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Facile preparation of *N*-acylsulfonamides by using sulfonyl isocyanate

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Abstract—*N*-Acylsulfonamide is widely used as a carboxylic acid bioisostere. A rapid and mild acyl sulfonamide preparation methodology from carboxylic acid and arylsulfonyl isocyanate in the presence of amine is described. The preparation of biologically active acylsulfonamide by our methodology is also presented.

The *N*-acylsulfonamide group is a versatile functional group, which is used as a carboxylic acid bioisostere in medicinal chemistry. For instance, an acylsulfonamide-bearing leukotriene antagonist, a cyclin-dependent kinase inhibitor, a hepatitis C virus (HCV) NS3 protease inhibitor, and a chemokine receptor inhibitor have recently been reported.[1] The group has a pK_a close to that of carboxylic acids and tetrazoles (pK_a 4–5),[2] which renders it a suitable carboxylic acid surrogate, yet it is stable under physiological conditions as well as chemical transformations. The utility of acylsulfonamide-equipped organocatalysts in certain enantioselective asymmetric reactions has also been reported.[3]

Typically, acylsulfonamide is prepared from the corresponding carboxylic acid and sulfonamide via a condensation reaction. Typical condensation reagents are *N*-ethyl-*N*′-(3,3-dimethylamino)-propylcarbodiimide (WSCDI) or a DCC–DMAP combination[4], 1,1′-carbonyldiimidazole (CDI)[5] or 2-chloro-*N*-methylpyridinium iodide.[6] More reactive carboxylic anhydrides[7] and acid chlorides[8] are also used. An alternative preparation uses sulfonyl chloride and carboxylic amide in the presence of base.[9] More recently, the synthesis of acylsulfonamide from aryl halide and sulfonamide mediated by combination of $Pd(OAc)_2$ and $Mo(CO)_6$ under microwave irradiation was also reported.[10] Although the utility of acylsulfonamide is widely recognized in the medicinal chemistry field, its preparation is sometimes difficult. We present here a mild and rapid preparation method for acylsulfonamides from carboxylic acids using *p*-toluenesulfonyl isocyanate in the presence of amine.[11]

Firstly, carboxylic acid **1a** was treated with *p*-toluenesulfonyl isocyanate in the presence of triethylamine in THF, causing evolution of CO_2. After a few minutes, when CO_2 evolution was complete, sulfonamide **2a** was obtained in 97% yield. As shown in Table 1, various functional groups, such as ester, halide, acetal, and olefin, are tolerant of these mild reaction conditions, and all reactions were completed within 20 min. When *N*-Cbz-L-glutamic acid α-benzyl ester and *p*-toluenesulfonyl isocyanate were allowed to react under these conditions, tosylamide **2f** was obtained quantitatively without the formation of pyroglutamate derivatives, as occurred in previously reported methods.[4] The enantiomeric excess of **2f** was determined by 400 MHz ^{1}H NMR analysis after conversion to the corresponding (*S*)-(α)-methylbenzyl amide after N-methylation using trimethyloxonium tetrafluorobarate.[12] The ee was over 99% and racemization was negligible. It is noteworthy that the highly sterically hindered carboxylic acid **1g** was also converted to the corresponding tosylamide in 81% yield.

There have been reports of racemization at the α-position during acylsulfonamide preparation from carboxylic acid and sulfonamide, because a strong base such

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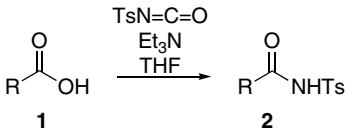
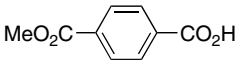
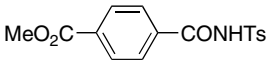
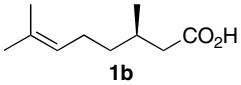
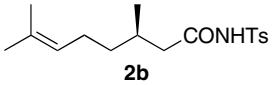
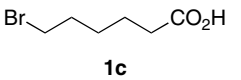
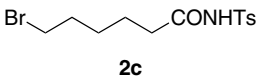
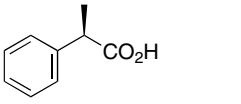
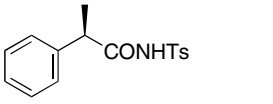
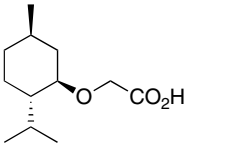
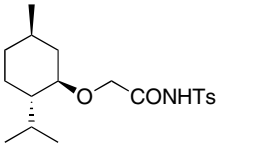
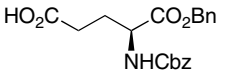
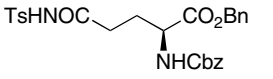
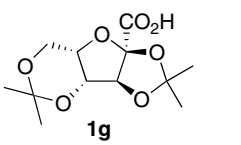
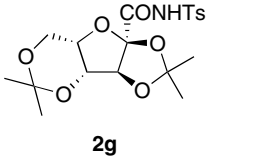
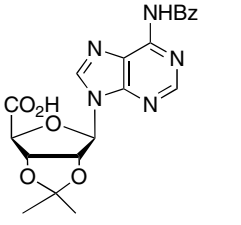
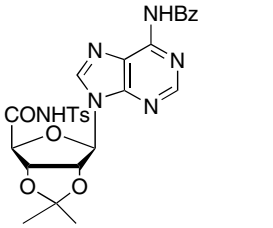
Table 1. The tosylamides preparation from carboxylic acids by *p*-toluenesulfonyl isocyanate



1 2

Substrate	Product	Yield (%)
 **1a**	 **2a**	97
 **1b**	 **2b**	85
 **1c**	 **2c**	96
 **1d**	 **2d**	Quant
 **1e**	 **2e**	83
 **1f**	 **2f**	Quant
 **1g**	 **2g**	81
 **1h**	 **2h**	89

as DMAP[4] or DBU[5] is required together with the condensation reagent. This was prevented by use of a solid–liquid two-phase system[13] or addition of sulfonyl chloride.[9] In our methodology, however, the chirality at the labile stereogenic benzylic center of **2d** remained completely unchanged. The methyl ester of carboxylic acid **1d** was determined by chiral HPLC to be 98% ee (DAICEL CHIRALCEL OJ, hexane/*i*-PrOH 9:1, 0.50 mL/min, 254 nm detection, retention time 9.8 min for (*R*), 11.3 min for (*S*)), and following methylation of **2d** with $TMSCH_2N_2$, *N*-methyl tosylamide was found to be 98% ee (DAICEL CHIRALCEL OJ, hexane/*i*-PrOH 9:1, 0.50 mL/min, 254 nm detection, retention time 17.2 min for (*S*), 20.1 min for (*R*)).

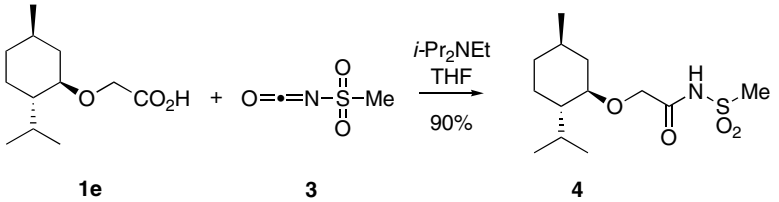
Furthermore, the potentially biologically active nucleoside derivative **2h**, which has been reported by Widlanski to be difficult to synthesize by other methods,[14] was readily prepared using our methodology.

As well as tosyl sulfonamides, other sulfonamides were also prepared using our method. For instance, methylsulfonyl isocyanate **3**, prepared according to Alper's procedure,[15] was allowed to react with carboxylic acid **1e** to give the corresponding sulfonamide **4** in 90% yield (Scheme 1).

Finally, potential antitumor agent diaryl acylsulfonamide **7**[16] was prepared from commercially available acid **5** and 4-chlorophenyl isocyanate **6** in 93% yield in 5 min at 50 °C; the yield was much improved compared to the reported one (Scheme 2).

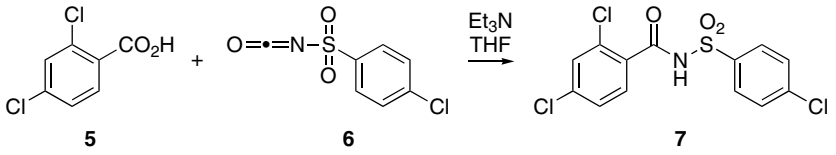
Our *N*-acylsulfonamide preparation method can be carried out under very mild conditions and can be applied to complex molecules. Because acylsulfonamides are wildly used in the medicinal chemistry field, we believe our preparation method will be useful in this area.

General procedure for synthesis of N-acylsulfonamide: Into a solution of acid (1.20 mmol) and triethylamine (0.18 mL, 1.32 mmol) in THF (5 mL), was added dropwise *p*-toluenesulfonyl isocyanate (0.20 mL, 1.32 mmol). The mixture was stirred at room temperature for 30 min under a N_2 atmosphere, and then *N*,*N*′-dimethyl-1,3-propanediamine (0.1 mL) was added to destroy the excess isocyanate. After 10 min, the mixture was diluted with $CHCl_3$ and washed with 1 M HCl aqueous solution. The aqueous layer was extracted with $CHCl_3$ and the combined extracted layers were washed with brine. After drying the extract over Na_2SO_4, the solvent was removed by evaporation. The residue was purified by silica gel column chromatography.



1e **3** **4**

Scheme 1. Preparation of methanesulfonyl amide.



Scheme 2. Preparation of anti-cancer reagent.

It is possible to omit the aqueous work-up; the compound can be purified directly after addition of *N*,*N*′-dimethyl-1,3-propanediamine by silica gel column chromatography.

Acknowledgments

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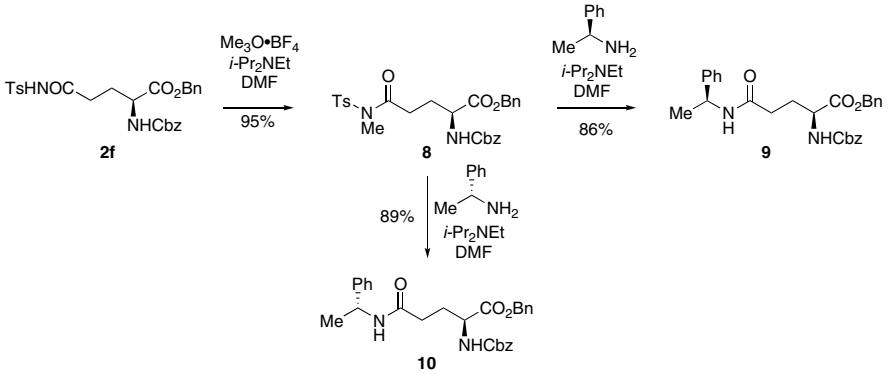
12. The methyl signal of (*S*)-(α)-benzylmethyl amide **9** appeared at 1.45 ppm in $CDCl_3$, whereas the methyl signal of (*R*)-(α)-benzylmethyl amide **10** appeared at 1.43 ppm. The trials of HPLC ee determination of **2f** and **8** by chiral HPLC (CHIRALPAK AS-H, CHIRALPAK AD-H, CHIRALCEL OD-H, CHIRALCEL OJ-H, CHIRALPAK IA, CHIRALPAK IB, CHIRALCEL OB, CHIRALPAK OT, CHIRALPAK OP) were failed.



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