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MICROWAVE ASSISTED ONE-POT SYNTHESIS AND CHARACTERIZATION OF BENZOXAZOLE CONTAINING MULTI SUBSTITUTED 1,2,3-TRIAZOLES

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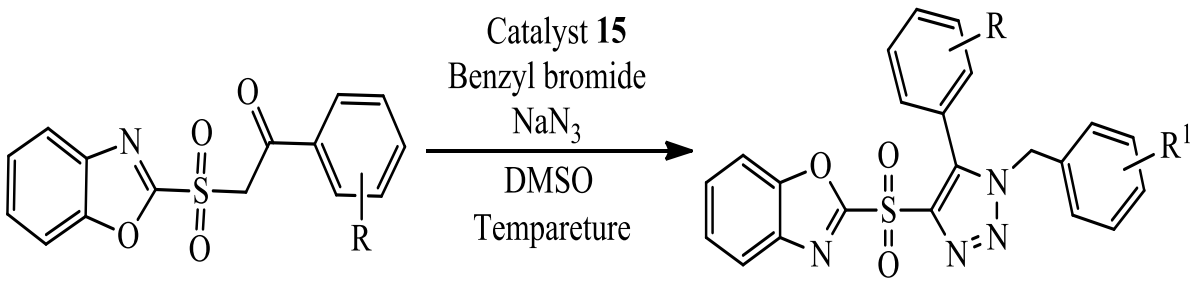
Abstract:- ***Developing a new method for the synthesis of highly functionalized 1,2,3-triazoles encouraged us to test the three-component reactions between 2-(benzo[d]oxazol-2-ylsulfonyl)-1-phenylethanone (14), benzyl bromide and sodium azide with the base under microwave condition. Herein, we would like to describe an efficient method for obtaining 1,4,5-trisubstituted-1,2,3-triazoles (Scheme 1). Our initial investigation was started with one pot [3+2] cycloaddition reaction of benzyl bromide, sodium azide and 2-(benzo[d]oxazol-2-ylsulfonyl)-1-phenylethanone (14) by following the previously reported literature condition[24]. However, the reaction did not proceed and the desired product 16a was not obtained (Table 1, entry 1). The same reaction was carried out above 80 °C temperature condition by using triethylamine (5 and 10 mol %) (15a) as catalyst the products were obtained in low yield (Table 1, entry 2). Our investigation of 15b, 15c, 15d, 15e and 15f as the catalysts showed that 15d (5 mol %) was optimal (Table 1, entries 3- 7). When the same reaction was carried out under microwave irradiation resulted in the generation of the desired product 16a in an excellent yield (Table 1, entry 8). It was also found that the loadings of catalyst could be increased to 10 mol% almost without affecting the yield of the desired products (Table 1, entry 9). Thus, the combination of 5 mol% of 15d in the presence of DMSO under microwave irradiation was the optimal reaction conditions. The compounds were further confirmed by spectral analysis data.***

Keywords: triazoles , benzoxazoles,sodium azide,MWI.



14 **16a-17e**

Scheme 1: MWI one-pot synthesis of fully substituted 1,2,3-triazoles

Introduction

Heterocyclic compounds containing 1,2,3-triazoles constitute one of the most active classes of compounds possessing diverse pharmacological activity. A brief account of the synthesis and biological importance of various heterocyclic linked 1,2,3-triazoles is furnished below

Piotrowska and co-workers[1] ported a new antiviral active isoxazolidine nucleotide analogues with a 1,2,3-triazole linker. The synthesized compounds were evaluated for their *in vitro* activity against a variety of DNA and RNA viruses. Compounds exhibited cytostatic activity at a higher micromolar range. Bennet and co-workers [2] reported the best example of 1,2,3-triazole containing molecule is tazobactam, **2** a β-lactamase inhibitor which is marketed in combination with the broad spectrum antibiotic piperacillin.

Synthesis of novel pyrazolyl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolylthiazoles using 1-tolylyl-4-acetyl-5-methyl-1,2,3-triazole as a precursor through a series of multistep reactions was discovered by Wahab and co-workers.[3] The compound was found to be a potent antimicrobial agent. Mohapatra research group[4] carried out a new tetracyclic fused 1,2,3-triazolyl benzodiazepine compounds as enzymatic protease inhibitors like serine protease.

Synthesis and evaluated for their *in vitro* antimycobacterial activity of some new dibenzofuran linked 1,2,3-triazoles reported by Yempala and co-workers.[5] The compound **5** was found to be a potent antitubercular agent with the lowest cytotoxicity against the HEK-293T cell line. Synthesis and screened for their antimicrobial and antimycobacterial activity of some new benzimidazole containing 1,2,3-triazoles reported by Gill and co-workers.[6] The compshowed excellent activity in both microbial and mycobacterial activity.

Synthesis novel chalcone-pyrrolo[2,1-c] [1,4]benzodiazepine (PBD) derivatives using alkane spacers and linked through a 1,2,3-triazole moiety by Kamal et al.[7] among all the derivatives the compound was found to be the more potent than a standard drug with MIC ranging from 0.12-2.03 μM against eleven different cancer cell lines.

Synthesis and evaluated for their *in vitro* antimycobacterial activity of some new dibenzofuran linked 1,2,3-triazoles reported by Yempala and co-workers.[8] The compound was found to be a potent antitubercular agent with the lowest cytotoxicity against the HEK-293T cell line.

Fray *et al.*[9] carried out a new 1,2,3-triazole substituted quinoxaline derivatives and screened for their biological function as N-methyl-D-aspartate (NMDA) receptor antagonists. Among all the derivatives compound possessed IC_{50}=7.6 nM for binding and EC_{50}=88 nM in the cortical wedge assay, data which compare favorably with the standard.

Synthesis and potent antifungal activity of new indole-triazole-amino acid derivatives were developed by Komatha and Palwinder research group[10] by using click chemistry condition.

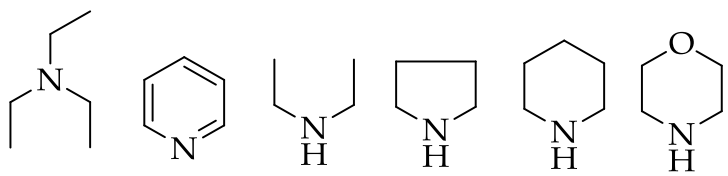
Minvielle group reported Indole–triazole conjugates are selective inhibitors andinducers of bacterial biofilms.[11]Synthesis and screened for their *in vitro* and *in vivo* anti-inflammatory activity of new benzoxazolinone based 1,2,3-triazoles using click chemistry approach by Haider group in 2013.[12]

Literature survey revealed that Benzoxazoles and 1,2,3-triazole have shown potential biological activities and based on the above mentioned facts, we aimed to design a moiety that embodied both the active pharmacophores in a single molecular framework. Benzoxazoles and 1,2,3-triazole constitutes an important class of heterocyclic compound possessing a wide range of therapeutic value, in the current investigation the one-pot synthesis of Benzoxazoles containing 1,2,3-triazole derivatives.

Table 1. Conditions used for preparation of **16a**[a]

Entry	Catalyst	Temperature (^{o}C)	Time (h)	Yield (%)
1	15a (5 mol %)	Rt	24	NR
2[b]	15a (5 mol %)	80	24	16, 22
3	15b (5 mol %)	100	24	18
4	15c (5 mol %)	100	20	38
5	15d (5 mol %)	100, 120,150	18	53, 55, 58
6	15e (5 mol %)	>100	18	31
7	15f (5 mol %)	>100	18	42
8	**15d (5 mol %)**	**MW/150 ^{o}C**	**30min**	**81**
9	15d (10 mol %)	MW/200 ^{o}C	30min	83

[a]*Reaction conditions*:1 (1.0 equiv), 1-bromohexane (1.3 equiv), NaN_3(1.3 equiv).[b] **2a** 5 mol% & 10 mol%,



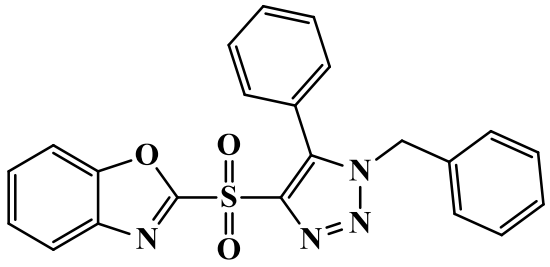
15a 15b 15c 15d 15e 15f

MATERIALS AND METHODS

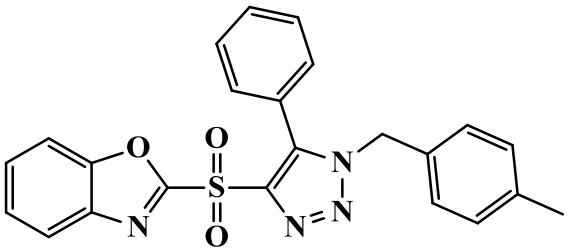
All the reagents and solvents were purchased from Aldrich/Merck and used without further purifications. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and Silica gel (100-200 mesh) was used for column chromatography. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with using ethylacetate /hexane (5/5) as eluent. Melting points were determined using a Cintex apparatus and are uncorrected. 400 MHz spectrometer was used to get ^{1}H-NMR spectra respectively. Coupling constant (*J*) values are presented in Hertz, spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded by using ESI–MS method.

Names & Structures of synthesized compounds16a-e &17a-e

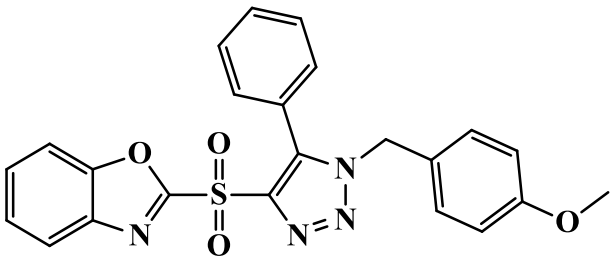
2-((1-benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d]oxazole (16a)



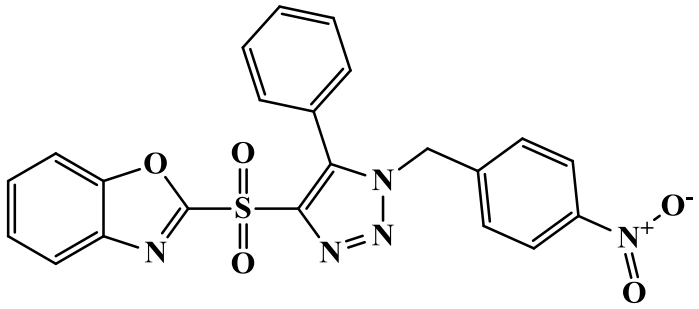
2-((1-(4-methylbenzyl)-5-phenyl-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d]oxazole (16b):



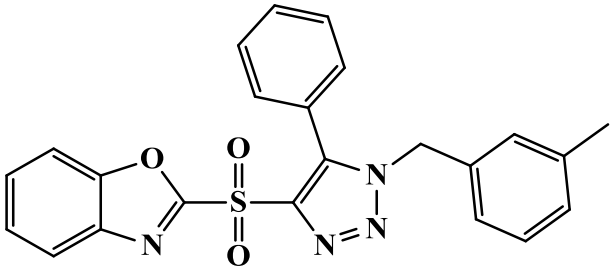
2-((1-(4-methoxybenzyl)-5-phenyl-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d] oxazole (16c):



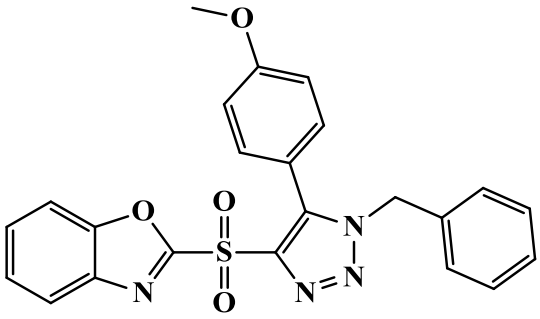
2-((1-(4-nitrobenzyl)-5-phenyl-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d]oxazole (16d):



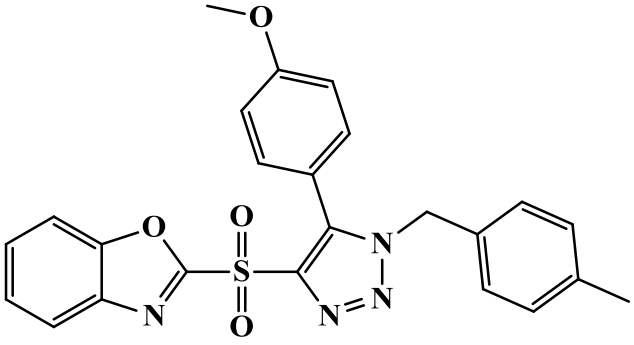
2-((1-(3-methylbenzyl)-5-phenyl-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d]oxazole (16e):



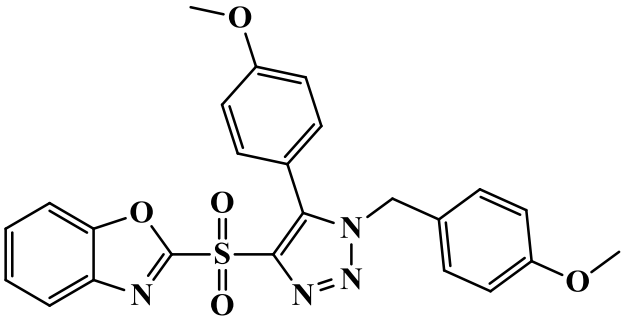
2-((1-benzyl-5-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)sulfonyl)benzo[d]oxazole (17a):



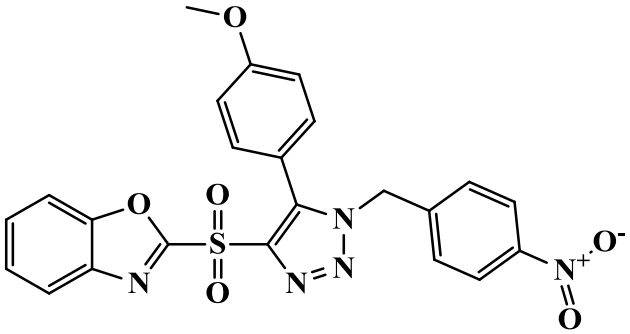
2-((5-(4-methoxyphenyl)-1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)sulfonyl) benzo[d]oxazole (17b):



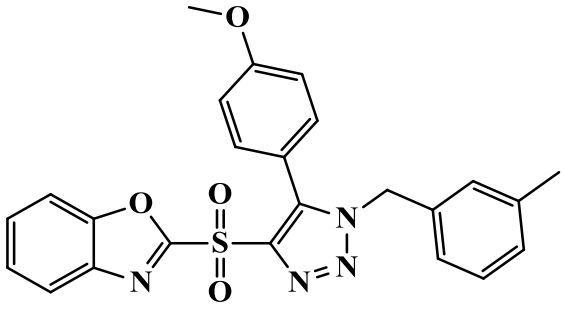
2-((1-(4-methoxybenzyl)-5-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)sulfonyl) benzo[d]oxazole (17c):



2-((5-(4-methoxyphenyl)-1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)sulfonyl) benzo[d]oxazole (17d):



2-((5-(4-methoxyphenyl)-1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)sulfonyl) benzo[d]oxazole (17e):



Spectral and Analytical data of synthesized compounds 16a-e &17a-e

16a: mp: 107-109 ^{o}C; IR (KBr, cm^{-1}) 3064, 1587, 1472, 1411; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.71 (m, 2H), 7.60 (d, *J* = 9.8 Hz, 2H), 7.47 (m, 4H), 7.42 – 7.26 (m, 6H), 5.32 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, DMSO) δ 160.23, 151.67, 136.31, 133.56, 132.42, 131.77, 130.89, 129.23, 128.71, 128.71, 128.54, 127.31, 127.13, 125.25, 123.32, 118.14, 110.20, 51.22. Anal. calcd. for $C_{22}H_{16}N_4O_3S$: C, 63.45; H, 3.87; N, 13.45. Found: C, 63.47; H, 3.83; N, 13.41; MS (ESI, m/z): 417 $[M+H]^+$.

16b: mp: 112-114 ^{o}C; IR (KBr, cm^{-1}) 3030, 1575, 1447, 1410; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.78 (m, 2H), 7.63 (s, 1H), 7.57 (s, 1H), 7.54 – 7.33 (m, 5H), 7.24 – 7.04 (m, 2H), 7.04 – 6.93 (m, 2H), 5.32 (s, 2H, N-CH_2), 2.26 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.83, 151.34, 137.89, 135.12, 134.30, 132.76, 131.40, 130.84, 130.09, 129.88, 129.04, 128.83, 127.13, 126.65, 125.81, 125.05, 123.62, 118.34, 111.40, 51.34, 21.51. Anal. calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.13; H, 4.24; N, 13.05; MS (ESI, m/z): 431 $[M+H]^+$.

16c: mp: z115-117 ^{o}C; IR (KBr, cm^{-1}) 2977, 1567, 1452, 1421; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 6 – 7.79 (m, 2H), 7.63 (s, 1H), 7.50 – 7.33 (m, 6H), 7.23 – 7.03 (m, 2H), 6.92 – 6.73 (m, 2H), 5.34 (s, 2H, N-CH_2), 3.82 (m, 3H, O-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.33, 158.23, 151.29, 136.78, 133.98, 132.67, 131.56, 130.98, 129.20, 128.98, 128.65, 128.13, 127.23, 126.88, 125.61, 123.78, 119.34, 117.08, 111.40, 55.44, 51.32. Anal. calcd. for $C_{23}H_{18}N_4O_4S$: C, 61.87; H, 4.06; N, 12.55. Found: C, 61.82; H, 4.09; N, 12.52; MS (ESI, m/z): 447 $[M+H]^+$.

16d: mp: 134-136 ^{o}C; IR (KBr, cm^{-1}) 3041, 1574, 1452, 1418; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 7.98 (m, 2H), 7.87 – 7.72 (m, 3H), 7.65 (t, *J* = 9.0 Hz, 2H), 7.52 – 7.40 (m, 6H), 5.42 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, DMSO) δ 160.63, 151.78, 138.04, 137.54, 135.10, 132.41, 131.34, 130.20, 129.88, 129.13, 128.43, 126.53, 125.45, 124.98, 124.21, 123.55, 117.34, 111.40, 51.23. Anal. calcd. for $C_{22}H_{15}N_5O_5S$: C, 57.26; H, 3.28; N, 15.18. Found: C, 57.31; H, 3.25; N, 15.13; MS (ESI, m/z): 462 $[M+H]^+$.

16e: mp: 122-124 ^{o}C; IR (KBr, cm^{-1}) 3079, 1557, 1470, 1419; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.79 (m, 2H), 7.63 – 7.57 (m, 2H), 7.54 – 7.40 (m, 5H), 7.37 (m, 1H), 7.13 (d, *J* = 13.1 Hz, 2H), 6.96 (s, 1H), 5.34 (s, 2H, N-CH_2), 2.32 (m, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.19, 151.87, 137.94, 137.24, 135.19, 132.47, 131.20, 130.80, 129.74, 129.03, 128.95, 128.53, 128.16, 127.90, 127.23, 124.46, 123.62, 118.34, 111.40, 51.42, 21.25. Anal. calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.11; H, 4.25; N, 13.06; MS (ESI, m/z): 431 $[M+H]^+$.

17a: mp: 136-138 ^{o}C; IR (KBr, cm^{-1}) 3044, 1569, 1461, 1418; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 4H), 7.45 (d, *J* = 13.8 Hz, 2H), 7.37 – 7.29 (m, 4H), 7.24 (s, 1H), 7.13 – 6.93 (m, 2H), 5.34 (s, 2H, N-CH_2), 3.81 (m, 3H, O-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 161.13, 158.67, 151.27, 136.10, 130.74, 130.02, 129.81, 129.01, 128.80, 128.73,128.34, 127.79, 125.45, 123.62, 118.34, 117.42,117.02, 110.40, 55.04, 51.52. Anal. calcd. for $C_{23}H_{18}N_4O_4S$: C, 61.87; H, 4.06; N, 12.55. Found: C, 61.89; H, 4.02; N, 12.59; MS (ESI, m/z): 447 $[M+H]^+$.

17b: mp: 153-155 ^{o}C; IR (KBr, cm^{-1}) 3041,1562, 1468, 1419; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 2H), 7.59 – 7.46 (m, 3H), 7.39 – 7.12 (m, 3H), 7.12 – 6.93 (m, 4H), 5.46 (s, 2H, N-CH_2), 3.83 (s, 3H, O-CH_3), 2.25 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.13, 158.81, 151.47, 137.72, 136.51, 132.67, 131.24, 130.62, 129.81, 129.61, 129.15, 128.34, 127.71, 125.35, 123.61, 119.67, 118.41, 117.61, 111.40, 55.04, 51.52, 21.13. Anal. calcd. for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.67; H, 4.35; N, 12.15; MS (ESI, m/z): 461 $[M+H]^+$.

17c: mp: 141-142 ^{o}C; IR (KBr, cm^{-1}) 2989, 1561, 1454, 1421; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 4H), 7.43 (d, *J* = 4.3 Hz, 2H), 7.22 – 7.12 (m, 1H), 7.12 – 6.92 (m, 3H), 6.92 –

6.72 (m, 2H), 5.35 (s, 2H,-N-CH_2), 3.86 (s, 3H, O-CH_3), 3.88 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.89, 159.13, 158.71, 150.92, 136.32, 131.14, 130.82, 129.81, 129.4, 128.23, 127.55, 126.34, 125.22, 123.41, 118.21, 117.88, 117.10, 114.89, 113.02, 111.43, 55.81, 55.10, 51.19. Anal. calcd. for $C_{24}H_{20}N_4O_5S$: C, 60.49; H, 4.23; N, 11.76. Found: C, 60.46; H, 4.28; N, 11.72; MS (ESI, m/z): 477 $[M+H]^+$

17d: mp: 161-163 ^oC; IR (KBr, cm^{-1}) 2987, 1565, 1467, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.00 (m, 2H), 7.63 (m, 2H), 7.60 – 7.46 (m, 3H), 7.45 (dd, J = 5.6, 4.2 Hz, 3H), 7.12 – 6.92 (m, 2H), 5.35 (s, 2H,-N-CH_2), 3.86 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, DMSO) δ 160.13, 159.61, 151.67, 147.88, 142.43, 136.19, 130.65, 130.27, 129.24, 128.55, 128.26, 127.91, 125.33, 124.56, 124.44, 123.12, 118.34, 117.42, 117.02, 110.40, 55.32, 51.55. Anal. calcd. for $C_{23}H_{17}N_5O_6S$: C, 56.21; H, 3.49; N, 14.25. Found: C, 56.25; H, 3.46; N, 14.21; MS (ESI, m/z): 492 $[M+H]^+$.

17e: mp: 145-147 ^oC; IR (KBr, cm^{-1}) 3074, 1565, 1467, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.50 (m, 5H), 7.43 (s, 1H), 7.34 (s, 1H), 7.16 – 7.09 (m, 3H), 6.99 (d, J = 29.3 Hz, 2H), 5.35 (s, 2H,-N-CH_2), 3.78 (s, 3H, O-CH_3), 2.41 – 2.36 (m, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.09, 158.92, 151.67, 138.04, 136.14, 135.12, 131.34, 131.32, 129.31, 128.67, 128.16, 126.61, 124.36, 122.55, 119.14, 118.12, 117.52, 111.47, 55.44, 51.62, 21.32. Anal. calcd. for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.67; H, 4.35; N, 12.13; MS (ESI, m/z): 461 $[M+H]^+$.

Conclusion

We have developed a versatile microwave assisted organocatalytic one-pot three component reaction that generates fully substituted 1,2,3-triazoles. This protocol highlights the metal-free conditions with high regioselectivity, and it provides an easy access to diversely functionalized 1,2,3-triazoles.

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