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metal-free cascade nucleophilic cyclization

Metal-free Synthesis of Polysubstituted Imidazolinone through Cyclization of Amidines with 2-Substituted Acrylates

Zhen Liu,[a] Yan-Shun Zhang,[b] Dr. Yin Wei,[b] Prof. Dr. Min Shi*[a,b]

Abstract: Polysubstituted imidazolinones were synthesized in a facile metal-free cascade nucleophilic cyclization of easily available amidines and 2-substituted acrylates. This protocol is distinguished by simple, mild, and catalyst-free reaction conditions with a broad substrate scope, affording the desired products in moderate to good yields and providing an efficient strategy for synthesis of polysubstituted imidazolinone.

Introduction

As one of the most valuable classes of *N*-heterocyclic compounds, imidazoles are the important structural motifs in many natural products[1] and pharmaceutical compounds[2] (Figure 1). Imidazolinones, as the derivative of imidazoles, also exist in many biologically active compounds and have wide applications in medicinal chemistry since many of them possess antihypertensive, antidiabetic, and antiinflammatory activities.[3] In recent years, the synthetic methods of these pivotal *N*-heterocyclic compounds have been extensively investigated.[4] However, these mainstream developments are generally limited to the transition metal-catalyzed methods.[5] For example, the synthesis of imidazole from the reaction of amidine with various electron-deficient alkenes or terminal alkyne has been developed by the groups of Neuville,[6] Chen,[7] and Li[8] using CuI, $CuCl_2 \cdot H_2O$ or $FeCl_3$ as the catalyst (Scheme 1). Although these transition metal catalyzed synthetic methods were very efficient to obtain the target products, the residual metals in products could be the biggest obstacle to apply them in drug synthesis because complicated purifying procedures caused higher costs.[9] From this point, developing metal-free synthetic strategies for the synthesis of imidazole core structures is still highly desirable.

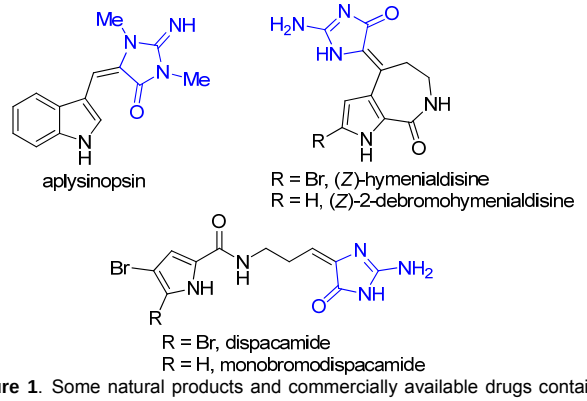
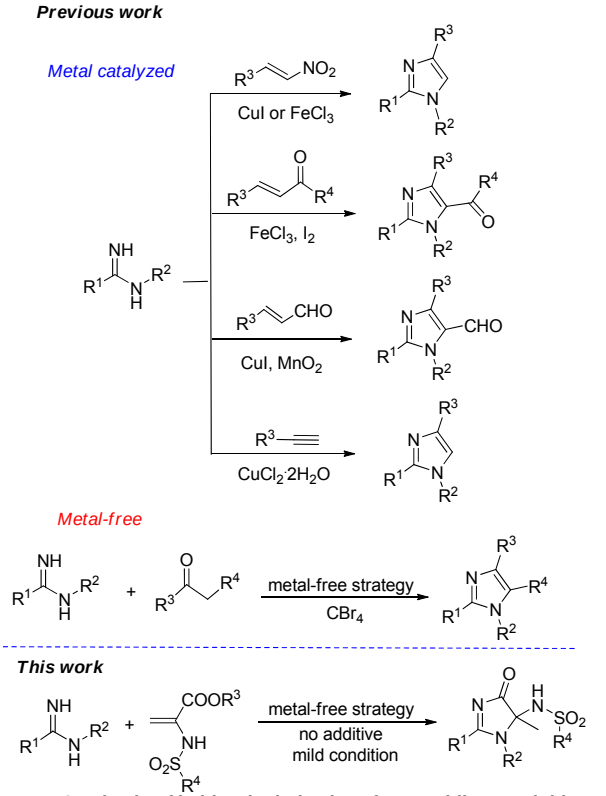


Figure 1. Some natural products and commercially available drugs containing Imidazolinones moiety.

In 2015, an efficient procedure for the preparation of 4,5-dihydro-1*H*-imidazol-5-one from aryl amidines and ketones under transition-metal free conditions has been described by Deng's group.[10] Mild conditions and metal-free operation are the advantages of this procedure. In 2017, a facile approach to synthesize polysubstituted imidazoles through a CBr_4-mediated tandem cyclization of amidines with 1,3-dicarbonyl compounds or ketones has been reported by Huang's group.[11] This synthetic strategy required CBr_4 as the halogenation reagent to initiate the reaction under metal-free conditions.



Scheme 1. Synthesis of imidazole derivatives from amidines and this work.

Although there are many synthetic methods to prepare imidazole, the facile synthetic approach to imidazolidone was rare. At the present stage, the main way to get imidazolone was based on the oxidation of imidazole using chloramine-B.[12] Thus, it is necessary to develop a new method for the synthesis of imidazolidone under environment-benign conditions. Considering that 2-substituted acrylates[13] have a similar structure as that of α,β-unsaturated esters, thus we envisaged that they might be able to undergo conjugated addition with amidine[14] as nucleophilic reagent, furnishing the cyclized product along with C-N bond formation. Herein, we wish to disclose a novel metal-free and atom-economical synthetic protocol for the preparation of polysubstituted imidazolinone through a one-step cyclization of amidines with 2-substituted acrylates under mild conditions.

Results and Discussion

To initiate our study, the reaction conditions were screened for the formation of imidazolinone **3aa** by using methyl 2-((4-methylphenyl)sulfonamido)acrylate **1a** and *N*-phenylbenzimidamide **2a** as model substrates and the results are summarized in Table 1. Firstly, we examined the solvent effects at 80 °C and identified that 1,2-dichloroethane (DCE) was more

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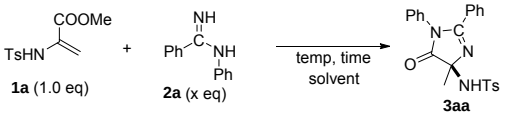
favorable to the reaction, giving **3aa** in 65% yield (entries 1-6). Next, we chose DCE as the solvent to realize the best reaction temperature. When the temperature was raise to 120 °C, the yield of **3aa** decrease to 60% as compared to 80 °C, suggesting that the reaction temperature was also an important factor to affect the reaction outcome (entry 7). Reducing the reaction temperature to 40 °C, the yield of **3aa** increased to 78% (entry 8). Next, we found that the desired product **3aa** could be obtained in 80% yield when the reaction was carried out at room temperature (entry 9). Subsequently, we tried to improve the yield further by changing the equivalent ratios of substrates. We found that decreasing the loading amount of **2a** to 1.0 equiv, 0.5 equiv or 0.3 equiv afforded **3aa** in 52%, 25% or 27% yields, respectively (entries 10-12) and increasing the loading amount of **2a** to 2.0 equiv or 3.0 equiv gave **3aa** in 81% yields (entries 13 and 14). Moreover, we also screened the reaction time and found that the yield of **3aa** reached its peak after the reaction was performed for 12 h (entries 15-18). Eventually, the best reaction conditions were identified as follows: mixing **1a** (1.0 equiv) with **2a** (1.5 equiv) in DCE at room temperature for 12 h.

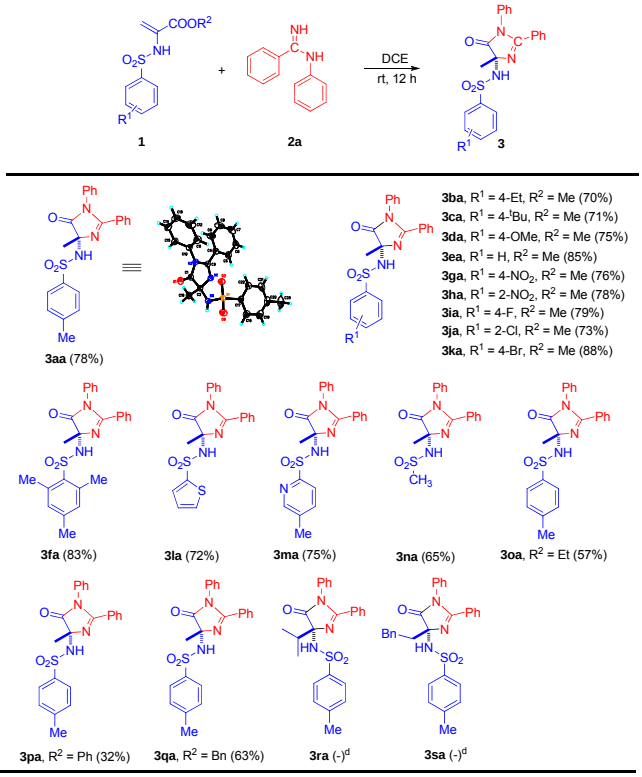
Table 1. Optimization of the Reaction Conditions for the Preparation of **3aa**



entry	solvent	temp (°C)	equiv	time (h)	yield [a,b] (%)
1	DCE	80	1.5	15	65
2	toluene	80	1.5	15	64
3	1,4-dioxane	80	1.5	15	55
4	THF	80	1.5	15	55
5	CH_3CN	80	1.5	15	50
6	DMF	80	1.5	15	46
7	DCE	120	1.5	15	60
8	DCE	40	1.5	15	78
9	DCE	rt	1.5	15	80
10	DCE	rt	1	15	52
11[c]	DCE	rt	0.5	15	25
12[d]	DCE	rt	0.3	15	27
13	DCE	rt	2	15	81
14	DCE	rt	3	15	81
15	DCE	rt	1.5	4	56
16	DCE	rt	1.5	8	65
17	**DCE**	**rt**	**1.5**	**12**	**80**
18	DCE	rt	1.5	16	80

[a]Reaction was run under the following conditions: a solution of **1a** (0.1 mmol) and **2a** (x mmol) in dry solvent (2.0 mL) at different temperature under argon atmosphere. [b]Yields were determined by ^{1}H NMR spectroscopic analysis of the crude mixture using trimethoxybenzene as the internal standard for calculating the yield. [c]**1a** (0.2 mmol) and **2a** (0.1 mmol) were used in the reaction. [d]**1a** (0.3 mmol) and **2a** (0.1 mmol) were used in the reaction.
DCE is 1,2-dichloroethane; THF is tetrahydrofuran; DMF is N,N-Dimethylformamide.

With the optimized reaction conditions in hand, the scope and generality of the reaction with regard to different acrylates were investigated, and the results are summarized in Scheme 2. Firstly, we investigated the substituent effect (R^1) of aryl group in sulfonamides of **1** on the reaction outcomes. As can be seen, for substrates **1b**-**1k** containing either electron-deficient or electron-rich aromatic rings, the reactions proceeded efficiently, affording the desired products **3ba**-**3ka** in moderate to good yields ranging from 70% to 88%. The results indicated that the electronic property of substituent at the aromatic ring did not have significant impact on the reaction outcome. Moreover, the substituent could also locate at the ortho-, meta- or para-position of the aromatic ring. The structure of **3aa**[15] has been unambiguously determined by X-ray diffraction. Its ORTEP drawing is shown in Scheme 2 and the CIF data are presented in the Supporting Information. Replacing the benzene ring in **1** with a heteroaromatic ring, such as thiophene (substrate **1l**) or pyridine (substrate **1m**), the reaction was also tolerated, affording the desired product **3la** or **3ma** in 72% and 75% yields, respectively. Meanwhile, substrate **1n** prepared from methanesulfonamide could also produce the desired product **3na** in 65% yield. Furthermore, the substituent R^2 in ester group was next investigated. Substrates **1o**-**1q**, in which R^2 = Et, Ph and Bn, could give the desired products **3oa**-**3qa** in 57%, 32% and 63% yields, respectively. These results corresponded to the leaving ability of R^2 groups. In addition, we also investigated the reactivity of non-terminal alkene substrates **1r** and **1s**. However, these substrates failed to give the desired products **3ra** and **3sa** under the standard conditions, presumably due to that the isomerization to the corresponding imine intermediate is not possible for both of them.

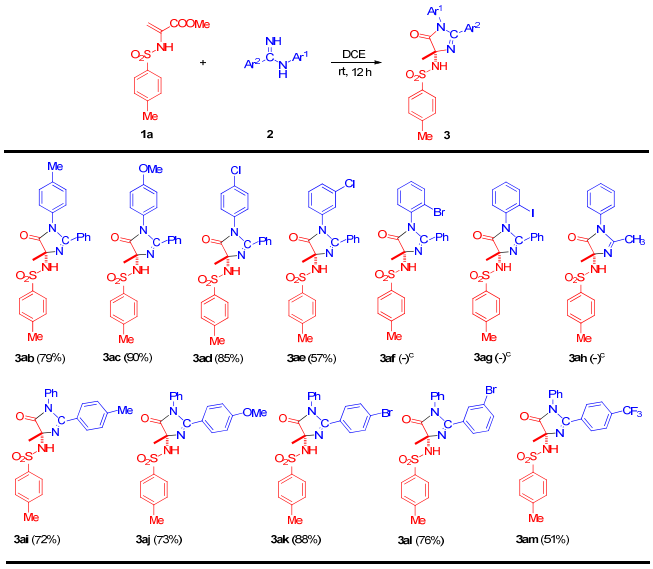


[a]Reaction conditions: **1** (0.2 mmol) and **2a** (0.3 mmol) in DCE (2.0 ml) at room temperature under argon atmosphere for 12 h. [b]isolated yield. [c]Toluene was used as the solution. [d]None of the desired product was produced.

Scheme 2. Substrate Scope of **1** for the Production of **3**.[a,b]

Next, we turned to investigate the reactivity of amidines **2** and the results are shown in Scheme 3. As can be seen from Scheme 3, the desired products **3ab**-**3ad** were obtained in moderate to good yields ranging 79–85% when Ar^1 was substituted by either the electron-rich group or the electron-deficient substituent at the para-position of the benzene ring. Obviously, for substrate **2e**, in which Ar^1 = meta-chlorobenzene, the reaction proceeded less efficiently, giving the corresponding product **3ae** in 57% yield. For amidines **2f** and **2g**, in which the ortho-position of Ar^1 group had substituent, the reaction did not go give the desired products **3af** and **3ag**, presumably due to the steric effect. In addition, we have also tried to introduce alkyl group as the substituent into amidine moiety. Amidine **2h**, in which Ar^2 has been replaced by a methyl group, failed to afford the desired product **3ah** in the reaction with **1a** under the standard conditions. This result suggested that alkyl amidine was not compatible in this reaction. Furthermore, as for the substituent at Ar^2 group such as amidines **2i**-**2l**, the reactions were also compatible, giving the target products **3ai**-**3al** in moderate to good yields ranging from 72-88% under the standard conditions. However, introducing a strongly electron-withdrawing CF_3 substituent into the benzene ring of amidine, the corresponding product **3am** was obtained in 51% yield perhaps due to that the

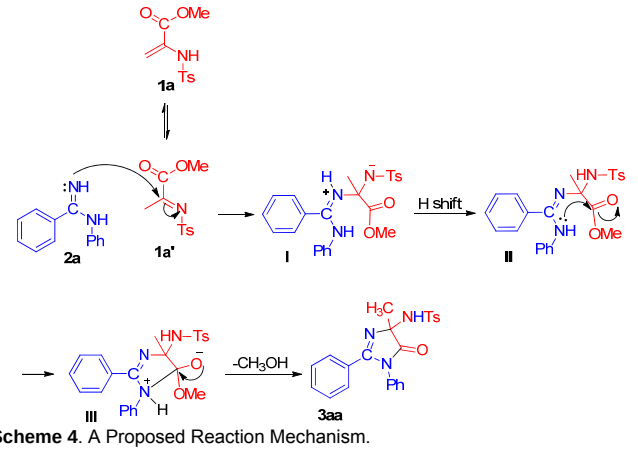
strongly electron-withdrawing CF_3 substituent decreased the nucleophilicity of *N* atom in imine.



[a]Reaction conditions: 1a (0.2 mmol) and 2 (0.3 mmol) in DCE (2.0 ml) at room temperature under argon atmosphere for 12 h. [b]Isolated yield. [c]None of the desired product was produced.

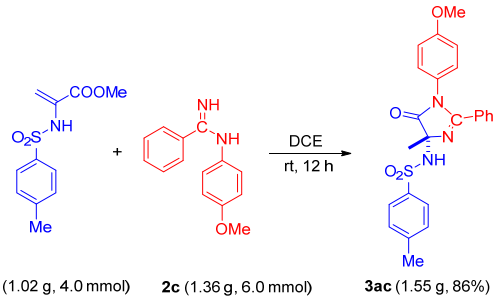
Scheme 3. Substrate Scope of **2** for the Production of **3**.[a,b]

As for the reaction mechanism, we initially proposed two possible reaction pathways shown in Supporting Information as Scheme S1 and Scheme S2. To verify the reaction mechanism, we conducted ^{1}H NMR spectroscopic tracing experiment. Upon mixing **1a** and **2a**, the rapid isomerization of **1a** to **1a'** (shown in Scheme 4) was observed and the signal of methoxyl ester group became weaker during the reaction proceeding (see Figures S1 and S2 in the Supporting Information). On the basis of these experimental results and the previous reports, a plausible reaction mechanism for this metal-free transformation has been outlined in Scheme 4. The reaction started with the nucleophilic attack of imino group of **2a** to NTs imino moiety of **1a'**, affording intermediate **I**, which underwent intramolecular H-shift to give intermediate **II**. Subsequently, intermediate **II** underwent a second intramolecular nucleophilic attack to give intermediate **III**. Then, the release of methanol took place to give the target product **3aa** (for an alternative possible reaction mechanism, please see Scheme S1 in the Supporting Information).



Scheme 4. A Proposed Reaction Mechanism.

The potential synthetic practicability of this method on gram-scale was next assessed. As shown in Scheme 5, the reaction of **1a** (1.02 g, 4 mmol) with **2c** (1.36 g, 6 mmol) produced **3ac** in 86% yield (1.55 g) under the optimized reaction conditions (Scheme 5).



1a (1.02 g, 4.0 mmol) **2c** (1.36 g, 6.0 mmol) **3ac** (1.55 g, 86%)

Scheme 5. Gram-Scale Experiment

Conclusions

In summary, we have demonstrated a facile metal-free approach to synthesize polysubstituted imidazolinones through a cascade sequence of inter- and intramolecular nucleophilic attack between amidines and 2-substituted acrylates with a broad substrate scope and good functional tolerance. The simple operation with inexpensive reagents and mild reaction conditions as well as gram-scale synthesis make this protocol efficient and practical. Further investigations on the application of this protocol to the synthesis of biologically active substances are underway.

Experimental Section

General methods: Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorous nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 400, 100 and 367 MHz, respectively. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz) and integration. Mass and High Resolution Mass Spectra (HRMS) spectra were recorded by DART or ESI method. The employed solvents were dry up by standard methods when necessary. Commercially obtained reagents were used without further purification. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF254) were used. Flash column chromatography was carried out using 300-400 mesh silica gel at increased pressure.

General Procedures for the Synthesis of 1a, 1m, 1n, 1o.:

Step 1: α-Ketoesters **1a**, **1o**, **1p**, and **1q** were synthesized starting from the corresponding commercially available pyruvic acid according to the previous literature. The pyruvic acid **S1** (10 mmol, 1.0 equiv), the alcohol **S2** (20 mmol, 2.0 equiv) and pyridine (25 mmol, 2.5 equiv) were dissolved in THF (10 mL), and the reaction mixture was cooled to 0 °C (see Supporting Information). Mesyl chloride (12 mmol, 1.2 equiv) was then added dropwise. The reaction mixture was then warmed to room temperature and stirred for 18 hours. The reaction was quenched with water (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were then dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by a flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1) to afford the desired α-ketoester **S3**

Step 2: A round-bottom flask equipped with a Dean-Stark trap was charged with α-ketoesters **S3** (10 mmol) p-$TsNH_2$ **S4** (11 mmol), a catalytic amount of p-TsOH, 4-methoxyphenol (0.1 mol %) and toluene (50 mL) (see Supporting Information). The stirred mixture was heated under reflux for 18 h, then concentrated in vacuo. The resulting mixture was taken up in DCM (100 mL), washed with saturated $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a silica gel chromatography to afford the desired products **1a**, **1o**, **1p**, and **1q**.

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General Procedures for the Synthesis of 1b-1n, 1r and 1s : A round-bottom flask equipped with a Dean-Stark trap was charged with methyl pyruvate (10 mmol), benzenesulfonamide **S5** (11 mmol), a catalytic amount of p-TsOH, 4-methoxyphenol (0.1 mol%) and toluene (50 mL). The stirred mixture was heated under reflux for 18 h and then concentrated in vacuo. The resulting yellow oil was taken up in DCM (100 mL), washed with saturated $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a silica gel chromatography to afford the desired products **1b**-**1n, 1r and 1s**.

General Procedure for the Synthesis of 2: A round bottom flask (25 mL in volume) was charged with NaH (60% in mineral oil) (360 mg, 15.0 mmol, 60%, 1.5 equiv). Under a stream of argon, DMSO (5 mL) was added, and the resulting suspension was cooled with an ice-water bath prior to the addition of the aniline **S6** (11.0 mmol, 1.1 equiv) and the carbonitrile **S7** (10.0 mmol) (see Supporting Information). The reaction mixture was kept at 0 °C for 30-60 min, and then stirred at room temperature until the starting material was consumed as monitored by TLC analysis. Ice-water (50 mL) was added while maintaining vigorous stirring. When the amidine precipitated upon addition of water, the solid was filtered off and dissolved in EtOAc (20 mL). In other cases, the aqueous layer was extracted with EtOAc (3 × 20 mL). The extracts were combined and washed with water (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified either by a silica gel chromatography or upon recrystallization to afford the desired product **2**.

Compound *3aa*: A white solid, 67.1 mg, 80% yield. M.P.: 227-229 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.83 (s, 1H, NH), 7.20 (d, *J* = 7.6 Hz, 4H, ArH), 7.25 (s, 1H, ArH), 7.29 (t, *J* = 7.2 Hz, 3H, ArH), 7.36-7.43 (m, 4H, ArH), 7.78 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.4, 78.3, 127.3, 127.4, 128.2, 128.5, 128.6, 128.8, 129.3, 129.4, 131.3, 134.4, 138.9, 143.4, 162.4, 180.9. IR (neat) ν 3250, 1754, 1619, 1592, 1490, 1329, 1315, 1300, 1151, 778, 696, 669 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_3S$ (M+H): 420.1376, Found: 420.1384.

Compound *3ba*: A white solid, 60.6 mg, 70% yield. M.P.: 155-157 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.22 (t, *J* = 7.6 Hz, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.67 (q, *J* = 7.6 Hz, 2H, CH_2), 6.50 (s, 1H, NH), 7.20-7.28 (m, 8H, ArH), 7.34-7.40 (m, 4H, ArH), 7.82 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 15.2, 24.3, 28.8, 78.4, 127.3, 127.4, 128.17, 128.19, 128.5, 128.6, 128.8, 129.4, 131.3, 134.4, 139.2, 149.4, 162.3, 181.1. IR (neat) ν 3246, 1756, 1592, 1490, 1331, 1300, 1153, 783, 702, 694, 655 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_3S$ (M+H): 434.1533, Found: 434.1541.

Compound *3ca*: A white solid, 65.5 mg, 71% yield. M.P.: 208-210 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.31 (s, 9H, $C(CH_3)_3$), 1.72 (s, 3H, CH_3), 6.59 (s, 1H, NH), 7.21-7.23 (m, 6H, ArH), 7.37-7.43 (m, 6H, ArH), 7.84 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.3, 31.1, 35.1, 78.3, 125.8, 127.0, 127.4, 128.2, 128.5, 128.6, 128.9, 129.4, 131.3, 134.4, 139.1, 156.1, 162.2, 181.1. IR (neat) ν 3258, 1746, 1595, 1490, 1332, 1297, 1157, 1112, 889, 762, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{26}H_{28}N_3O_3S$ (M+H): 462.1846, Found: 462.1853.

Compound *3da*: A white solid, 65.3 mg, 75% yield. M.P.: 197-200 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.24 (s, 1H, NH), 6.85 (d, *J* = 8.8 Hz, ArH), 7.19-7.22 (m, 2H, ArH), 7.26 (d, *J* = 7.2 Hz, 2H, ArH), 7.31-7.33 (m, 2H), 7.35-7.40 (m, 4H, ArH), 7.83 (d, *J* = 8.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.4, 55.5, 78.4, 113.8, 127.4, 128.2, 128.5, 128.6, 128.8, 129.3, 129.4, 131.3, 133.6, 134.4, 162.2, 162.8, 181.0. IR (neat) ν 3249, 1751, 1595, 1491, 1446, 1329, 1296, 1265, 1147, 1090, 1024, 1011, 893, 829, 766 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_4S$ (M+H): 436.1326, Found: 436.1331.

Compound *3ea*: A white solid, 68.9 mg, 85% yield. M.P.: 220-223 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.72 (s, 3H, CH_3), 6.53 (s, 1H, NH), 7.20-7.29 (m, 6H, ArH), 7.35-7.43 (m, 6H, ArH), 7.52 (t, *J* = 7.4 Hz, 1H, ArH), 7.91 (d, *J* = 7.7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.4, 78.3, 127.2, 127.4, 128.2, 128.51, 128.54, 128.7, 128.8, 129.4, 162.4, 181.0. IR (neat) ν 3257, 1759, 1622, 1490, 1452, 1358, 1328, 1300, 1153, 772, 750 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{20}N_3O_3S$ (M+H): 406.1220, Found: 406.1227.

Compound *3fa*: A white solid, 74.3 mg, 83% yield. M.P.: 236-238 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.72 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.58 (s, 6H, CH_3), 6.28 (s, 1H, NH), 6.91 (s, 2H, ArH), 7.16-7.20 (m, 6H, ArH), 7.35-7.39 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 20.9, 22.9, 24.7, 78.2, 127.3, 128.0, 128.5, 128.5, 128.8, 129.4, 131.3, 131.8, 134.3, 136.4, 138.3, 141.9, 162.0, 181.3. IR (neat) ν 3225, 1739, 1623, 1491, 1354, 1302, 1151, 780, 772, 707, 694, 660 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{26}N_3O_3S$ (M+H): 448.1689, Found: 448.1697.

Compound *3ga*: A white solid, 68.4 mg, 76% yield. M.P.: 218-220 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.75 (s, 3H, CH_3), 7.21 (d, *J* = 6.0 Hz, 2H, ArH), 7.27-7.31 (m, 4H, ArH), 7.40-7.44 (m, 4H, ArH), 8.03 (d, *J* = 8.8 Hz, 2H, ArH), 8.17 (d, J = 8.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.2, 78.7, 123.9, 127.3, 128.2, 128.4, 128.5, 128.6, 128.8, 129.5, 131.7, 134.0, 147.5, 149.8, 162.8, 180.9. IR (neat) ν 3199, 1749, 1609, 1528, 1348, 1299, 1162, 1092, 737, 699, 682 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{19}N_4O_5S$ (M+H): 451.1071, Found: 451.1078.

Compound *3ha*: A white solid, 70.3 mg, 78% yield. M.P.: 215-218 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.75 (s, 3H, CH_3), 6.55 (s, 1H, NH), 7.22 (d, *J* = 6.8 Hz, 2H, ArH), 7.26-7.30 (m, 4H, ArH), 7.34-7.45 (m, 5H, ArH), 7.60-7.64 (m, 1H, ArH), 7.80 (dd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH). ^{13}C NMR (CD_2Cl_2, TMS, 100 MHz) δ 24.2, 78.4, 125.4, 127.3, 128.2, 128.3, 128.6, 128.63, 129.4, 130.7, 131.5, 132.7, 133.6, 134.5, 135.6, 147.3, 162.1, 179.7. IR (neat) ν 3179, 1745, 1618, 1541, 1493, 1368, 1322, 1307, 1163, 1120, 997, 853 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{19}N_4O_5S$ (M+H): 451.0897, Found: 451.0904.

Compound *3ia*: A white solid, 66.9 mg, 79% yield. M.P.: 201-203 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.71 (s, 3H, CH_3), 6.88 (s, 1H, NH), 7.05 (t, *J* = 8.8 Hz, 2H, ArH), 7.20-7.31 (m, 6H, ArH), 7.35- 7.43 (m, 4H, ArH), 7.89-7.92 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.3, 78.5, 115.8 (d, *J* = 22.5 Hz), 127.3, 128.3, 128.5 (d, *J* = 8.2 Hz), 128.7, 129.4, 130.0 (d, *J* = 9.3 Hz), 131.4, 134.3, 138.1 (d, *J* = 3.2 Hz), 162.4, 163.7, 181.1. ^{19}F NMR ($CDCl_3$, CFCl3, 376 MHz) δ -105.52- -105.59 (m, 1F). IR (neat) ν 3147, 1750, 1591, 1493, 1448, 1321, 1308, 1161, 1150, 1090, 897, 835, 766 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{19}FN_3O_3S$ (M+H): 424.1126, Found: 424.1133.

Compound *3ja*: A white solid, 64.1 mg, 73% yield. M.P.: 278-280 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.72 (s, 3H, CH_3), 6.09 (s, 1H, NH), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 7.13-7.20 (m, 5H, ArH), 7.35-7.45 (m, 5H, ArH), 7.54 (d, *J* = 7.6 Hz, 1H, ArH), 7.83 (d, *J* = 8.0 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 23.7, 78.0, 127.6, 128.0, 128.4, 128.76, 128.80, 128.9, 129.7, 130.3, 130.9, 131.5, 131.9, 134.0, 134.9, 140.7, 161.2, 181.3. IR (neat) ν 3277, 1758, 1567, 1493, 1302, 1157, 1025, 994, 763, 701 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{19}ClN_3O_3S$ (M+H): 440.0830, Found: 440.0838.

Compound *3ka*: A white solid, 85.0 mg, 88% yield. M.P.: 210-212 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.71 (s, 3H, CH_3), 7.19 (d, *J* = 6.4 Hz, 2H, ArH), 7.26-7.27 (m, 4H, ArH), 7.36-7.42

(m, 4H, ArH), 7.51 (d, *J* = 8.4 Hz, 2H, ArH), 7.73 (d, *J* = 8.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.2, 78.5, 127.3, 127.5, 128.3, 128.4, 128.6, 128.7, 128.8, 129.4, 131.5, 131.9, 134.2, 141.0, 162.5, 181.0. IR (neat) v 3258, 1755, 1615, 1575, 1491, 1333, 1154, 1072, 768, 695 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{19}BrN_3O_3S$ (M+H): 484.0325, Found: 484.0332.

Compound *3la*: A white solid, 59.2 mg, 72% yield. M.P.: 198-201 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.73 (s, 3H, CH_3), 6.32 (s, 1H, NH), 6.97-6.99 (m, 1H, ArH), 7.18-7.20 (m, 2H, ArH), 7.26 (t, *J* = 7.2 Hz, 2H, ArH), 7.34-7.43 (m, 6H, ArH), 7.51-7.52 (m, 1H, ArH), 7.63-7.65 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.4, 78.5, 126.9, 127.3, 128.2, 128.51, 128.54, 128.8, 129.4, 131.3, 132.0, 132.6, 134.2, 143.0, 162.7, 180.7. IR (neat) v 3265, 1761, 1624, 1491, 1447, 1336, 1301, 1154, 1021, 774 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{18}N_3O_3S_2$ (M+H): 412.0784, Found: 412.0792.

Compound *3ma*: A white solid, 63.0 mg, 75% yield. M.P.: 244-246 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.70 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.64 (s, 1H, NH), 7.15-7.24 (m, 6H, ArH), 7.36-7.44 (m, 5H, ArH), 7.64 (d, *J* = 8.0 Hz, 1H, ArH), 8.56 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 18.5, 24.0, 78.1, 121.1, 127.3, 128.1, 128.4, 128.5, 128.7, 129.3, 131.2, 134.3, 137.1, 137.6, 150.3, 156.1, 162.2, 180.3. IR (neat) v 3093, 1754, 1595, 1493, 1446, 1337, 1305, 1164, 1104, 704, 672 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{21}N_4O_3S$ (M+H): 421.1329, Found: 421.1336.

Compound *3na*: A white solid, 44.6 mg, 65% yield. M.P.: 172-174 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.71 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 6.13 (s, 1H, NH), 7.14-7.16 (m, 2H, ArH), 7.27-7.31 (m, 2H, ArH), 7.34-7.44 (m, 6H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 24.4, 44.3, 78.2, 127.3, 128.3, 128.5, 128.6, 128.7, 129.3, 131.4, 134.1, 163.0, 181.0. IR (neat) v 3534, 1752, 1624, 1595, 1498, 1331, 1309, 1148, 1131, 975, 776, 696 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{18}N_3O_3S$ (M+H): 344.1063, Found: 344.1071.

Compound *3oa*: A white solid, 47.8 mg, 57% yield. M.P.: 227-229 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.70 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.20 (s, 1H, NH), 7.19-7.22 (m, 4H, ArH), 7.25-7.30 (m, 4H, ArH), 7.35-7.40 (m, 4H, ArH), 7.78 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.4, 78.3, 127.3, 127.4, 128.2, 128.5, 128.6, 128.8, 129.3, 129.4, 131.3, 134.4, 139.0, 143.4, 162.3, 180.9. IR (neat) v 3250, 1754, 1619, 1592, 1490, 1329, 1315, 1300, 1151, 778, 696, 669 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_3S$ (M+H): 420.1376, Found: 420.1384.

Compound *3pa*: A white solid, 26.8 mg, 32% yield. M.P.: 227-229 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.68 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.83 (s, 1H, NH), 7.17-7.21 (m, 4H, ArH), 7.23-7.29 (m, 4H, ArH), 7.34-7.39 (m, 4H, ArH), 7.76 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.4, 78.3, 127.3, 127.4, 128.2, 128.5, 128.6, 128.8, 129.3, 129.4, 131.3, 134.4, 139.0, 143.4, 162.3, 180.9. IR (neat) v 3250, 1754, 1619, 1592, 1490, 1329, 1315, 1300, 1151, 778, 696, 669 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_3S$ (M+H): 420.1376, Found: 420.1384.

Compound *3qa*: A white solid, 52.8 mg, 63% yield. M.P.: 227-229 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.20 (s, 1H, NH), 7.19-7.22 (m, 4H, ArH), 7.25-7.30 (m, 4H, ArH), 7.35-7.40 (m, 4H, ArH), 7.78 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.4, 78.3, 127.3, 127.4, 128.2, 128.5, 128.6, 128.8, 129.3, 129.4, 131.3, 134.4, 138.9, 143.3, 162.3, 180.9. IR (neat) v 3250, 1754, 1619, 1592, 1490, 1329, 1315, 1300, 1151, 778, 696, 669 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_3S$ (M+H): 420.1376, Found: 420.1384.

Compound *3ab*: A white solid, 68.4 mg, 79% yield. M.P.: 94-96 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.08-7.20 (m, 6H, ArH), 7.22-7.32 (m, 5H, ArH), 7.39 (t, *J* = 7.2 Hz, 1H, ArH), 7.77 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.2, 21.5, 24.3, 78.3, 127.2, 127.3, 128.2, 128.7, 128.9, 129.3, 130.0, 131.2, 131.7, 138.5, 139.1, 143.2, 162.4, 185.4. IR (neat) v 3279, 1757, 1623, 1579, 1514, 1336, 1297, 1153, 1089, 1006, 888, 812, 757, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_3S$ (M+H): 434.1533, Found: 434.1538.

Compound *3ac*: A white solid, 80.8 mg, 90% yield. M.P.: 102-104 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.62 (s, 1H, NH), 6.89 (d, *J* = 8.8 Hz, 2H, ArH), 7.13-7.20 (m, 4H, ArH), 7.25 (t, *J* = 8.0 Hz, 2H, ArH), 7.31 (d, *J* = 7.2 Hz, 2H, ArH), 7.39 (t, *J* = 7.2 Hz, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 20.5, 23.3, 54.4, 77.1, 113.6, 126.0, 126.2, 127.2, 127.63, 127.64, 127.8, 128.3, 130.2, 138.0, 142.2, 158.4, 161.5, 180.4. IR (neat) v 3241, 1757, 1609, 1597, 1510, 1297, 1247, 1152, 1091, 1029, 813, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_4S$ (M+H): 450.1482, Found: 450.1488.

Compound *3ad*: A white solid, 77.0 mg, 85% yield. M.P.: 100-102 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H,CH_3), 2.37 (s, 3H, CH_3), 6.74 (s, 1H, NH), 7.14-7.20 (m, 4H, ArH), 7.27-7.28 (m, 4H, ArH), 7.35 (d, *J* = 8.8 Hz, 2H, ArH), 7.40-7.44 (m, 1H, ArH), 7.76 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.1, 78.4, 127.2, 128.3, 128.4, 128.7, 128.8, 129.3, 129.6, 131.5, 132.9, 134.3, 139.0, 143.4, 161.9, 181.0. IR (neat) v 3257, 1759, 1611, 1597, 1491, 1305, 1152, 1089, 1004, 891, 812, 699, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{21}ClN_3O_3S$ (M+H): 454.0987, Found: 454.0994.

Compound *3ae*: A white solid, 51.7 mg, 57% yield. M.P.: 118-120 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.66 (s, 1H, NH), 7.05-7.07 (m, 1H, ArH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.27-7.29 (m, 6H, ArH), 7.31-7.33 (m, 1H, ArH), 7.41-7.45 (m, 1H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.6, 24.2, 78.4, 125.7, 127.2, 127.6, 128.3, 128.4, 128.8, 129.4, 130.3, 131.5, 134.8, 135.5, 138.9, 143.4, 161.7, 180.8. IR (neat) v 3194, 1745, 1590, 1478, 1309, 1155, 1093, 997, 893, 762, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{21}ClN_3O_3S$ (M+H): 454.0987, Found: 454.0990.

Compound *3ai*: A white solid, 62.4 mg, 72% yield. M.P.: 198-200 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.70 (s, 1H, NH), 7.03 (d, *J* = 8.0 Hz, 2H, ArH), 7.15-7.22 (m, 6H. ArH), 7.35-7.41 (m, 3H, ArH), 7.77 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 21.5, 24.3, 78.3, 125.7, 127.3, 127.5, 128.5, 128.8, 128.9, 129.3, 129.3, 134.5, 139.1, 141.8, 143.2, 162.2, 181.2. IR (neat) v 3252, 1752, 1628, 1491, 1330, 1301, 1151, 894, 810, 768, 698, 673 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_3S$ (M+H): 434.1533, Found: 434.1540.

Compound *3aj*: A white solid, 65.6 mg, 73% yield. M.P.: 227-229 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.68 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.22 (s, 1H, NH), 6.73 (d, *J* = 9.2 Hz, 2H, ArH), 7.19-7.24 (m, 6H, ArH), 7.37-7.43 (m, 3H, ArH), 7.77 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.6, 24.5, 55.3, 78.2, 113.6, 120.7, 127.3, 127.5, 128.5, 129.3, 129.4, 130.7, 134.7, 139.0, 143.3, 161.8, 161.9, 181.1. IR (neat) v 3172, 1727, 1599, 1509, 1318, 1303, 1262, 1173, 1153, 1088, 1029, 806, 768, 665, 717 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_4S$ (M+H): 450.1482, Found: 450.1491.

Compound *3ak*: A white solid, 87.5 mg, 88% yield. M.P.: 114-116 °C. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.69 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.10 (s, 1H, NH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 7.21 (t, *J* = 8.4 Hz, 4H, ArH), 7.38-7.42 (m, 5H, ArH), 7.76 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.6, 24.3, 78.3, 126.2, 127.2, 127.4, 127.5, 128.8, 129.4, 129.5, 130.3, 131.5, 134.1, 138.9, 143.5, 161.5, 180.8. IR (neat) v 3526, 1755,

1615, 1590, 1502, 1333, 1310, 1152, 1012, 896, 818, 697, 678 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{21}BrN_3O_3S$ (M+H): 498.0482, Found: 498.0490.

Compound *3al*: A white solid, 75.6 mg, 76% yield. M.P.: 97-99 °C. ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.70 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.56 (s, 1H, NH), 7.02-7.07 (m, 2H, ArH), 7.21 (d, *J* = 6.4 Hz, 2H, ArH), 7.27 (d, *J* = 7.2 Hz, 2H, ArH), 7.38-7.52 (m, 5H, ArH), 7.80 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.6, 24.1, 78.2, 110.0, 122.5, 127.1, 127.3, 127.4, 128.8, 129.5, 129.5, 130.4, 131.8, 134.0, 134.3, 139.0, 143.5, 160.9, 181.0. IR (neat) v 3521, 1758, 1615, 1591, 1499, 1424, 1332, 1304, 1151, 1094, 901, 812, 695 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{21}BrN_3O_3S$ (M+H): 498.0482, Found: 498.0490.

Compound *3am*: A white solid, 49.7 mg, 51% yield. M.P.: 102-105 °C. ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.72 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.43 (s, 1H, NH), 7.21 (d, *J* = 6.8 Hz, 4H, ArH), 7.40-7.44 (m, 5H, ArH), 7.52 (d, *J* = 7.2 Hz, 2H, ArH), 7.77 (d, *J* = 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.5, 24.2, 78.5, 123.4 (q, *J* = 271.0 Hz), 125.2 (q, *J* = 3.6 Hz), 127.1, 127.5, 128.8, 129.3, 129.35, 129.6, 132.1, 132.9 (q, *J* = 32.7 Hz), 133.9, 138.9, 143.5, 161.2, 180.8. ^{19}F NMR ($CDCl_3$, $CFCl_3$, 376 MHz) δ -63.12 (s, 3F). IR (neat) v 3092, 1758, 1596, 1493, 1411, 1323, 1304, 1153, 1130, 1092, 1066, 1015, 856 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{21}F_3N_3O_3S$ (M+H): 488.1160, Found: 488.1167.

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[15] CCDC 1913943 (for **3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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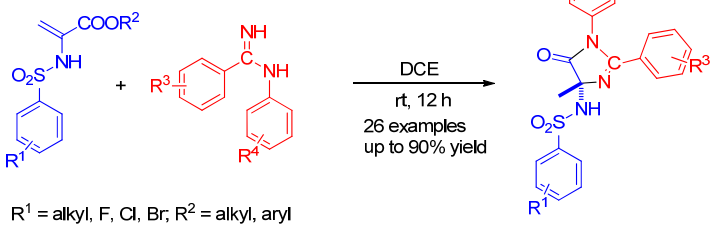
metal-free cascade nucleophilic cyclization

Zhen Liu, Yan-Zhun Zhang, Yin Wei and Min Shi* _____ **Page – Page**

nucleophilic cyclization !



R^1 = alkyl, F, Cl, Br; R^2 = alkyl, aryl
R^3 = alkyl, Cl, Br; R^4 = alkyl, Cl, Br, I

transition metal-free !
simple and mild conditions !
broad substrate scope !
gram-scale synthesis !

Metal-free Synthesis of Polysubstituted Imidazolinone through Cyclization of Amidines with 2-Substituted Acrylates

A facile metal-free cascade nucleophilic cyclization of amidines with 2-substituted acrylates has been developed, producing polysubstituted imidazolinone derivatives in moderate to good yields with a broad substrate scope.