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Facile synthesis of 5′-(*N*-acyl sulfonamide) derivatized nucleosides

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Abstract—The acylation of several primary sulfonamides with N_6-benzoyl-2′,3′-isopropylidene-5′-carboxylic acid-5′-deoxyadenosine (**1**) is described. Literature methods for the construction of the *N*-acyl sulfonamide functionality proved ineffective for synthesizing 5′-*N*-acyl sulfonamide derivatives of **1**. The combination of DCC/DMAP provided the mild conditions necessary to effect coupling of the protected nucleoside acid with various primary sulfonamides in good to high yield.

Acylation of a primary sulfonamide results in the formation of an *N*-acyl sulfonamide. An attractive feature of synthesizing *N*-acyl sulfonamides in this fashion is the variety of structures that can be easily accessed.[1] Structures obtained in this manner have significant potential for use in biological applications. Their acidity (pK_a 4–5)[2,3] renders them suitable carboxylic acid surrogates,[3,4] while their resistance to chemical and enzymatic hydrolysis[5] makes them amenable for use as enzyme inhibitors.[6] In addition, *N*-acyl sulfonamide analogs of arachidonic acid metabolites have been shown to induce tyrosine phosphorylation cascades.[7] Despite the many uses of *N*-acyl sulfonamides, little attention has been paid to their application in nucleoside chemistry. The incorporation of the *N*-acyl sulfonamide functionality into nucleosides would nicely compliment the emerging use of sulfonate,[8] sulfamate,[9] sulfonamide[8b,10] and *N*-acyl sulfamide[11] functional groups as phosphate surrogates.

In principle, acylation of sulfonamides can be accomplished by the reaction of a sulfonamide with anhydrides,[4d,12] esters[13] or acid chlorides.[14] Alternately, direct condensation of a carboxylic acid with a sulfonamide in the presence of either *N*-ethyl-*N*′-(3,3-dimethylamino)-propylcarbodiimide hydrochloride (EDC·HCl)[4d,15] or 1,1′-carbonyldiimidazole (CDI)[16] should also provide *N*-acyl sulfonamides. Another method for construction of this functional group uses 2-chloro-*N*-methylpyridinium iodide (Mukaiyama's reagent).[17] We desired to acylate a variety of sulfonamides using N_6-benzoyl-2′,3′-isopropylidene-5′-carboxylic acid-5′-deoxyadenosine (**1**).[18] However, the previously cited procedures proved ineffective. For example, acylation of tosyl sulfonamide with **1**, using Ishizuka's procedure,[14b] provided the desired product in only 30% yield. Drummond's protocol[16] gave only a slightly better yield of 35%. Further, an attempt to acylate methane sulfonamide using this protocol also provided unsatisfactory results. Both Guzzo and Pelletier have reported procedures using EDC·HCl and 4-dimethylaminopyridine (DMAP). The former method calls for a full equivalent, whereas the latter uses a catalytic amount. Using these to acylate tosyl sulfonamide gave yields of 40 and 33%, respectively. Entries 1–5 in Table 1 summarize these results.

We find that the combination of dicyclohexylcarbodiimide (DCC) and one full equivalent of DMAP in methylene chloride gave facile coupling between various sulfonamides and **1**. As in other procedures[15,19] that employ diimides to construct *N*-acyl sulfonamides, our method requires reaction times of between 2 and 4 days at room temperature. Entries 6–12 in Table 1 summarize the yields obtained for the acylation of a variety of sulfonamides using the DCC/DMAP combination. It can be seen that reasonable yields are obtained for acylation of all primary sulfonamides investigated. However, secondary sulfonamides investigated here were not acylated under the reported conditions (Table 2). Methylene chloride was found to be a suitable solvent in all cases except during the acylation of Boc-protected sulfanilamide (entry 11), where the addi-

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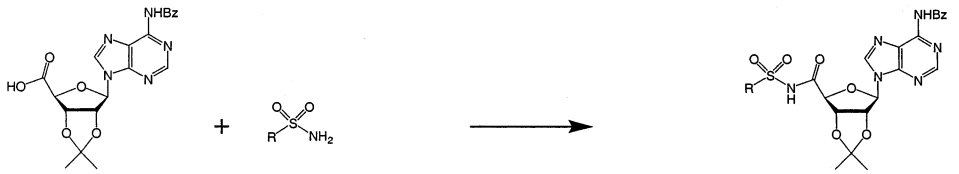
Table 1. Comparison of existing procedures to new procedure



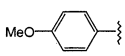
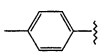
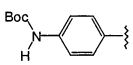
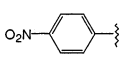
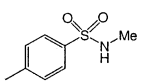
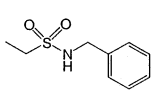
Entry	R=	Reagents	Yield of 2 (%)	Ref
1		a) oxalyl chloride b) KOH	30	14b
2		a) CDI, Δ b) DBU, Δ	35	16
3	Me	a) CDI, Δ b) DBU, Δ	30	16
4		EDC·HCl DMAP (cat)	33	15b
5		EDC·HCl DMAP (1 eq)	40	15a
6	Me	DCC DMAP (1 eq)	95	
7	Et	DCC DMAP (1 eq)	84	
8	*i*-Pr	DCC DMAP (1 eq)	65	
9		DCC DMAP (1 eq)	91	
10		DCC DMAP (1 eq)	93	
11		DCC DMAP (1 eq)	74	
12		DCC DMAP (1 eq)	83	

Table 2. Yields for attempted *N*-acylation of secondary sulfonamides

Entry	Sulfonamide	Reagents	*N*-acylated Product (%)	Recovered Sulfonamide (%)
13		DCC DMAP (1 eq)	0	90
14		DCC DMAP (1 eq)	0	79

tion of either tetrahydrofuran or ethyl acetate in methylene chloride (20% v/v) increased the yield by 10% after 2 days.

This methodology is particularly well suited for the acylation of sulfonamides using 5′-nucleoside carboxylates. The acylation is conducted under neutral condi-

tions with mild reagents. These conditions accommodate the often complex functionalities associated with protected nucleosides. The methodology was found to be quite versatile in that all primary aliphatic and aryl sulfonamides investigated were acylated in moderate to good yield. Finally, the products were easily obtained in high purity by chromatography on silica gel.

General procedure for acylation of a sulfonamide with 1

To an argon purged flame dried flask is added N_6-benzoyl-2′,3′-isopropylidene-5′-carboxylic acid-5′-deoxyadenosine (500 mg, 1.175 mmol), dicyclohexylcarbodiimide (267 mg, 1.293 mmol), 4-dimethylaminopyridine (158 mg, 1.293 mmol) and nosyl sulfonamide (475 mg, 2.351 mmol). The mixture is then dissolved in 11 ml freshly distilled methylene chloride and allowed to stir under an argon atmosphere at room temperature. After 4 days, Amberlite 120H resin is added and the reaction stirred for an additional 15 minutes. After filtering through a glass-fritted funnel, the filtrate is evaporated under reduced pressure and the remaining solid is purified on silica gel (10% acetone/methylene chloride followed by 5% methanol/methylene chloride) to provide 597 mg (83%) of a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.13 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.21 (d, 2H), 8.05 (d, 2H), 7.92 (d, 2H), 7.64 (t, 1H), 7.55 (t, 2H), 6.31 (s, 1H), 5.30 (d, 1H), 5.12 (d, 1H), 4.44 (s, 1H), 1.53 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.89, 162.62, 151.99, 151.47, 150.79, 150.02, 148.37, 143.65, 133.51, 132.41, 128.51, 128.47, 128.26, 125.26, 123.32, 112.70, 90.26, 88.51, 84.27, 83.84, 26.86, 25.09.

FAB-MS (positive mode): m/z calcd for $C_{26}H_{24}N_7O_9S$ (MH^+): 610.1356; found: 610.1356.

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