Burgess Reagent ([Methoxycarbonylsulfamoyl]triethylammonium Hydroxide, Inner Salt): Dehydrations and More

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Dedicated to Prof. Dr. Bernd Giese on the Occasion of his 60th Birthday

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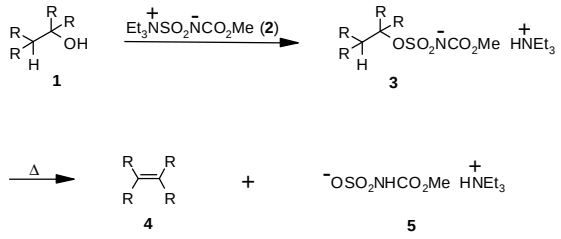
Contents

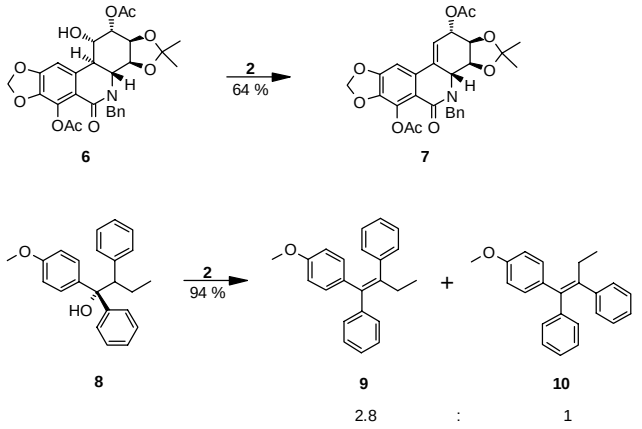
1. Formation of Alkenes

In 1970, E. Burgess *et al*. [1] discovered, that treatment of secondary and tertiary alcohols **1** with the inner salt of (methoxycarbonylsulfamoyl)triethylammonium hydroxide (**2**) causes their smooth dehydration to the corresponding olefines **4** [2]. A mechanism has been proposed for the reaction, which involves a stereospecific *syn*-elimination *via* ion-pair formation from an intermediate sulfamate **3**, comparable to the Chugaev elimination of dithiocarbonate (xanthate) esters and following Saytzeff's rule [1]. Kinetic and spectroscopical data are consistent with an initial rate-limiting formation of an ion-pair followed by a fast *cis*-β-proton transfer to the departing anion (Scheme 1).



Scheme 1 Mechanism of the Burgess dehydration

The *syn*-selectivity is mainly observed in the dehydration of secondary alcohols, as demonstrated by the transformation **6**→**7**, one of the last steps in the total synthesis of the phenanthridone alkaloid narciclasine [3]. This first example in Scheme 2 shows also an advantage of the Burgess reagent over many competitive dehydration methods, which are usually acid-mediated and often accompanied by rearrangements and ether formation resulting from high reaction temperatures and low pH values. The mild conditions of the Burgess dehydration (low temperature, neutral medium) enable the high-yielding transformation of acid-sensitive species.



Scheme 2 Dehydration of secondary and tertiary alcohols

Because of the good leaving group abilities of the intermediate sulfamic acid ester **3**, the products of an E1 elimination are observed where stabilized carbenium ions are accessible. This is especially the case for tertiary alcohols, which seem to react under milder conditions than secondary ones, but less *cis*-selective [4]. In an attempt to prepare analogs of the anti-estrogen tamoxifen, the same 2.8 : 1 mixture of (*Z*) and (*E*)-alkenes **9** and **10** is obtained from both diastereomeric alcohols **8** (Scheme 2) [5].

Generally, if conjugation with other C–C or C–O double bonds is possible, the formation of the new double bond takes this direction [6]. Wagner–Meerwein rearrangements and allylic shifts are less likely, but not completely suppressed by **2**. Mixtures of products are also obtained, where elimination can occur across a number of possible C–C bonds. For instance, cyclic alcohols with a hydroxy group and an alkyl substituent at the same ring carbon atom produce usually both *endo*- and *exo*cyclic alkenes [1, 7]. During the total synthesis of the sesquiterpene isocanambrin, **12** and **13** are obtained with Burgess reagent in 90% yield, whereas attempted dehydration of this seven-membered ring with acidic reagents led mainly to ring contraction *via* cationic rearrangement (Scheme 3) [7c].

In an attempt to synthesize cyclopropenone *S*,*S*-acetals by dehydration of the spiro alcohol **14** only the etherification product **15** was generated (Scheme 3) [8]. The compatibility of the Burgess reagent with many functionalities, *e.g*. halogens, epoxides, alkenes, alkines, aldehydes, ketones, acetals,

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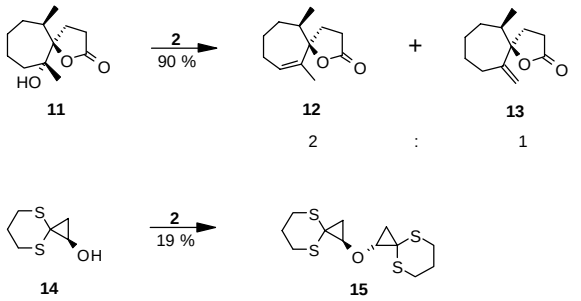
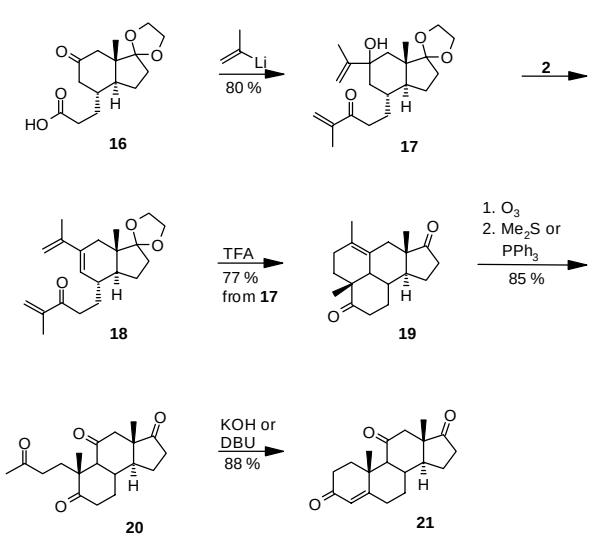


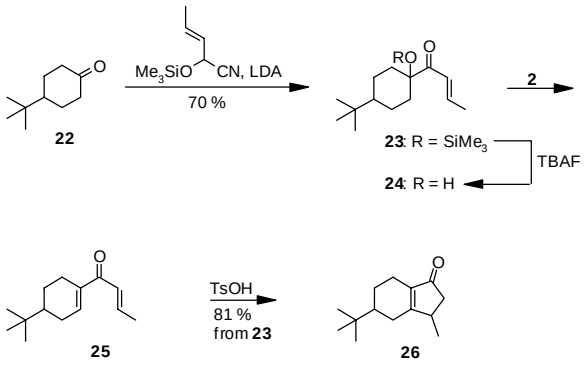
Scheme 3 Dehydration of secondary and tertiary alcohols

esters, secondary amides, makes it an attractive technique for the introduction of C–C double bonds into highly functionalized molecules. For instance, the total syntheses of several complex natural products with antibiotic [9] and anticancer [10] activity relied on selective dehydration reactions with **2**. The Burgess reagent plays an important role in Stork's brilliant stereospecific five-step approach from indanonepropionic acids like **16** to the tetracyclic 11-ketosteroid nucleus of several cortical hormones (Scheme 4) [11]. Key step is the intramolecular Diels–Alder reaction of trienone **18**, whose diene system is introduced by regioselective Burgess dehydration of carbinol **17**. This sequence was used for the concise construction of cortisone [11a], adrenosterone (**21**) [11a,b], 11-ketoprogesterone [11c] and 11-ketotestosterone [11d].



Scheme 4 Synthesis of adrenosterone (**21**)

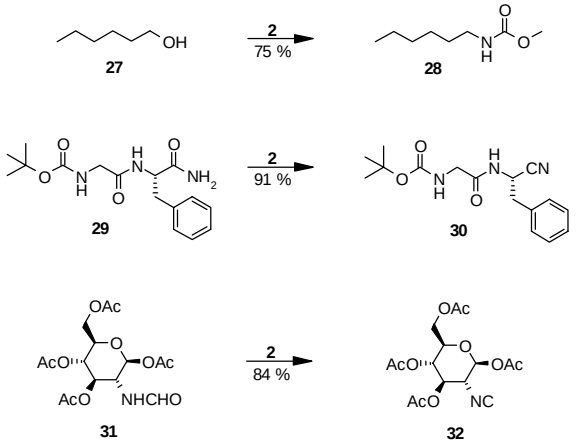
The Burgess dehydration of α'-hydroxy vinyl ketones such as **24** and the subsequent Nazarov cyclization of the resulting acid-labile dienone **25** represent a short three-carbon annelation route to cyclopentenones **26**, which is especially of interest in terpene chemistry (Scheme 5) [12].



Scheme 5 Synthesis of cyclopentenones

2. Formation of Carbamates (Urethanes)

In contrast to their secondary and tertiary counterparts, primary alcohols are usually converted with Burgess reagent to carbamates (**27**→**28**, Scheme 6), because for the decomposition of the intermediate primary alkyl *N*-methoxycarbonylsulfamate salt a S_N2 pathway is energetically more favourable than an E_i reaction [1, 13]. The subsequent hydrolysis of the carbamates provides an useful transformation of primary alcohols into primary amines.



Scheme 6 Dehydration of primary alcohols and amides

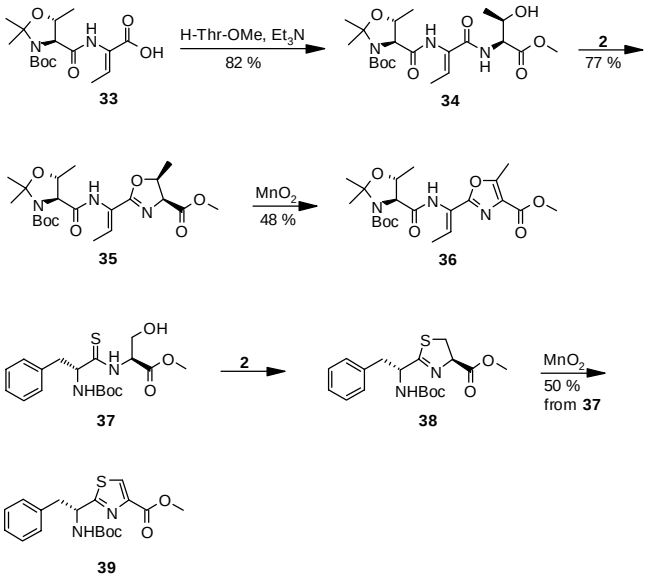
3. Formation of Nitriles

The dehydration of primary amides to nitriles is achieved by Burgess reagent at room temperature (**29**→**30**, Scheme 6) [14]. The excellent chemoselectivity of this reaction enables the presence of several other functionalities. In the same way, Burgess reagent converts formamides into isocyanides (**31**→**32**, Scheme 6) [15], ureas into carbodiimides [16] and primary nitro alkanes into nitrile oxides [17].

4. Formation of Oxazolines and Thiazolines

Early in the nineties the potential of Burgess reagent was extremely broadened by Wipf's cyclodehydration chemistry.

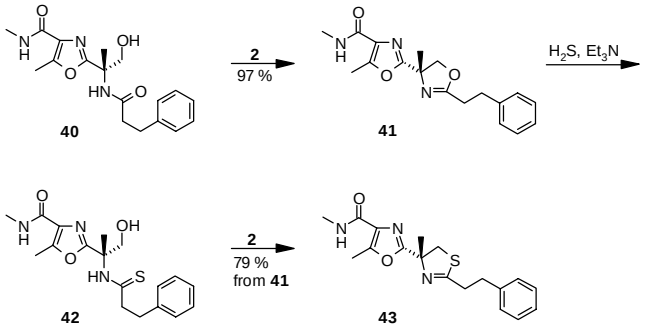
Herein (*N*-2-hydroxyethyl)-amides and (*N*-2-hydroxyethyl)-thioamides are converted with **2** into oxazolines [18] and thiazolines [19] by dehydrative cyclization. These partially saturated five-membered heterocycles have recently attracted considerable attention as pharmacophores of peptidomimetics in medicinal chemistry [20], as chiral ligands in transition metal catalyzed asymmetric synthesis [21] and as common feature of several biologically highly active marine cyclopeptides [22]. The unique properties of Burgess reagent solve some problems, which often arise in classical oxazoline and thiazoline syntheses. The cyclization of serine and threonine derivatives or other 2-acylamino alcohols to oxazolines takes place without β-lactam, aziridine and dehydroamino acid side product formation as often obtained with other methods [18, 23]. The comparable transformation of β-hydroxythioamides to thiazolines proceeds with less than 3% epimerization at the C-2 *exo* methine position, which always is a problem using other reagents [19, 24]. A wide range of protocols is available for the oxidative aromatization of oxazolines and thiazolines to the corresponding oxazoles and thiazoles. Therefore, the Burgess cyclodehydration opens an easy access to unique substituted heterocycles (Scheme 7).



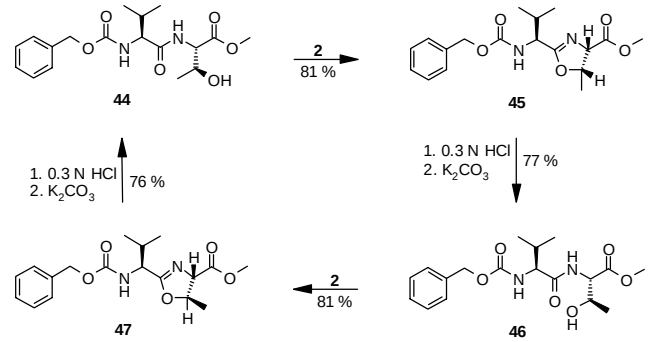
Scheme 7 Cyclodehydration of β-hydroxyamides and β-hydroxythioamides

A direct oxazoline → thiazoline conversion can be realized *via* thiolysis of oxazolines with hydrogen sulfide and triethylamine in methanol and subsequent cyclodehydration of the resulting β-hydroxythioamides [25]. The ring opening of the oxazoline occurs regioselectively. Scheme 8 demonstrates, that the double employment of Burgess reagent allows a short transformation of (*N*-hydroxyethyl)-amide **40** into thiazoline **43** [25a,e,f].

The cyclodehydration of β-hydroxyamides, in which the hydroxy group is attached to an asymmetric carbon atom, to an oxazoline can be utilizied for the selective inversion of configuration at this chiral centre [26]. The mild acidic hydrolysis of the oxazoline **45** affords an intermediate *O*-acyl amine, which smoothly undergoes a base-catalyzed intramolecular *O*→*N*-acyl shift to regenerate the amide backbone, resulting in a clean epimerization of the β-carbon atom [26c,d]. The repetition of this sequence allows the convenient interconversion of threonine and *allo*-threonine (a nonproteinogenic amino acid) in peptide segments (Scheme 9).



Scheme 8 Oxazoline → thiazoline conversion



Scheme 9 Wipf inversion of β-aminoalcohols

These cyclodehydration possibilities with the Burgess reagent have been a major driving force for the total syntheses of important densely functionalized marine [27] and terrestrial [28] natural products. The synthesis of complex structures with several five-membered heterocycles is often facilitated by the fact, that treatment of precursors with more than one β-hydroxyamide or β-hydroxythioamide function with excess Burgess reagent results in simultaneous double [27a,c] or triple [25a,b,e] cyclodehydration to bis- or trisoxazolines and -thiazolines.

Recently, also a polyethyleneglycol-linked version of **2** has been applied to the cyclodehydration of β-hydroxyamides and β-hydroxythioamides [29]. Major advantages of this polymer-supported reagent are its ease of preparation on large scale, its stability under oxidative and wet conditions, its readily separation from the reaction mixture and its superior yields in the synthesis of labile oxazolines [29c].

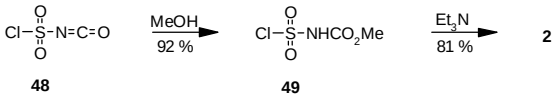
Besides oxazolines and thiazolines, also other heterocycles have been obtained by direct cyclodehydration with Burgess reagent, for instance oxazoles from 2-acylamino carbonyl compounds [30], 1,3,4-oxadiazoles from 1,2-diacylhydra-

zines [31], 1,3-oxazines from γ-hydroxyamides [32], 1,3-thiazines from γ-hydroxythioamides [32] and thiazepines from δ-hydroxythioamides [32].

5. Miscellaneous Uses and Preparation

The application of Burgess reagent was also reported in the facile formation of organotin reagents like vinyltributyltin [33] and tributyltin isocyanate [34]. Besides this, a ring contraction of the macrolide antibiotic oleandomycin's six-membered oleandrose sugar unit to a 3-methoxy-4-vinylfuranosyl system has been accomplished by Burgess reagent [35].

Burgess reagent is a crystalline and commercially available compound. It is readily prepared in high yield on a 1.5 mol scale from chlorosulfonyl isocyanate (**48**) in two steps (Scheme 10) [7b].



Scheme 10 Preparation of Burgess reagent

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