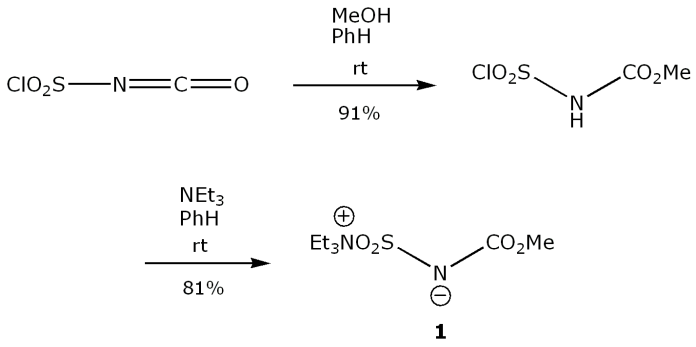
Synthetic applications of Burgess reagent

The Burgess reagent has been introduced in 1968 (1) and shown shortly afterwards to act as a mild and selective dehydrating reagent (2). Next to its importance in the construction of olefins from secondary and tertiary alcohols, the Burgess reagent was also utilized to promote several other transformations of great synthetic values in medicinal chemistry. In this Atlanchim letter, we will present a brief overview of the uses of this reagent.

Preparation

The reagent ([methoxycarbonylsulfamoyl]triethylammonium hydroxide, inner salt) is easily prepared in two simple steps from chlorosulfonyl isocyanate as shown in the following scheme (1,3). The white crystalline solid **1** (m.p : 71-72°C from toluene) is air and moisture sensitive and, as such, needs to be stored in the cold and under an inert atmosphere.



1

Vicinal dehydration from secondary and tertiary alcohols

Burgess reagent proved useful in the installation of a double bond from elaborated structures adorned with several sensitive functionalities. An illustration is shown with the creation of the enoate motif present at carbon C-21 in macrocycle **3**. The transformation **2** → **3** (one of the final steps in Evans synthesis of bryostatine) was best accomplished following a two-step protocol featuring an aldolisation reaction followed by a Burgess reagent-induced dehydration (4).

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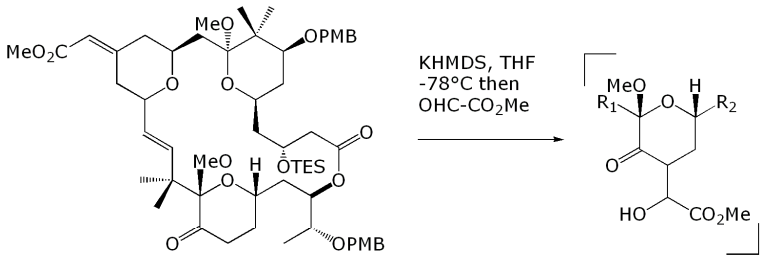

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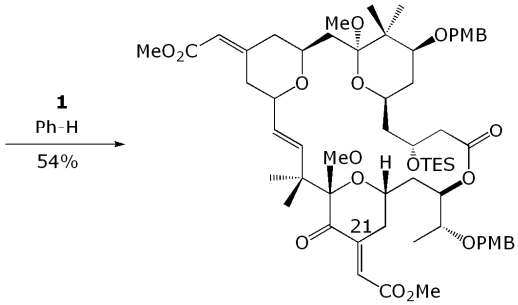
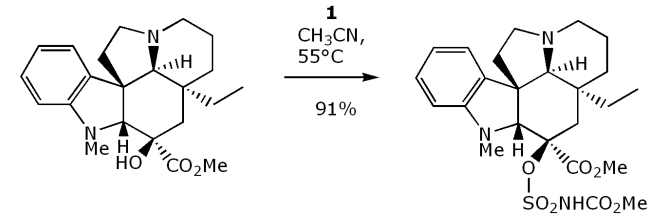
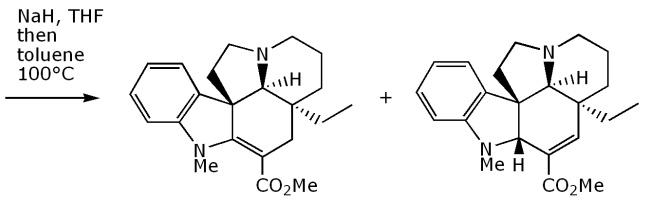


3 *E:Z* > 12:1

Another example can be found in the synthesis of minovine **6**, an alkaloid isolated from *Vinca minor*. Dehydration of intermediate **4** could not be achieved in a direct single procedure with the Burgess reagent but was successively accomplished in a stepwise procedure. Thus, exposure of **4** to reagent **1** in acetonitrile provided the sulfamidate **5** in excellent yield. Treatment of the latter with NaH followed by heating at 100°C in toluene, afforded the natural product **6** along with its undesired isomer **7** which was thought to arise, at least in part, via the formation of a transient aziridinium species (5).

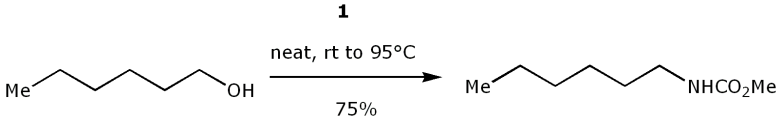


4 **5**

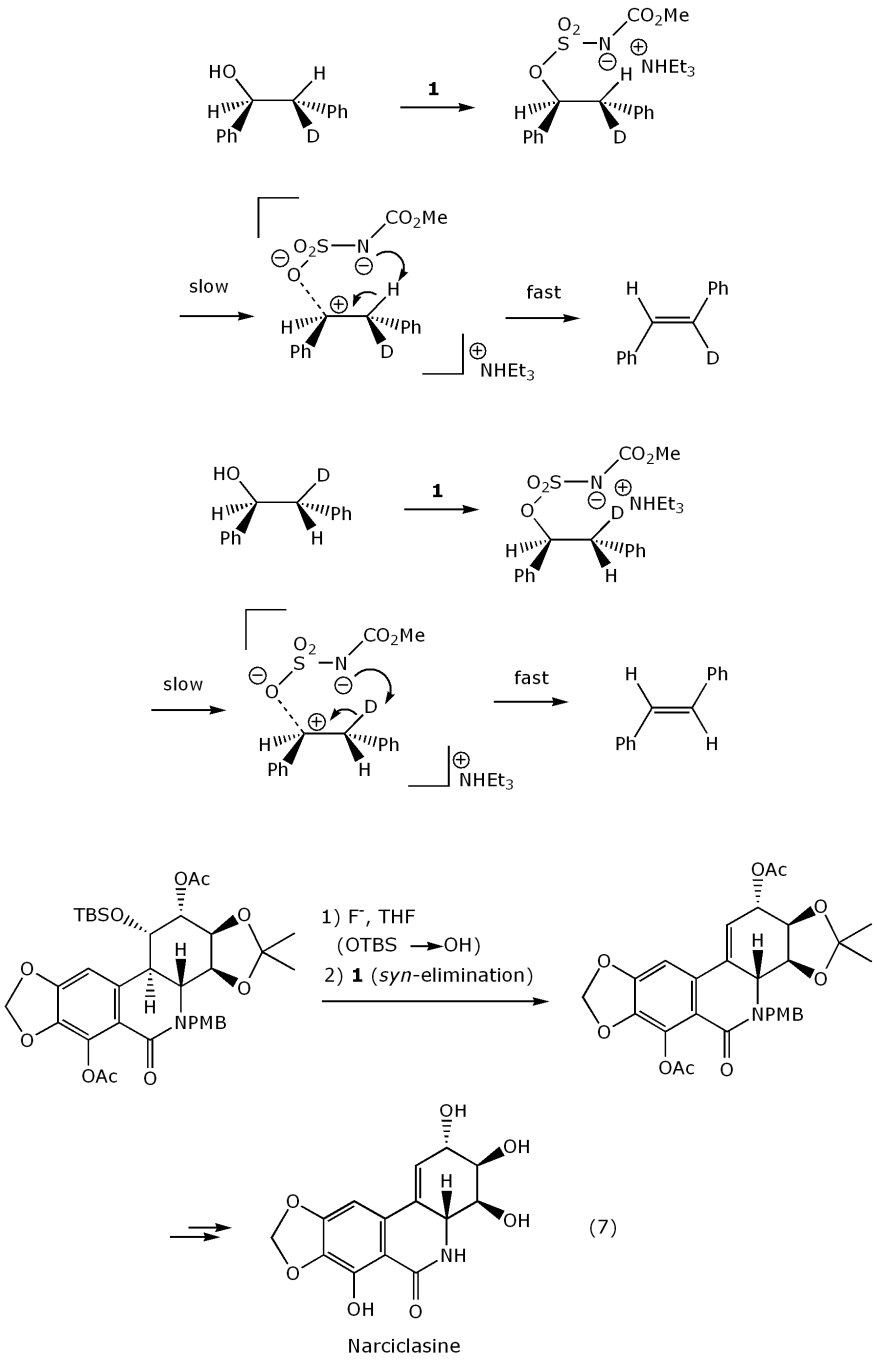


6 (39%) **7** (53%)

In contrast to secondary and tertiary alcohols, primary alcohols lead to the formation of urethanes when exposed to the action of the Burgess reagent (3,6).



As shown by Burgess in its seminal papers (2,3), the dehydration usually proceeds via a *syn*-elimination. The results of a kinetic study of the dehydration of the *erythro*- and *threo*-2-deuterio-1,2-diphenylethanols helped to pinpoint the reaction mechanism. These results were consistent with a rate-limiting formation of an ion pair followed by a rapid *syn*-□-proton transfer, thereby precluding a conformational reorganisation.



Such a clear-cut mechanism is not always operating, in particular in examples where the formation of a stabilized carbocation is possible. Obtention of isomeric olefins, possibly arising from Wagner-Meerwein rearrangement, thus resulted. Conformationnal effects can also drive the reaction towards the formation of *anti*-elimination products.

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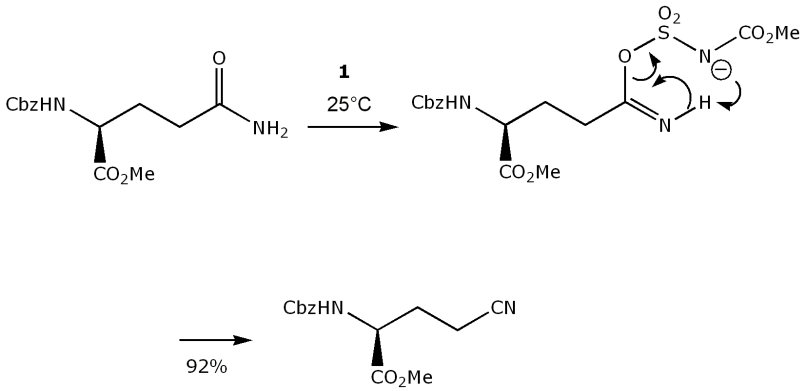
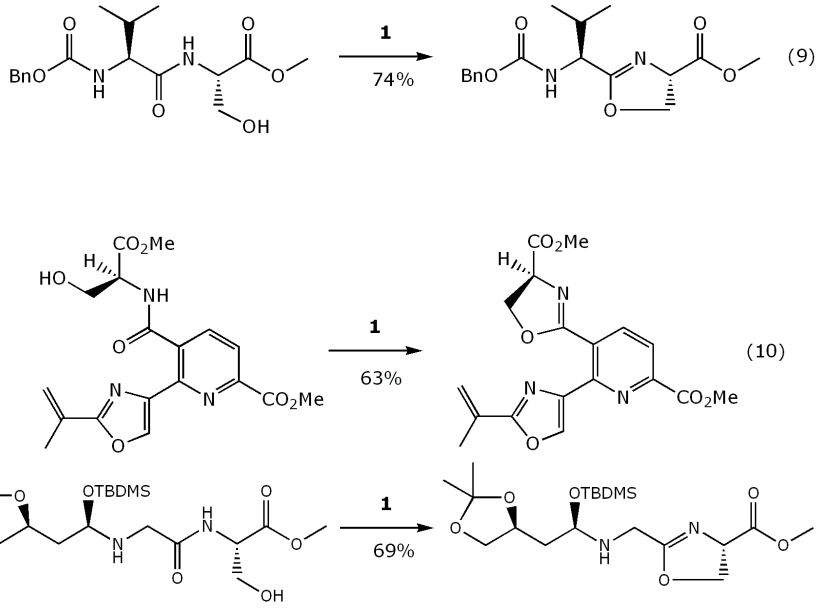
Other dehydration reactions. Formation of nitriles, isocyanides and nitrile oxides

The Burgess reagent has been used in dehydration of primary amides, formamides and primary nitroalkanes to generate nitriles, isocyanides and nitrile oxides, respectively. These reactions are carried out in smooth conditions and occurred without alteration of the stereochemistry of the molecules. Dehydration of a glutamine derivative is presented as an illustration (8).



Synthesis of 4,5-dihydro-oxazoles (2-oxazolines) and 4,5-dihydro-thiazoles (2 thiazolines)

In 1992 P. Wipf and C.P. Miller disclosed that a series of serine and threonine derivatives, when treated with the Burgess reagent, led to the formation of 4,5-dihydro-oxazoles rather than to elimination products (9). An intramolecular sulfonate substitution mechanism accounts for the formation of the heterocycles. The reaction proved to be of quite general scope and occurred without notable erosion of chirality. Some representative examples are given below (10, 11).



The transformation takes place with inversion of configuration at the chiral carbon bearing the sulfonate leaving group (intramolecular SN_2 substitution). As a consequence, selective hydrolysis of the oxazole ring leads to the starting □-hydroxy-□-amino acid derivative with inversion of configuration at the substitution site. If this latter derivative is subjected to a second cyclodehydration protocol to form a new 4,5-dihydro-oxazole component, then the whole

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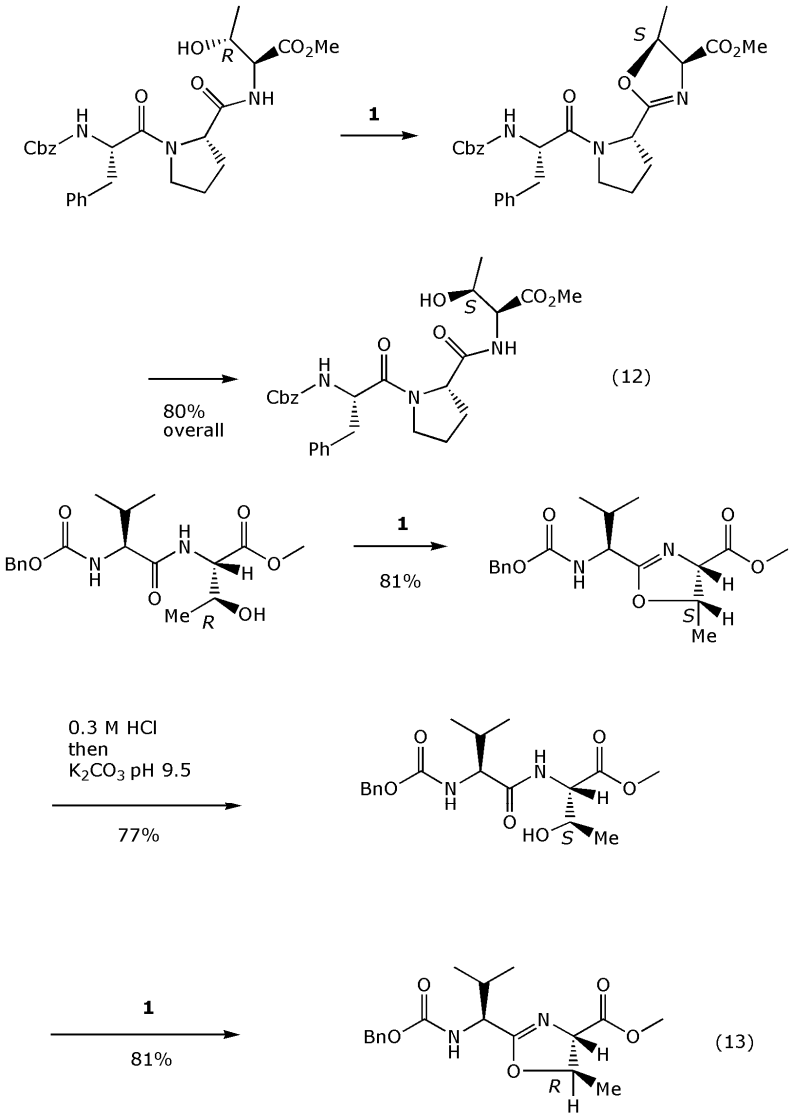
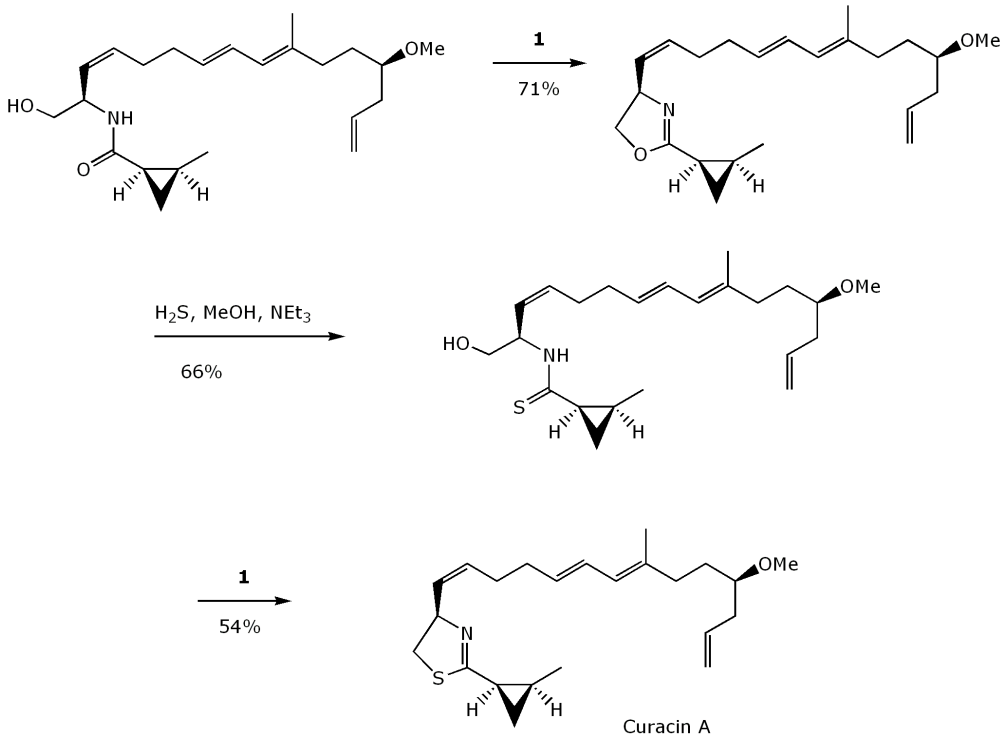
sequence takes place with conservation of the initial stereochemistry at the substitution site (two consecutive inversions).

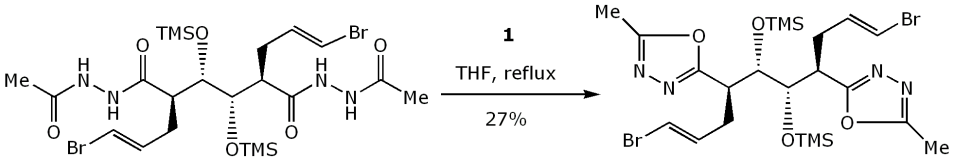


The use of Burgess reagent is also suitable for formation of 4,5-dihydro-thiazoles. It is worth mentioning that 4,5-dihydro-oxazole → 4,5-dihydro-thiazole conversion may be achieved via the formation of an intermediate thiamide (14). Oxidation of the 4,5-dihydro-oxazole and 4,5-dihydro-thiazole rings towards their corresponding oxazole and thiazole rings may be achieved in a single operation (usual oxidation conditions : NBS-radical initiator, MnO_2, CCl_4 or $BrCCl_3$-DBU).



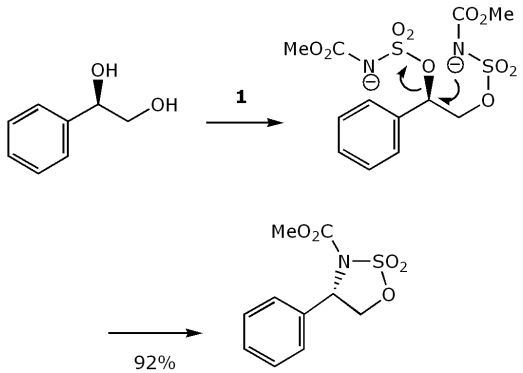
Synthesis of 1,3,4-oxadiazoles

1,3,4-Oxadiazoles may be synthesized by cyclodehydration of diacylhydrazines with the Burgess reagent. In the course of a work aimed at synthesizing malarial plasmepsin inhibitors, symmetrical and unsymmetrical 1,3,4-bis-oxadiazoles were prepared following this strategy (15).

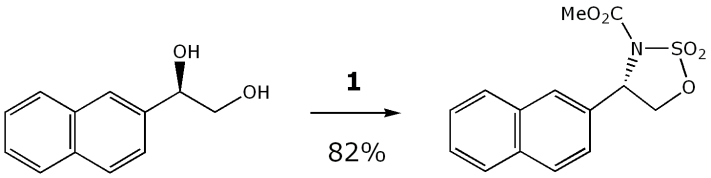


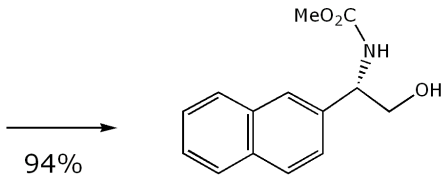
Stereoselective synthesis of □-amino-alcohols via cyclic sulfamidates precursors.

Nicolaou et al. recently showed that exposure of 1,2-diols to an excess of Burgess reagent (typically 2.5 equiv in THF at reflux for 1h) afforded cyclic sulfamidates (16). For example, styrene-diol gives mainly the sulfamidate arising from substitution at the more activated benzylic leaving group. The reaction occurs with inversion of configuration at the benzylic carbon (S_N2 type mechanism).

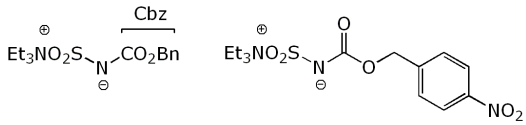


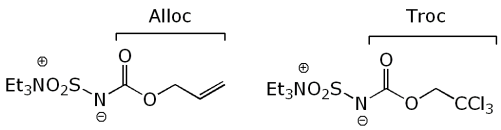
Treatment of cyclic sulfamidates with aqueous HCl in dioxane at ambient temperature affords N-protected □-amino-alcools in excellent yields. One representative example is shown in the following scheme.





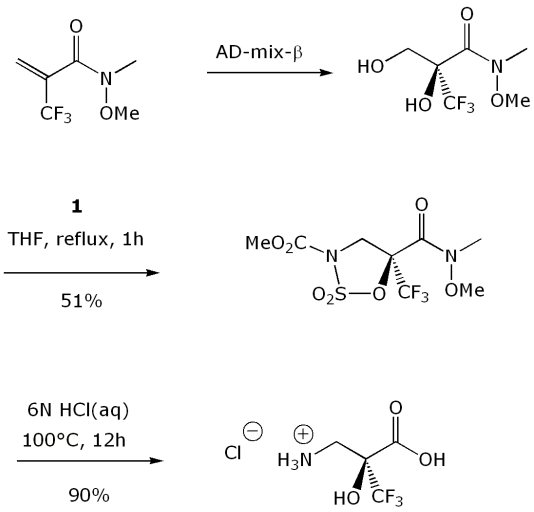
Burgess-type reagents with more easily removable ester moieties were also synthesized and shown to react in a similar way.



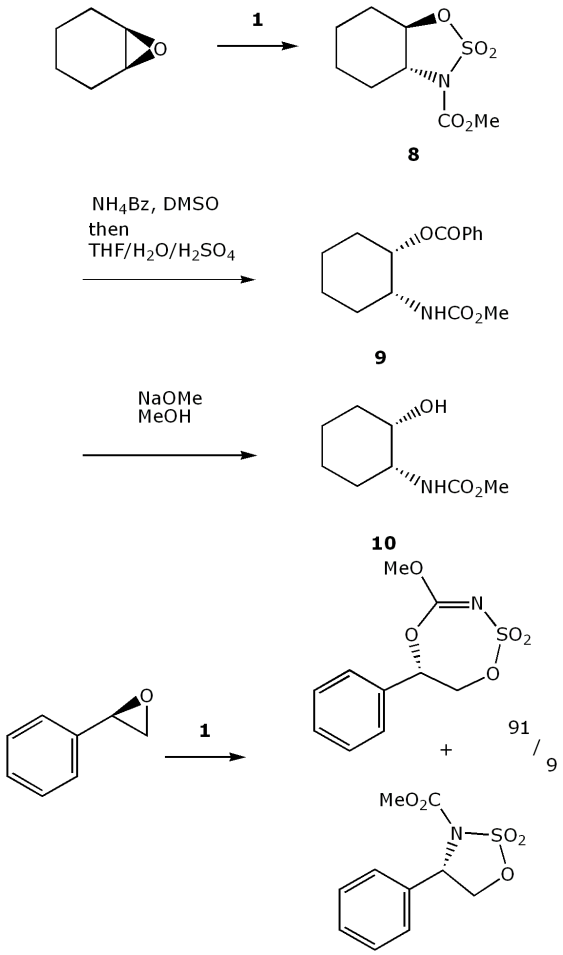


Variants of the original Burgess reagent

A practical synthesis of (*S*)-□-trifluoromethylisoserine via a cyclic sulfamidate intermediate has been recently reported (17).

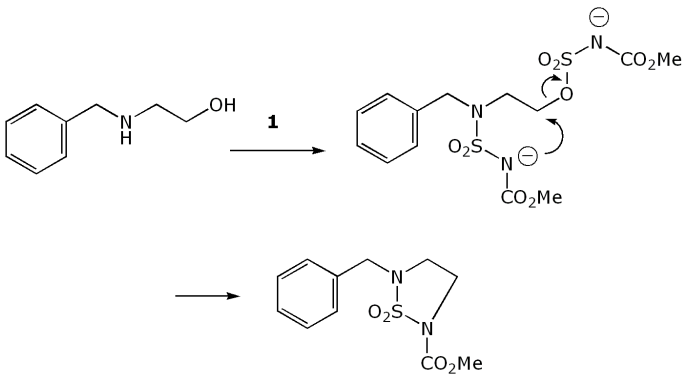


Obtention of cyclic sulfamidates was also reported by treatment of epoxides with an excess of Burgess reagent in an ethereal solvent (18). For example, cyclohexene oxide led to the formation of sulfamidate **8** (64% yield) which could be easily transformed into the protected *cis*-amino alcohol **10** via its benzoate **9**. It is interesting to remark that this sequence of reactions provides access to *cis*-amino alcohols from epoxide with double inversion of configuration. Styrene oxide behave differently as the major product of the reaction is a seven membered-ring system.



Synthesis of nonsymmetrical sulfamides

Sulfamides have proven to be particularly attractive in medicinal chemistry due to the diverse array of their biological activities. They have also been employed with success in asymmetric synthesis. Quite similarly to the behaviour of 1,2-diols shown above, amino alcohols and amines were found to react with an excess of Burgess reagent to give cyclic and acyclic sulfamides in good to excellent yields (19). Typical examples are pictured in the following scheme.



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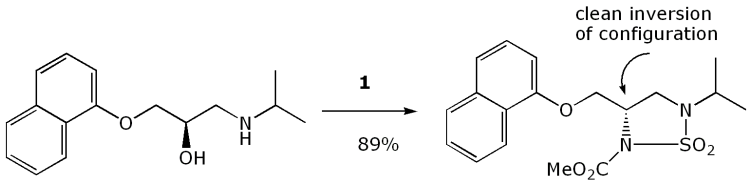
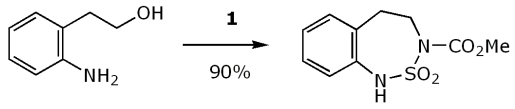
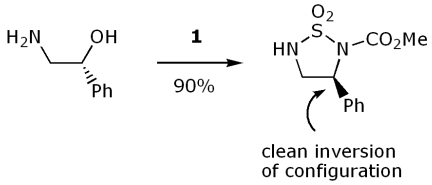
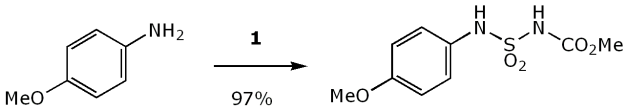
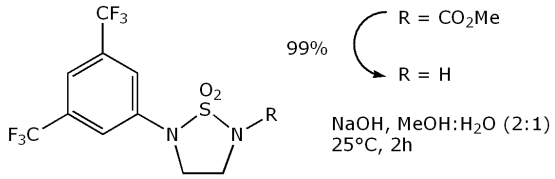


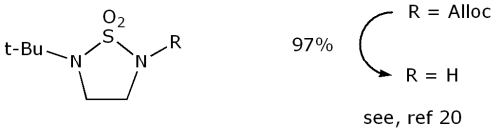


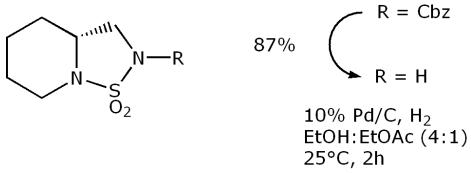




Finally, deprotection of sulfamides obtained from Burgess and related Burgess reagents have been accomplished in excellent yields to give nonsymmetrical, monosubstituted sulfamides.

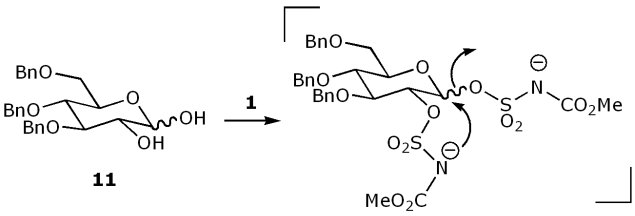






Stereoselective synthesis of □- and □-glycosylamines

Glycosylamines are prominent in glycopeptides and glycoproteins and exhibit selective RNA-binding properties. A practically simple synthesis of both □- and □-glycosylamines based on the property of the Burgess reagent to form cyclic sulfamidates from 1,2-diols has been recently reported (21). For example, the glucose derivative **11** when treated with a 2.5 excess of Burgess reagent in refluxing THF/CH_2Cl_2 for 6h, selectively afforded the □-disposed sulfamidate **12**. Subsequent treatment of **12** with sodium azide in DMF at 60°C delivered the □-disposed N-protected □- glycosylamine **13**.



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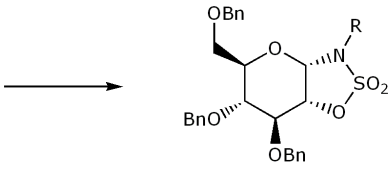
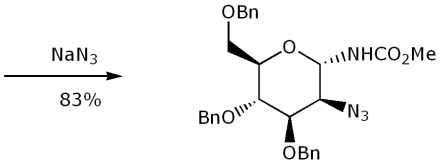


12

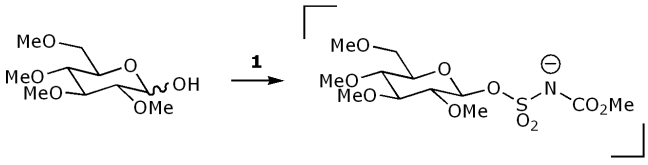
R = CO_2Me α:β 8:1

R = Alloc α:β 15:1

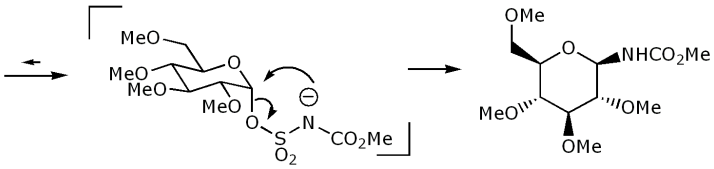


13

In contrast, anomeric alcohols bearing a C-2 protection led to the direct formation of □-glycosylamine derivatives when exposed to an excess of Burgess reagent. Such a stereochemical result can be accounted for by assuming that, similarly to the established preference of anomeric triflates to exist as □-anomers, intermediate **16** is favored over intermediate **15**.



14 15



16 17 β:α >20:1

Conclusion

The above examples have underlined the impressive power of the Burgess reagent to effect various transformations of synthetic interest in very mild conditions, and new applications are certainly to be expected in the future. In this context, the preparation of a polymer-bound version of the reagent, with better shelf-life (22,23), should bring a new impetus for further developments.

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