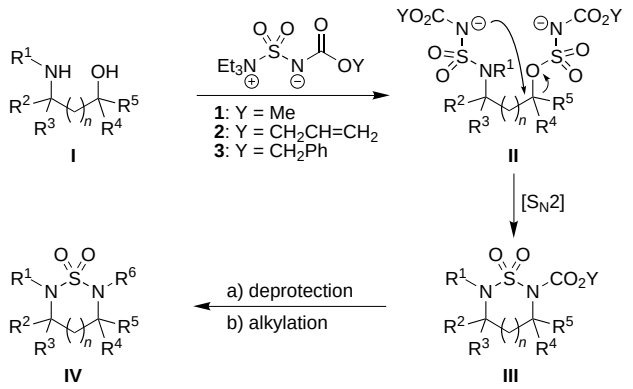
A New Method for the Synthesis of Nonsymmetrical Sulfamides Using Burgess-Type Reagents**

K. C. Nicolaou,* Deborah A. Longbottom, Scott A. Snyder, Annie Z. Nalbanadian, and Xianhai Huang

Within the realm of proven pharmacophores, the sulfamide functional group (thiadiazine-1,1-dioxide) stands out as one of the most important structural motifs found in high affinity protein ligands and pharmaceutically useful agents. Indeed, a survey of the recent patent literature reveals several hundred proprietary documents illustrating that the incorporation of a sulfamide group within a suitable scaffold, often cyclic, leads to compounds with an impressive and diverse array of biological activity.[1] Among the numerous applications of sulfamides, these agents have proven to be particularly effective as inhibitors of key enzymes including HIV protease[2] and serine protease,[3] and have demonstrated utility as both agonists and antagonists of critical molecular receptors such as those used to regulate endogenous levels of serotonin[4] and histamine.[5] Beyond their clear significance in the treatment of disease, cyclic sulfamides have also been employed with considerable success as chiral ligands and auxiliaries,[6] and constitute an increasingly popular set of building blocks within the field of supramolecular chemistry.[7]

Despite the indisputable utility of these compounds, existing routes for their synthesis, particularly in a cyclic setting, are far from ideal. For example, typical procedures to fashion cyclosulfamides rely upon the reaction of a diamine with either SO_2Cl_2 or $H_2NSO_2NH_2$ at elevated temperatures,[8] conditions which often lead to a low yield of product as a result of the concomitant formation of polycondensation side-products. Equally problematic is the relative scarcity of suitable diamines for these reactions from commercial sources[9] and the difficulties associated with their laboratory preparation. While these issues have led to the development of several alternative protocols for sulfamide synthesis,[10] these additional synthetic technologies have proven amenable only to specific substrate classes and have not yet alleviated the need for multistep protocols. Most significantly, none of these methods has enabled the efficient and selective synthesis of nonsymmetrical *N*,*N*′-disubstituted cyclosulfamides (**IV**, Scheme 1), perhaps the most versatile class of these compounds for generating pharmaceutically relevant molecular diversity. Herein, we provide a general and widely applicable solution for the synthesis of these diverse classes of sulfamides, which enables for the first time the reliable and efficient formation of this highly desirable structural moiety (**IV**).



Scheme 1. Proposed conversion of amino alcohols (**I**) into cyclic sulfamides (**III**) using Burgess (**1**) and related reagents (**2** and **3**) and further elaboration leading to nonsymmetrically substituted, structurally diverse products (**IV**).

Drawing insight from our recent discovery[11] that β-amino alcohols can be smoothly synthesized with excellent chiral integrity from precursor diols through a novel cyclization reaction initiated by the Burgess reagent (**1**, Scheme 1)[12] and related compounds (**2** and **3**),[11] we anticipated that application of this protocol to an amino alcohol starting material (**I**) would result in a monoprotected, nonsymmetrical cyclic sulfamide (**III**) in a single, stereocontrolled operation through the delineated mechanism (Scheme 1). Assuming that this reaction course could be successfully realized in preference to the typical rearrangement/dehydration pathways promoted by these reagents,[13] subsequent deprotection of the carbamate in **III**, followed by substitution with an appropriate electrophile, would then provide access to an assorted collection of sulfamides (**IV**) with the potential to incorporate diversity at all possible sites.

To test this attractive hypothesis, a representative set of commercially available secondary β-amino alcohols was investigated. Most gratifyingly, exposure of all substrates listed in Table 1 to excess Burgess reagent (**1**) in refluxing THF for 8 h led to the formation of the desired cyclic sulfamide product in high yield, regardless of the nature of the group attached to the amine. Of particular note is that neither placement of the amine in a hindered cyclic setting (entry 4) nor addition of a bulky *tert*-butyl substituent (entry 3) retarded product formation. This latter substrate constitutes a particularly effective test for the power of this synthetic technology, as starting materials bearing this functionality have generally proven recalcitrant to sulfamide formation with currently available methods.[4] Of equal importance, all

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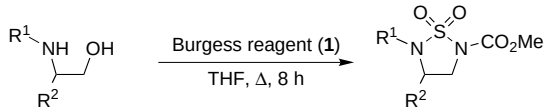
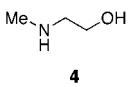
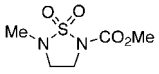
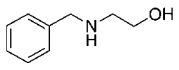
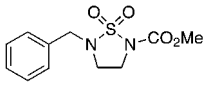
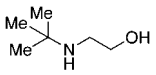
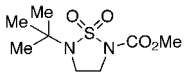
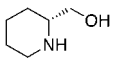
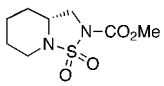
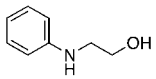
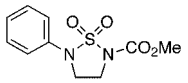
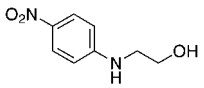
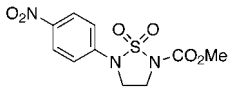
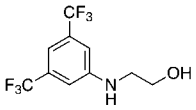
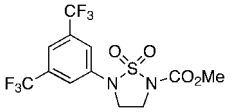
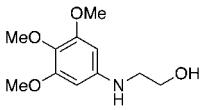
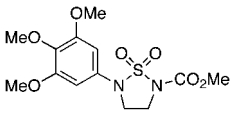
Table 1. Synthesis of five-membered nonsymmetrical cyclic sulfamides from precursor secondary β-amino alcohols using Burgess reagent (**1**): initial investigations.



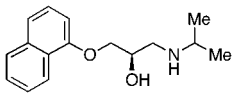
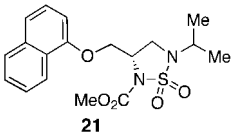
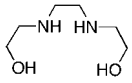
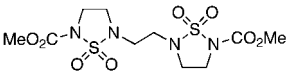
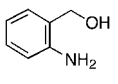
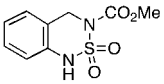
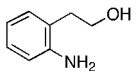
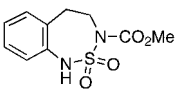
Entry	Starting material	Product	Yield [%]
1	 **4**	 **5**	75
2	 **6**	 **7**	85
3	 **8**	 **9**	81
4	 **10**	 **11**	77
5	 **12**	 **13**	92
6	 **14**	 **15**	75
7	 **16**	 **17**	82
8	 **18**	 **19**	69

aniline-derived systems (entries 5–8) proved readily amenable to the cyclization process regardless of the electron-withdrawing (entries 6 and 7) or -donating (entry 8) properties of the appended aromatic ring; these results are indicative of the versatility of this intramolecular Burgess-mediated cyclization.[14]

While certainly satisfied by this initial success in which the two nitrogen atoms of the sulfamide product had been effectively differentiated, we next sought to more fully probe the limits of the Burgess-mediated sulfamide synthesis by exploring more challenging substrates. As shown in Table 2, the use of a chiral secondary alcohol (entry 1), even in a relatively hindered context **20**, failed to engender any particular difficulties (although extension of the reaction time beyond the standard 8 h of heating was required to optimize yields), and led to **21** with clean inversion of configuration. A double cyclization seeking to generate a bis-sulfamide (**23**, entry 2) was also smoothly effected. The reduced yield in this case was solely a consequence of difficulties encountered during isolation of this polar product. Finally, following optimization of the reaction conditions, extension of the sulfamide cyclization to ring sizes beyond the five-membered products formed in the previous examples also proved to be possible. Initial efforts in this regard focused on **24** (entry 3), wherein commencing the reaction at 0 °C for 1 h and then warming to ambient temperature for 5 h led to the desired product (**25**) in 45 % yield. All other conditions examined provided no improvement on this yield; they gave only greater amounts of decomposition and led us to conclude that the activated primary benzylic alcohol was responsible. Fundamentally, however, the formation of other sulfamide-containing rings should not prove to be as problematic if a non-benzylic alcohol is employed instead. For this reason, alcohol **26** was examined and, to our delight, the seven-membered ring analogue (**27**, entry 4) was readily generated in 90 % yield through a cyclization reaction that is less favorable both enthalpically and entropically than that to form a six-membered ring. The smooth generation of **27** is additionally significant because this bicyclic product is analogous to the benzodiazepine motif, a molecular scaffold that has been the subject of intensive biological investigations and the source of several clinically employed agents.[15]

Based on the successful cyclization of the latter two primary aryl amine substrates in Table 2, we were hopeful that primary aliphatic amino alcohols would perform equally well as both sides of the resultant sulfamide product could then be substituted in turn, thus leading to greater structural diversity. Unfortunately, all four substrates examined within this class (Table 3, entries 1–4) gave rather disappointing yields of sulfamide products which led either to decomposition or to

Table 2. Synthesis of nonsymmetrical cyclic sulfamides from precursor amino alcohols using Burgess reagent (**1**): exploration of additional substrate classes and development of optimized reaction conditions.

Entry	Starting material	Product	Yield [%]
1	 **20**	 **21**	89[a]
2	 **22**	 **23**	55[b]
3	 **24**	 **25**	45[c]
4	 **26**	 **27**	90[d]

[a] THF, Δ, 21 h. [b] THF, Δ, 8 h. [c] 0 °C, 1 h, then 25 °C, 5 h. [d] THF, Δ, 2 h.

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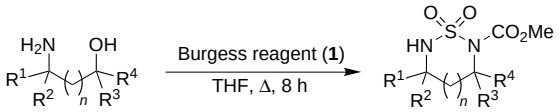
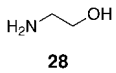
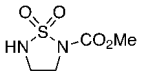
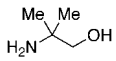
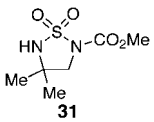
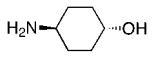
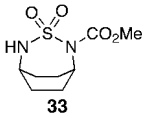
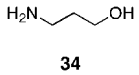
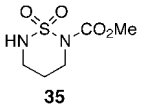
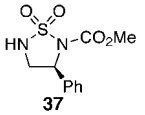
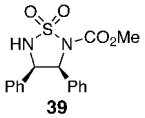
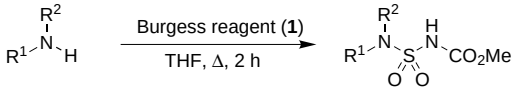
Table 3. Synthesis of monoprotected cyclic sulfamides from precursor primary amino alcohols using Burgess reagent (**1**).

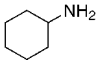
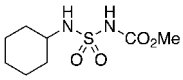
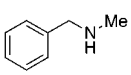
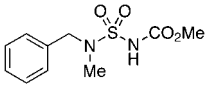
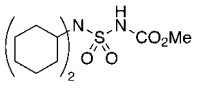
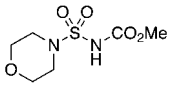
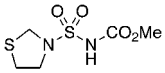
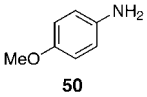
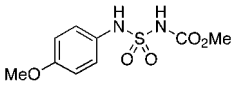
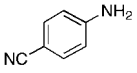
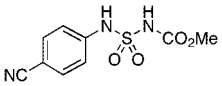
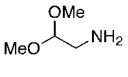
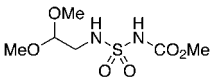


Entry	Starting material	Product	Yield [%]
1	 **28**	 **29**	62
2	 **30**	 **31**	39
3	 **32**	 **33**	34
4	 **34**	 **35**	42
5	 **36**	 **37**	90[a]
6	 **38**	 **39**	76[a]

[a] 0 °C, 1 h, then 25 °C, 5 h.

Table 4. Synthesis of nonsymmetrical linear sulfamides from precursor amines using Burgess reagent (**1**).



Entry	Starting material	Product	Yield [%]
1	 **40**	 **41**	83
2	 **42**	 **43**	91
3	 **44**	 **45**	82
4	 **46**	 **47**	87
5	 **48**	 **49**	73
6	 **50**	 **51**	97
7	 **52**	 **53**	66
8	 **54**	 **55**	98[a]

[a] −10 to 25 °C, 24 h.

the formation of side-products resulting from undesired rearrangements. In retrospect, however, the poor performance of these substrates in an intramolecular cyclization relative to their secondary amine counterparts is not so surprising, as in the absence of an additional alkyl or aryl substituent, the nitrogen atom is less nucleophilic, and requires a longer reaction time and provides a greater opportunity for decomposition/rearrangement. The modest yields observed in these examples, however, do not really constitute a limitation in strategy as the quantitative debenzylation of **7** (Table 1, entry 2) using Pearlman's catalyst provided a route to the same product **29** (Table 3, entry 1), thus alleviating the need to start with ethanolamine (**28**). As such, this approach provides a tactic to sequentially substitute both sides of any cyclic sulfamide product, if so desired. Finally, in contrast with the results in the rest of Table 3, the utilization of primary aliphatic amines in conjunction with a secondary benzylic alcohol (Table 3, entries 5 and 6) led to good product yields when the reaction was performed at low temperature. As such, these unanticipated results suggest that there is a subtle interplay between substrate structure and particular reaction conditions to facilitate sulfamide formation in synthetically useful yield.

Beyond the synthesis of cyclic sulfamides, we have also verified that Burgess reagent (**1**) can smoothly effect the generation of nonsymmetrical, linear sulfamides from all classes of amines in excellent yield (Table 4). While this same conversion is more typically achieved by adding the amine to an appropriate chlorosulfonylisocyanate derivative,[5,16] the present conditions provide a mild alternative which avoids the use of these rather toxic and corrosive agents directly on the reaction substrate.

Finally, we should note that since all of the preceding examples of sulfamide synthesis in Tables 1–4 led to products with methyl carbamate protection we tested the ability of our recently reported novel benzyloxycarbonyl (Cbz) and allyloxycarbonyl (Alloc) Burgess-type reagents (**2** and **3**, Scheme 1)[11,17] to perform the same transformations. Most gratifyingly, in all cases examined, these reagents provided the desired product in yields that were equivalent to those obtained with the original Burgess reagent (**1**). As such, this method of sulfamide synthesis, whether for cyclic or linear systems, can be tailored with a variety of protecting groups to fit the particular needs of the test molecule. In line with several reports,[18] our own studies have revealed that subsequent deprotection (Table 5) is easily achieved with conventional procedures and readily followed by substitution of appropriate electrophiles. Thus general and efficient syn-

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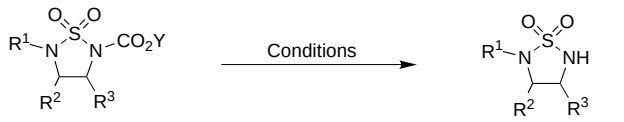
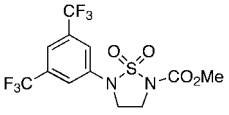
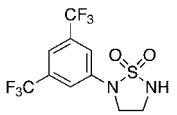
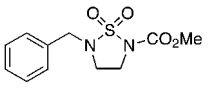
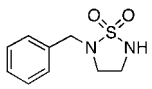
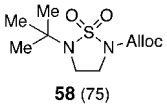
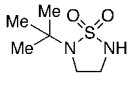
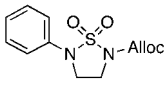
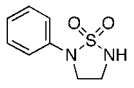
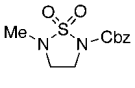
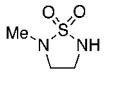
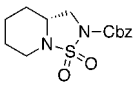
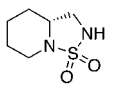
Table 5. Deprotection of cyclic sulfamides to yield nonsymmetrical, monosubstituted sulfamides.



Entry	Starting material (Yield [%])[a]	Product	Yield [%]
1	 **17**	 **56**	99[b]
2	 **7**	 **57**	99[b]
3	 **58** (75)	 **59**	97[c]
4	 **60** (82)	 **61**	98[c]
5	 **62** (82)	 **63**	84[d]
6	 **64** (75)	 **65**	87[d]

[a] Yield in parentheses is that for synthesis of the starting material. [b] NaOH, MeOH:H_2O (2:1), 25 °C, 2 h. [c] $Pd(OAc)_2$ (10 mol %), 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt (20 mol %), $HNEt_2$ (40 equiv), MeCN:H_2O (1:1), 25 °C, 15 min. [d] 10 % Pd/C, H_2, EtOH:EtOAc (4:1), 25 °C, 2 h.

thesis of compounds represented by structure **IV** (Scheme 1) has been realized.

In conclusion, we have developed a practical and high-yielding method for the efficient, one-step synthesis of diverse classes of *N*,*N*′-differentiated sulfamides from a wide range of amino alcohols and simple amines using Burgess-type reagents. This synthetic technology constitutes a marked improvement over those currently in the literature, and should extend the potential applications of sulfamides not only within chemical biology and medicinal chemistry, but also in the fields of asymmetric synthesis and supramolecular chemistry. At a more fundamental level, this methodology, in conjunction with additional applications currently under development in these laboratories, serves to delineate new pathways in which the power of the Burgess reagent and its relatives can be applied to effect transformations of critical importance in chemical synthesis.

Experimental Section

Representative procedure: The desired Burgess reagent (**1**–**3**, 1.25 mmol, 2.5 equiv) was added in one portion to a stirred solution of amino alcohol (0.5 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was then subjected to the conditions defined in the Tables. Upon completion, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with 1N HCl (30 mL). The aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography on silica gel then provided the desired products in the yields quoted.[18]

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[17] We would like to emphasize that all of our reported novel Burgess-type reagents (including **2** and **3**) are readily isolable, can be purified through trituration with toluene, and then stored at 0 °C for several months; the recent use of **3** in solution by a Merck group, therefore,[13d] should not be taken as a sign of instability in the solid form.
[18] Notes: 1) For the synthesis of nonsymmetrical linear sulfamides (Table 4), only 1.3 equiv of Burgess reagent is used to facilitate the reaction process. 2) HCl salts of the starting amines and amino alcohols do not provide good conversion into the desired product. The free base must be isolated prior to reaction with **1**–**3**. 3) Removal of protecting groups was carried out by using conventional protocols: CO_2Me: NaOH, MeOH:H_2O (2:1), 25 °C, 2 h;[19] Cbz: 10 % Pd/C, H_2, EtOH:EtOAc (4:1), 25 °C, 5 h;[20] Alloc: $Pd(OAc)_2$ (10 mol %), 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt (20 mol %), $HNEt_2$ (40 equiv), MeCN:H_2O (1:1), 25 °C, 15 min;[21] Bn: 20 % $Pd(OH)_2$/C, H_2 (60 psi), EtOH:EtOAc (4:1), 25 °C, 24 h.[22] Subsequent alkylation was carried out by using a conventional protocol: sulfamide, NaH, DMF, 0 °C to 25 °C then alkyl halide, tetrabutylammonium iodide (cat), 25 °C 4 h.[2d,5]
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$[Os^{III}(tpy)(Cl)(NCCH_3)(NSAr)]$: Reversible Reduction of Acetonitrile by Os^{III}–Sulfilimido Complexes**

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Earlier reports have revealed an extensive electron–proton, reversible redox chemistry based on the $Os^{V/IV}$ couples $[Os^{V}(tpy)(Cl)_2\{NN(CH_2)_4O\}]^+/[Os^{IV}(tpy)(Cl)_2\{N(H)-N(CH_2)_4O\}]^+$ (tpy = 2,2′:6,2″-terpyridine, $N(CH_2)_4O$ is a morpholide),[1] $[Os^{V}(tpy)(Cl)_2\{NS(3,5\text{-}C_6H_3Me_2)\}]^+/[Os^{IV}(tpy)(Cl)_2\{NS(H)(3,5\text{-}C_6H_3Me_2)\}]^+$,[2] and $[Os^{V}(Tp)(Cl)_2(NPEt_2)]/[Os^{IV}(Tp)(Cl)_2\{NP(H)Et_2\}]$ (Tp = tris(pyrazolyl)borate).[3] These couples are reminiscent of oxo/hydroxo/aqua couples such as *cis*-$[Ru^{IV}(bpy)_2(py)(O)]^{2+}$/*cis*-$[Ru^{III}(bpy)_2(py)(OH)]^{2+}$ and *cis*-$[Ru^{III}(bpy)_2(py)(OH)]^{2+}$/*cis*-$[Ru^{II}(bpy)_2(py)(H_2O)]^{2+}$ (bpy = 2,2′-bipyridyl, py = pyridyl), where the change in proton content between oxidation states is a consequence of differences in proton acidity of several orders of magnitude.[4]

We report here the existence of a related electron–proton chemistry, but based on the reversible two-electron reduction of a nitrile ligand and the couples $[Os^{III}(tpy)(Cl)(N{\equiv}CCH_3)(NSAr)]$ / $[Os^{III}(tpy)(Cl)(NH{=}CHCH_3)(NSAr)]$ (Ar = C_6H_5, 4-MeC_6H_4, 3,5-$Me_2C_6H_3$). At more negative potentials, the Os^{III}–imino complexes undergo further reduction and solvolysis to give $[Os^{III}(tpy)(Cl)(NCCH_3)(NSAr)]$ and $CH_3CH_2NH_2$.

A rapid reaction occurs when *cis*-$[Os^{VI}(tpy)(Cl)_2(N)]^+$ ($[\mathbf{1}]^+$) and aromatic thiols (C_6H_5SH, 4-MeC_6H_4SH, or 3,5-$Me_2C_6H_3SH$) are mixed in CH_3CN under N_2 at room temperature [Eq. (1)]. The products are *cis*-

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