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AN IMPROVED PROTOCOL FOR AZOLE SYNTHESIS WITH PEG-SUPPORTED BURGESS REAGENT

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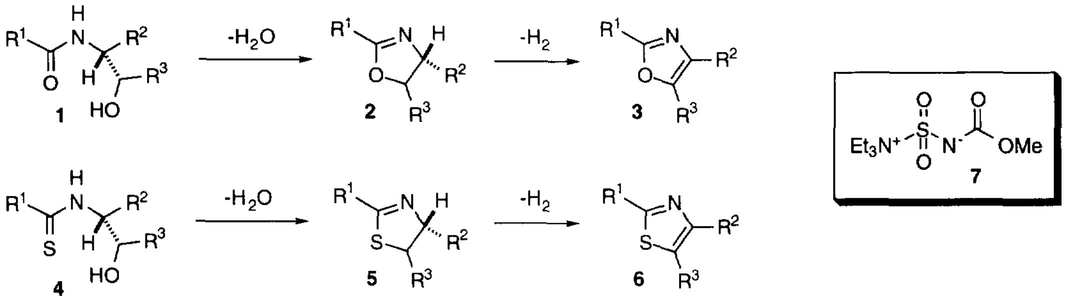
Abstract: A polyethyleneglycol-linked version of Burgess reagent was developed and applied toward the cyclodehydration of β-hydroxy amides and thioamides. The desired oxazolines and thiazolines were obtained in high yields and excellent purities. The major advantages of the polymer bound reagent are its improved ease of handling and greatly increased yields in the synthesis of labile oxazolines.

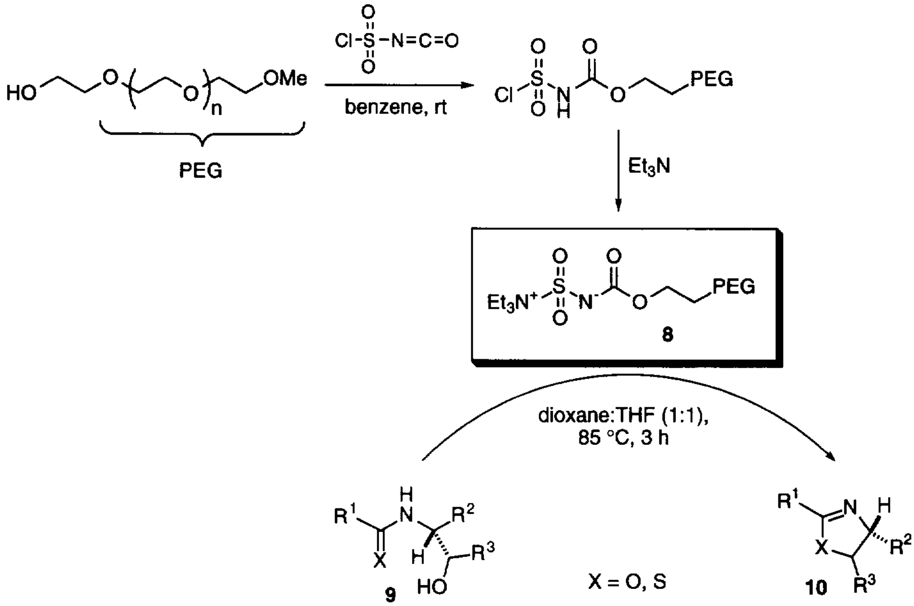
The cyclodehydration of N-(hydroxyethyl)amides and -thioamides is an important method for the preparation of oxazolines and thiazolines as well as oxazoles and thiazoles (Scheme 1). These five-membered heterocycles are found in many biologically active synthetic and natural products and are useful auxiliaries in stereocontrolled synthesis.[1] Even with configurationally labile and highly functionalized substrates, cyclodehydration with Burgess reagent[2] (methyl N-(triethylammonium-sulfonyl)carbamate, **7**) provides oxazolines **2** and thiazolines **5** of high stereochemical purity.[3] Accordingly, this protocol has successfully been applied to natural products total synthesis.[4]

Scheme 1



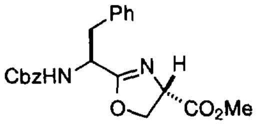
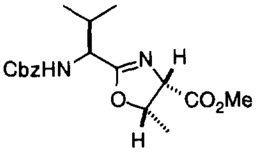
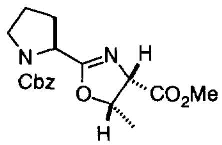
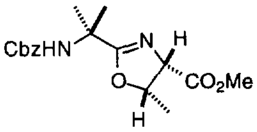
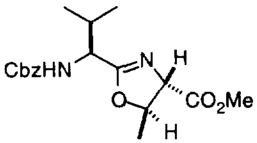
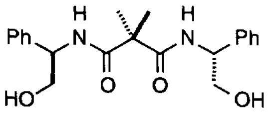
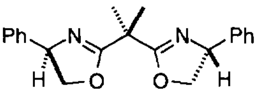
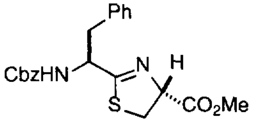
The commercially available Burgess reagent **7** is oxidation and moisture sensitive, needs to be stored at low temperature, and has nonetheless a limited shelf-life. Cyclodehydration yields are highest with freshly prepared reagent and tend to be batch-dependent. In the course of investigating modifications of **7** with more desirable physical properties, we systematically varied amine and ester components and achieved significant relative increases in reactivity but no major improvements in stability. Attachment of Burgess reagent to modified Merrifield resin was unsuccessful, but condensation with polyethyleneglycol (PEG) and related polyethers led to useful new reagents with markedly different reactivity profiles. Coupling of chlorosulfonyl isocyanate to dry M_W 750 PEG monomethylether, for example, followed by treatment with 2.2 equiv of Et_3N, led to the polymer-linked Burgess variant **8** that, compared to **7**, gave superior yields of oxazolines and thiazolines and maintained considerable reactivity even after extended storage at or below room temperature (Scheme 2, Table 1).[5]

Scheme 2



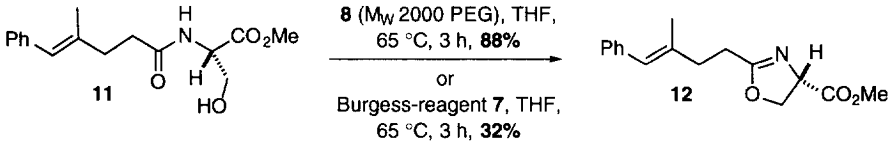
Cyclodehydration of serine as well as threonine derived peptides with polymer-supported **8** in hot dioxane/THF (1:1) occurred cleanly and provided oxazolines **10** in ca. 10-20% higher yields than standard Burgess reagent (Table 1). After completion of the reaction, the polymer was readily removed. In most cases, filtration through a short plug of silica gel with hexanes/EtOAc (1:1 to 1:8) led directly to pure product, since most minor side products and the remainder of the reagent remained absorbed in the polyethyleneglycol matrix and the silica gel. Due to the neutral reaction conditions, <2% epimerization at α- or β-carbons or elimination to dehydroamino acids[3] were detected by NMR spectroscopy. The reaction is stereospecific, e.g. an *allo*-threonine derivative was converted to the *trans*-oxazoline (entry 5) whereas cyclodehydration of a threonine residue, which occurs via S_N2-displacement of the side-chain hydroxyl group,[3b] provided *cis*-oxazolines (entries 2-5). Double cyclodehydration in the presence of 3 equiv of **8** gave bisoxazoline in excellent yield (entry 6). Thiazoline formation from thioamides[3d] was similarly successful under standard conditions (entry 7). A particularly impressive example for the use of polymer-supported Burgess reagent is shown in Scheme 3. Hydroxyamide **11** was converted in 88% yield to the sensitive oxazoline **12** using M_W 2000 PEG-linked **8**, whereas the maximum yield that was obtained with reagent **7** was 32%.[6] Therefore, the use of polyetheylene glycol modified cyclodehydrating agent led to a nearly three-fold improvement in the efficiency of this reaction.

Table 1. Cyclodehydration of hydroxy amides and thioamides with polymeric **8** (Scheme 2).

Entry	Hydroxy amide **9**	Azole **10**	Yield [%]
1	Cbz-Phe-Ser-OMe		88
2	Cbz-Val-Thr-OMe		90
3	Cbz-Pro-Thr-OMe		85
4	Cbz-Aib-Thr-OMe		88
5	Cbz-Val-*a*Thr-OMe		76
6			80
7	Cbz-Phe-ψ(CSNH)Ser-OMe		98

In summary, the use of the new polymeric PEG-linked Burgess reagent **8** offers considerable advantages for azole synthesis: First and foremost, the polymeric reagent is highly reactive for hydroxyl group activation and yet provides fewer side-products of reagent-induced oxazoline decompositions. With standard Burgess reagent, degradation of acid-sensitive oxazolines under the reaction conditions can considerably reduce the yield. The polymeric reagent is easily prepared on large scale and provides superior reproducibility. It is added as a concentrated solution in THF or benzene to the hydroxy amide or thioamide dissolved in dry dioxane or THF. Cyclodehydration occurs exceptionally cleanly and with <2% epimerization, and most minor side-products are readily removed with the polymer by filtration through silica gel.

Scheme 3



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References and Notes

1. For recent leading references, see: (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (c) van Koten, G. *Pure Appl. Chem.* **1994**, *66*, 1455. (d) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771.
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4. See, for example: (a) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (b) Shin, C.; Nakamura, Y.; Okumura, K. *Chem. Lett.* **1993**, 1405. (c) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477. (d) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705. (e) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (f) Okonya, J. F.; Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 1932. (g) Boden, C. D. J.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 6153. (h) Wipf, P. Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224. (i) Li, G.; Warner, P. M.; Jebaratnam, D. J. *J. Org. Chem.* **1996**, *61*, 778. (j) Hoemann, M. Z.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 953.
5. Typical experimental procedures are as follows:

   A solution of 5.88 g (7.8 mmol) of PEG monomethylether (M_w 750) in 20 mL of benzene was dried azeotropically for 24 h in a Dean Stark apparatus and subsequently added dropwise to a solution of $ClS(O)_2NCO$ in 20 mL of dry benzene. The reaction mixture was stirred at 25 °C for 1 h, concentrated *in vacuo* and dried overnight *in vacuo* to yield a pale yellow residue which was used without further purification. A solution of this residue in 35 mL of benzene was added dropwise to a solution of 2.5 mL (17.3 mmol) of Et_3N in 15 mL of benzene. The reaction mixture turned darker with concomitant formation of insoluble Et_3NHCl, and was stirred at 25 °C for 30 min, filtered, concentrated *in vacuo*, and dried *in vacuo* for 2-3 d to yield 6.2 g (82%) of polymer-linked Burgess reagent. The tan colored reagent was used without further purification.

   A solution of 100 mg (0.28 mmol) of Cbz-Val-Thr-OMe in 1.5 mL of dioxane/THF (1:1) was treated with 400 mg (0.41 mmol) of PEG-Burgess reagent and heated at 85 °C for 3 h. The reaction mixture was concentrated *in vacuo* and filtered or chromatographed through SiO_2 (EtOAc/Hexanes 1:1) to yield 85 mg (90%) of the desired oxazoline as a colorless oil. For the spectroscopic characterization of this oxazoline, see ref. 4a.
6. These experiments were performed by Mr. Greg Hayes in the context of synthetic studies toward phenoxan in our laboratories.

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