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Synthesis of acyl[^{35}S]sulfonamides: Coupling of high specific activity [^{35}S]methane sulfonamide with acids and acid chlorides

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Direct coupling of high specific activity [^{35}S]methanesulfonamide, generated from [^{35}S]methanesulfonyl chloride and ammonia, with acids and acid chlorides afforded the corresponding [^{35}S]acyl sulfonamides in excellent yields. Examples of high specific activity [^{35}S]acyl sulfonamides were prepared containing functionality that can be further elaborated through carbon–carbon or carbon–nitrogen bond forming reactions.

Keywords: [^{35}S]methanesulfonamide; [^{35}S]methanesulfonyl chloride; acyl sulfonamide

Introduction

Radioligands labeled with high specific activity sulfur (greater than 750 Ci/mmol) have proven to be very useful tools in biological applications, such as receptor binding and receptor occupancy, and offer advantages over ^{3}H or ^{125}I labeled radioligands.[1] Although the preparation of several high specific activity [^{35}S]sulfonamides[2] and [^{35}S]sulfones[3] have been reported, we sought to expand the potential functionality of sulfur-35 labeled biologically relevant molecules to include acyl sulfonamide containing radioligands. Acyl sulfonamides can be formed by reaction of an amide with methanesulfonyl chloride; however, the rigorous reaction conditions (NaH, refluxing conditions, and long reaction times) precludes this methodology from being adapted to sulfur-35 syntheses.[4] Reports have also shown that methanesulfonamide can generally be coupled with acids and acid chlorides by using EDC, DCC, and DMAP to form acyl sulfonamides in good yields.[5] Herein, we report the synthesis of high specific activity [^{35}S]acyl sulfonamides through the coupling of high specific activity [^{35}S]methanesulfonamide with representative acids and acid chlorides.

Experimental

General experimental procedure

All reagents and solvents used were of ACS grade or higher and used without further purification. [^{35}S]Methanesulfonate (1400 Ci/mmol) was purchased from Perkin-Elmer. All unlabeled compounds were prepared and structurally identified by NMR and LC/MS analysis. Reactions were monitored by HPLC with comparisons made with authentic unlabeled materials. Final labeled compounds were identified by co-elution with authentic unlabeled compounds. Radiochemical purities were determined by HPLC (Rainin Model SD-200, Varian PDA-2 detector, and a Beta-Ram detector (IN/US Systems Inc.)) using the method as described. (Luna C18(2) 4.6 × 150 column; mobile phase A = 0.1% TFA in water, B=CH_3CN; gradient 30–100% B over 20 min.) Semi-preparative chromatography was performed using Rainin Model SD-200 pumps, Rainin UV detector: 254 nm, and Zorbax SB-C8 9.4 × 250 mm column. General purification method A (A = 0.1% TFA in water, B=CH_3CN; gradient 20–80% B over 45 min; flow rate 5 mL/min). LC/MS analyses were performed on a Finningan LXQ mass spectrometer. NMR spectra were recorded on Bruker Avance II 300 MHz spectrometer. Liquid scintillation counting was performed on a Perkin-Elmer Tri-Carb Model 2900Tr. [^{35}S]Methanesulfonyl chloride was prepared from reaction of oxalyl chloride with commercially available [^{35}S]methanesulfonate according to the published procedure.[2]

Synthesis of [^{35}S]methanesulfonamide

A methylene chloride stock solution of [^{35}S]methanesulfonyl chloride (2.0 mCi/mL, 2 mL) was distilled at atmospheric pressure (68 °C) by using a water cooled short-path distillation apparatus with 2-inch vigreux column to a volume of approximately 200 uL. The concentrated solution was added by syringe to 250 uL of saturated ammonia/methylene chloride,† and the mixture stirred for 1.5 h at room temperature. The reaction mixture was concentrated by nitrogen stream to approximately 100 uL (1.85 mCi) and aliquoted as needed.

Synthesis of 4-iodo-N-(methyl[^{35}S]sulfonyl)benzamide (representative procedure of coupling of acid with [^{35}S]methanesulfonamide)

4-Iodobenzoic acid (3 mg, 0.012 mmol), EDC (3 mg, 0.016 mmol), and DMAP (4 mg, 0.033 mmol) were combined in methylene chloride (200 uL). [^{35}S]methanesulfonamide (1.85 mCi) in methylene chloride (100 uL) was added, and the mixture stirred overnight at room temperature. HPLC analysis showed 85% radiochemical conversion to the desired [^{35}S]acyl sulfonamide. The mixture was diluted with methanol and water and purified by semi-preparative HPLC (method A) to afford

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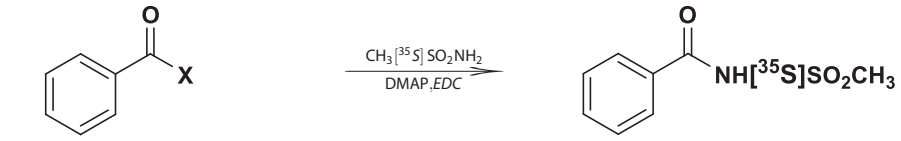
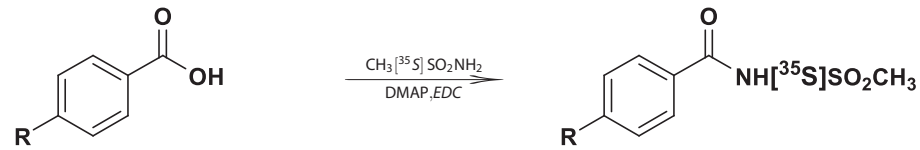
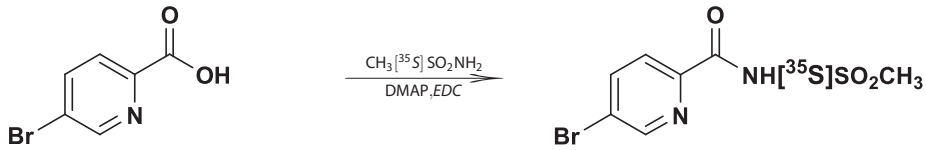
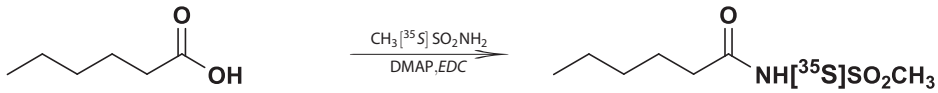
† *It is important to use ammonia/methylene chloride solution as ammonia/dioxane or ammonia/THF led to significant hydrolysis of the [^{35}S]methanesulfonyl chloride during [^{35}S]methanesulfonamide formation. Any remaining excess ammonia may react to form unlabeled primary amide, which is easily separable by preparative HPLC.*

Table 1. Syntheses of [35S]acyl sulfonamides

	Radiochemical yield (%)*
 X = OH, Cl	85, 72
 R = I, OCH3	78, 72
	78
	75

*Isolated radio chemical yields

1.56 mCi (78% isolated radiochemical yield) of 4-iodo-*N*-(methyl[^{35}S] sulfonyl)benzamide.

Synthesis of N-(methyl[^{35}S]sulfonyl)benzamide (representative procedure of coupling of acid chloride with [^{35}S]methanesulfonamide)

Benzoyl chloride (3.5 mg, 0.025 mmol) and Hunig's base (8 uL, 0.045 mmol) were combined in methylene chloride (200 uL). [^{35}S]methanesulfonamide (2 mCi) in methylene chloride (100 uL) was added, and the mixture stirred overnight at room temperature. HPLC analysis showed 87% radiochemical conversion to the desired [^{35}S]acyl sulfonamide. The mixture was diluted with methanol and water and purified by semi-preparative HPLC (method A) to afford 1.45 mCi (72% isolated radiochemical yield) of *N*-(methyl[^{35}S]sulfonyl)benzamide.

Results and discussion

High specific activity [^{35}S]methanesulfonamide was prepared in excellent yields from [^{35}S]methanesulfonyl chloride by quenching the sulfonyl chloride with a saturated ammonia/methylene chloride solution. Following concentration, which removed excess ammonia, a stock solution of the [^{35}S]methanesulfonamide in methylene chloride was generated. Subsequent coupling of the [^{35}S]methanesulfonamide with aromatic and aliphatic acids or acid chlorides proceeded smoothly and efficiently using EDC and DMAP or Hunig's base, respectively, in methylene chloride, affording the corresponding [^{35}S]acyl sulfonamides in high yields. A summary of our results (Table 1) demonstrates that the yields of [^{35}S]acyl sulfonamides in all cases were high for both aryl and aliphatic acid derivatives. Additionally, [^{35}S]acyl sulfonamides were formed containing bromide, iodide, and methoxy (a latent potential triflate group),[3] which allow further functionalization through Pd catalyzed carbon–carbon or carbon–nitrogen couplings. A halogenated nicotinic acid derivative was also formed in high yield (entry 3). Isolation of the [^{35}S]acyl sulfonamides from the reaction mixtures by semi-preparative HPLC was straightforward and afforded clean [^{35}S]products with greater than 98% radiochemical purity.

Conclusion

We have developed a synthetic methodology that provides facile access to high specific activity [^{35}S]acyl methanesulfonamides for biological applications by direct coupling of aryl and aliphatic carboxylic acids and acid chlorides to [^{35}S]methanesulfonamide under mild conditions. These coupling reactions are high yielding, robust, and tolerant of functionality. This flexibility allows further elaboration to tailor the radioligand to suit the needs of the biological study.

Conflict of Interest

The authors did not report any conflict of interest.

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