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Burgess reagent in organic synthesis†

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Abstract

Methyl *N*-(triethylammoniumsulfonyl)carbamate, also known as Burgess regent, is a mild yet powerful dehydrating agent. Usefulness of the regent in various synthetic transformations and in the synthesis of various heterocyclic systems has been reviewed.

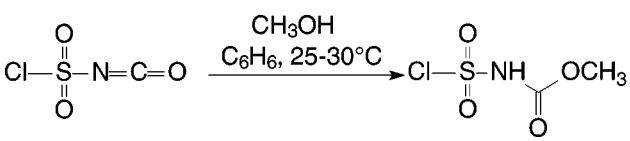
Keywords: Burgess regent, dehydrating agent, heterocycles, cyclodehydration.

1. Introduction

Methyl *N*-(triethylammoniumsulphonyl)carbamate (**1**), also known as Burgess reagent,[1] is a mild and selective dehydrating agent, and can be successfully utilized for the preparation of alkenes from alcohols. However, it went into oblivion for nearly a decade soon after its discovery by E. M. Burgess in 1968. It was Peter Wipf who brought it to the attention of organic chemists through its extensive use in the formation of 5-membered heterocycles from their acyclic precursors. An interesting feature of this reagent is that the dehydration is a pyrolytic reaction which can be effected below 100°C. The reagent is highly soluble in most of the common organic solvents including nonpolar ones, even though it is formulated as a salt. The dehydration takes place through a variant of Ei mechanism resulting in *syn*-elimination. The reagent is also known to bring about many important transformations such as preparation of isocyanides, nitriles, and nitrile oxides from formamides, primary amides and nitroalkanes, respectively. The most noteworthy application has been in the cyclodehydration of hydroxy amides and thioamides to afford the corresponding heterocycles. Because of the mild conditions required as well as the selectivity observed, the reagent has received wide acceptance in natural product synthesis. It is intended in this review to give an updated overview of the reagent.

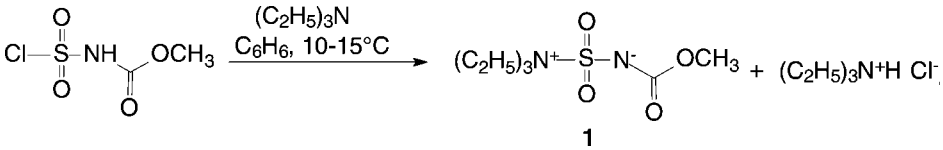
2. Preparation of the reagent

The inner salt **1** is prepared from two readily available chemicals, i.e. chlorosulfonyl isocyanate and triethylamine via a two-step (eqns 1and 2) preparation as outlined below.[2]



(1)

†Dedicated to Prof. S. C. Bhattacharyya.
*Author for correspondence.



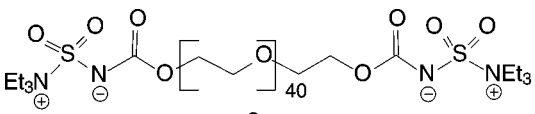
(2)[2]

1

Step 1: Anhydrous methanol in dry benzene is added dropwise to a solution of chlorosulfonyl isocyanate in benzene at 25–30°C over a period of 0.5 h. The mixture is stirred for 0.5 h before olefin-free hexane is added and the flask is cooled to 0–5°C. The moisture-sensitive product is removed by filtration, washed twice with hexane and dried under reduced pressure to afford white crystals of methyl (chlorosulfonyl) carbamate (yield 88–92%, m.p. 72–74°C).

Step 2: Methyl (chlorosulfonyl)carbamate in dry benzene is added dropwise to a solution of triethylamine in anhydrous benzene at 10–15°C over a period of 1 h with constant shaking. The resulting mixture is stirred at 25–30°C for additional 0.5 h and then filtered to remove triethylamine hydrochloride. Evaporation of the filtrate under reduced pressure gives light tan needles. It is dissolved in anhydrous THF and on cooling the inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide **(1)** is precipitated as colorless needles (yield 84–86%, m.p. 70–72°C). The reagent is oxidation and moisture sensitive, and needs to be stored at low temperature.

A polyethyleneglycol (PEG)-linked version[3,4] **2** of Burgess reagent (**1**) has been developed by Wipf and coworkers, and shown to be very effective in cyclodehydration of hydroxy amides. The polymer-bound reagent has better shelf-life than the parent reagent. It can be prepared on a laboratory scale as follows. A solution of polyethyleneglycol (3 mmol, M_x = 2000) in dry benzene (30 ml) is added dropwise to a solution of $ClSO_2NCO$ (6.3 mmol) in 10 ml of dry benzene. The reaction mixture is stirred for 1 h, concentrated *in vacuo* to yield a colorless residue. A solution of this residue in 20 ml of dry benzene is added dropwise to a solution of Et_3N (11.4 mmol) in 10 ml of dry benzene. The reaction mixture is stirred at 25°C for 1 h, filtered, concentrated and dried *in vacuo* to yield (88%) polymer-linked Burgess reagent **(2)**.

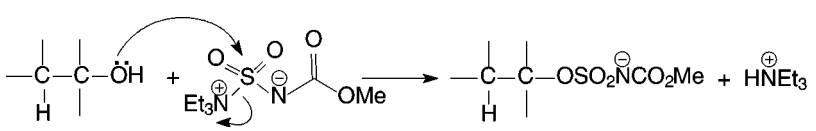


(2a)

2

3. Mechanism

The mechanism of action by which Burgess reagent works is now believed to be a variant of Ei mechanism (eqn 4). It is proposed on the basis of dehydration of *threo* and *erythro*-2- deuterio-1,2-diphenylethanol, studied in detail by Burgess *et al.*[5] The first step, i.e. the formation of sulfamate ester, takes place in hydrocarbon solvents (eqn 3) at or below 30°C by the interaction of an alcohol with the reagent (**1**).



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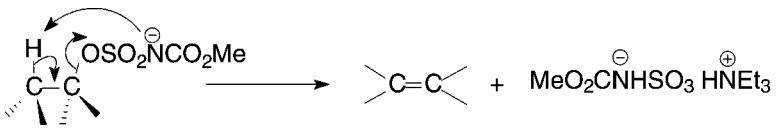
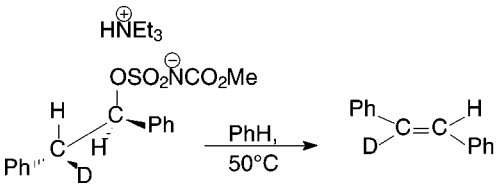


(4)

When heated/irradiated by microwave, this sufamate ester undergoes pyrolysis. Ionization of the α carbon bearing the sulfamate group (which is also the rate-determining step) results in an ion pair whose collapse involves rapid transfer of the β hydrogen from cation to anion. Geometrical constraints require that this abstracted hydrogen is *syn* with respect to the leaving group. The leaving group has good incipient proton nucleophilicity even in solvents of low polarities. Furthermore, it has multiple H^+ acceptor sites. So, the free energy of the process is lowered owing to an increased positive entropy contribution. As a result, the proton capture becomes favorable. This reduces the degree of ion-pairing character and consequently the carbonium ion rearrangements. Thus, *erythro* and *threo*-2-deuterio-1,2-diphenylethyl-*N*-carbomethoxy sulfamates on decomposition give α-deuterio *trans*-stilbene (eqn 5) and protio *trans*-stilbene (eqn 6), respectively, in accordance with the mechanism of *syn* elimination.



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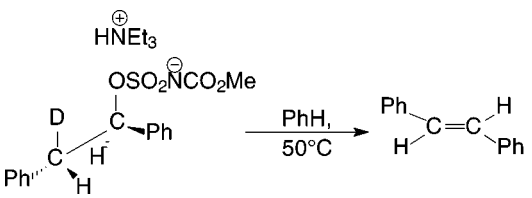
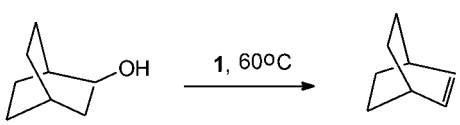


(6)

4. Applications

4.1. *Dehydration of alcohols*

The nature of the alcohol group (secondary, tertiary and homoallylic), its configuration and the environment are the primary factors that govern the course of the reaction. Secondary and tertiary alcohols (eqns 7 and 8), when treated with Burgess reagent (**1**) in an aprotic solvent, afford the corresponding olefins in 70–90% yields.[6]



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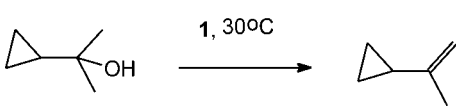
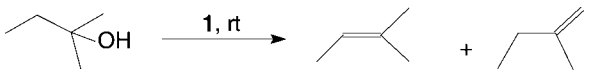


(8)

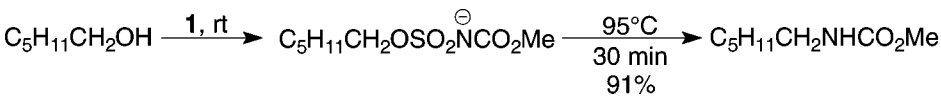
It has been observed that the product formation follows Saytzef 's rule in majority of the cases (eqn 9).[5]



(2.4 : 1) (9)

Primary alcohols, in contrast to secondary and tertiary alcohols, yield the corresponding carbamates (eqns 10 and 11) in excellent yields, instead of the expected terminal olefins.

With *N*-carbomethoxysulfomate salts derived from primary alcohols, an S_N2 pathway becomes energetically more favorable as compared to the Ei counterpart and urethanes result from the thermolysis of these salts (eqns 10 and 11).[5]



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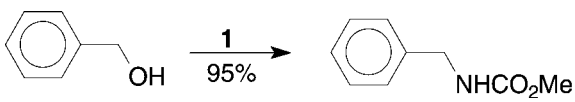
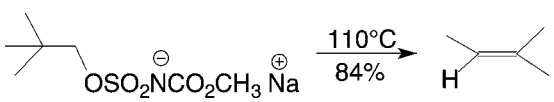


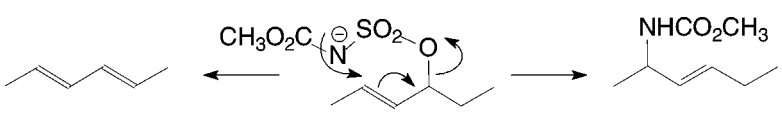
(11)

However, for a primary sulfamate ester in which there are steric restrictions to a bimolecular displacement, Ei pathway becomes operative following a rearrangement at the high temperature (eqn 12).



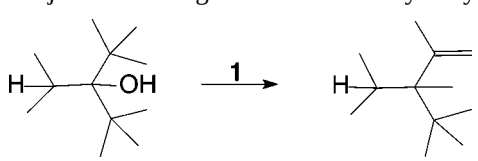
(12)

When the reaction is applied to an allylic alcohol either elimination or an S_Ni rearrangement ensues depending upon the experimental conditions. For example, the thermal decomposition (80°C, solid-state decomposition) of sodium 4-hex-2-enyl *N*-carbomethoxysulfamate (eqn 13) provides, after hydrolytic decomposition, the rearranged urethane **(4)** in 94% yield, while the diene **(3)** is obtained in 73% yield from the reaction in triglyme solution.[5]



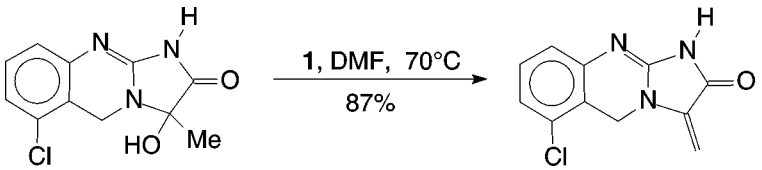
3 **4** (13)

While tertiary alcohols normally undergo dehydration under milder conditions, they are also subject to rearrangements followed by dehydration (eqn 14).[5]



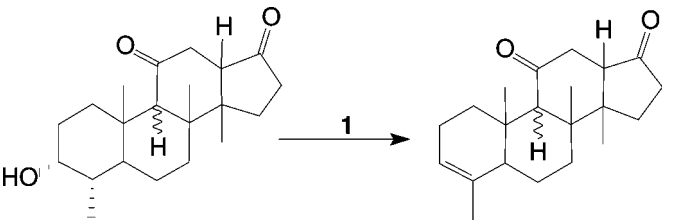
(14)

A tertiary alcohol present in a heterocycle-like quinazolinone (eqn 15) moiety can be smoothly dehydrated with the reagent (**1**) to the corresponding olefinic compound in high yield.



(15)[7]

Although the *cis* elimination is generally accepted, there are cases where deviations are observed. In cases where carbonium ion is stabilized by substituents or a more stable configuration can be attained by rearrangements, the normal *cis* elimination products are not observed. For example, steroidal alcohol (eqn 16) provides the corresponding olefinic steroid via a *trans* elimination.



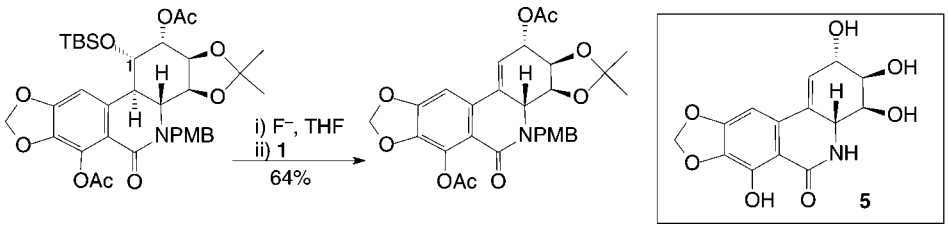
(16)[8]

The compatibility of a saturated ketone, α,β-unsaturated ketone, aromatic ring, triple bond, acetate, and bismethylenedioxy function with the reagent (**1**) and mild reaction conditions (low temperature, neutral medium), the satisfactory yields which are obtained as well as the unexpected nature of some products in some cases makes it an attractive tool for the introduction of double bonds. The results[9] of dehydration of various steroidal molecules examined are presented in Table I.

The reagent **1**, because of its mild nature, has found wide application in natural product synthesis. The phenanthridone alkaloids of the narciclasine family are reported to exhibit antitumor activity. Rigby's first total synthesis of (+)-narciclasine (**5**) has utilized Burgess reagent (**1**) as a dehydrating agent to promote a *cis* elimination. The double bond required at C-1 was introduced by selective deprotection of the hydroxyl group at this location followed by dehydration with Burgess reagent in 64% yield (eqn 17).

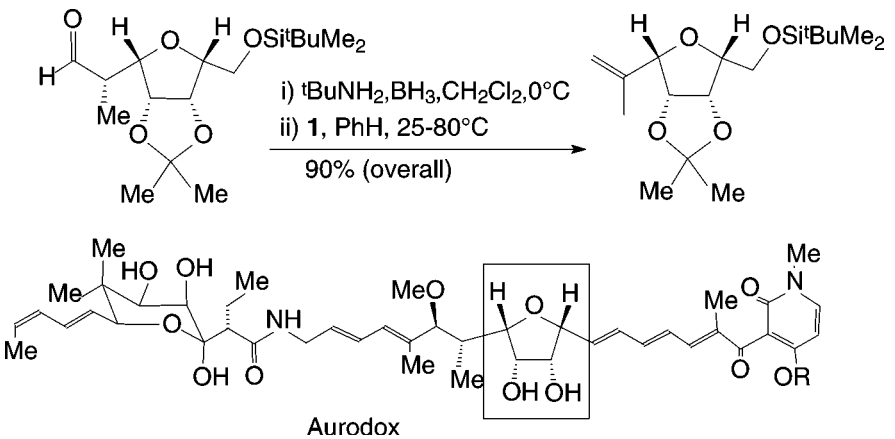
Table I
Products and yields of compounds formed by the dehydration of steroidal alcohols

Steroidal alcohols	Steroidal olefins formed	Yield (%)
3α-Hydroxy-5α-androstan-17-one	5α-Androst-2-ene-17-one	75
3β-Hydroxy-5α-androstan-17-one	5α-Androst-2-ene-17-one	52
3β-Hydroxy-5α-cholestane	5α-Cholest-2-ene	63
3β-Hydroxy-cholest-5-ene	Cholesta-3,5-diene	27
11β, 17α, 21-Trihydroxy-17:20, 20:21-bismethylenedioxypregn-4-ene-3,20-dione	17α, 21-dihydroxy-17:20, 20:21-bismethylenedioxypregna-4, 9(11)diene-3,20-dione	96



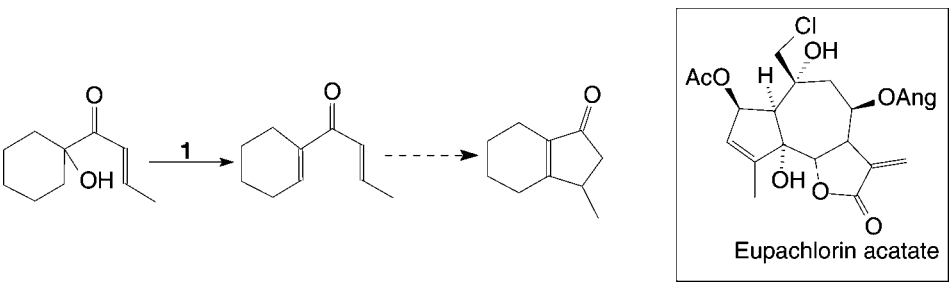
(17)[10]

Dolle and Nicolaou have reported the total synthesis of aurodox and efrotomycin which belong to a newly discovered class of narrow spectrum antibiotics known as elfamycins. Burgess reagent (**1**) was used for the construction of tetrahydrofuran fragment of the elfamycins (eqn 18).[11] It is noteworthy that a primary alcohol can be dehydrated contrary to the general notion.



(18)[2]

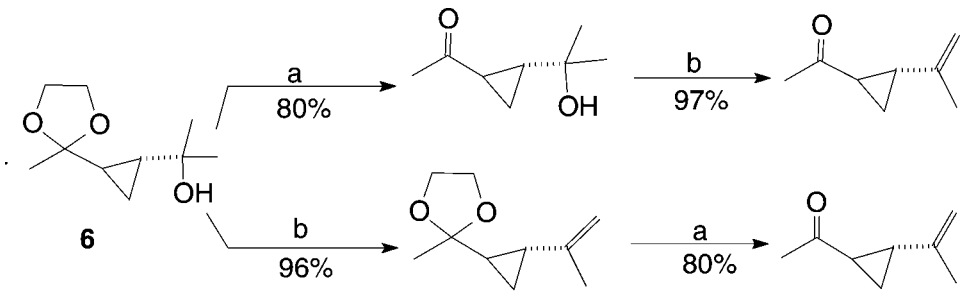
Nazarov cyclization is an important method of formation of a cyclopentenone from its acyclic precursor. It can be extended to cyclopentenone annulation providing a number of sesquiterpenoid lactones (e.g. eupachlorin acetate) of biological interest. The generation of the intermediate dienones from their hydroxy precursors is, however, a serious problem due to the fact that the conventional dehydrating agents give rise to lactone side products. The problem can be overcome by the use of Burgess reagent (**1**) (eqn 19).



(19)[12]

The tertiary alcohol **(6)** is used for the synthesis of the diterpene plant growth regulator, portulal.[13] Dehydration of tertiary alcohol **(6)** (Scheme 1) with conventional reagents such as thionyl chlo-

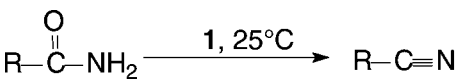
ride or phosphorus tribromide in pyridine failed or gave low yields of the desired alkenes. On the other hand, the use of Burgess reagent resulted in clean dehydration of the cyclopropylcarbinyl alcohol system **(6)**.



Scheme 1.

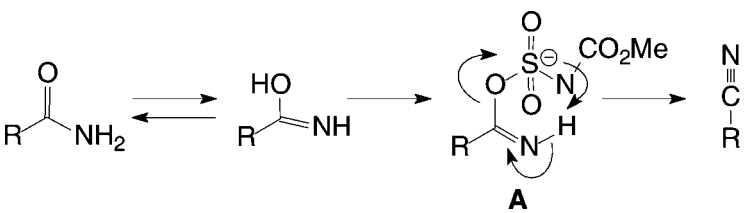
4.2. *Nitriles from primary amides*

The dehydration of primary amides offers a convenient route to nitriles. Reagents, which are commonly employed for this transformation, are often inappropriate in the presence of other functional groups and therefore require protection or an entirely alternative synthesis. Burgess reagent can, however, be used efficiently for this transformation (eqn 20).



(20)[14]

Examples in Table II demonstrate the excellent chemoselectivity of the reagent and its inertness to various functional groups. The observed chemoselectivity may be the result of kinetically faster formation of intermediate **A** (eqn 21) versus the formation of similar species for secondary alcohols (entry 1).

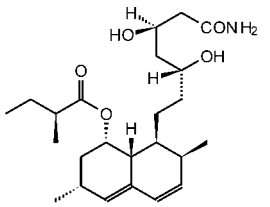
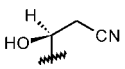
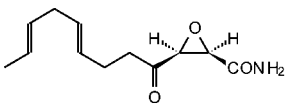
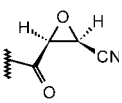
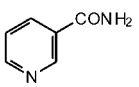
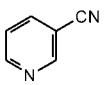
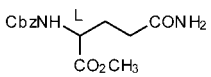
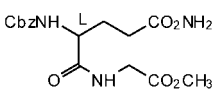
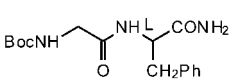


(21)

4.3. *Isocyanides from formamides*

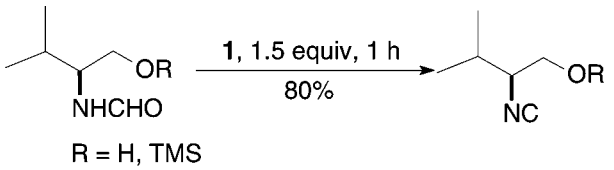
Isocyanides are versatile compounds, which participate in a range of synthetically important transformations. Among the variety of methods available, dehydration of formamides is the most popular route and Burgess reagent can be effectively applied for this functional group interconversion (eqns 22–24).[15] The Burgess reagent readily converts formamides into isocyanides in high yields and is particularly effective for substrates containing halide-sensitive TMS ether groups.

Table II
Formation of nitriles from primary amides by dehydration

Entry	Starting amide	Product	Yield (%)	Comments
1			82	–CN formation, even in the presence of secondary –OH group.
2			85	No epoxide ring opening is observed.
3			92	—
4			92	No racemerization is observed.
5			88	No epimerization is observed.
6			91	No epimerization is observed.

4.4. *Nitrile oxides from nitroalkanes*

Nitrile oxides readily cycloadd to a variety of alkenes to generate isoxazolines which represent an extremely useful class of heterocycles. Nitrile oxides, in most of the cases, are highly reactive intermediates which are produced *in situ* in the presence of a dipolarophile. They can undergo either cycloaddition to form isoxazoles or dimerization to give furoxanes. Two general routes are normally used for generating nitrile oxides: dehydrogenation of aldoximes via the formation of hydroxamoyl halides or dehydration of primary nitro compounds. The latter method is however most useful due to its easy set-up. A wide variety of reagents are available for this, out of which DAST (diethylaminosulfur trifluoride) and Burgess reagent are found to be most effective (Scheme 2).[16]



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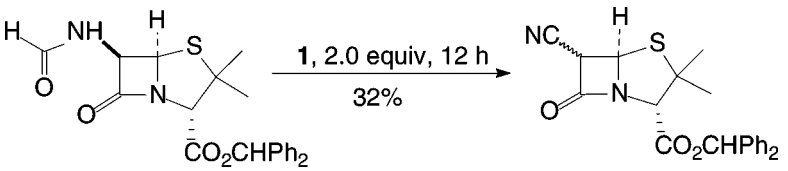

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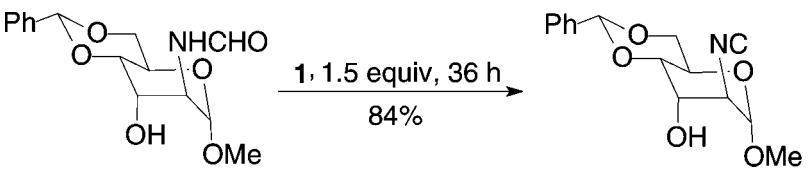
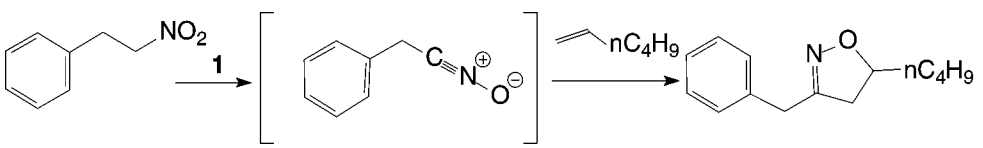


(24)

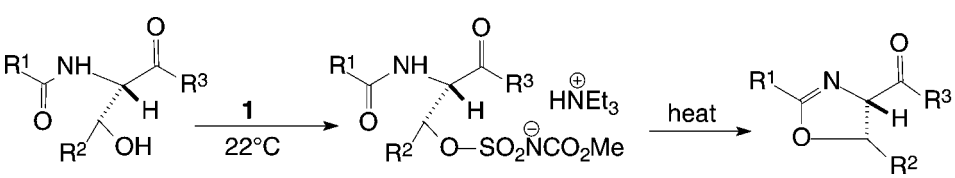


Scheme 2.

4.5. *Synthesis of heterocycles (Wipf cyclodehydration protocol)*

In recent years, the most notable application of the reagent has been in the cyclodehydration of hydroxy amides and thioamides leading to the corresponding heterocycles.

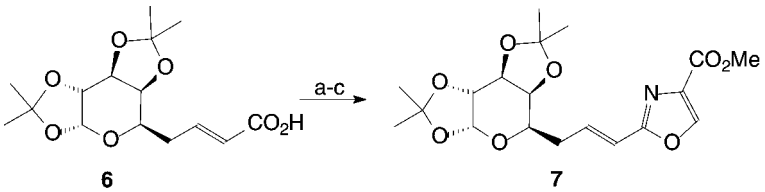
Dihydrooxazoles are important as synthetic intermediates and form an integral part of many biologically active natural products. Generally, tedious multistep sequences have been used for the preparation of these heterocycles. Cyclization of hydroxy amino acids with Burgess reagent **(1)**, on the other hand, provides a new single step approach for the synthesis of dihydrooxazoles from serine and threonine derivatives (eqn 25).



(25)[17]

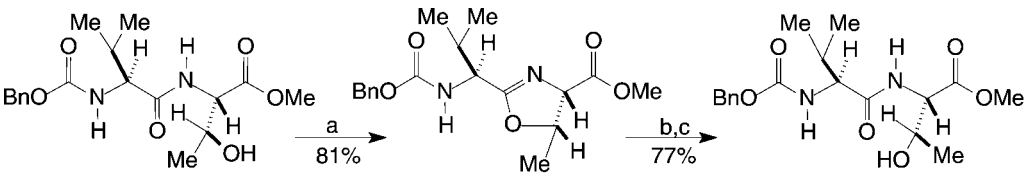
The absence of β-lactam, dehydroamino acid or aziridine side products and the mild neutral reaction conditions allow the successful application of this protocol in the synthesis of a large number of natural products (e. g. phorboxazole synthesis, eqn 26). As expected, cyclodehydration takes place with the inversion of the configuration at β-position. This has been exploited in the

stereospecific synthesis of peptide analogs through side chain epimerization. Wipf and Miller have used Burgess cyclodehydration protocol to get an oxazoline followed by selective hydrolysis with K_2CO_3 (Scheme 3).[18]



(26)[19]

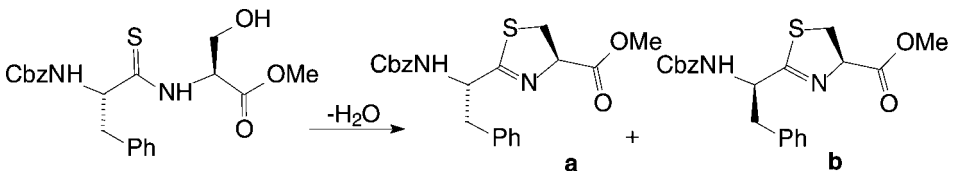
a) $ClCO_2CH_2CHMe_2$, NMM, -25°C, 15 min, then L-serine methylester hydrochloride, rt, 3 h, 72%; .
b) **1**, THF, reflux, 2 h, 71%; c) $CuBr_2$, DBU, HMTA, CH_2Cl_2, rt, 75%.



a) **1**, THF, 70°C, 2 h; b) 0.3N HCl/THF, 30 min; c) K_2CO_3, pH 9.5, 2 h.

Scheme 3.

The formation of thiazolines from β-hydroxy thioamides under TsCl/Et_3N, $SOCl_2$, and Mitsunobu conditions leads to extensive epimerization at the C(2) *exo* methine position. In contrast, thiazolines of >94% diastereomeric purity are isolated when Burgess reagent protocol is applied (eqn 27 and Table III).



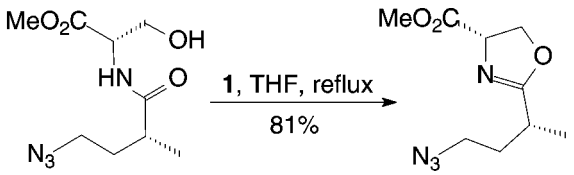
(27)[20]

It is to be noted that cyclodehydrative formation of dihydrooxazoles from hydroxy amides with a chiral center at C-2 proceeds with minimum epimerization at the chiral center (eqn 28).

The Wipf cyclodehydration protocol can be performed on 2-acylamino ketones for direct obtention of oxazoles in high yields (eqn 29). However, the reactions have to be conducted under

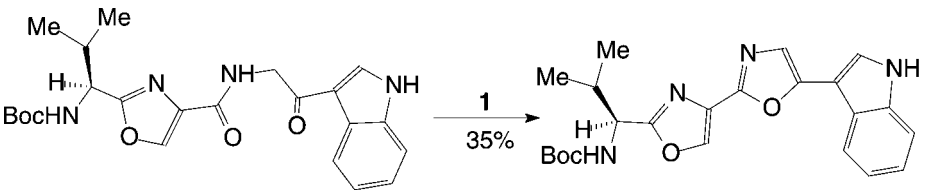
Table III
Comparison of efficiency of Burgess reagent with other reagents

Entry	Method	Yield (%)	Ratio (*a*/*b*)
1	TsCl, Et_3N, CH_2Cl_2, 42°C, 1 h	40	1:1
2	i) $SOCl_2$, 0°C, 2 h; ii) Pyridine, THF, 0°C, 15 min	49	1:1
3	Ph_3P, DIAD, CH_2Cl_2, -78 to 22°C, 30 min	80	78:22
4	Burgess reagent (**1**), THF, 65°C, 10 min	96	>97:3



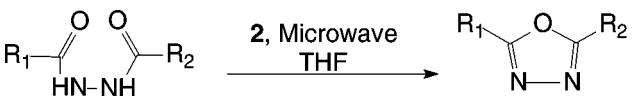
(28)[21]

monomode microwave irradiation. The routine thermal conditions seem to afford poorer yields of the products.



(29)[22]

Similarly, a variety of 1,3,4-oxadiazoles can be synthesized from 1,2-diacylhydrazines by cyclodehydration with Burgess reagent (**1**) in moderate to poor yields. However, the yields can be dramatically improved if the reactions are carried out using polymer-supported reagent **2** under single-mode microwave conditions (eqn 30 and Table IV).



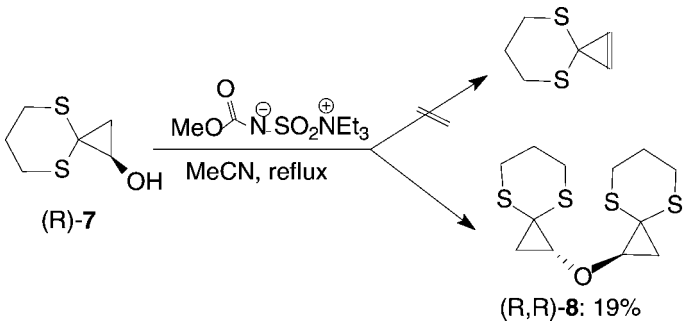
(30)[23]

4.6. *Miscellaneous reactions*

The use of Burgess reagent (**1**) in many occasions leads to unexpected products. Cited below are a few such examples. Cyclopropanone dithioacetals with an additional electron by withdrawing ring substituent are particularly useful, especially if available in optically active form. Apart from substitution chemistry, the electron-withdrawing group can be eliminated to give cyclopropenone dithioacetals. The latter compounds are sulfur analogs of cyclopropenone acetals and may be more useful for [3+2] cycloadditions with some alkenes. In this respect, Schwarz *et al.*[24] attempted dehydration of *(R)*-**7** with Burgess reagent (**1**). But, they isolated the unusual etherification product *(R, R)*-**8**, instead of the expected elimination product. This observation suggests an unusual S_N process with the retention of the configuration (Scheme 4).

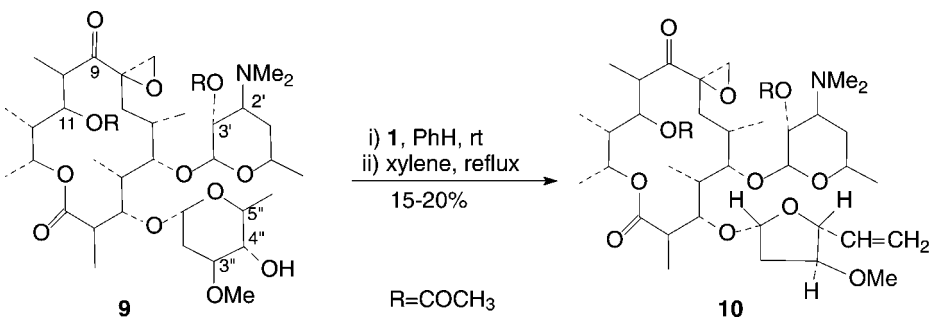
Table IV
Synthesis of 1,3,4-oxazolines from 1, 2-diacylhydrazines by cyclodehydration

Entry	R_1	R_2	%Yield
1	Ph	Ph	96
2	2-Nitrophenyl	Me	95
3	3-Methoxyphenyl	Me	95
4	2-Furyl	Ph	86
5	2-Chlorophenyl	Me	70



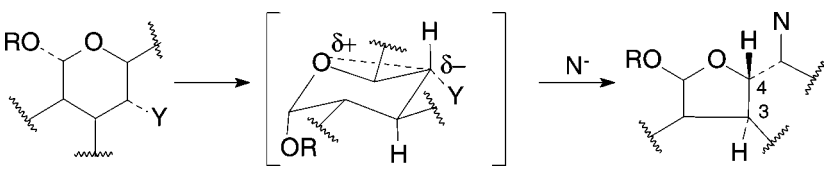
Scheme 4.

The attempted dehydration of 14-membered ring macrolide antibiotic oleandomycin (**9**) with Burgess reagent (**1**) resulted in an unusual ring contraction of the neutral oleandrose sugar (eqn 31).



(31)[25]

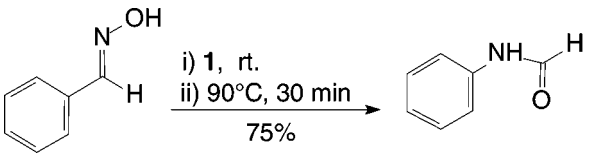
Conformational studies of oleandomycin suggest that the oleandrose sugar exists in a chair form in which the ring oxygen exists in *trans*-antiparallel relationship with the 4″ alcohol functionality. This is a favorable condition for ring contraction of pyranosides to furanosides because 1,3-oxonium ion participation can take place in the developing carbonium ion (eqn 32).



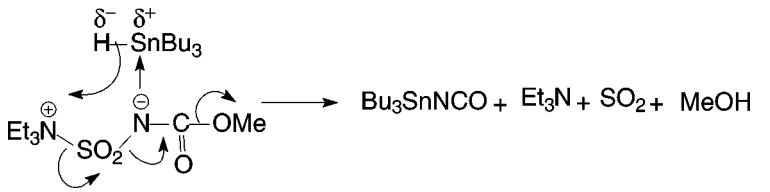
(32)[25]

Beckmann rearrangement of syn-benzaldehyde oxime: In a further application, the treatment of *syn*-benzaldehyde oxime with **1** at ambient temperature under dry atmosphere followed by thermolysis (90°C) and hydrolysis provided the Beckmann rearrangement product, formanilide, in modest yield (eqn 33).

Synthesis of tributyltin isocyanate can be accomplished in nearly quantitative yield by an unprecedented reaction of tributyltin hydride with Burgess reagent (**1**) at 80°C (eqn 34). This synthesis supersedes the previous synthesis of the isocyanate.



(33)[5]

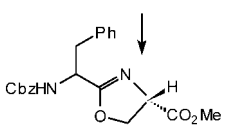
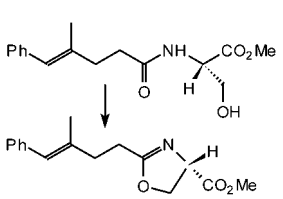
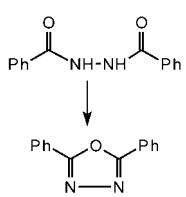
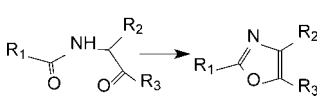


(34)[26]

5. Conclusions

The Burgess reagent (**1**), though moisture and oxidation sensitive, is superior to the conventional reagents used for dehydration. It is compatible with a broad range of functionalities which include

Table V
Comparison of efficiency of different forms of Burgess reagent

Entry	Reaction	**1**	**2**	**1**+M.W.	**2**+M.W.
1	Cbz—Phe—Ser— OMe 	60–70%	88%	—	—
2		32%	88%	—	—
3[23]		40%	40%	—	96%
4[27]					
	R^1= Me, R^2= H, R^3= Ph	78%	—	80%	—
	R^1= Ph, R^2= H, R^3= Ph	84%	—	93%	—

mutiple bonds, oxo group, heterocyclic rings, epoxides, etc. Both nonpolar and polar aprotic solvents can be used with the reagent. However, it is to be noted that the yields of the products are batch-dependent. The *syn* stereospecificity of the reagent complements the known reagents which normally result in *trans* elimination.

The PEG-supported Burgess reagent **(2)** offers many advantages. It is more stable than the parent reagent and can be handled easily. The yields of the products with reagent **2** are often higher. It is likely that it can be used for automated synthesis and combinatorial technologies. Furthermore, improvement in the yields can be achieved by carrying out a reaction under microwave irradiation (100 W) in a shorter period of time. Examples cited in Table V highlight the efficiency of reagents **1** and **2**.

Acknowledgements

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