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Graphical Abstract

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_N_-Sulfonyl Acetylketenimine as A Highly Reactive Intermediate for Synthesis of _N_-Aroylsulfonamides

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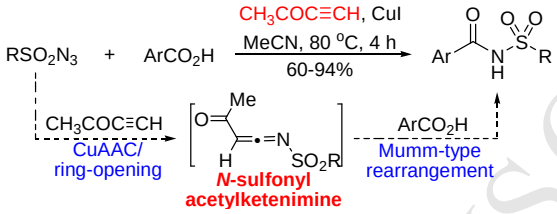

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ABSTRACT

A highly reactive intermediate *N*-sulfonyl acetylketenimine was generated from an ynone-participated CuAAC/ring-opening method. Its unique structure allowed it to react with aryl carboxylic acids to give *N*-aroylsulfonamides via a novel Mumm-type rearrangement.

1. Introduction

Many organic reactive intermediates are too energetic to be directly isolated or identified spectroscopically. But, they can be trapped by suitable reagents to convert into stable derivatives. Thus, discovery of new reactive intermediates not only benefits understanding of the mechanisms, but also becomes an essential part of organic synthesis.[1] Many reactive intermediates have played important roles in the development of synthetic methods, such as ketenes **1**, ketenimines **2** and *N*-sulfonyl ketenimines **3** (Fig. 1).[2] Although these intermediates have significantly different applications, their structures are different only in one atom or one functional group.

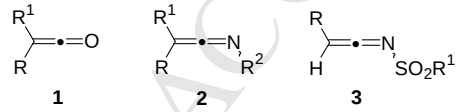
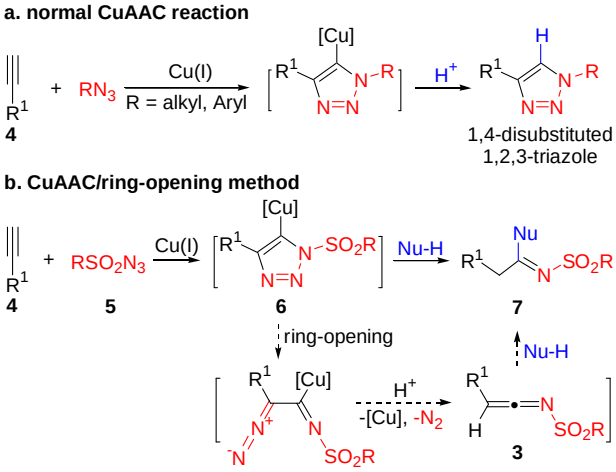


Figure 1. Structures of the reactive intermediates **1**-**3**.

The first efficient generation of *N*-sulfonyl ketenimines **3** was reported by Chang's group in 2005.[3] As shown in Scheme 1, normal CuAAC reaction[4] [copper(I)-catalyzed azide-alkyne cycloaddition] produced only 1,4-disubstituted 1,2,3-triazoles. However, when CuAAC reaction was carried out with sulfonyl azide **5**, the intermediate **6** underwent a ring-opening reaction to generate a reactive intermediate *N*-sulfonyl ketenimines **3**.[5] In the presence of a nucleophile, the intermediates **3** was trapped to give a chain product **7**.[6] This CuAAC/ring-opening method in fact is a one-pot multi-component reaction.

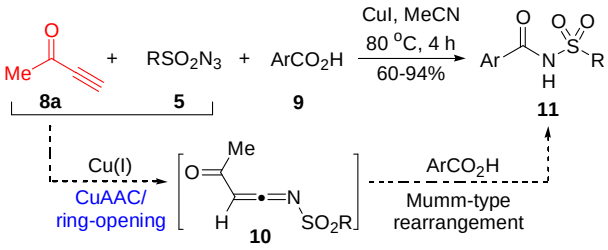


Scheme 1. Generation of *N*-sulfonyl ketenimines **3**.

By the electron-withdrawing effect of the sulfonyl group, both electrophilicity and polarization of *N*-sulfonyl ketenimines **3** were enhanced significantly. Thus, ketenimines **3** easily underwent nucleophilic additions with *C*-, *N*-, *O*- or *S*-nucleophiles and [2 + 2] cycloadditions. In the past decade, this CuAAC/ring-opening method was well-developed and the versatile reactions of *N*-sulfonyl ketenimines **3** were well-reviewed.[2c-d] Interestingly, ynones usually were not employed in this method although many of them are commercially available.[7]

Herein, we report a novel ynone-participated CuAAC/ring-opening method as shown in Scheme 2. 3-Butyn-2-one (**8a**) and

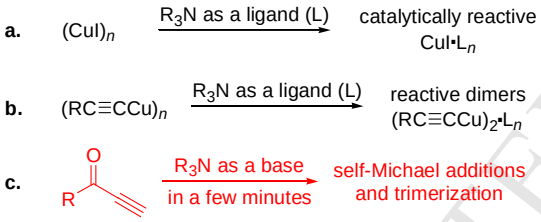
sulfonyl azide **5** underwent a CuAAC/ring-opening process to generate a highly reactive intermediate *N*-sulfonyl acetylketenimine **10**, which was then trapped by aryl carboxylic acids **9** to give a series of *N*-aroylsulfonamides **11** via a Mumm-type rearrangement.



Scheme 2. *N*-Sulfonyl acetylketenimine **10** as a highly reactive intermediate.

2. Results and Discussion

Investigation showed that CuI/R_3N is the most efficient catalytic system for CuAAC/ring-opening method. As shown in Scheme 3a-3b, R_3N is an essential ligand (L) that serves two purposes:[8] (a) to dissociate the polymeric $(CuI)_n$ into the catalytically reactive $CuI{\cdot}L_n$ species; (b) to dissociate the *in situ* formed polymeric $(RC{\equiv}CCu)_n$ into the reactive dimers $(RC{\equiv}CCu)_2{\cdot}L_n$. However, the terminal ynones can not survive in the presence of R_3N because R_3N is also functioned as a base to efficiently catalyze the self-Michael addition and the trimerization of ynones within a few minutes (Scheme 3c).[9] These results may well explain why ynones did not be used in CuAAC/ring-opening method.

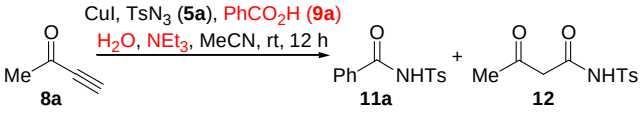


Scheme 3. Possible reasons why ynones did not be used.

Further investigation indicated that $(CuI)_n$ can be dissociated into catalytically reactive Cu(I) species in CH_3CN[10] and $(RC{\equiv}CCu)_n$ can be dissociated into the reactive dimers using carboxylic acids as additives.[8,11] Thus, a group of conditional experiments in CH_3CN were tested by using 3-butyn-2-one (**8a**), TsN_3 (**5a**) and H_2O (Nu-H) as model substrates in the presence of $PhCO_2H$ (**9a**). As shown in Table 1, an inseparable mixture was obtained in the presence of Et_3N (entry 1). The product **12** was obtained in 88% yield via a normal CuAAC/ring-opening pathway without Et_3N (entry 2). Interestingly, when 0.5 equivalents of $PhCO_2H$ were used, an unexpected product *N*-benzoyltosylamide (**11a**) was separated in 15% yield besides the product **12** (entry 3). In the absence of H_2O, **11a** was obtained as a single product in 30% yield when one equivalent of $PhCO_2H$ was used (entry 4). The results in entries 5 and 6 indicated that both CuI and 3-butyn-2-one (**8a**) were essential to the formation of **11a**.

The results in Table 1 indicate that the products **11a** and **12** may come from two competitive reactions of the same intermediate. Therefore, a possible pathway is proposed as shown in Scheme 4. Initially, **5a** and **8a** gave a new reactive

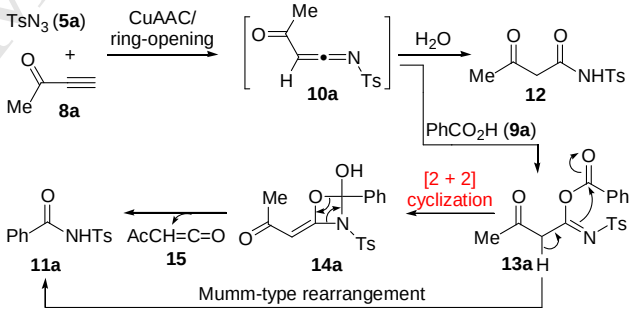
Table 1. A group of conditional tests and the results.[a]



entry	$PhCO_2H$ (eq.)	H_2O (eq.)	Et_3N (eq.)	**11a**/**12** (%)[b]
1	0.1	1	1	inseparable mixture
2	0.1	1	---	0/88
3	0.5	1	---	15/53
4	1	---	---	30/0
5[c]	1	---	---	0/0
6[d]	1	---	---	0/0

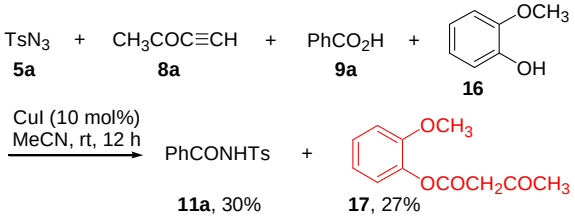
[a] A mixture of **5a** (0.5 mmol), **8a** (0.5 mmol), CuI (0.05 mmol) and others in MeCN (3 mL) was stirred at room temperatures for 12 h. [b] Isolated yields. [c] The reaction without CuI. [d] The reaction without **8a**.

intermediate **10a**. When **10a** was attacked by a nucleophile H_2O or $PhCO_2H$ (**9a**), the expected **12** or **13a** was produced, respectively. However, the isoimides **13a** underwent further an intramolecular cyclization to give a [2 + 2] product **14a**. Finally, **11a** was obtained via a ring-opening of **14a** with the release of acetylketene (**15**). The conversion of **13a** into **11a** in fact was a Mumm-type rearrangement.[12] In a typical Mumm rearrangement, the *O*,*N*-acyl migration of the isoimides went through a four-membered ring transition state[13] and a cleavage of the acyl-oxygen (C–O) bond. However, by the electron-withdrawing and conjugating effects of the acetyl group, both a C–O bond and a C–N bond in the four-membered ring of **14a** were cleaved. To the best of our knowledge, this is the first example of Mumm-type rearrangement involving two-bond cleavages.



Scheme 4. A proposed pathway for the formation of **11a** and **12**.

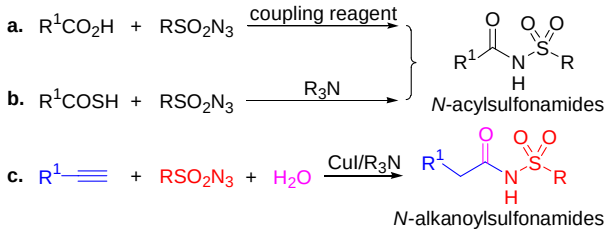
The attempts to isolate the intermediate **13a** failed due to its instability.[13] However, the acetylketene (**15**) was successfully trapped as shown in Scheme 5. When 2-methoxyphenol (**16**) was added into the reaction, the desired 2-methoxyphenyl 3-oxobutanoate (**17**) was obtained in 27% yield.



Scheme 5. An experiment to trap acetylketene **15**.

We then attempted to develop a new method for the synthesis of *N*-acylsulfonamides based on our above findings. Investigation showed that *N*-acylsulfonamides are a type of sulfonamides with special properties. They have similar acidity (pK_a = 4-5) to

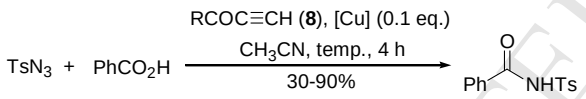
carboxylic acids, but are stable under physiological conditions and in chemical transformations. Therefore, they often serve as carboxylic acid bioisosteres in drug design and synthesis.[14] Numerous methods have been developed for the synthesis of *N*-acylsulfonamides by coupling the derivatives between carboxylic acid and sulfonamide.[14] Prominent among them are those protocols developed recently using sulfonyl azides as alternatives of sulfonamides, by which clean products and high efficiency were achieved (Scheme 6a,[15] 6b,[16] and 6c[17]). The method-7c is actually a CuAAC/ring-opening method, which is limited to the synthesis of *N*-alkanoylsulfonamides because an extra CH_2 forms unavoidably in the conversion of alkyne into an acyl group.



Scheme 6. Some methods for the synthesis of *N*-acylsulfonamides.

Thus, we were encouraged to further optimize the synthesis of **11a**. As shown in Table 2, the yield of **11a** was influenced significantly by the temperature, and the best results were obtained in refluxing CH_3CN (entries 1-2). Other ynones **8b-8d** also could be used for this method, but with lower efficiency (entries 3-5). The results in entries 6-9 indicated that this conversion can be catalyzed by many copper salts. Finally, entry 2 was assigned as the standard conditions for its clean product and easy work-up.

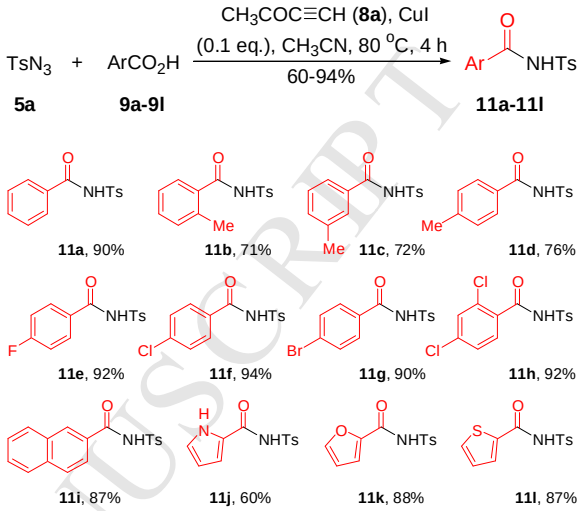
Table 2. Conditional tests for the synthesis of **11a**.[a]



Entry	R in **8**	[Cu(I)]	temp. (°C)	**11a** (%)[b]
1	CH_3- (**8a**)	CuI	25	32[c]
2	CH_3- (**8a**)	CuI	80	90
3	*n*-C_5H_{11}- (**8b**)	CuI	80	85
4	EtO- (**8c**)	CuI	80	67
5	Ph- (**8d**)	CuI	80	53
6	CH_3- (**8a**)	CuBr	80	88
7	CH_3- (**8a**)	CuCl	80	83
8	CH_3- (**8a**)	$Cu(OAc)_2 \cdot H_2O$	80	87
9	CH_3- (**8a**)	$Cu(acac)_2$	80	90

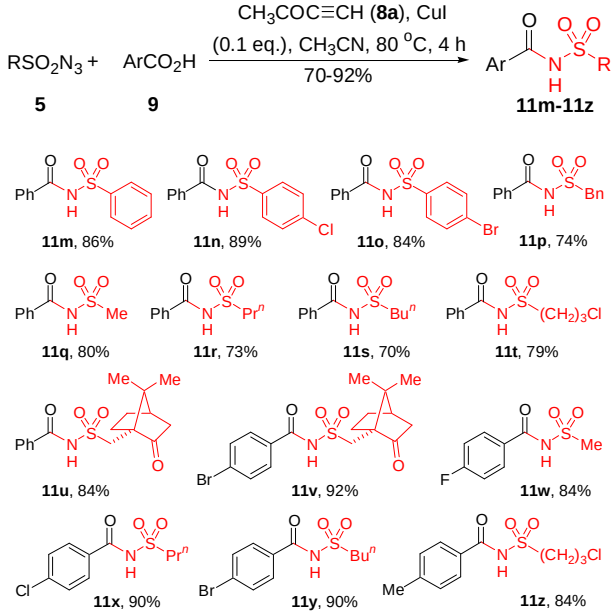
[a] A mixture of **5a** (0.5 mmol), **9a** (0.75 mmol), **8** (0.75 mmol) and Cu-catalyst (0.05 mmol) in MeCN (3 mL) was stirred at the given temperatures for 4 h. [b] Isolated yields. [c] 12 h.

To generalize this method, its scope was tested by using different substrates. As shown in Scheme 7, products **11a-11l** were synthesized in good to excellent yields by fixing tosyl azide (**5a**). This method was very suitable for those aromatic acids substituted by electrically neutral groups. However, the benzoic acids substituted by strong EDG or EWG gave unacceptable yields (for example, the products from 4-methoxybenzoic acid and 4-nitrobenzoic acid were obtained in 13% and 6% yields, respectively). These results can be well explained by the mechanism described in Scheme 5. For example, EWG on **9a** is unfavorable for the conversion of **10a** into **13a**, while EDG on **9a** is unfavorable for the conversion of **13a** into **14a**. As was expected, the aliphatic acids ($MeCO_2H$ and *n*-$PrCO_2H$) gave only complicated mixtures because the intermediate isoimides (**13**) are a type of acylating reagent[18] and the isoimides generated from aliphatic acids (the derivatives of **13**) have the most reactivity. Thus, their acetyl carbonyl was attacked preferentially by another acid[13d,18] to form an anhydride rather than carrying out a *O*,*N*-acyl migration.



Scheme 7. Synthesis of the products **11a-11l**.

This method has wide scope of sulfonyl azides (Scheme 8). Both aryl and alkyl sulfonyl azides gave the corresponding **11m-11o** and **11p-11z**, respectively, in good to excellent yields.



Scheme 8. Synthesis of the products **11m-11z**.

3. Conclusions

In summary, by careful investigation, the reason why ynones did not be used in CuAAC/ring-opening method was well elucidated. Furthermore, an ynone-participated CuAAC/ring-opening method was developed under neutral conditions to efficiently generate a highly reactive intermediate *N*-sulfonyl

acetylketenimine. Since this ketenimine has a unique structure bearing two EWGs (acetyl and sulfonyl groups), it has much higher reactivity than normal ketenimines and even *N*-sulfonyl ketenimines. Finally, a novel method for the synthesis of *N*-aroylsulfonamides was developed.

4. Experimental Section

4.1. General

All melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All spectra of ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM-ECA 400 spectrometer in DMSO-d_6 or $CDCl_3$. TMS was used as an internal reference and *J* values are given in Hz. HRMS were obtained on a Bruker micrOTOF-Q II spectrometer.

*4.2. A typical procedure for synthesis of N-[(4-methylphenyl)sulfonyl]benzamide (**11a**).*

To a solution of benzoic acid (**9a**, 61 mg, 0.5 mmol), TsN_3 (**5a**, 148 mg, 0.75 mmol) and CuI (9.6 mg, 0.05 mmol) in MeCN (3 mL) was added but-3-yn-2-one (51 mg, 0.75 mmol). After the mixture was stirred at 80 °C for 4 h (monitored by TLC), the solvent was removed. The residue was purified by a flash chromatography [silica gel, 1% MeOH and 20% EtOAc in petroleum ether (60–90 °C)] to give 124 mg (90%) of product **5a** as a white solid, mp 140−142 °C (lit.[19] 148−150 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.05−8.04 (m, 2H), 7.85−7.83 (m, 2H), 7.54−7.51 (m, 1H), 7.41−7.38 (m, 2H), 7.34−7.26 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 145.2, 135.4, 133.4, 131.0, 129.6 (2C), 128.8 (2C), 128.5 (2C), 127.9 (2C), 21.6.

The products **11b-11z** were prepared by the similar procedure.

*4.2.1. N-[(4-Methylphenylsulfonyl)]-2-methylbenzamide (**11b**).*

103 mg (71%), white solid, mp 113−114 °C (lit.[20a] 114−116 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.33−7.29 (m, 3H), 7.17−7.13 (m, 2H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 145.0, 137.8, 135.5, 132.0, 131.6, 131.5, 129.5 (2C), 128.4 (2C), 127.3, 125.8, 21.6, 20.0.

*4.2.2. N-[(4-Methylphenylsulfonyl)]-3-methylbenzamide (**11c**).*

104 mg (72%), white solid, mp 121−123 °C (lit.[20a] 132−134 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.65−7.62 (m, 2H), 7.32−7.24 (m, 4H), 2.41 (m, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 145.0, 138.7, 135.5, 134.1 (2C), 131.0, 129.5 (2C), 128.6, 128.5 (2C), 124.9, 21.6, 21.1.

*4.2.3. N-[(4-Methylphenylsulfonyl)]-4-methylbenzamide (**11d**).*

110 mg (76%), white solid, mp 138−140 °C. (lit.[20b] 137−138 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 145.0, 144.2, 135.6, 129.5 (2C), 129.4 (2C), 128.5 (2C), 128.3, 127.9 (2C), 21.6, 21.5.

*4.2.4. N-[(4-Methylphenylsulfonyl)]-4-fluorobenzamide (**11e**).*

135 mg (92%), white solid, mp 107−109 °C (lit.[20c] 114−116 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 7.97−7.92 (m, 2H), 7.91−7.89 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.33−7.27 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0 (d, *J* = 249.8 Hz), 164.3, 144.3, 136.6, 131.4 (d, *J* = 9.5 Hz, 2C), 129.5 (2C), 128.1 (d, *J* = 2.9 Hz), 127.8 (2C), 115.7 (d, *J* = 22.9 Hz) (2C), 21.1.

*4.2.5. N-[(4-Methylphenylsulfonyl)]-4-chlorobenzamide (**11f**).*

145 mg (94%), white solid, mp 175−176 °C (lit.[20b] 169−170 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 7.91−7.86 (m, 4H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 144.4, 138.2, 136.5, 131.2, 130.4 (2C), 129.6 (2C), 128.7 (2C), 127.8 (2C), 21.1.

*4.2.6. N-[(4-Methylphenylsulfonyl)]-4-bromobenzamide (**11g**).*

159 mg (90%), white solid, mp 141−143 °C (lit.[20a] 199−201 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.80−7.78 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 144.4, 136.4, 131.7 (2C), 130.6, 130.4 (2C), 129.6 (2C), 127.8 (2C), 127.3, 21.1.

*4.2.7. N-[(4-Methylphenylsulfonyl)]-2,4-dichlorobenzamide (**11h**).*[20d]

158 mg (92%), white solid, mp 154−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.38−7.35 (m, 3H), 7.30−7.27 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 145.6, 138.7, 135.2, 132.1, 131.8, 130.5, 130.3, 129.7 (2C), 128.7 (2C), 127.8, 21.8.

*4.2.8. N-(4-Methylphenyl)-2-naphthamide (**11i**).*

141 mg (87%), white solid, mp 154−155 °C. (lit.[20e] 106−110 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.58 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 8.00−7.93 (m, 4H), 7.86−7.84 (m, 1H), 7.68−7.59 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 144.3, 136.6, 134.9, 131.8, 129.8, 129.6 (2C), 129.3, 128.8, 128.7, 128.3, 127.8 (2C), 127.7, 127.1, 124.1, 21.1.

*4.2.9. N-(4-Methylphenyl)-pyrrole-2-carboxamide (**11j**).*

79 mg (60%), white solid, mp 124−125 °C (lit.[15] 160 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 11.72 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.14−7.12 (m, 1H), 7.02−7.01 (m, 1H), 6.14−6.12 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 144.0, 137.1, 129.4 (2C), 127.6 (2C), 125.1, 123.3, 114.9, 109.5, 21.1.

*4.2.10. N-(4-Methylphenyl)-furan-2-carboxamide (**11k**).*[20f]

117 mg (88%), white solid, mp 124−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 0.9 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 3.7 Hz, 1H), 6.53−6.51 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 145.8, 145.2, 145.1, 135.5, 129.5 (2C), 128.5 (2C), 118.0, 112.9, 21.6.

*4.2.11. N-(4-Methylphenyl)-thiophene-2-carboxamide (**11l**).*[20c]

122 mg (87%), white solid, mp 174−176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.07−8.06 (m, 1H), 7.94−7.93 (m, 1H), 7.89−7.87 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.20−7.17 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 144.4, 136.5, 136.4, 134.7, 132.3, 129.6 (2C), 128.6, 127.8 (2C), 21.6.

*4.2.12. N-(Phenylsulfonyl)benzamide (**11m**).*

112 mg (86%), white solid, mp 147−149 °C. (lit.[19] 165 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.04−8.02 (m, 2H), 7.88−7.86 (m, 2H), 7.73−7.69 (m, 1H), 7.66−7.59 (m, 3H), 7.50−7.46 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 139.6, 133.6, 133.3, 131.6, 129.1 (2C), 128.6 (2C), 128.4 (2C), 127.7 (2C).

*4.2.13. N-[(4-Chlorophenyl)sulfonyl]benzamide (**11n**).*

131 mg (89%), white solid, mp 172−174 °C. (lit.[19] 186 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.04−8.00 (m, 2H), 7.88−7.85 (m, 2H), 7.74−7.71 (m, 2H), 7.65−7.60 (m, 1H), 7.51−7.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 138.6, 138.5, 133.3, 131.5, 129.7 (2C), 129.3 (2C), 128.6 (2C), 128.5 (2C).

*4.2.14. N-[(4-Bromophenyl)sulfonyl]benzamide (**11o**).*[20g]

142 mg (84%), white solid, mp 168−170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 7.95−7.93 (m, 2H), 7.88−7.85 (m, 4H), 7.63−7.60 (m, 1H), 7.50−7.46 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 138.8, 133.4, 132.2 (2C), 131.4, 129.8 (2C), 128.6 (2C), 128.5 (2C), 127.7.

*4.2.15. N-(Benzylsulfonyl)benzamide (**11p**).*

102 mg (74%), white solid, mp 137−138 °C. (lit.[20h] 145−147 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.91−7.89 (m, 2H), 7.66−7.63 (m, 1H), 7.53−7.38 (m, 2H), 7.39−7.33 (m, 5H), 4.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 133.3, 131.7, 130.8 (2C), 129.1, 128.6 (4C), 128.5 (3C), 58.0.

*4.2.16. N-(Methylsulfonyl)benzamide (**11q**).*[20g]

80 mg (80%), white solid, mp 126−128 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 7.95−7.93 (m, 2H), 7.67−7.63 (m, 1H), 7.54−7.50 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 133.2, 131.7, 128.6 (2C), 128.4 (2C), 41.4.

*4.2.17. N-(Propylsulfonyl)benzamide (**11r**).*

83 mg (73%), white solid, mp 75−76 °C. (lit.[20i] 119 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.95−7.93 (m, 2H), 7.67−7.63 (m, 1H), 7.54−7.50 (m, 2H), 3.50 (t, J = 7.6 Hz, 2H), 1.79−7.93 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 133.2, 131.7, 128.6 (2C), 128.5 (2C), 54.0, 16.8, 12.5.

*4.2.18. N-(Butylsulfonyl)benzamide (**11s**).*

84 mg (70%), yellow oil (lit.[20i] 65 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.91 (d, J = 7.8 Hz, 2H), 7.62−7.58 (m, 1H), 7.49−7.45 (m, 2H), 3.59 (t, J = 7.8 Hz, 2H), 1.87−1.79 (m, 2H), 1.51−1.42 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.6, 130.9, 128.8 (2C), 128.0 (2C), 53.2, 25.0, 21.2, 13.4.

*4.2.19. N-[(3-Chloropropyl)sulfonyl]benzamide (**11t**).*

103 mg (79%), white solid, mp 113−114 °C. IR (KBr) ν 3165, 2705, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.88 (d, J = 7.3 Hz, 2H), 7.62−7.58 (m, 1H), 7.49−7.45 (m, 2H), 3.76 (t, J = 7.1 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 2.36−2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.8, 130.7, 128.9 (2C), 128.0 (2C), 50.9, 42.2, 26.3. HRMS (ESI-TOF) (*m/z*) calcd for $C_{10}H_{12}ClNO_3S$, $[M+Na]^+$ 284.0119; found 284.0120.

*4.2.20. N-[(1R)-(+)-Camphorsulfonyl)]-benzamide (**11u**).*

141 mg (84%), yellow oil. IR (KBr) ν 3413, 3255, 1744, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.92 (m, 2H), 7.59−7.56 (m, 1H), 7.47−7.44 (m, 2H), 4.03 (d, J = 15.1 Hz, 1H), 3.57 (d, J = 15.1 Hz, 1H), 2.39−2.28 (m, 2H), 2.11−2.01 (m, 2H), 1.86−1.77 (m, 2H), 1.42−1.36 (m, 1H), 1.07 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 165.9, 133.2, 131.4, 128.7 (2C), 128.1 (2C), 58.7, 51.1, 48.5, 42.6, 42.4, 26.9, 25.4, 19.6, 19.5; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{21}NO_4S$, $[M+Na]^+$ 358.1083; found 358.1088.

*4.2.21. N-[(1R)-(+)-Camphorsulfonyl)]-4-bromo-benzamide (**11v**).*

190 mg (92%), white solid, mp 164−166 °C. IR (KBr) ν 3413, 3128, 2963, 1735, 1698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 7.89−7.86 (m, 2H), 7.74−7.72 (m, 2H), 3.90 (d, J = 15.1 Hz, 1H), 3.45 (d, J = 15.1 Hz, 1H), 2.38−2.31 (m, 2H), 2.06−2.04 (m, 1H), 1.98−1.88 (m, 2H), 1.65−1.58 (m, 1H), 1.44−1.38 (m, 1H), 1.01 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 214.0, 165.8, 131.6 (2C), 131.2, 130.6 (2C), 127.1, 58.0, 49.6, 47.9, 42.0, 41.0, 26.4, 24.5, 19.4, 19.3; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{20}BrNO_4S$, $[M+Na]^+$ 436.0189; found 436.0190.

*4.2.22. N-(Methylsulfonyl)-4-fluorobenzamide (**11w**).*

91 mg (84%), white solid, mp 91−93 °C. IR (KBr) ν 3414, 3251, 3031, 1677 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.04−8.00 (m, 2H), 7.38−7.33 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 165.0 (d, J = 250.8 Hz), 131.5 (d, J = 9.5 Hz) (2C), 128.3 (d, J = 2.9 Hz), 115.7 (d, J = 21.9 Hz, 2C), 41.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_8FNO_3S$, $[M+Na]^+$ 240.0101; found 240.0105.

*4.2.23. N-(Propylsulfonyl)-4-chlorobenzamide (**11x**).*

117 mg (90%), white solid, mp 131−133 °C. IR (KBr) ν 3412, 3233, 2920, 1677 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.59−7.57 (m, 2H), 3.50 (t, J = 7.6 Hz, 2H), 1.79−1.69 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 138.2 (2C), 130.4 (2C), 128.8 (2C), 54.0, 16.8, 12.5; HRMS (ESI-TOF) (*m/z*) calcd for $C_{10}H_{12}ClNO_3S$, $[M+Na]^+$ 284.0119; found 284.01122.

*4.2.24. N-(Butylsulfonyl)-4-bromobenzamide (**11y**).*

144 mg (90%), white solid, mp 118−120 °C. IR (KBr) ν 3416, 3278, 2957, 1695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 7.88−7.86 (m, 2H), 7.73−7.72 (m, 2H), 3.51 (t, J = 7.3 Hz, 2H), 1.72−1.64 (m, 2H), 1.43−1.37 (m, 2H), 0.88−0.84 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 131.7 (2C), 130.8, 130.5 (2C), 127.3, 52.0, 24.9, 20.7, 13.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_{11}H_{14}BrNO_3S$, $[M+Na]^+$ 341.9770; found 341.9773.

*4.2.25. N-[(3-Chloropropyl)sulfonyl]-4-methylbenz-amide (**11z**).*

116 mg (84%), white solid, mp 139−141 °C. IR (KBr) ν 3413, 3241, 2926, 1707 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.4 Hz, 2H), 3.77 (t, J = 5.7 Hz, 2H), 3.66 (t, J = 7.3 Hz, 2H), 2.38 (s, 3H), 2.18−2.15 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 143.8, 129.2 (2C), 128.8, 128.6 (2C), 49.9, 43.0, 26.6, 21.1; HRMS (ESI-TOF) (*m/z*) calcd for $C_{11}H_{14}ClNO_3S$, $[M+Na]^+$ 298.0275; found 298.0272.

*4.3. 2-Methoxyphenyl 3-oxobutanoate (**17**).*[7]

28 mg (27%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 1H), 7.09−7.06 (m, 1H), 7.00−6.94 (m, 2H), 3.83 (s, 3H) , 3.69 (s, 2H) , 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 165.2, 150.9, 139.3, 127.3, 122.6, 120.8, 112.4, 55.8, 49.8, 30.0.

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