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Convenient Synthesis of Salicylanilide Sulfonates from 1,2,3-Benzotriazin-4(3*H*)-ones and Organosulfonic Acids *via* Denitrogenative Cross-Coupling

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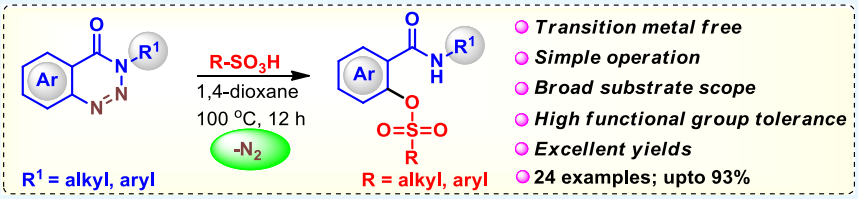

ABSTRACT: An efficient and straightforward approach to synthesize salicylanilide aryl and alkyl sulfonates from 1,2,3-benzotriazin-4(3*H*)-ones and organosulfonic acids is described. This protocol is operationally simple and scalable, exhibits a broad substrate scope with high functional group tolerance, and affords the desired products in good to high yield. Application of the reaction is also demonstrated by converting the desired product to synthetically useful salicylamides in high yields.

INTRODUCTION

Sulfonate ester is one of the key functional groups that received paramount attention owing to their diverse applications in various fields like synthetic chemistry,[1] material science,[2] and pharmaceutical chemistry.[1d] They have also been explored as synthetic auxiliaries, intermediates, protecting groups, and activating groups.[1c] Furthermore, sulfonate ester derivatives have been utilized as the bifunctional DNA alkylating agents (such as busulfan and treosulfan),[3] monoamine oxidase A inhibitors,[4] $P2X_7$ receptor antagonist,[5] phospho-STAT3 inhibitor,[6] and antimicrotubule agents with antibacterial and antifungal properties (*e.g.*, secnidazole sulfonate)[7] as shown in Figure 1, in clinical settings. As a result, the creation of these bioactive molecules containing sulfonate esters is in great demand.

In recent years, metal-catalyzed denitrogenative annulation and cross-coupling reactions of 1,2,3-benzotriazin-4(3*H*)-ones have emerged as an effective protocol to prepare heterocycles and *ortho*-substituted benzamide derivatives.[8] Conversely, such types of reactions in the absence of metal catalysts are hardly studied.[9,10] Literature report reveals that acid-mediated denitrogenative cross-coupling reactions of 1,2,3-benzotriazin-4(3*H*)-ones in the absence of metal catalysts have been reported but remain underdeveloped.[10]

For instance, Raffa's research group reported the acetic acid-mediated synthesis of 2-iodobenzamides in the presence of potassium iodide.[10a] Subsequently, Kishore and colleagues discovered the formation of 2-azido benzamide intermediates during the synthesis of 4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones.[10b] Tang *et al.* demonstrated an organic-dye catalyzed denitrogenative phosphorylation of 1,2,3-benzotriazin-4(3*H*)-ones.[9] Meanwhile, we also described trifluoroacetic acid-mediated *ortho*-hydroxylated benzamide synthesis from 1,2,3-benzotriazin-4(3*H*)-ones.[11] More recently, acid-mediated heteroannulation of benzotriazinones using sodium sulfide to synthesize benzo[*c*][1,2]dithiol-3-ones was reported by the research group of Zhou.[12]

In the past few years, we have been investigating denitrogenative cross-coupling reactions of 1,2,3-benzotriazin-4(3*H*)-ones to prepare *ortho*-substituted benzamides.[13] During our studies on the synthesis of *ortho*-hydroxylated benzamides, we discovered that the reaction of 1,2,3-benzotriazin-4(3*H*)-one (**1a**) with *para*-toluenesulfonic acid (*p*-TSA) (**2a**) yields (phenylcarbamoyl)phenyl 4-methyl benzenesulfonate **3a** in a 65% yield.[11] This result is noteworthy because the metal-free approaches toward the direct arylation of organosulfonic acids are scarcely studied, particularly the synthesis of *ortho*-sulfonylated benzamides from 1,2,3-benzotriazin-4(3*H*)-ones has not been reported.[14] Representative examples include a metal-free arylation of oxygen nucleophiles using diaryliodonium salts in the presence of a base by the research group of Olofsson (Scheme 1a)[15] and an efficient iodobenzene-catalyzed synthesis of aryl sulfonate esters from aminoquinolines by Shen and co-workers (Scheme 1b).[16] Given the

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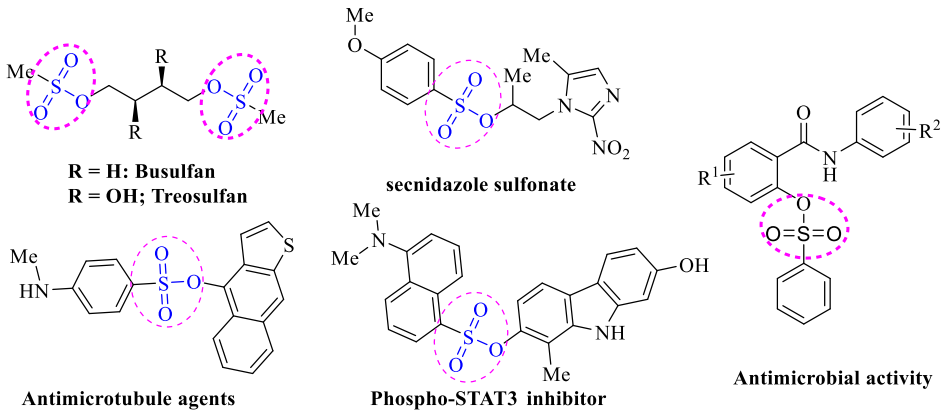
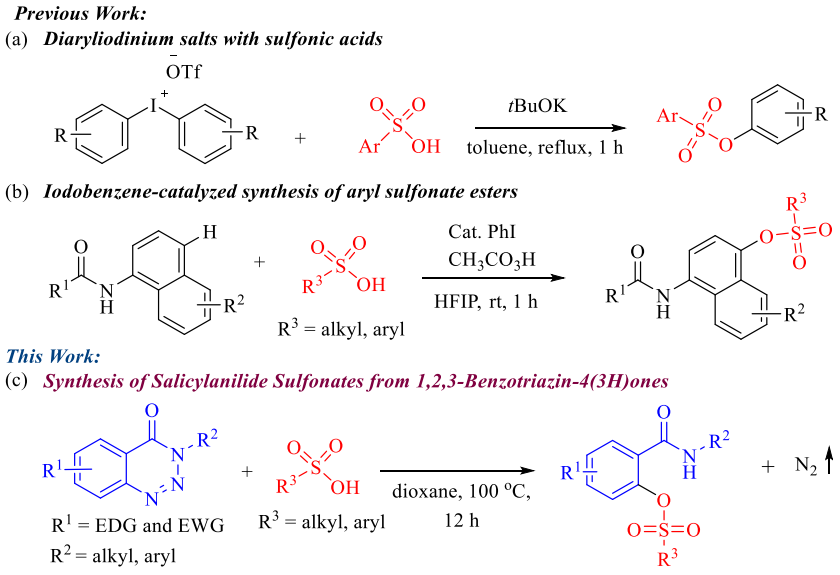


Figure 1. Selective examples of bioactive scaffolds containing sulfonate ester core.

Scheme 1. Strategies toward the Synthesis of Sulfonate Esters

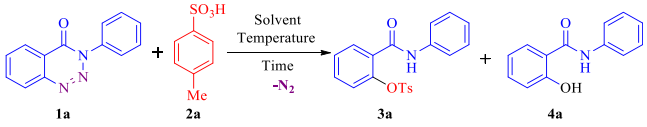


significance of sulfonate esters in bioactive molecules and the utility of 1,2,3-benzotriazin-4(3*H*)-ones in the acid-mediated cross-coupling reactions, we have investigated the synthesis of *ortho*-sulfonylated benzamides. It's worth mentioning that this reaction has a broad substrate scope and gives the desired products in good to high yields under mild conditions.

RESULTS AND DISCUSSION

We continued our investigation on the denitrogenative *ortho*-sulfonylation reaction of 1,2,3-benzotriazin-4(3*H*)-one **1a** using *p*-TSA **2a** as the coupling partner (Table 1). We initially screened the reaction of **1a** and **2a** with different solvents at 80 °C for 12 h (entries 2−6). Among the solvents that we tested, 1,4-dioxane gave **3a** in 72% yield, while the remaining solvents such as toluene, tetrahydrofuran (THF), 1,2-dichloroethane (DCE), and xylene furnished the desired product in moderate yields. Finally, upon increasing the reaction temperature to 100 °C and the *p*-TSA equivalent to 1.5, the reaction yielded **3a** in high yield (98%; entry 8). It is important to mention that a minor amount (7−11%) of *ortho*-hydroxylated benzamide **4a** was also observed while carrying out the reaction using toluene, DCE, and xylene as solvents (entries 2, 4, and 5, respectively).

Table 1. Optimization Reaction Conditions[a]



entry	p-TSA, **2a** (equiv)	solvent	*T* (°C)	time (h)	**3a** (%)[b]	**4a** (%)
1	1.0	toluene	100	12	65	25
2	1.0	toluene	80	12	54	8
3	1.0	THF	80	12	47	
4	1.0	DCE	80	12	41	7
5	1.0	xylene	80	12	45	11
6	1.0	dioxane	80	12	72	
7	1.5	dioxane	80	12	81	
8	**1.5**	**dioxane**	**100**	**12**	**98 (92)**[c]	
9	2.0	dioxane	100	12	96	trace
10	1.0	dioxane	100	12	89	
11	1.5	dioxane	Rt	12		

[a]Reaction conditions are as follows: **1a** (0.40 mmol), **2a** (1.0−2.0 equiv.), solvent (3 mL), temperature (°C), and time (h). [b]GC-MS yields. [c]Isolated yield.

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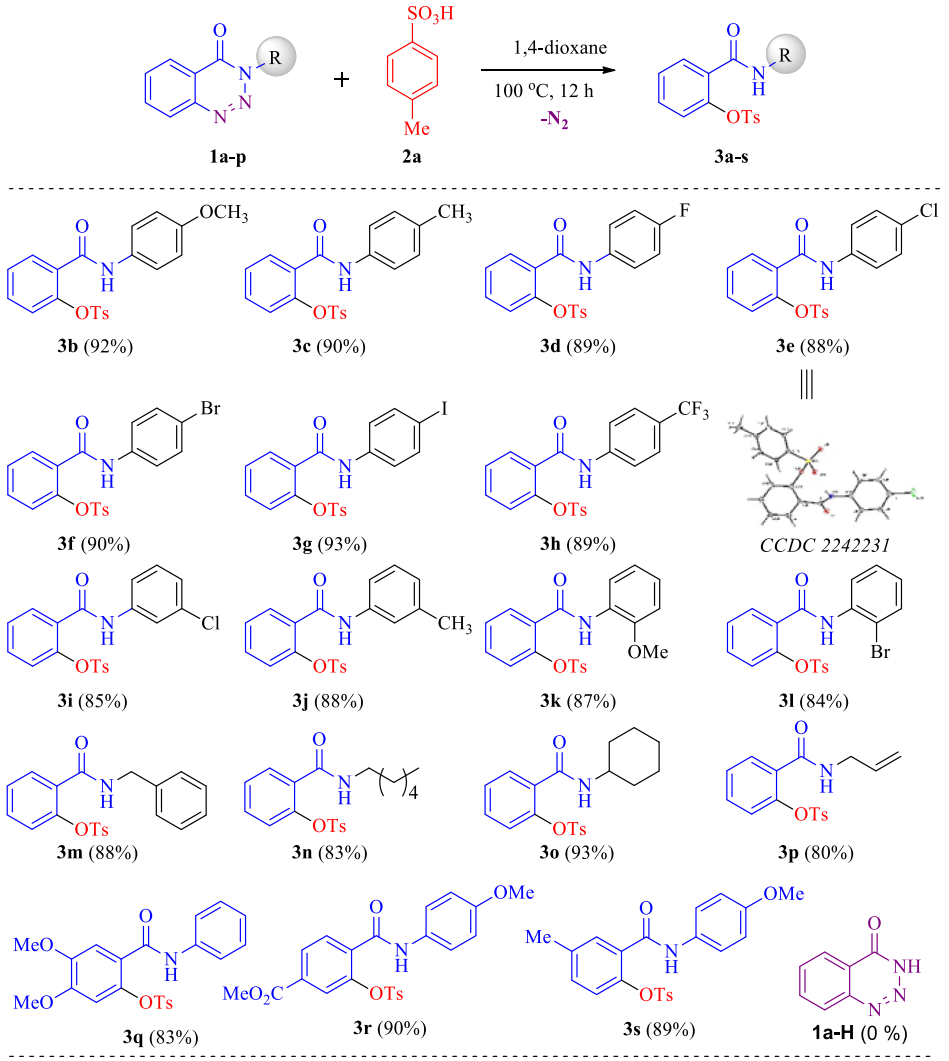
Scheme 2. Scope of N-Substituted 1,2,3-Benzotriazin-4(3*H*)-ones[a,b]



[a]All the reactions were carried out using 1,2,3-benzotriazin-4(3*H*)-ones **1** (0.40 mmol), **2a** (0.60 mmol), and 1,4-dioxane (3 mL); temperature (100 °C); time (12 h). [b]Isolated yields.

With the optimal conditions in hand (entry 8, Table 1), we then explored the scope of this metal-free denitrogenative *ortho*-sulfonation reaction (Scheme 2). The present protocol is highly general and works well with a wide range of substituted benzotriazin-4(3*H*)-ones. To our delight, electron-donating groups (4-OMe, 4-Me), halogens (4-F, 4-Cl, 4-Br, and 4-I), and electron-withdrawing groups (4-CF_3) at the para-position of *N*-aryl-substituted 1,2,3-benzotriazin-4(3*H*)-ones gave corresponding products in high yields (**3b**−**3h**, 88−93%). The structure of the *ortho*-sulfonylated product **3e** was unambiguously confirmed by single-crystal X-ray analysis. Additionally, meta-substituted (3-Cl and 3-Me) 1,2,3-benzotriazin-4(3*H*)-ones also delivered the desired products **3i** and **3j** in 85% and 88% yields, respectively. Interestingly, sterically hindered *ortho*-substituted 1,2,3-benzotriazin-4(3*H*)-ones (**1k** and **1l**) were also well-tolerated under these reaction conditions and offered *ortho*-sulfonylated benzamides **3k** and **3l** in good yields. On the other hand, *N*-alkyl-substituted 1,2,3-benzotriazin-4(3*H*)-ones such as benzyl- (**1m**), *n*-hexyl- (**1n**), cyclohexyl- (**1o**), and allyl- (**1p**) efficiently participated in the reaction, yielding the corresponding products **3m**−**3p** in good to high yields (80−93%). It is also noteworthy that other substituted 1,2,3-benzotriazin-4(3*H*)-ones, such as 6,7-dimethoxy-1,2,3-benzotriazin-4(3*H*)-one (**1q**) and 7-methylester-1,2,3-benzotriazin-4(3*H*)-one (**1r**) and methyl-1,2,3-benzotriazin-4(3*H*)-one (**1s**), reacted well with *p*-TSA under the standard reaction conditions, yielding the desired products **3q**−**3s** in 83−90% yields (Scheme 2). Surprisingly, unsubstituted 1,2,3-benzotriazin-4(3*H*)-one (**1a**−**H**) failed to give the desired product **3**.

To demonstrate the versatility of the developed methodology, we examined the reactivity of various organosulfonic acids (**2b**−**2f**) with 1,2,3-benzotriazin-4(3*H*)-one (**1a**) under the optimized reaction conditions (Scheme 3). Unsubstituted, *ortho*-chlorinated, and 2,4-dimethyl-substituted benzene sulfonic acids delivered the *ortho*-sulfonated benzamides **3t**−**3v** in 85−92% yields. Notably, trifluoromethanesulfonic acid (CF_3SO_3H) and methanesulfonic acid (CH_3SO_3H) gave the corresponding products **3w** and **3x** in 85 and 88% yields, respectively.

We also tested the practicality of this protocol by performing a reaction on a gram scale (Scheme 4). Under the optimized conditions, the gram-scale denitrogenative *ortho*-sulfonylation reaction of **1a** with **2a** proceeded smoothly, and the desired product **3a** was obtained in a comparable yield (3.1 g, 85%).

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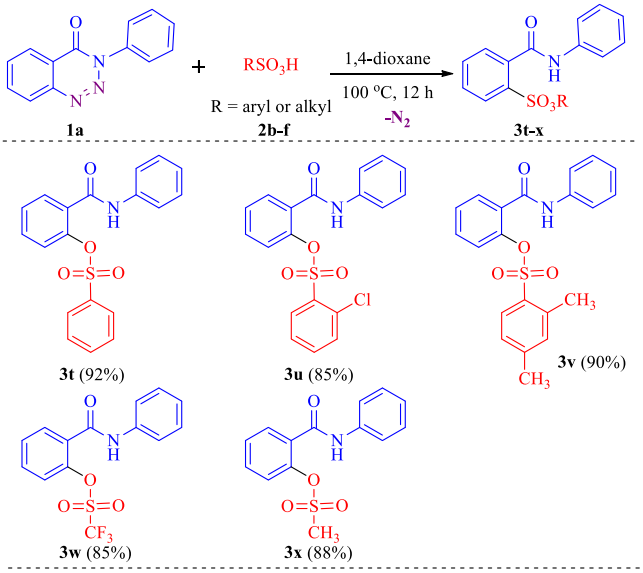
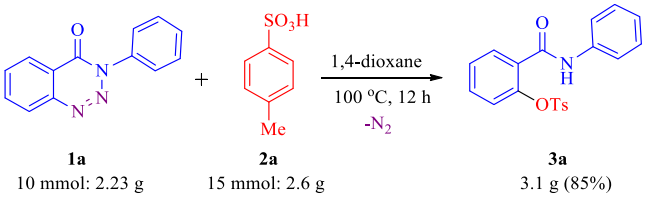
Scheme 3. Scope of Various Organosulfonic Acids[a,b]



[a]All the reactions were carried out using 1,2,3-benzotriazin-4(3*H*)-one **1a** (0.40 mmol), **2b−f** (0.60 mmol.), 1,4-dioxane (3 mL), temperature (100 °C), and time (12 h). [b]Isolated yields.

Scheme 4. Gram-Scale Synthesis of 3a



To demonstrate the utility of the present reaction, a series of biologically significant salicylamide derivatives were successfully synthesized (Scheme 5). Gratifyingly, *N*-aryl and *N*-alkyl salicylanilide sulfonates underwent hydrolysis and provided the corresponding salicylamides (**4a−4d**) in good to high yields.

A plausible mechanism for metal-free *ortho*-sulfonation of 1,2,3-benzotriazin-4(3*H*)-one is provided in Scheme 6. Initially, the reaction proceeds through a reversible ring opening of 1,2,3-benzotriazinone (**1a**) in the presence of sulfonic acid generating the benzene diazonium intermediate **A**. Subsequent nucleophilic attack of the sulfonate ion on the diazonium intermediate (**A**) results in *ortho*-sulfonylated benzamide (salicylanilide sulfonate) **3** with the extrusion of molecular nitrogen as a sole byproduct.

CONCLUSIONS

In summary, we have successfully developed a metal-free denitrogenative sulfonylation reaction of 1,2,3-benzotriazin-4(3*H*)-ones using *p*-TSA as an efficient sulfonylating agent. This protocol is simple to execute, has a broad substrate scope and good functional group tolerance, and affords the desired salicylanilide aryl and alkyl sulfonates in good to high yields. Moreover, the present methodology provides a promising alternative for the synthesis of salicylamides in high yields.

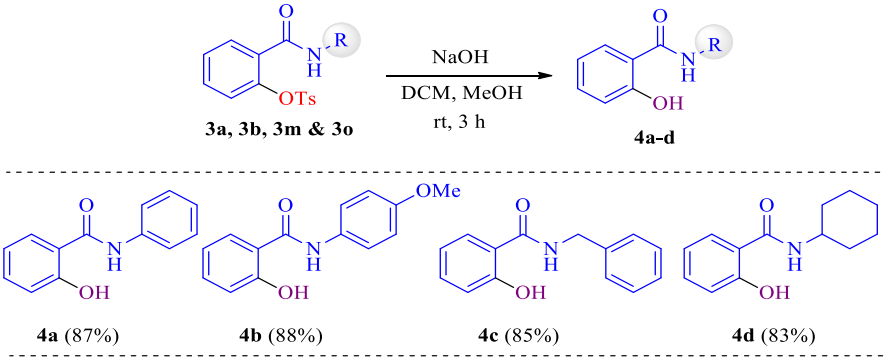
EXPERIMENTAL SECTION

Materials and Methods. All experiments were carried out in oven-dried glassware. Flash column chromatography was performed on 100−200 mesh silica gel. ^{1}H and ^{13}C NMR spectroscopy was performed on a Bruker BBFO (400 MHz and 500 MHz) spectrometer. Chemical shifts were determined relative to the residual solvent peaks ($CDCl_3$, δ = 7.26 ppm for ^{1}H NMR, δ = 77.0 ppm for ^{13}C NMR). The mass spectra (ESI-MS) were recorded on an Agilent 6200 Series Q-TOF LC/MS spectrometer. The starting materials 1,2,3-benzotriazin-4(3*H*)-ones (**1a−s**) were prepared according to the literature procedure.[8b,h] All the reactions were conducted under an air atmosphere unless otherwise stated.

*General Procedure for the Synthesis of Salicylanilide Sulfonates (**3**).* A sealed tube containing 1,2,3-benzotriazin-4(3*H*)-ones (**1**) (0.4 mmol), organosulfonic acid (0.6 mmol), and 1,4-dioxane (3 mL) was stirred at room temperature for 2 min. The sealed tube was placed in a preheated oil bath at 100 °C and stirred for 12 h. After completion of the reaction, the mixture was allowed to cool and then diluted with ethyl acetate (10 mL). The reaction mixture was washed three times with 10 mL of water, and the organic layer was separated. The separated organic layer was then dried over $MgSO_4$ and concentrated under a vacuum to remove the solvent. The residue was purified by silica gel column chromatography using a suitable eluent (hexane/ethyl acetate) to afford the desired pure product **3.**

*Typical Procedure for the Gram-Scale Synthesis of 2-(Phenylcarbamoyl)phenyl 4-Methyl Benzenesulfonate (**3a**).* To a sealed tube containing 3-phenylbenzo[*d*][1,2,3] triazin-4(3*H*)-one (**1a**) (2.23 g, 10 mmol), *p*-TSA (2.6 g, 15 mmol) and 1,4-dioxane (30 mL) were added, and the mixture was stirred at room temperature for 2 min. The sealed tube was then placed in a preheated oil bath at 100 °C for 12 h. After

Scheme 5. Synthesis of *ortho*-Hydroxylated Benzamides



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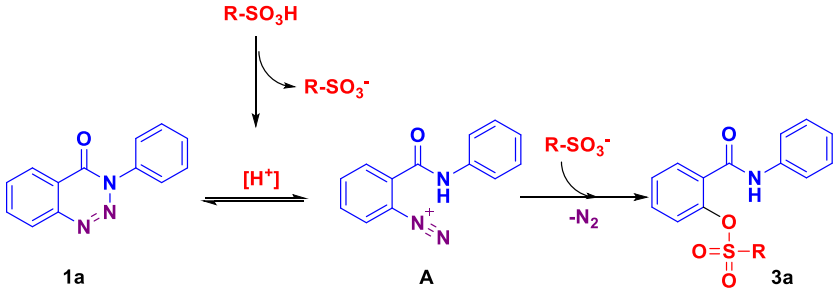
Scheme 6. Proposed Mechanism



completion of the reaction, the mixture was cooled and diluted with ethyl acetate (100 mL). The reaction mixture was then poured into 100 mL of water and shaken well. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum. The resulting residue was purified by silica gel column chromatography using a suitable eluent (hexane/ethylacetate; 8:2) to afford the desired pure product 2-(phenylcarbamoyl)phenyl 4-methylbenzenesulfonate (**3a**) in 85% (3.1 g) yield.

*General Procedure for the Synthesis of Salicylamide Derivatives (**4**).*[17] To a sealed tube containing 0.2 mmol of compound **3**, 3 mL of a 9:1 mixture of dichloromethane and methanolic sodium hydroxide solution was added. The resulting mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the solvent was removed under reduced pressure, and the remaining mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum. The resulting residue was purified using silica gel column chromatography with a suitable eluent to obtain the desired pure product **4**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02165.

Spectral data for the compounds **3a−x** and **4a−d** and copies of ^1H and ^{13}C NMR spectra (PDF)

Single-crystal analysis data for the compound **3e** (CCDC 2242231) (CIF)

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Author Contributions

†R.K. and K.M. contributed equally.

Notes

The authors declare no competing financial interest.

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