture of the 2*H*-azirine ring followed by cyclization to the observed products.[20] Each step of the rearrangement is thermally induced, and the rates and products were not influenced by oxygen, radical inhibitors, or small amounts of acids and bases. It is interesting to note that 5-alkoxyisoxazoles have been reported to undergo a facile thermally induced skeletal rearrangement to alkyl 1-azirine-3-carboxylates.[21] This rearrangement provides good analogy for the first step of the proposed sequence. The literature also contains several references dealing with the thermal rearrangement of 4-isoxazolines.[22-26] Most of the rearrangements observed with these systems can also be attributed to a ring-contraction–ring-expansion sequence.

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Supplementary Material Available. Complete experimental data for this communication will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1976.

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Sulfoxonium Salts as Reagents for the Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

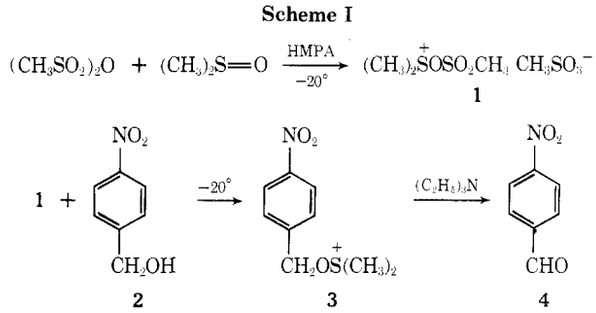
Summary: The generality of using sulfoxonium salts for oxidation of alcohols to carbonyl derivatives is illustrated.

Sir: We wish to report on a new method for the oxidation of alcohols to carbonyl derivatives which complements our previously described dimethyl sulfoxide–acetic anhydride procedure.[1] Since none of the previous methods based on dimethyl sulfoxide[2-4] give satisfactory results with all classes of compounds, our finding that reagents such as *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, methanesulfonic anhydride, benzoyl chloride, and cyanuric chloride react with dimethyl sulfoxide (DMSO) at −20° to give sulfoxonium complexes useful in oxidizing alcohols to carbonyl derivatives opens up the possibility of choosing among these mild oxidative reagents to obtain good yields.

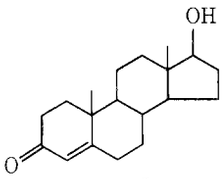
We have found that *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, or methanesulfonic anhydride[5] with dimethyl sulfoxide in hexamethylphosphoramide (HMPA) at −20° oxidize secondary alcohols to ketones and primary alcohols to aldehydes in high yields. The overall mechanistic sequence is depicted in Scheme I for the oxidation of *p*-nitrobenzyl alcohol **2** to *p*-nitrobenzaldehyde **4**.

The following example demonstrates the simplicity and efficiency of the oxidative process and illustrates the typi-

Scheme I



cal ratio of reactants and solvents used. A solution of *p*-nitrobenzyl alcohol **2** (8 mmol) in 15 ml of HMPA and 6 ml of DMSO was cooled to −20° and methanesulfonic anhydride (16 mmol) added. After 3.5 hr at −20°,[6] triethylamine (32 mmol) was added and the mixture allowed to stand at room temperature for 10 min. Pouring into ice and water and filtration gave *p*-nitrobenzaldehyde (**4**) in 88% yield. Most of the exploratory work was carried out by oxidation of testosterone (**5**) to 4-androstene-3,17-dione (**6**). For example, methanesulfonic anhydride and DMSO in HMPA (−20°, 3 hr) gave **6** (99%), mp 168–170° (lit.[7] mp 170–171°). Thin layer chromatography (tlc) showed insignificant amounts of methylthiomethyl ether **7** which can be a troublesome impurity in DMSO oxidations.[1,3] With methanesulfonyl chloride the reaction was incomplete (5 hr) and tlc showed additional impurities. *p*-Toluenesulfonyl chloride–DMSO and **5** in HMPA (5 hr, −20°) gave **6** in high yield without significant amounts of by-product **7**; however, some of the excess *p*-toluenesulfonyl chloride necessary for efficient conversion of **5** to **6** remained in the product. Recrystallization gave **6** (77%), mp 170–171°. Both benzenesulfonyl chloride and toluenesulfonic anhydride oxidized **5** to **6** (~85% yields) while benzoyl chloride in DMSO and HMPA at −20° gave **6** in 75% yield. The solvents HMPA and dichloromethane are satisfactory but HMPA is superior because it gives cleaner products.



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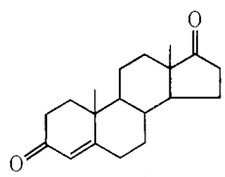

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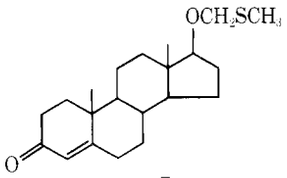

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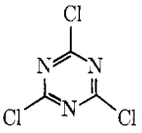
The generality of using sulfoxonium salts for oxidations of alcohols to carbonyl derivatives is illustrated by the use of cyanuric chloride and DMSO in HMPA. Cyanuric chloride (4 mmol) and testosterone **5** (4 mmol) in DMSO (3 ml) and HMPA (8 ml) (5 hr, −20°) gave, after addition of triethylamine (16 mmol), **6**, mp 167–169°, in 99% yield. Only a trace of by-product **7** was present as determined by tlc. Under similar conditions (5 hr, −20°)[8] *p*-nitrobenzyl alcohol **2** and cyanuric chloride gave a mixture (~1:1) of aldehyde **4** and *p*-nitrobenzyl chloride. Oxidations with cyanuric chloride **8** are visualized as occurring *via* intermediates **9**, **10**, and **11**. The intermediacy of ylides in conversions of sulfoxonium salts of type **10** has been established in previous studies[9] on oxidations with DMSO.

Oxidation of 1-adamantylmethanol with methanesulfonic anhydride and DMSO in HMPA (16 hr, −20°) gave 1-adamantylcarboxaldehyde (67%) while benzoin (5 hr, −20°) gave benzil in 99% yield. Yohimbine (**12**) with methanesulfonic anhydride in HMPA–CH_2Cl_2 gave **13**[10] (75%), mp 249–251° dec, while with cyanuric chloride **13** was obtained in 56% yield.[11]

The methanesulfonic anhydride and cyanuric chloride procedures have special merit since both are commercially available, polar solvents can be used, and the products from these reagents on aqueous work-up are water-soluble triethylamine salts. Cyanuric chloride is inexpensive and less toxic than *N,N*-dicyclohexylcarbodiimide and thus



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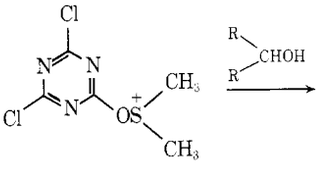

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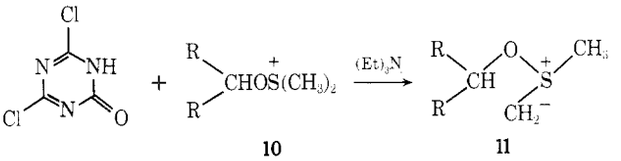
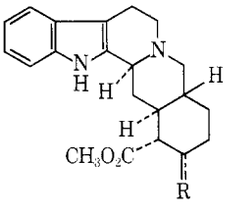
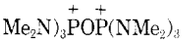


10 **11**



12, R = H, OH

13, R = O



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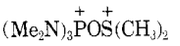

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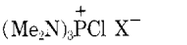

16, X = Cl

17, X = ClO_4

has advantages for large scale work. Methanesulfonic anhydride gives good yields of primary aldehydes, in contrast to acetic anhydride–DMSO where primary alcohols are not consistently oxidized in good yields.

Some consideration must be given to the possibility that intermediate **15** is involved in oxidations involving HMPA as solvent because *p*-toluenesulfonyl chloride and HMPA are reported[12] to give **14**. Reagents **16** and **17** have been reported[13] as useful in peptide synthesis and, if **15** is an intermediate in formation of alkoxysulfonium salts, some evidence on this point should be obtained by a study of the reaction of **16** and **17** with DMSO.[14] At present there is no necessity for invoking intermediate **15** since the oxidations reported also proceed in other solvents such as dichloromethane.

The use of compounds of type **16** and **17** for oxidations in DMSO, as well as a pmr study of the intermediates involved in the oxidations reported, is under investigation.

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(14) Phosphonitrilic chloride–DMSO in HMPA–CH_2Cl_2 (−20°) oxidized **5** to **6** in 78% yield.

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Intramolecular Homoconjugate Addition. A Simple Entry to Functionalized Pyrrolizidines and Indolizidines

Summary: Intramolecular alkylation of amines by activated cyclopropanes, followed by lactam formation, gives functionalized bicyclic nitrogen heterocycles.

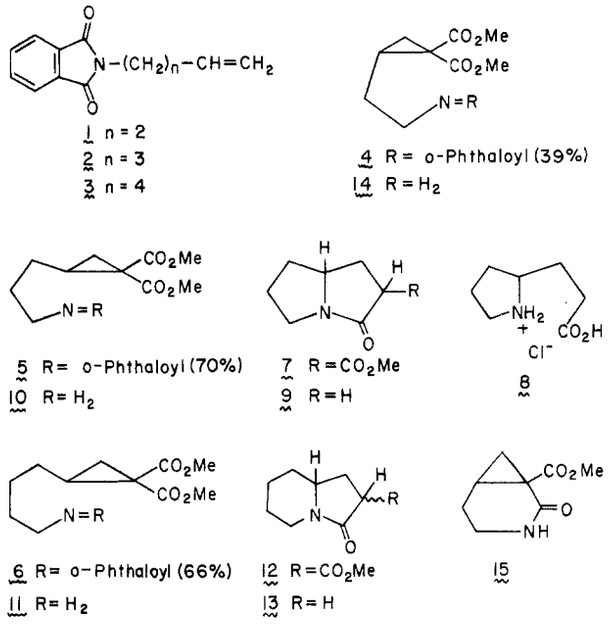
Sir: Recently we reported a new approach to the synthesis of functionalized carbocyclic ring system.[1] The method involves the generation of an anionic carbon center in juxtaposition with a cyclopropane ring which is so substituted as to render it vulnerable to nucleophilic attack. Below, we demonstrate the applicability of this concept to heterocyclic synthesis in the context of facile constructions of the pyrrolizidine[2] and indolizidine[2a] ring systems from readily available precursors.

The phthalimido olefins **1**,[3a] **2**,[3b] and **3**,[4a] mp 25.5–26.5°, were prepared by the alkylation of potassium phthalimide with 4-bromo-1-butene, 5-bromo-1-pentene, and 6-bromo-1-hexene, respectively. The cyclopropanes **4**,[4] mp 124–125°, **5**,[4] mp 84–85°, and **6**, mp[4] 91–92°, were prepared in the yields shown[5] by cyclopropanation of the corresponding olefins with dimethyl diazomalonate (*e.g.*, for the case of **4**, 0.107 mol of diazo compound added dropwise over 0.5 hr to a mixture of 0.094 mol of **1** and 130 mg of copper bronze which was heated at 140° under nitrogen).

Reaction of **5** with hydrazine (1.1 equiv of hydrazine to 1 equiv of **5** in methanol under reflux for 15 hr) gave the lactam ester **7**[4a] in quantitative recovery. Hydrolysis and decarboxylation of this compound (10% aqueous HCl, reflux 15 hr) is accompanied by ring opening. The pyrrolidine propionic acid salt, **8**, so produced,[6] was not purified. Esterification by MeOH–HCl produced the ester hydrochloride which was converted to the known[7] pyrrolizid-3-one (**9**) in 93% overall yield from **5**.

When the hydrazinolysis was conducted at room temperature, the intermediate amino diester **10** was isolated in 65% yield. Purification of **10**[4a] was rendered difficult by its tendency to undergo partial conversion to **7** on chromatography. Hence, for preparative purposes, direct conversion of **5** → **7** is the preferred method.

It appears reasonable to postulate that, in the pathway from **10** (or **5**) → **7**, internal alkylation of the amine by the activated cyclopropane occurs before lactamization. The reverse order of steps seems unlikely since it would require formation of a seven-membered lactam and, more seriously, necessitate an endocyclic[8] displacement during the alkylation step.



Preliminary experimentation revealed that the conditions required for conversion of amino diester **11**[4a] [obtained by room temperature hydrazinolysis (*cf.* above) of phthalimido diester **6**] to the epimeric indolizidine derivatives **12** are considerably more drastic than those required for the case of **10** → **7**. The considerably more facile formation of a pyrrolidine relative to a piperidine *via* intramolecular homoconjugate addition finds precedent in the carbocyclic series.[1] Hence, more vigorous hydrazinolysis conditions (1.1 equiv of hydrazine in MeOH at 115°, sealed tube, 15 hr) were employed for the conversion of **6** → **12**. The known epimeric mixture[9] thus obtained in crude form was carried through the same sequence of reactions as for the case of **7** to give 3-indolizidone **13**[7] in 82% overall from **6**. By the same reasoning set forth in the case of **10**, the most likely pathway from **11** → **12** involves intramolecular alkylation followed by lactamization.

The formation of **7** and **12** from **10** and **11**, respectively, corresponds to intramolecular homoconjugate addition *via* what has been termed the spiro mode.[1] As in the case of the carbocyclic series, no products corresponding to the alternative fused mode of attack are observed when the spiro mode[1] gives five- or six-membered primary ring products. In this connection it was of interest to examine the chemistry of amino diester **14** which might, in principle, have given, as primary products, an azetidine *via* the spiro mode or a pyrrolidine through the fused mode. Both processes have precedent,[1] though under drastic conditions, in the carbocyclic series.[1] In practice, depthaloylation of **4** *via* hydrazinolysis in methanol at room temperature gives upon work-up the desired **14**[4a] (63%). Upon standing in neat form, **14** cyclizes to give lactam ester **15** mp 133–136°.[4] No evidence for intramolecular homoconjugate addition was observed in this instance. However, these results do not constitute a valid test of the feasibility of the ring opening reactions, since lactamization prevents their occurence.[8]

Further studies of heterocyclic synthesis *via* activated cyclopropanes are in progress as are adaptations of this scheme to the synthesis of related alkaloids.[2a]

Acknowledgments. This research was supported by PHS Grant C.A. 12107-09. Facilities for nmr spectra were supported by PHS Grant RR-00292-03.