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N-(*tert*-Butoxycarbonyl)-*N*-[(triethylenediammonium)sulfonyl]azanide: A Convenient Sulfamoylation Reagent for Alcohols

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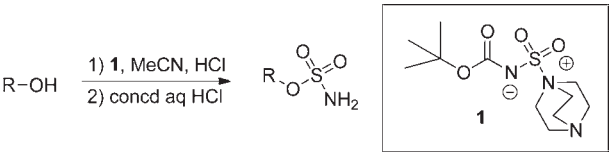
ABSTRACT



A convenient and efficient procedure is described for the sulfamoylation of alcohols using *N*-(*tert*-butoxycarbonyl)-*N*-[(triethylenediammonium)-sulfonyl]azanide (1). The ambient temperature stable reagent 1 reacts with phenols as well as primary and secondary alcohols to give high to modest yields. The relative reaction rate of substrates was determined (primary > phenol > secondary ≫ tertiary). The reagent's utility as a selective sulfamoylation reagent with polyols is also demonstrated.

Compounds containing the sulfamate function have recently gained prominence in pharmaceutical research as anticonvulsant, antibiotic, and antitumor agents.[1] The reported approaches to installation of a sulfamoyloxy group on alcohols are very limited.[2] Selective sulfamoylation on polyols is unprecedented in the literature. The most common method of making sulfamate derivatives from alcohols requires *in situ* formation of sulfamoyl chloride starting with chlorosulfonyl isocyanate and formic acid.[3] Due to the high reactivity of sulfamoyl chloride, polyol systems containing primary and secondary alcohols require a protecting group strategy for selective sulfamoylation of primary alcohols.[4] Additionally, sulfamoyl chloride decomposes quickly in solution, which often forces the use of a large excess to achieve complete conversion to the desired product.[3a] Furthermore, scale-up of sulfamoyl chloride according to this procedure using solvents other than DMA and NMP could lead to uncontrollable runaway behavior with explosive gas evolution.[3a]

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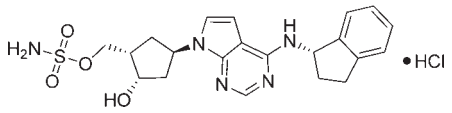


Figure 1. MLN4924.

As part of our effort to improve the synthesis of MLN4924 (Figure 1), an investigational small molecule inhibitor of Nedd-8 activating enzyme currently in phase I clinical trials, novel sulfamoylating reagents were investigated.[5] The key properties of a desirable reagent were defined to include solid-state stability, safety, and reactivity. Selectivity for 1° vs 2° in a diol system was also considered. The approach to the process friendly sulfamoylation reagent was based on Burgess-type reagent **2** (Figure 2) reported by Winum.[3a] A derivative of the original Burgess reagent **3**,[6b−g] **2** reacts with various amines and anilines to afford sulfamides at rt. However, **2** is not reactive toward alcohols. Structural modification of **2** led to the development of Burgess-type reagent **1**, an ambient temperature stable solid, suitable for large scale selective sulfamoylation of a 1,3 diol intermediate in the synthesis of MLN4924.[5b] This paper describes the general reactivity and utility of the novel sulfamoylating reagent **1** toward various alcohols.

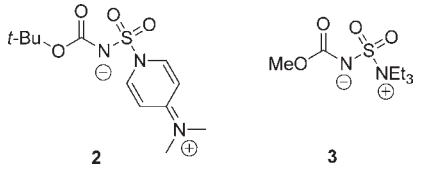
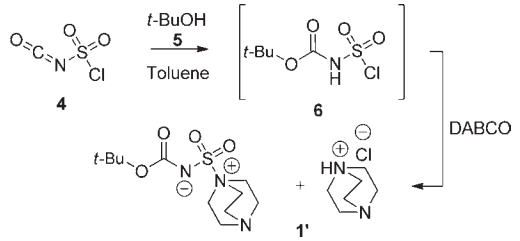


Figure 2. Previous Burgess-type reagents.

Similar to the preparation of **2**,[6e] an optimized procedure to make reagent **1** was developed with an efficient isolation process. Chlorosulfonylisocyanate (**4**) and *tert*-butyl alcohol (**5**) react together in toluene to give *N*-(*tert*-butoxycarbonyl)sulfamoyl chloride (**6**), which reacts further with 2.0 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford the desired sulfamoylation reagent **1** plus an equiv of DABCO·HCl salt (Scheme 1). Due to the rapid decomposition of **1** in water, the product is collected by filtration with DABCO·HCl salt as a 1:1 mixture (**1′**) in quantitative yield.[5] A number of multi-kilogram scale batches of **1′** were prepared according to this procedure. Reagent **1′** has been kept at ambient temperatures (20−23 °C) up to one year without detectable decomposition by NMR or loss of reactivity when used in test reactions.

Scheme 1. Preparation of Sulfamoylation Reagent **1′**



In order to establish an optimal protocol for screening the reactivity of **1′** with various alcohols, the reaction of **1′** with 3-hydroxypropylbenzene (**7a**) was investigated under various conditions (Table 1). The rate of conversion from **7a** to **7b** was evaluated as a function of solvent, amounts of **1′**, and acid catalyst added.

Since Burgess-type reagents are known to be unstable in solution,[7] a group of minimally nucleophilic solvents were selected and the sulfamoylation reaction was run at ambient temperature with 2.0 equiv of **1′**. Low reaction rates were observed for a number of common solvents, such as MTBE, 1,4-dioxane, and THF, due to the poor solubility of reagent **1′** (Table 1, entries 1−3). Among the solvents showing promising reaction rates, sulfolane and NMP gave the slowest conversions (Table 1, entries 4 and 5). The reaction was much faster in MeCN (Table 1, entry 6). A combination of MeCN and NMP showed no improvement compared with using MeCN alone (Table 1, entry 7). The best conversion rate was observed when DCM was used as the reaction solvent (Table 1, entry 8). However, DCM was not selected as the standard solvent in this study because of its environmental concerns.[8] All the solvents tested failed to provide a complete conversion of **7a** to **7b** with 2.0 equiv of **1′**. In most of the solvents, the reaction stalled after 17 h at 70−80% conversion. Increasing the initial amount of **1′** to 4.0 equiv showed minimal impact (Table 1, entry 9) presumably due to the solution stability issue combined with poor solubility of **1**. Subsequent addition of more reagent **1′**, however, successfully drove the reaction to completion (Table 1, entry 10). It was later discovered that this reaction could also be accelerated with a small amount of anhydrous HCl (Table 1, entries 11 and 12). This result was likely due to protonation of the nitrogen anion in reagent **1** to provide a quaternary salt **1″** (Scheme 2) which should be more reactive toward nucleophiles.

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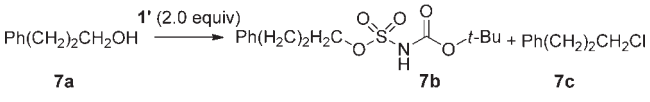
Table 1. Determining Optimal Conditions for Reaction of **1′** with Alcohol **7a**

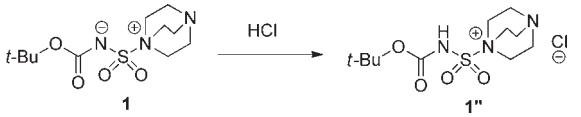


entry	solvent	acid/ equiv	conversion (%)[a] (time)	**7c** (%)[a]
1	MTBE	none	10 (17 h)	0
2	1,4-dioxane	none	18 (17 h)	0
3	THF	none	33 (17 h)	0
4	sulfolane[b]	none	46 (17 h)	0
5	NMP	none	38 (17 h)	0
6	MeCN	none	31 (3 h), 72 (17 h)	0
7	MeCN/NMP[c]	none	66 (17 h)	0
8	DCM	none	94 (17 h)	0
9[d]	MeCN	none	77 (17 h)	0
10[e]	MeCN	none	100 (17 h + 24 h)	0
11	MeCN	HCl[f]/0.1	77 (3 h)	<1
12	MeCN	HCl[f]/0.2	100 (3 h)	1–2
13	MeCN	HCl[f]/0.4	100 (3 h)	6
14	MeCN	HCl[f]/1.0	100 (3 h)	10
15[g]	MeCN	HCl[f]/0.4	100 (3.5 h)	10
16[g]	MeCN	MsOH/0.4	100 (2 h)	9
17[g]	MeCN	AcOH/0.4	95 (17 h)[h]	24

[a] Area under curve of HPLC traces. [b] Reaction run at 30 °C. [c] 1:1 ratio of solvents. [d] 4.0 equiv of **1′** was used. [e] 4.0 equiv of **1′** plus another 1.5 equiv of **1′**. [f] 4 M HCl in dioxane. [g] Reactions were performed on a 3 g scale versus a 0.1 g scale for the other entries. [h] Unknown products were also observed.

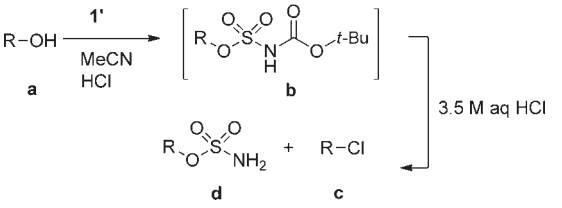
The conversion of **7a** increased to 77% in 3 h with the addition of 0.1 equiv of 4 M HCl in dioxane (Table 1, entry 11) vs 31% without any HCl (Table 1, entry 6), and the reaction was complete if 0.2 equiv of HCl (Table 1, entry 12) was used. When the reaction was scaled to 3 g, it was not complete with 0.2 equiv of HCl and 0.4 equiv of HCl was found to be optimal (Table 1, entry 15). As more HCl was introduced to the reaction mixture, the corresponding chloride (**7c**) was formed as a minor impurity (Table 1, entries 11–14) likely due to nucleophilic displacement of the sulfamoyl group. Other acids were also tested and demonstrated a similar acceleration effect (Table 1, entries 16 and 17). Unfortunately, the levels of **7c** were not reduced due to the existence of DABCO·HCl salt in reagent **1′**. Having successfully met our reaction criteria on the 3 g scale, the standard protocol for this study was established. The alcohol substrate **7a** was charged to a slurry of reagent **1′** (2.0 equiv) in MeCN, followed by the addition of 0.4 equiv of HCl in dioxane. The reaction mixture was allowed to stir at ambient temperature until complete consumption of **7a**.

Scheme 2. Effect of HCl Catalyst



Various alcohols (**a**) were selected and subjected to the standard sulfamoylation conditions to afford intermediates **b**. The Boc group was readily removed by addition of 3.5 M aqueous HCl to provide the targeted sulfamates **d**. The desired products were isolated after aqueous workup. The results are summarized in Table 2.

Table 2. Reactivity of **1′** toward Diverse Alcohols



entry	R	substrate ID	product (yield, %[a])	impurity (yield, %[b])
1	$PhCH_2CH_2CH_2$–	**7a**	**7d** (88)	**7c** (10)
2	$PhCH_2CH_2$–	**8a**	**8d** (90)	**8c** (8)
3	$PhCH_2CH_2CH(CH_3)$–	**9a**	**9d**[c] (84)	**9c** (5)
4	$PhCH_2CH(CH_3)$–	**10a**	**10d** (93)	**10c** (5)
5	$PhCH_2CH_2C(CH_3)_2$–	**11a**	none	
6	$PhCH_2C(CH_3)_2$–	**12a**	none[d]	
7	Ph–	**13a**	**13d** (94)	
8	*p*-MeO, Ph–	**14a**	**14d** (99)	
9	*p*-F, Ph–	**15a**	**15d** (64)[e]	
10	Bn–	**16a**	none	**16c** (>50)
11	*p*-MeO, $PhCH_2$–	**17a**	none	**17c** (100)
12	$EtCH_2CH{=}CHCH_2$–	**18a**	none	
13	$EtCH_2C{\equiv}CCH_2$–	**19a**	none	

[a] Isolated yield. [b] Yield determined by NMR integration of isolated crude product. [c] Product was collected after basic work up as it decomposed easily during acidic aq. workup. [d] NMR of reaction mixture indicated that elimination to the olefin occurred when reaction was forced with addition of 1.0 equiv of HCl in the first step. [e] Starting material **15a** was observed in the crude product.

High yields were obtained for primary alcohols (Table 2, entries 1 and 2). Secondary alcohols reacted slightly slower, yet still gave excellent yields (Table 2, entries 3 and 4). Although the original Burgess reagent **3** was first introduced as a mild dehydration reagent,[9] no olefin formation was observed even in the reactions of substrates **8a** and **10a** with reagent **1′**. Reagent **1′** was not reactive with tertiary alcohols presumably due to steric hindrance, and starting materials were recovered under the standard conditions (Table 2, entries 5 and 6). Phenol substrate **13a** was as reactive (Table 2, entry 7) as primary alcohols **7a** and **8a**. As expected, electron enriched phenol **14a** reacted faster (Table 2, entry 8), while electron poor phenol **15a** reacted much more slowly (Table 2, entry 9). The major side product of this sulfamoylation reaction is the corresponding chloride **c**. In most cases, less than 10% of chloride **c** was observed in product **d** (Table 2, entries 1–4). For benzyl alcohols, **16a** provided benzyl chloride **16c** as the major product in the reaction mixture (Table 2, entry 10), and

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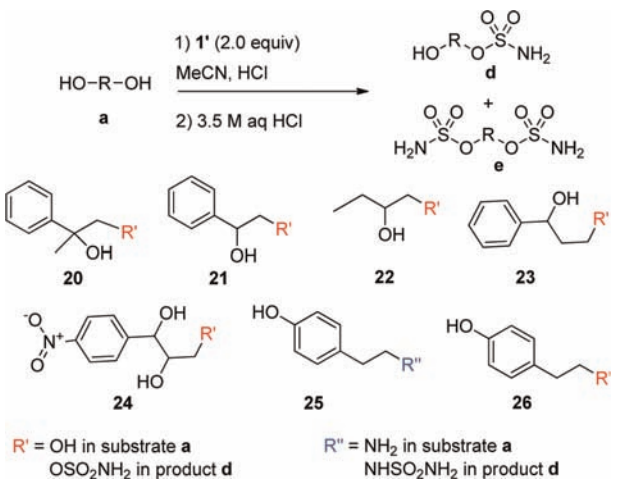
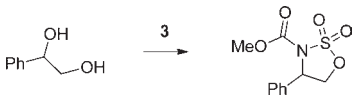
Table 3. Selectivity of **1′** towards Polyols



entry	substrate	product (yield, %)	byproduct (yield, %)
1	**20a**	**20d** (99)[a]	undetectable
2	**21a**	**21d** (78)[a]	undetectable
3	**22a**	**22d** (16),[b] (47)[b,c]	**22e** (23),[b] (11)[b,c]
4	**23a**	**23d** (70)[a]	undetectable
5	**24a**	**24d** (93)[a]	undetectable
6	**25a**	**25d** (63),[b] (79)[b,c]	**25e** (19),[b] (10)[b,c]
7	**26a**	**26d** (79)[b,d]	**26e** (10)[b]

[a] Isolated yield. [b] Yield determined by NMR integration of isolated crude product. [c] 1.5 equiv of **1′** was used. [d] Chloride (8%) was also obtained.

Scheme 3. Ring Formation from 1,2-Diols with Burgess Reagent



electron rich derivative **17a** formed chloride **17c** exclusively in this reaction (Table 2, entry 11). Allylic alcohol **18a** and 2-yn-1-ol **19a** provided messy reactions, and no desired products were observed (Table 2, entries 12 and 13).

The rate constants for 1°, 2°, and phenolic alcohols **8a**, **10a**, and **14a** were experimentally determined. Rate constants were determined via the method of initial rates under pseudo-first-order conditions. The relative rates of reaction followed the trend 1° > phenol > 2° (3.1:2.7:1). On the basis of these rate differences, the monosulfamoylation of polyols should be feasible with some degree of selectivity.

To demonstrate the selectivity of reagent **1′**, sulfamoylation of a set of polyols was carried out under the standard protocol. The results are summarized in Table 3.

For 1,2-diol substrates **20a** and **21a**, no bis byproduct (**e**) was observed (Table 3, entries 1 and 2) and the desired products were isolated in high yields. High yield and selectivity were also obtained with 1,2,3-triol substrate **24a** (Table 3, entry 5). Reducing the steric hindrance of the 2° alcohol in **22a** led to significant formation of bis byproduct **22e** with 2.0 equiv of **1′**. The low isolated yield was likely due to loss during workup caused by the aqueous solubility of **22d** and **22e**. However, a high ratio of mono vs bis products was readily obtained when 1.5 equiv of **1′** was added to the reaction. The isolated yield was also improved with extra extractions of the aqueous layer (Table 3, entry 3). It was noteworthy that the ring formation with 1,2-diols highlighted in the literature using the original Burgess reagent **3** was not observed in cases of **20a**, **21a**, and **24a** (Scheme 3).[10] **1′** was presumably bulky enough to inhibit formation of bis sulfamoylation intermediates leading to the five membered sulfamidate rings for those 1,2-diols. However, the ring formation was indeed detected by MS at a low level (< 5%) in the case of substrate **22a** where bis sulfamoylation occurred. A 1,3-diol substrate **23a** provided 70% isolated product and no bis byproduct (Table 3, entry 4). Although developed as a sulfamoylation reagent for alcohols, it was predictable that **1′** is preferentially reactive toward more nucleophilic amines and anilines (Table 3, entry 6). In the cases where two competing functional groups are similarly reactive (Table 3, entries 6 and 7), only the favored mono product (**d**) was formed and bis products (**e**) were also obtained in 19% and 10% yield respectively. Similar to entry 3, the formation of bis product could be minimized by reducing the amount of Burgess-type reagent **1′** added (Table 3, entry 6).

A novel Burgess-type reagent, *N*-(*tert*-butoxycarbonyl)-*N*-[(triethylenediammonium)sulfonyl]azanide, a triethylenediammonium hydrochloride salt mixture (**1′**), has been demonstrated to be a convenient sulfamoylating reagent for alcohols. It gives high yields under mild conditions for primary, secondary, and phenyl alcohols. It is readily prepared on the kilogram scale and can be stored under ambient conditions (20 °C, 40s% RH) for 6 months. It also reacts selectively with unprotected polyols (primary > phenol > secondary ≫ tertiary).

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Supporting Information Available. Experimental procedures, spectral and analytical data for the products, and kinetic study data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.