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Efficient synthesis of arylsulfamides by reaction of amines with arylsulfamoyl imidazolium triflate

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Abstract—Arylsulfamoyl imidazolium triflates, readily prepared from the corresponding chlorides, react with amines under neutral conditions to form arylsulfamides in high yields. This methodology, which contrasts with the slow and inefficient reactions of amines with arylsulfamoyl chlorides, is applied to the synthesis of arylsulfamide **3a**, a bioisotere of muraglitazar.

The peroxisome proliferate-activated receptors (PPARs) are members of the nuclear receptor superfamily that play key roles in the regulation of lipid metabolism and storage.[1] The three mammalian PPARs (PPARα, PPARγ, and PPARδ), identified thus far, are important molecular targets for the development of drugs for the treatment of human metabolic diseases, inflammation, and cancer.[1,2] A number of PPAR agonists (α-, γ-, and dual-α/γ selective) have been identified for clinical development.[3–6] Two thiazolidinediones, rosiglitazone[7] and pioglitazone,[8] represent a novel class of insulin-sensitizing PPARγ agonists and are used clinically as antidiabetic drugs. Members of the fibrate drug class, such as fenofibrate and bezafibrate, which lower triglycerides and elevate HDL levels, are weak PPARα agonists and are used for the treatment of dyslipidemia.[1] Recently, muraglitazar/BMS-298585 (Fig. 1), a novel non-thiazolidinedione PPAR dual-α/γ agonist with efficacious glucose and lipid-lowering activities is in clinical development for the treatment of type 2 diabetes and dislipidemia.[9]

As part of recent studies targeted at the development of potent PPAR ligands, we identified arylsulfamide **3a**, a bioisotere of muraglitazar, as potential PPAR agonist. In designing a synthesis of this substance, we recognized that the preparation of alkylsulfamides is generally performed by reacting the corresponding alkylsulfamoyl chlorides with amines in the presence of base, the typical Schotten-Bauman process.[10] Following this protocol, we attempted to prepare arylsulfamide **3a** by reacting amino ester **1a**[9] with arylsulfamoyl chloride **2a**[11] in the presence of Hunig's base (Scheme 1). However, the yield of this process was disappointingly low (less than 10%). Attempts to improve the efficiency of this reaction by varying the base and solvent were unsuccessful. We believe that the low yield is due in part to a side reaction promoted by base or liberated chloride nucleophile. To

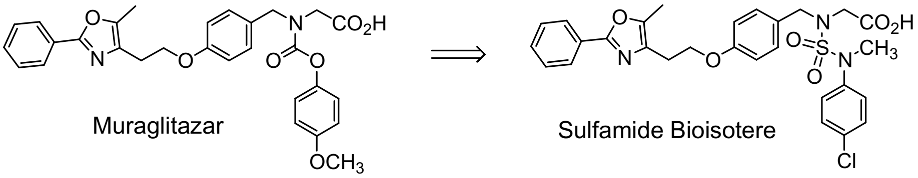

Figure 1. Muraglitazar and its sulfamide bioisotere.

Keywords: Arylsulfamide; Arylsulfamoyl chloride; Arylsulfamoyl imidazolium triflate; PPAR agonist.

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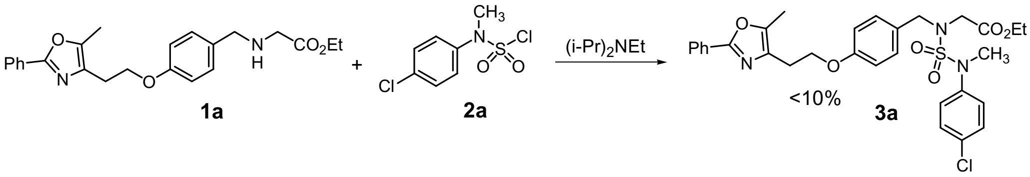
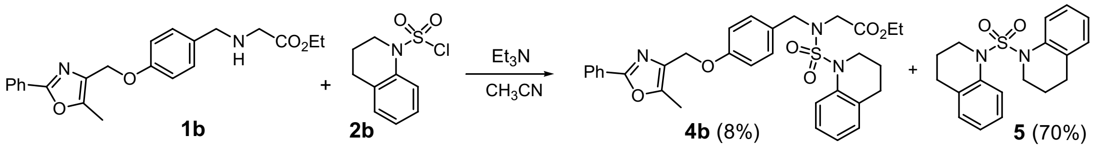


Scheme 1.

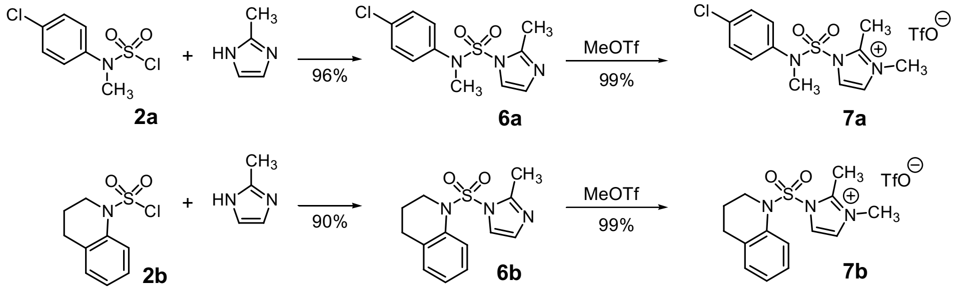


Scheme 2.

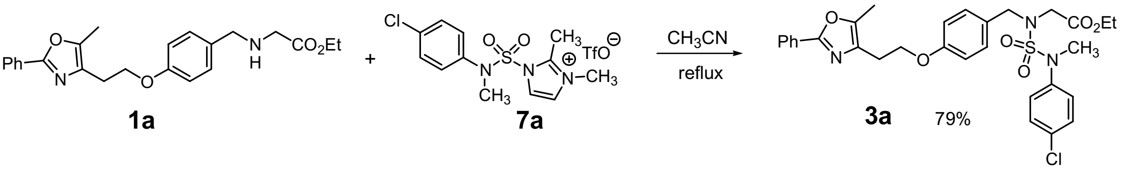
probe this issue further, reaction of arylsulfamoyl chloride **2b** with amine **1b** was carried out (Scheme 2). This process produced a small amount of desired sulfamide **4b** (8%) and the undesired symmetrical sulfamide **5** as a major (70%) product.

The need for arylsulfamide **3a** in our PPAR agonist studies stimulated a search for an efficient procedure for its preparation. Our observations suggested that it would be advantageous to have a sulfamoylating agent that does not possess a nucleophilic leaving group and that reacts with amines under mild conditions in the absence of added base. A survey of the literature revealed that arylsulfonyl imidazolium triflates are superior sulfamoylating agents as compared to arylsulfonyl chlorides.[12] A recent report, describing the synthesis of alkylsulfamides, utilized highly reactive alkylsulfamoyl imidazolium triflates that are prepared from 1,1′-sulfonyldiimidazole.[13] Unfortunately, 1,1′-sulfonyldiimidazole is a very expensive starting material (1 g = ca. $55 USD, Aldrich) and, as a result, it is not applicable to large scale syntheses. In addition, there are no reported examples of the preparation or reactions of arylsulfamoyl imidazolium triflates.

Consequently, studies to develop new methods to prepare arylsulfamoyl imidazolium triflates were initiated. We quickly found that arylsulfamoyl 2-methylimidazole **6a** is easily prepared from the corresponding, readily available arylsulfamoyl chloride **2a** by reaction with 2-methylimidazole in acetonitrile (Scheme 3). Subsequent methylation of the imidazole nitrogen of **6a** with MeOTf produced arylsulfamoyl imidazolium triflate **7a**.[14] Importantly, reaction of triflate **7a** with amino ester **1a** proceeded to cleanly afford the desired arylsulfamide **3a** in high yield (79%) (Scheme 4).[15] This result demonstrates that a change of the sulfamoylating agent from the arylsulfamoyl chloride **2a** to the more reactive arylsulfamoyl imidazolium triflate **7a** greatly enhances reactivity toward the amine **1a**.



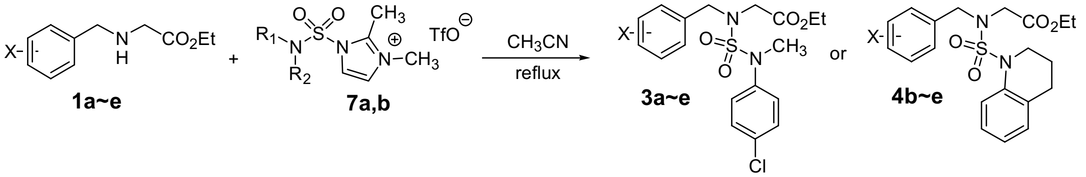
Scheme 3.

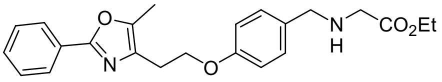
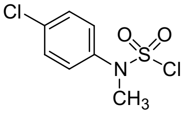
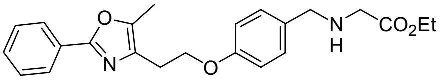
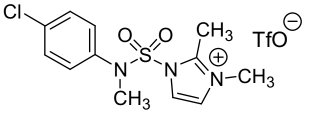
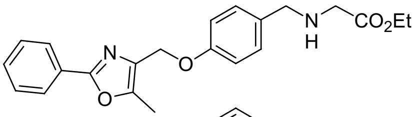
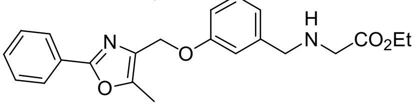
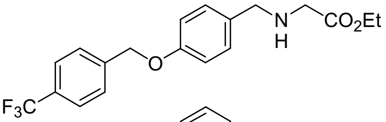
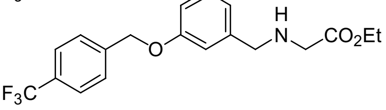
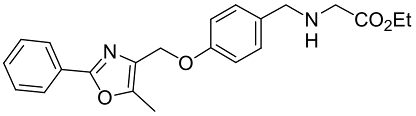
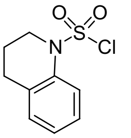
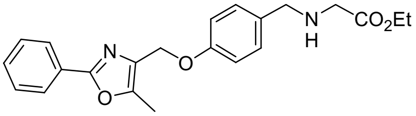
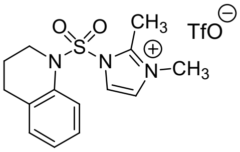
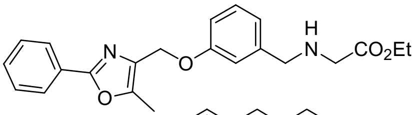
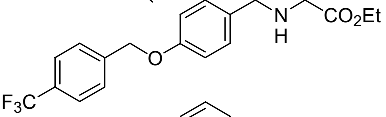
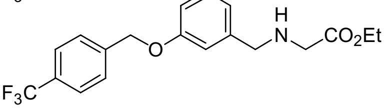


Scheme 4.

In order to test the generality of the new methodology, we studied reactions of arylsulfamoyl imidazolium triflate **7a** with various amines. In nearly all cases, reactions took place to generate arylsulfamides[15] in high yields (Table 1). Tetrahydroquinolinesulfonyl imdazolium triflate **7b** was also prepared from the corresponding sulfamoyl chloride **2b** by using the same reaction conditions employed to form **7a**. Reactions of

Table 1. Syntheses of arylsulfamides by reactions of arylsulfamoyl imidazolium triflates with amines



Entry	Amine	Sulfamoylating agent	Yield[a] of sulfamide (%)
1	 **1a**	 **2a**	**3a** (7)
2	 **1a**	 **7a**	**3a** (79)
3	 **1b**	**7a**	**3b** (84)
4	 **1c**	**7a**	**3c** (72)
5	 **1d**	**7a**	**3d** (72)
6	 **1e**	**7a**	**3e** (76)
7	 **1b**	 **2b**	**4b** (8)
8	 **1b**	 **7b**	**4b** (95)
9	 **1c**	**7b**	**4c** (70)
10	 **1d**	**7b**	**4d** (79)
11	 **1e**	**7b**	**4e** (75)

[a] Isolated and purified yields with silica gel chromatography.

7b with amines also provided sulfamides in high yields.

In summary, the above studies have shown that arylsulfamoyl imidazolium triflates can be readily prepared from the corresponding chlorides and that they display high reactivity with amines, in processes carried out under neutral conditions that efficiently generate arylsulfamide. Finally, this methodology was successfully applied to the synthesis of arylsulfamide **3a**, a potential bioisotere of muraglitazar.

Acknowledgements

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14. (a) *N*-Methyl-*N*-(4-chlorophenyl)sulfamoyl-2-methylimidazole (**6a**): To a solution of 2-methylimidazole (5.5 g, 66 mmol) in CH_3CN (50 mL) at 0 °C was slowly added a solution of *N*-methyl-*N*-(4-chlorophenyl)sulfamoyl chloride (**2a**) (7.2 g, 30 mmol) in CH_3CN (15 mL). The mixture was warmed to room temperature and stirred overnight, and concentrated in vacuo. The residue was subjected to silica gel chromatography (Hex–EA = 1:1) affording pure **6a** as a white crystalline solid, 8.2 g (96%). Mp: 82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.33 (s, 3H), 6.91 (s, 1H), 7.03 (d, 2H, $J = 6.60$ Hz), 7.14 (s, 1H), 7.36 (d, 2H, $J = 6.60$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.13, 39.74, 119.63, 127.65, 128.40, 129.87, 134.99, 146.45. (b) *N*-Methyl-*N*-(4-chlorophenyl)sulfamoyl-2,3-dimethylimidazolium triflate (**7a**): To a solution of **6a** (1.46 g, 5.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 0.61 mL (5.36 mmol) of methyl triflate. After being stirred for 2 h at 0 °C, the reaction mixture was concentrated in vacuo to give **7a** (2.29 g, 99%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 3H), 3.55 (s, 3H), 3.96 (s, 3H), 7.19 (s, 1H), 7.30 (s, 1H), 7.43 (d, 2H, $J = 6.70$ Hz), 7.54 (d, 2H, $J = 6.70$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.94, 36.59, 40.44, 120.68, 122.84, 129.14, 130.27, 136.00, 136.67, 146.50.
15. Typical procedure for arylsulfamide from arylsulfamoyl imidazolium triflate and amine: A solution of arylsulfamoyl imidazolium triflate **7a** (4.95 g, 11 mmol) and amine **1b** (3.80 g, 10 mmol) in CH_3CN (40 mL) was stirred overnight at reflux. The mixture was concentrated in vacuo giving a residue, which was subjected to silica gel chromatography (Hex/EA = 4:1) affording sulfamide **3b** (4.91 g, 84%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J = 7.15$ Hz), 2.44 (s, 3H), 3.27 (s, 3H), 3.81 (s, 2H), 4.16 (q, 2H, $J = 7.15$ Hz), 4.42 (s, 2H), 4.98 (s, 2H), 6.95–8.03 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.54, 14.15, 38.82, 47.38, 52.00, 61.32, 62.30, 115.05, 126.14, 127.14, 127.34, 127.42, 128.02, 128.72, 129.19, 130.10, 130.15, 132.78, 136.64, 141.23, 147.15, 158.06, 160.06, 169.50. MS *m*/*z* 583 (M^+, 3), 379 (6), 172 (100). Sulfamide **3c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J = 7.15$ Hz), 2.24 (s, 3H), 3.28 (s, 3H), 3.85 (s, 2H), 4.16 (q, 2H, $J = 7.15$ Hz), 4.47 (s, 2H), 4.96 (s, 2H), 6.85–8.02 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.53, 14.14, 38.83, 47.60, 52.55, 61.34, 62.21, 114.73, 114.89, 121.31, 126.16, 127.47, 128.00, 128.70.