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MULTICOMPONENT CYCLOCONDENSATIONS OF β-KETOSULFONES WITH ALDEHYDES AND AMINOAZOLE BUILDING BLOCKS

Eugene S. Gladkov,[a,b*] Valentin A. Chebanov,[a] Sergey M. Desenko,[a] Oleg V. Shishkin,[a] Svetlana V. Shishkina,[a] Doris Dallinger,[b] and C. Oliver Kappe[b*]

[a] State Scientific Institution "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Lenin Ave, 60, Kharkiv, Ukraine, 61001, gladkov@isc.kharkov.com

[b] Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria, oliver.kappe@uni-graz.at

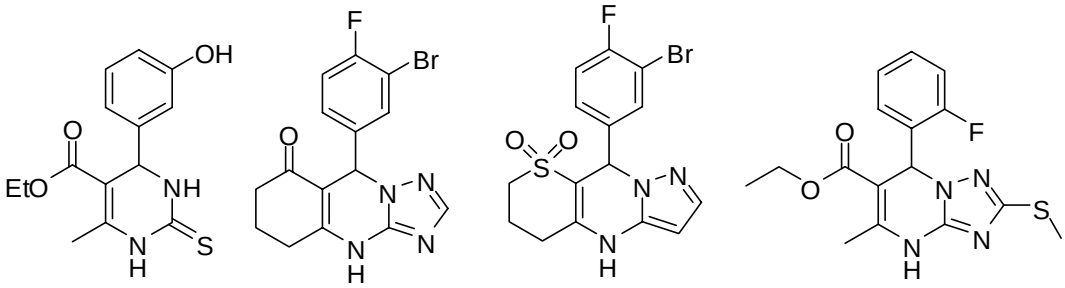
Abstract – The multicomponent reaction of methylsulfonylacetone (or α-methylsulfonylacetophenone) with aromatic aldehydes and aminoazoles (or urea) under microwave irradiation to yield 5,8-dihydroimidazolo[1,2-*a*]pyrimidines and 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines was studied. The influence of the type of aminoazole building block on the reactivity was established. In addition, an unusual reaction pathway for the Biginelli-type condensation of methylsulfonylacetone with aldehydes and urea leading to non-classical Hantzsch-type dihydropyridines was found.

INTRODUCTION

Partially hydrogenated pyrimidines and azolopyrimidines play an important role in medicinal chemistry. Some of these nitrogen-containing heterocycles (Figure 1) are known as mitotic kinesin Eg5 inhibitors, cardiovascular vasodilators, calcium channel blocking agents, potassium channel inhibitors and openers.[1,2] One of the most facile synthetic routes to dihydroazolopyrimidines is based on the Biginelli- or Hantzsch-type cyclocondensation of aldehydes with aminoazoles and CH-acidic compounds. There is ample precedent in the literature for the synthesis of fused azolopyrimidines by treatment of 3-amino-1,2,4-triazole, 5-aminotetrazole and 5-aminopyrazoles with aldehydes and acetoacetic acid derivatives, pyruvic acids or cyclic β-diketones.[2-4]

The known pharmacological activity of heterocycles containing both a sulfone and azolopyrimidine moiety (Figure 1)[2] stimulated our interest in the multicomponent reaction of β-ketosulfones with aromatic aldehydes and aminoazoles containing a guanidine fragment or with urea.[5] We here report on microwave-assisted[6] one-pot multicomponent cyclocondensations involving aromatic aldehydes containing substituents with different electronic nature, acyclic β-ketosulfones and aminoazoles such as 2-aminobenzimidazole (**3**) and 3-amino-1,2,4-triazole (**4**).

Figure 1. Selected examples of biologically active dihydropyrimidines.[1,2]

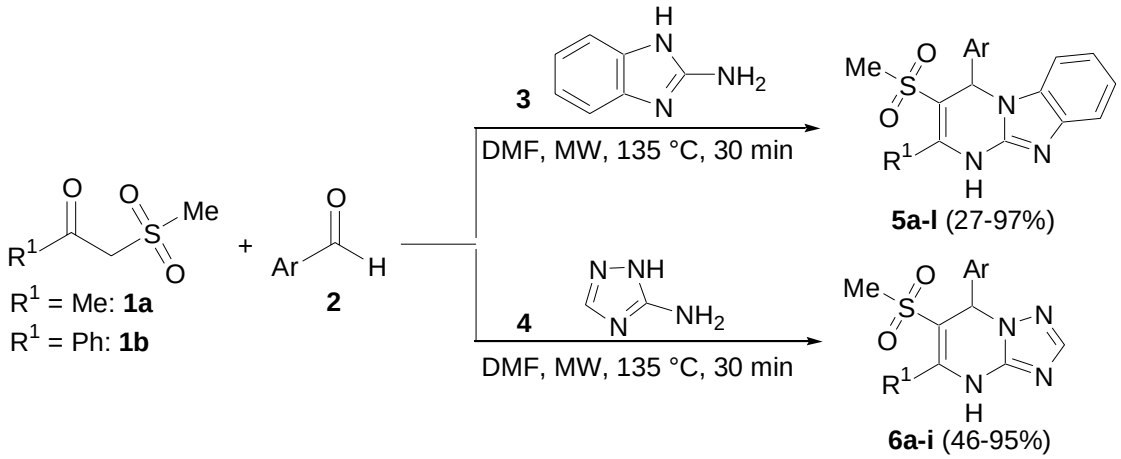


RESULTS AND DISCUSSION

In the course of our investigations we found that the microwave-assisted three-component condensation of benzimidazole **3**, methylsulfonylacetone (**1a**) or α-methylsulfonylacetophenone (**1b**), and the appropriate aromatic aldehyde **2** in DMF at 135 °C for 30 minutes led to the formation of the corresponding 5,8-dihydroimidazolo[1,2-*a*]pyrimidines **5a-l** (see Scheme 1 and Table 1). Applying the same reaction conditions for the triazole building block **4** the corresponding 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines **6a-i** were isolated in moderate to excellent yields (Scheme 1, Table 1). The purification step consists of simple product precipitation by addition of acetone. The reaction with 5-aminotetrazole was unsuccessful. Although a variety of different reaction conditions were tested, only unreacted starting materials could be isolated. An explanation for this unreactivity could be the decrease in nucleophilicity comparing 3-amino-1,2,4-triazole and 2-aminobenzimidazole with 5-aminotetrazole. The same observations regarding the reactivity characteristics for these aminoazoles have already been reported before.[7]

The structures of compounds **5a-l** and **6a-i** were established by elemental analysis, MS-spectrometry and NMR-spectroscopy (see Experimental Part). The ^{1}H NMR spectra of heterocycles **5a-l** and **6a-i** exhibit the following signals: characteristic resonances for the aromatic rings (6.5–8.0 ppm), a singlet for the Ar-CH proton (~ 6.5 ppm), a broad singlet for the amino group (10.0-11.5 ppm) and signals for other functional groups, including the SO_2CH_3 functionality at ~ 2.7 ppm. The formation of the isomeric products resulting from condensation at the N1 rather than at the N3 position of the dihydropyrimidine

ring can be excluded based on ^{1}H NMR spectra. In related structural cases[8] the NH protons are shifted upfield by 2-3 ppm. Additionally, the absence of a coupling between the methine and the NH-group strongly corraborates the formation of isomers **5** and **6**.



Scheme 1. Biginelli-type multicomponent reactions.

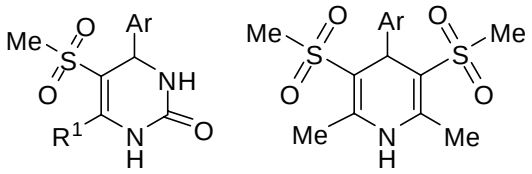
Table 1. Synthesis of 5,8-dihydroimidazolo[1,2-*a*]pyrimidines **5a-l** and 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines **6a-i**.

Entry	Diamine	R^1	Ar	Yield [%][a]
5a	**3**	Me	Ph	95
5b	**3**	Me	4-Cl-Ph	97
5c	**3**	Me	4-MeO-Ph	85
5d	**3**	Me	4-Me-Ph	90
5e	**3**	Me	4-F-Ph	85
5f	**3**	Me	2-MeO-Ph	73
5g	**3**	Ph	Ph	65
5h	**3**	Ph	4-Cl-Ph	70
5i	**3**	Ph	4-MeO-Ph	65
5j	**3**	Ph	2-MeO-Ph	55
5k	**3**	Ph	4-Br-Ph	47
5l	**3**	Ph	3-MeO-Ph	27
6a	**4**	Me	Ph	80
6b	**4**	Me	4-Cl-Ph	95
6c	**4**	Me	4-MeO-Ph	70
6d	**4**	Me	4-Me-Ph	92
6e	**4**	Me	4-F-Ph	88
6f	**4**	Ph	Ph	46
6g	**4**	Ph	4-Cl-Ph	60
6h	**4**	Ph	4-MeO-Ph	52
6i	**4**	Ph	2-MeO-Ph	45

[a] Yields refer to isolated yields of pure compound.

The investigation of the classical three-component Biginelli reaction involving equimolar amounts of urea, β-ketosulfone **1a** and aldehydes **2** under the same reaction conditions as described above (135 °C, 45 min) was another objective of the present work. However, when methylsulfonylacetone **1a** was employed as CH-acidic building block the anticipated Biginelli dihydropyrimidines **7** (Figure 3) were not obtained. According to MS-spectra and elemental analysis the isolated compounds contained two equivalents of ketosulfones, one equivalent of aldehyde and ammonia. This composition would correspond to classical Hantzsch dihydropyridines such as **8** (Figure 3). The formation of Hantzsch-type dihydropyridines as reaction products could be expected according to literature data.[9] However, the presence of two doublets at ~4.4 and 4.9 ppm (J ~ 5.6–6.0 Hz) and a doublet of doublets at 3.9 ppm in the ^{1}H NMR spectra allowed us to reject this hypothesis.

Figure 3. Biginelli and Hantzsch reaction products.



The structures of the synthesized compounds were established with the aid of X-ray diffraction analysis. The X-ray study of a single crystal of compound **9d** demonstrated that it was 6-methyl-5-methylsulfonyl-2-methylsulfonylmethyl-4-(4-methylphenyl)-1,4-dihydropyridine (Scheme 2, Figure 4). The dihydropyridine ring adopts an asymmetric boat conformation. Deviations of the N(1) and C(3) atoms from the mean plane of remaining atoms of the ring are -0.15 Å and -0.32 Å, respectively. The N(1)-C(1) bond (1.362(4) Å) is somewhat shortened and the C(1)-C(2) bond (1.351(4) Å) is slightly elongated compared to equivalent N(1)-C(5) and C(4)-C(5) bonds (1.383(4) Å and 1.320(4) Å, respectively). This redistribution of electron density in the dihydropyridine ring can be caused probably by the conjugation between the lone pair of the nitrogen atom and the methylsulfonyl group. The repulsion between the methyl substituent and the neighboring atoms (the shortened intramolecular contacts H(8b)… S(1) 2.89 Å (the van der Waals radii sum[10] is 3.01 Å), H(8c)…H(1N) 2.28 Å (2.34 Å)), probably results in some twisting of the C(1)-C(2) double bond (the C(8)-C(1)-C(2)-S(1) torsion angle is 6.9(4)°). The phenyl substituent has a pseudoaxial orientation and it is turned almost perpendicular to the average plane of the heterocycle (the C(1)-C(2)-C(3)-C(10) and C(2)-C(3)-C(10)-C(11) torsion angles are 96.9(3)° and 115.3(3)°, respectively).

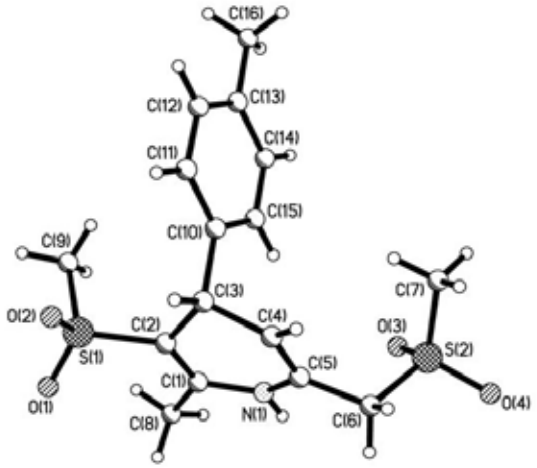
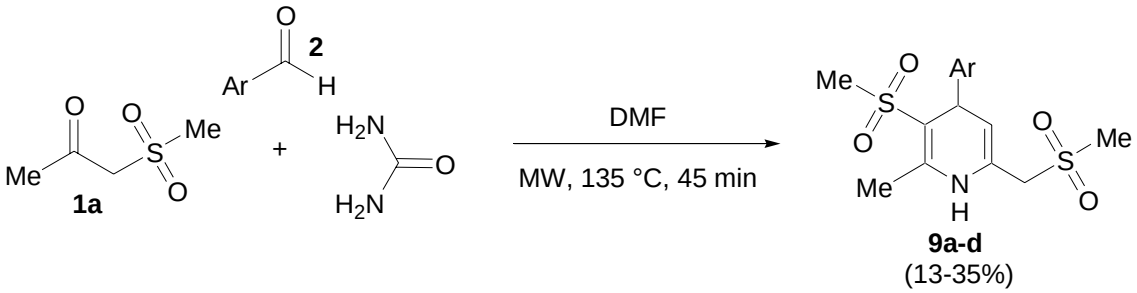


Figure 4. Molecular structure (X-ray diffraction data) of 6-methyl-5-methylsulfonyl-2-methylsulfonylmethyl-4-(4-methylphenyl)-1,4-dihydropyridine (**9d**).

Surprisingly, based on our findings from the X-ray diffraction analysis, the multicomponent reaction of β-ketosulfone **1a,** aromatic aldehydes **2** and urea yielded unusual Hantzsch dihydropyridines **9a-d** (Scheme 2), which were formed after elimination of ammonia from urea and participation of the methyl group as CH-acid center instead of the more reactive methylene.[11] However, the yields in these reactions were rather poor, an no exact investigation on the mechanism of this interesting transformation has been performed.



Scheme 2. Synthesis of dihydropyridines via Hantzsch-type reaction.

Table 2. Isolated Yields of Dihydropyridines **9a-d**.

Entry	Ar	Yield [%]
9a	Ph	13
9b	4-Cl-Ph	25
9c	4-MeO-Ph	35
9d	4-Me-Ph	20

Performing the reaction with two equivalents of β-ketosulfone **1a**, one equivalent of the appropriate aldehyde and urea allowed an improvement of the target compound yields, but still remained insufficient (Table 2). No positive result neither in an enhancement of the yield nor in obtaining the expected dihydropyrimidine structure of the isolated compounds was achieved when the solvents (methanol, ethanol, acetic acid or their mixtures), catalyst type (no catalyst, HCl, $Yb(OTf)_3$), temperature (70–160 °C) or heating conditions (MW in sealed vials, MW in open vials, conventional heating) were varied. Only dihydropyridines **9a-d** together with starting materials and unidentified byproducts could be detected by HPLC in the reaction mixture.

In conclusion, microwave-assisted multicomponent reactions of methylsulfonylacetone or α-methylsulfonylacetophenone with various aromatic aldehydes and aminoazoles or urea were studied. Rapid procedures for the synthesis of 5-methylsulfonyl-5,8-dihydroimidazolo[1,2-*a*]pyrimidines and 5-methylsulfonyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines were developed. An influence of the nature of the aminoazole building block on the reactivity was established: the yields of the target dihydropyrimidines decreased from 2-aminobenzimidazole to 3-amino-1,2,4-triazole, while 5-aminotetrazole did not react at all. Additionally, an unusual direction of the Biginelli reaction of methylsulfonylacetone with aldehydes and urea leading to non-classical Hantzsch-type 6-methyl-5-methylsulfonyl-2-methylsulfonylmethyl-4-aryl-1,4-dihydropyridines was found.

EXPERIMENTAL

Melting points of all synthesized compounds were determined with a Kofler or Gallenkamp melting point apparatus. The NMR spectra were recorded in DMSO-d_6 at 360 MHz (90,5 MHz for ^{13}C) with a Bruker AMX-360 and at 200 MHz with a Varian Mercury VX-200 spectrometer. The MS spectra were measured on a GC-MS Varian 1200L (ionizing voltage 70 eV) instrument or on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (positive APCI) mode. Elemental analysis was realized on EuroVector EA-3000.

All microwave-assisted experiments were carried out in a Discover single-mode microwave instrument from CEM producing controlled irradiation at 2450 MHz.

X-ray diffraction study. Crystals of **9d** are monoclinic. At the 293 K a = 5.503(3), b = 18.423(2), c = 16.758(9) Å, β = 93.06(4)°, V = 1697(1) Å^3, M_r = 355.46, Z = 4, space group $P2_1/n$, d_{calc}= 1.392 g/cm^3, μ (MoK_α) = 0.333 mm $^{-1}$, F(000) = 752. Intensities of 10636 reflections (2978 independent, R_{int} = 0.062) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scans, $2\Theta_{max}$ = 50°). The structure was solved by direct method using SHELXTL package.[12] Positions of hydrogen atoms were located from electron density difference maps and refined by “riding”

model with $U_{iso} = nU_{eq}$ of non-hydrogen atom bonded with given hydrogen atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). The hydrogen atom participated in the hydrogen bond was refined in isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation using 2940 reflections was converged to $wR_2 = 0.080$ ($R_1 = 0.042$ for 1414 reflections with $F>4\sigma(F)$), S = 0.771). Atomic coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 649116).

Starting α-methylsulfonylacetophenone **1b** was obtained by a known method.[13]

Preparation of methylsulfonylacetone 1a. 2.50 g (0.245 mol) of sodium methanesulfinate was dissolved in 20 mL of ethanol and 2.25 g (0.245 mol, 1.94 mL) of chloroacetone was added into the mixture. After refluxing for 2 h and cooling, the reaction mixture was poured onto 200 mL of ice-water, extracted with chloroform (3 x 50 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and the resulting sulfone was precipitated from a chloroform solution by addition of hexane. Sulfone **1a** was obtained in 73% yield (2.43 g). Mp 53-54 ^{o}C (lit., 54).[14]

General procedure for the preparation of 5,8-dihydroimidazolo[1,2-*a*]pyrimidines 5a-l and 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines 6a-i. A mixture of aminoazole **3** or **4** (1.0 mmol), β-ketosulfone **1a** or **1b** (1.0 mmol) and the appropriate aldehyde **2** (1.0 mmol) in 1.0 mL of DMF was irradiated at 135 ^{o}C for 30 min in a 25 mL round-bottom flask with a short air condenser under open-vessel conditions. After cooling, 10 mL of acetone were added and the reaction mixture was refluxed for 2-3 min. After cooling to rt, the mixture was kept at -5 ^{o}C overnight. The formed precipitate was filtered, washed with MeOH and dried at 50 °C in the drying oven to give the target dihydroazolopyrimidine. When it was necessary the product additionally was crystallized from DMF-MeOH (1:2).

5a ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.43 (s, 3H), 2.62 (s, 3H), 6.49 (s, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.30 (m, 5H), 7.42 (d, *J* = 7.6 Hz, 2H), 11.07 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 17.8, 44.9, 55.6, 106.9, 110.5, 117.4, 120.9, 122.5, 127.9, 128.9, 129.2, 131.8, 140.9, 142.6, 145.7, 146.1. *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$ (%): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.71; H, 4.99; N, 12.45. MS: Calcd MS for $[M+1]^+$ 340.10. Found: 340.6 (M+1, 96), 260.5 (100), 184.6 (29), 135.5 (10). Mp 295-296 ^{o}C (with decomposition).

5b ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.44 (s, 3H), 2.73 (s, 3H), 6.54 (s, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.37 (m, 4H), 7.45 (d, *J* = 8.6 Hz, 2H), 11.07 (bs, 1H). Anal. Calcd for $C_{18}H_{16}ClN_3O_2S$ (%): C, 57.83; H, 4.31; N, 11.24. Found: C, 57.78; H, 4.30; N, 11.32. MS: Calcd MS for $[M+1]^+$ 374.07. Found: 373.9 (M+1, 100), 294.1 (80). Mp 302 ^{o}C (with decomposition).

5c ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.41 (s, 3H), 2.61 (s, 3H), 3.68 (s, 3H), 6.43 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.97 (t, J = 7.4 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 7.30 (m, 4H), 11.13 (s, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 17.8, 45.0, 55.5, 56.0, 107.0, 110.5, 114.5, 117.4, 120.8, 122.4, 129.2, 131.8, 132.9, 142.6, 145.7, 159.6. *Anal.* Calcd for $C_{19}H_{19}N_3O_3S$ (%): C, 61.77; H, 5.18; N, 11.37. Found: C, 61.84; H, 5.20; N, 11.45. MS: Calcd MS for $[M+1]^+$ 370.11. Found: 370.2 (M+1, 100), 290.1 (57). Mp 290 °C (with decomposition).

5d ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.21 (s, 3H), 2.42 (s, 3H), 2.61 (s, 3H), 6.44 (s, 1H), 6.96 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.4 Hz, 2H), 7.31 (m, 4H), 10.98 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 17.9, 21.1, 45.0, 56.3, 106.9, 110.5, 117.4, 120.9, 122.4, 127.8, 129.7, 131.8, 138.0, 138.3, 142.6, 145.7, 146.0. *Anal.* Calcd for $C_{19}H_{19}N_3O_2S$ (%): C, 64.57; H, 5.42; N, 11.89. Found: C, 64.49; H, 5.42; N, 11.75. MS: Calcd MS for $[M+1]^+$ 354.12. Found: 354.4 (M+1, 100), 274.3 (69). Mp 302 °C (with decomposition).

5e ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.43 (s, 3H), 2.69 (s, 3H), 6.53 (s, 1H), 6.97 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.16 (m, 2H), 7.35 (dd, J = 8.0 Hz, 2H), 7.49 (dd, J = 8.0 Hz, 2H), 11.06 (bs, 1H). *Anal.* Calcd for $C_{18}H_{16}FN_3O_2S$ (%): C, 60.49; H, 4.51; N, 11.76. Found: C, 60.37; H, 4.50; N, 11.60. MS: Calcd MS for $[M+1]^+$ 358.09. Found: 357.9 (M+1, 100), 277.8 (33). Mp 296 °C (with decomposition).

5f ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.08 (s, 3H), 2.40 (s, 3H), 3.74 (s, 3H), 6.63 (s, 1H), 6.97 (m, 4H), 7.18 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 10.93 (bs, 1H). *Anal.* Calcd for $C_{19}H_{19}N_3O_3S$ (%): C, 61.77; H, 5.18; N, 11.37. Found: C, 61.87; H, 5.23; N, 11.42. MS: Calcd MS for $[M+1]^+$ 370.11. Found: 370.2 (M+1, 100), 290.1 (32). Mp 286-287 °C (with decomposition).

5g ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.45 (s, 3H), 6.68 (s, 1H), 7.04 (m, 2H), 7.39 (m, 5H), 7.56 (m, 7H), 11.21 (bs, 1H). *Anal*. Calcd for $C_{23}H_{19}N_3O_2S$ (%): C, 68.81; H, 4.77; N, 10.47. Found: C, 68.41; H, 4.70; N, 10.53. MS: Calcd MS for $[M+1]^+$ 402.12. Found: 402.6 (M+1, 100), 322.5 (57). Mp 261-262 °C.

5h ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.52 (s, 3H), 6.73 (s, 1H), 6.90 (dd, 2H), 7.09 (m, 4H), 7.50 (m, 7H), 11.2 (bs, 1H). *Anal.* Calcd for $C_{23}H_{18}ClN_3O_2S$ (%): C, 63.37; H, 4.16; N, 9.64. Found: C, 63.11; H, 4.34; N, 9.62. MS: Calcd MS for $[M+1]^+$ 436.08. Found: 436.3 (M+1, 95), 356.2 (100). Mp 250 °C.

5i ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.57 (s, 3H), 3.93 (s, 3H), 6.64 (s, 1H), 6.93 (d, J = 8.5 Hz, 2H), 7.04 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.52 (m, 7H), 10.30 (bs, 1H). *Anal.* Calcd for $C_{24}H_{21}N_3O_3S$ (%): C, 66.80; H, 4.91; N, 9.74. Found: C, 66.59; H, 4.85; N, 9.88. MS: Calcd MS for $[M+1]^+$ 432.13. Found: 432.1 (M+1, 65), 352.3 (100). Mp 257 °C.

5j ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.33 (s, 3H), 3.79 (s, 3H), 6.77 (s, 1H), 7.00 (m, 4H), 7.23 (d, J = 7.6 Hz, 1H), 7.31 (m, 2H), 7.49 (m, 5H), 7.65 (d, J = 7.6 Hz, 1H), 11.16 (bs, 1H). *Anal.* Calcd for $C_{24}H_{21}N_3O_3S$ (%): C, 66.80; H, 4.91; N, 9.74. Found: C, 66.66; H, 4.84; N, 9.87. MS: Calcd MS for

$[M+1]^+$ 432.13. Found: 432.1 (M+1, 100), 352.3 (65). Mp 254-255 °C.

5k ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.52 (s, 3H), 6.71 (s, 1H), 7.02 (t, J = 7.4 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.54 (m, 9H), 11.32 (bs, 1H). *Anal.* Calcd for $C_{23}H_{18}BrN_3O_2S$ (%): C, 57.51; H, 3.78; N, 8.75. Found: C, 57.45; H, 3.70; N, 8.77. MS: Calcd MS for $[M+1]^+$ 480.03. Found: 480.1 (M+1, 100), 402.1 (37), 322.3 (51). Mp 261 °C.

5l ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.55 (s, 3H), 3.74 (s, 3H), 6.66 (s, 1H), 7.06 (m, 5H), 7.35 (m. 2H), 7.50 (m, 6H), 11.35 (bs, 1H). *Anal.* Calcd for $C_{24}H_{21}N_3O_3S$ (%): C, 66.80; H, 4.91; N, 9.74. Found: C, 66.72; H, 4.83; N, 9.80. MS: Calcd MS for $[M+1]^+$ 432.13. Found: 432.1 (M+1, 56), 352.3 (100). Mp 242-243 °C.

6a ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.39 (s, 3H), 2.69 (s, 3H), 6.31 (s, 1H), 7.30 (m, 5H), 7.68 (s, 1H), 11.06 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 17.7, 44.9, 60.1, 106.5, 127.8, 129.0, 129.1, 141.1, 146.4, 147.4, 150.8. *Anal.* Calcd for $C_{13}H_{14}N_4O_2S$ (%): C, 53.78; H, 4.86; N, 19.30. Found: C, 53.65; H, 4.90; N, 19.17. MS: Calcd MS for $[M+1]^+$ 291.08. Found: 291.4 (M+1, 41), 211.6 (100). Mp 298-299 °C.

6b ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.38 (s, 3H), 2.77 (s, 3H), 6.33 (s, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.67 (s, 1H), 11.25 (bs, 1H). *Anal.* Calcd for $C_{13}H_{13}ClN_4O_2S$ (%): C, 48.07; H, 4.03; N, 17.25. Found: C, 48.20; H, 4.07; N, 17.30. MS: Calcd MS for $[M+1]^+$ 325.04. Found: 325.3 (M+1, 22), 245.2 (100). Mp 282-283 °C.

6c ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.39 (s, 3H), 2.69 (s, 3H), 3.73 (s, 3H), 6.26 (s, 1H), 6.90 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 7.67 (s, 1H), 11.01 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 17.6, 44.9, 55.6, 59.5, 106.6, 114.5, 129.1, 133.2, 150.7, 159.7. *Anal.* Calcd for $C_{14}H_{16}N_4O_3S$ (%): C, 52.49; H, 5.03; N, 17.49. Found: C, 51.87; H, 4.98; N, 17.23. MS: Calcd MS for $[M+1]^+$ 321.09. Found: 321.3 (M+1, 56), 241.5 (100). Mp 281 °C.

6d ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.26 (s, 3H), 2.39 (s, 3H), 2.69 (s, 3H), 6.26 (s, 1H), 7.15 (m, 4H), 7.66 (s, 1H), 10.94 (bs, 1H). *Anal.* Calcd for $C_{14}H_{16}N_4O_2S$ (%): C, 55.25; H, 5.30; N, 18.41. Found: C, 55.17; H, 5.22; N, 18.50. MS: Calcd MS for $[M+1]^+$ 305.10. Found: 305.2 (M+1, 94), 225.4 (100). Mp 297 °C.

6e ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.39 (s, 3H), 2.76 (s, 3H), 6.35 (s, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.68 (s, 1H), 10.84 (bs, 1H). *Anal.* Calcd for $C_{13}H_{13}FN_4O_2S$ (%): C, 50.64; H, 4.25; N, 18.17. Found: C, 50.59; H, 4.25; N, 18.25. MS: Calcd MS for $[M+1]^+$ 309.07. Found: 308.8 (M+1, 44), 229.0 (100). Mp 284 °C.

6f ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.47 (s, 3H), 6.50 (s, 1H), 7.46 (m, 10H), 7.72 (s, 1H), 11.23 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 45.7, 60.2, 108.2, 127.9, 128.5, 129.1, 129.4, 129.9, 130.5, 132.9, 141.0, 147.2, 147.6, 151.0. *Anal.* Calcd for $C_{18}H_{16}N_4O_2S$ (%): C, 61.35; H, 4.58; N, 15.90. Found: C, 61.42; H, 4.65; N, 15.95. MS: Calcd MS for $[M+1]^+$ 353.1. Found: 353.0 (M+1, 57), 272.9 (100). Mp

266 °C.

6g ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.55 (s, 3H), 6.55 (s, 1H), 7.49 (m, 5H), 7.58 (m, 4H), 7.74 (s, 1H), 11.27 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 45.6, 59.5, 107.9, 128.5, 129.4, 129.8, 129.9, 130.6, 132.8, 133.7, 140.1, 147.2, 147.8, 151.1. *Anal.* Calcd for $C_{18}H_{15}ClN_4O_2S$ (%): C, 55.88; H, 3.91; N, 14.48. Found: C, 56.12; H, 3.88; N, 14.70. MS: Calcd MS for $[M+1]^+$ 387.06. Found: 386.9 (M+1, 27), 306.8 (100). Mp 226 °C.

6h ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.48 (s, 3H), 3.75 (s, 3H), 6.46 (s, 1H), 6.97 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.54 (m, 5H), 7.71 (s, 1H), 11.19 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 45.7, 55.6, 59.6, 108.3, 114.7, 128.5, 129.2, 129.8, 130.5, 133.0, 133.1, 147.1, 150.9, 159.9. *Anal.* Calcd for $C_{19}H_{18}N_4O_3S$ (%): C, 59.67; H, 4.74; N, 14.65. Found: C, 59.24; H, 4.83; N, 14.39. MS: Calcd MS for $[M+1]^+$ 383.11. Found: 383.1 (M+1, 100), 303.3 (76). Mp 270 °C.

6i ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.32 (s, 3H), 3.76 (s, 3H), 6.58 (s, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.38 (m, 2H), 7.45 (m, 5H), 7.65 (s, 1H), 11.09 (bs, 1H). *Anal.* Calcd for $C_{19}H_{18}N_4O_3S$ (%): C, 59.67; H, 4.74; N, 14.65. Found: C, 59.34; H, 4.66; N, 14.25. MS: Calcd MS for $[M+1]^+$ 383.11. Found: 383.2 (M+1, 39), 303.4 (100). Mp 251-252 °C.

General procedure for the preparation of 6-methyl-5-methylsulfonyl-4-aryl-2-methanesulfonyl-methyl-1,4-dihydropyridine 9a-d. A mixture of 60 mg (1.0 mmol) of urea, 272 mg (2.0 mmol) of 2-methylsulfonylacetone (**1a**) and 1.0 mmol of the appropriate aldehyde **2** in 1.0 mL of DMF was irradiated at 135 °C for 45 min in a 25 mL round-bottom flask equipped with a short air condenser under open-vessel conditions. After cooling, 10 mL of acetone were added and the reaction mixture was refluxed for 2-3 min. After cooling to rt, the mixture was kept at -5 °C overnight. The formed precipitate was filtered, washed with MeOH and dried at 50 °C in the drying oven to give dihydropyridine products **9a-d**. In some cases the product was additionally recrystallized from DMF-MeOH (1:1).

9a ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.19 (s, 3H), 2.84 (s, 3H), 3.14 (s, 3H), 3.90 (dd, J = 14.6 Hz, J = 24.3 Hz, 2H), 4.48 (d, J = 6.0 Hz, 1H), 4.97 (d, J = 6. Hz, 1H), 7.42 (m, 5H), 8.45 (bs, 1H). *Anal.* Calcd for $C_{15}H_{19}NO_4S_2$ (%): C, 52.76; H, 5.61; N, 4.10. Found: C, 52.71; H, 5.65; N, 4.11. MS: Calcd MS for $[M+1]^+$ 342.08. Found: 342.4 (M+1, 100). Mp 204 °C.

9b. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.21 (s, 3H), 2.56 (s, 3H), 2.87 (s, 3H), 3.91 (dd, J = 37.8 Hz, J = 14.3 Hz, 2H), 4.53 (d, J = 5.6 Hz, 1H), 4.98 (d, J = 5.6 Hz, 1H), 7.25 (d, 2H), 7.37 (d, 2H), 8.53 (bs, 1H). *Anal.* Calcd for $C_{15}H_{18}ClNO_4S_2$ (%): C, 47.93; H, 4.83; N, 3.73. Found: C, 47.90; H, 4.85; N, 3.77. MS: Calcd MS for $[M+1]^+$ 376.04. Found: 376.1 (M+1, 12) 296.0 (100). Mp 218-219 °C.

9c ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.18 (s, 3H), 2.44 (s, 3H), 2.88 (s, 3H), 3.71 (s, 3H), 3.90 (dd, J = 41.8 Hz, J = 14.3 Hz, 2H), 4.44 (d, J = 5.6 Hz, 1H), 4.96 (d, J = 5.6 Hz, 1H), 6.86 (d, 2H), 7.16 (d, 2H),

8.42 (bs, 1H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 18.2, 45.7, 55.5, 57.1, 105.9, 109.1, 114.2, 114.4, 125.7, 129.1, 139.6, 146.2, 158.5. *Anal.* Calcd for $C_{16}H_{21}NO_5S_2$ (%): C, 51.73; H, 5.70; N, 3.77. Found: C, 51.70; H, 5.75; N, 3.81. MS: Calcd MS for $[M-1]^+$ 370.1. Found: 370.2 (M-1, 100). Mp 217 °C.

9d ^{1}H NMR (DMSO-d_6, 360 MHz): δ 2.17 (s, 3H), 2.24 (s, 3H), 2.43 (s, 3H), 2.85 (s, 3H), 3.90 (dd, J = 42.8 Hz, J = 14.3 Hz, 2H), 4.45 (d, 1H, J = 6.0 Hz), 4.94 (d, J = 6.0 Hz, 1H), 7.08 (d, 2H), 7,12 (d, 2H), 8.41 (bs, 1H). *Anal.* Calcd for $C_{16}H_{21}NO_4S_2$ (%): C, 54.06; H, 5.95; N, 3.94. Found: C, 54.08; H, 5.99; N, 3.91. MS: Calcd MS for $[M+1]^+$ 356.1. Found: 355.9 (M+1, 29) 276.1 (100). Mp 201-202 °C.

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