

Lanthanide triflate catalyzed generation of *N*-acyliminium ions from α -amido sulfones: the synthesis of (1-alkyl-1-aryl)methyl phenyl sulfones

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Abstract—The reaction of α -amido sulfones with various aromatic and heteroaromatic compounds in the presence of a catalytic amount of lanthanide triflate provides a facile route for the synthesis of (1-alkyl-1-aryl)methyl phenyl sulfones.

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Nucleophilic addition to imines and their derivatives is useful for the synthesis of amine derivatives.¹ The main difficulties encountered in utilizing these addition reactions due to the low electrophilic aptitude of the C=N bond have been augmented by activation with Lewis acids,² the presence of electron-withdrawing substituents at the nitrogen atom,^{3,4} and the in situ formation of *N*-acyliminium ions⁵ from α -amido sulfones.⁶ The ease in preparation of various α -amido sulfones has made the reactions involving *N*-acyliminium ions the most attractive route for introducing various substituents at the α -carbon of an amine.

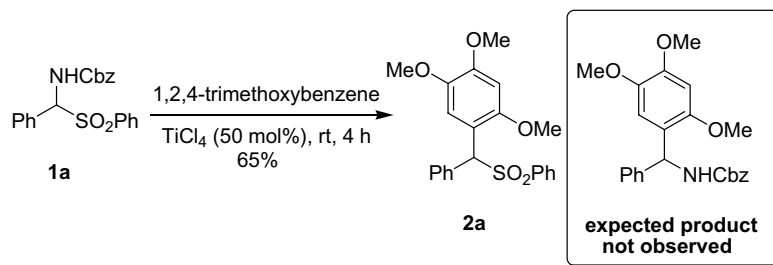
Petrini and co-workers demonstrated that the *N*-acyliminium ions, generated from α -amido sulfones with TiCl₄ at low temperature, reacted with various nucleophiles such as allyltrimethylsilane, enol derivatives, aromatic and heteroaromatic compounds and organometallic reagents to give the expected C–C bond formation products.⁷ A recent publication by the same research group on the Friedel–Crafts reaction of indoles with α -amido sulfones promoted by Montmorillonite K-10 giving the unexpected 3-(1-arylsulfonylalkyl)indoles prompted us to report our results in this area.⁸

Our work started a few years ago with attempts to perform the Friedel–Crafts alkylation using α -amido sulfones mediated by mild Lewis acids, particularly the lanthanide triflates. In a preliminary study, α -amido sulfone **1a**^{6b,9} was treated with 50 mol% of TiCl₄ in CH₂Cl₂ at room temperature for 15 min in order to preform the *N*-acyliminium ion. 1,2,4-Trimethoxybenzene was added to the mixture, and the reaction was allowed to proceed at rt for 4 h. In contrast to Petrini's work,^{7d} we obtained sulfone **2a** as the product without any indication of formation of the expected adduct (Scheme 1). The use of 1 equiv of TiCl₄ led to a low yield of **2a** (42%). Employing the conditions reported by Petrini^{7d} (2 equiv TiCl₄, CH₂Cl₂, –78 °C) with our substrates, no identifiable products could be isolated, and all of the 1,2,4-trimethoxybenzene was recovered. Our results are similar to those reported by Petrini using Montmorillonite K-10 as the Lewis acid.⁸ A number of Lewis acids were screened (Table 1). In the absence of any Lewis acid, no product could be detected. It was found that among the non-lanthanide Lewis acids screened (entries 1–3 and 7–9), BF₃–Et₂O and In(OTf)₃ performed equally well. For the lanthanide triflates (entries 4–6) a catalytic amount (20 mol%) of Yb(OTf)₃ gave a good yield of sulfone **2a**, Table 1.^{10,11} Ytterbium triflate was used to study the scope of this reaction due to the ease of handling the reagent and the reaction in general was much cleaner.

The reaction of various α -amido sulfones with 1,2,4-trimethoxybenzene gave (1-alkyl-1-aryl)methyl phenyl

Keywords: *N*-Acyliminium ions; Lanthanide triflates; Catalytic reactions.

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Scheme 1.

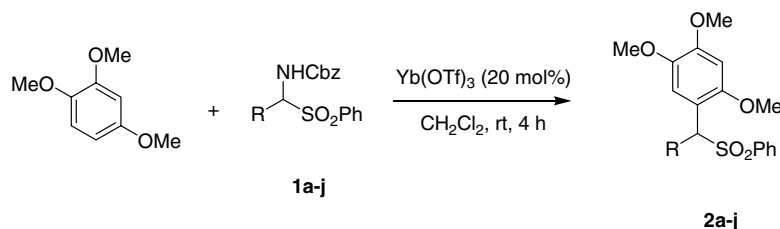
Table 1. Lewis acid optimization

Entry	Lewis acid (mol%)	Yield (%)
1	TiCl ₄ (50)	65
2	BF ₃ –Et ₂ O (50)	72
3	In(OTf) ₃ (20)	74
4	Yb(OTf) ₃ (20)	76
5	Sm(OTf) ₃ (20)	60
6	Hf(OTf) ₄ (20)	55
7	Cu(OTf) ₂ (20)	49
8	Sc(OTf) ₃ (20)	44
9	Sn(OTf) ₂ (20)	19

sulfones in good yields (Table 2). The reaction of α -amido sulfone **1j** (Table 2, entry 10) gave a low yield of **2j** due to competing proton loss from the firstly formed *N*-acyliminium ion intermediate to yield the correspond-

ing enamine in 47% yield. The structure of compound **2j** was confirmed by single crystal X-ray diffraction analysis (Fig. 1).¹²

The synthetic utility of this process was further demonstrated by the reaction of α -amido sulfones **1a,b** and **1e** with other aromatic and heteroaromatic compounds. The reaction gave moderate to good yields of the corresponding adducts (Table 3). Activated 1,3-dimethoxybenzene led to moderate to good yields of the sulfone products (entries 4, 8 and 12). However the reaction of **1a** with less activated aromatic compounds, that is, anisole and 1,4-dimethoxybenzene resulted in low yields, 11% and 13%, respectively. Heteroaromatic compounds **3a–c** gave lower yields than the activated aromatic compound **3d**. This may be due to complexation between the heteroaromatic compound and the Lewis acid which inhibits further reaction. It should be noted that the reaction of *N*-methylindole with α -amido sulfones **1a,b** and **1e** under our catalytic conditions yielded the corresponding phenyl sulfonyl products **2k**, **2o** and **2s** in 48%, 40% and 43% yields, respectively. We believe that the reaction mechanisms that are involved in our study are similar to those reported by Petrini.⁸

Table 2. Reactions of α -amido sulfones **1a–j** with 1,2,4-trimethoxybenzene promoted by Yb(OTf)₃¹⁰

Entry	α -Amido sulfone		Sulfone	Yield ^a (%)
	1a–j	R		
1	1a	Ph	2a	76
2	1b	Ph(CH ₂) ₂	2b	84
3	1c	Et	2c	74
4	1d	CH ₃ (CH ₂) ₆	2d	58
5	1e	CH ₂ =CH(CH ₂) ₈	2e	84
6	1f	<i>i</i> -Pr	2f	68
7	1g	Et ₂ CH	2g	76
8	1h	<i>sec</i> -Bu	2h	45
9	1i	<i>c</i> -C ₆ H ₁₁	2i	53
10 ^b	1j	Ph ₂ CH	2j	27

^a Isolated yields after chromatographic purification.

^b Competing formation of the enamine derivative, Ph₂C=CHNHCbz, (47%) after benzenesulfinic acid was eliminated from the α -amido sulfone occurred.

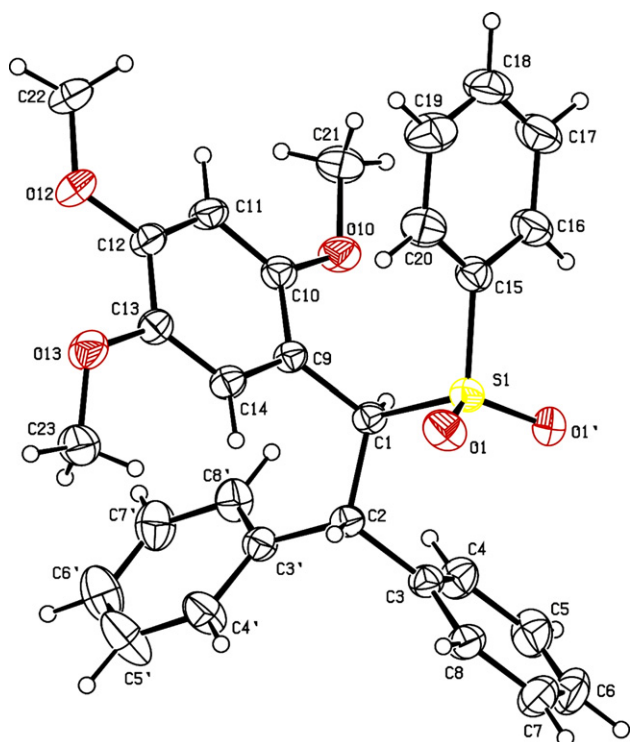


Figure 1. ORTEP plot of the X-ray crystal structure of compound **2j**.

Table 3. Reactions of α -amido sulfones **1a–b** and **1e** with various aromatic and heteroaromatic compounds promoted by Yb(OTf)₃¹⁰

	$\begin{array}{ccc} \text{NHCbz} & & \text{Ar} \\ & \xrightarrow{\text{ArH 3}} & \\ \text{R}-\text{C}-\text{SO}_2\text{Ph} & \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt, 4 h}]{\text{Yb(OTf)}_3 (20 \text{ mol}\%)} & \text{R}-\text{C}-\text{SO}_2\text{Ph} \\ \mathbf{1} & & \mathbf{2k-v} \end{array}$			
	1a R = Ph 1b R = Ph(CH ₂) ₂ 1e R = CH ₂ =CH(CH ₂) ₈	3a ArH = N-Methylindole 3b ArH = 2-Methylfuran 3c ArH = Thiophene 3d ArH = 1,3-Dimethoxybenzene		
Entry	α -Amido sulfone	ArH	Sulfone	Yield ^a (%)
1	1a	3a	2k	48
2		3b	2l	25
3		3c	2m	55
4		3d	2n	62
5	1b	3a	2o	40
6		3b	2p	32
7		3c	2q	23
8		3d	2r	50
9	1e	3a	2s	43
10		3b	2t	56
11		3c	2u	7
12		3d	2v	68

^a Isolated yields after chromatographic purification.

In conclusion, we have demonstrated that the reaction of α -amido sulfones with aromatic and heteroaromatic compounds using Yb(OTf)₃ as the catalyst is quite general and the products are (1-alkyl-1-aryl)methyl phenyl sulfones. The reactions took place under mild reaction

conditions at ambient temperature. Further investigation of the reaction under other conditions is currently in progress in our laboratory.

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 - Typical experimental procedure:* The α -amido sulfone (1 mmol) in a 50 mL round-bottomed flask was placed in an ALDRICH Atmos bag and the bag was evacuated and flushed with argon gas three times. Yb(OTf)₃ (20 mol %) was placed into the same round-bottom flask before it was stoppered with a septum. Dried CH₂Cl₂ (10 mL) was added into the reaction flask and the reaction mixture was stirred at room temperature for 15 min. To the resulting pale yellow solution was added dropwise an aromatic compound (1 mmol) and stirring was continued at room temperature (32 °C) for 4 h, followed by quenching with water (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL), brine (10 mL), dried (MgSO₄) and filtered. The solvent was removed (aspirator then vacuo) to give a crude product, which was purified by radial chromatography.
 - All isolated compounds were characterized by means of spectroscopic techniques (¹H NMR, ¹³C NMR, IR, MS). Molecular formulae of new compounds were confirmed by either HRMS or elemental analysis. Spectral data of known compounds were compared with those of compounds previously reported.
 - X-ray crystal data for **2j**: C₂₉H₂₈O₅S·CH₂Cl₂, *M_r* = 573.54, triclinic, space group *P1*, *a* = 11.4682(6), *b* = 12.0578(4), *c* = 12.4248(7) Å, α = 106.755(3)°, β = 116.559(2)°, γ = 91.467(3)°, *V* = 1447.4(1) Å³, *T* = 298(2) K, *Z* = 2, *D_c* = 1.316 g cm⁻³, μ = 0.334 mm⁻¹, a total of 10,426 reflections were collected and 5482 were unique. *R*1 = 0.0663 [*I* > 2σ(*I*)], *wR*2 = 0.1946 (all data). Crystallographic data (excluding structure factors) for compound **2j** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 632874. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).