Mol Divers
DOI 10.1007/s11030-015-9633-z

FULL-LENGTH PAPER

Synthesis of diverse pyrazole-4-sulfonyl chlorides starting from 2-(benzylthio)malonaldehyde

Pavlo A. Sokolyuk[1,2] · **Ivan S. Kondratov**[2,3] · **Olexiy V. Gavrylenko**[1,2] · **Andrey A. Tolmachov**[1,2]

Received: 3 May 2015 / Accepted: 25 August 2015

Abstract A series of pyrazole-4-sulfonyl chlorides was obtained by a convenient 2-step method starting from synthetically available 2-(benzylthio)malonaldehyde. The method can be applied for the effective multi-gram synthesis of diverse pyrazole-containing sulfonyl chlorides which are mostly not available by other methods.

Keywords Heterocycles · Pyrazole · Sulfonyl chlorides · Sulfonamides · Oxidation · Chlorination · Cyclization · Hydrazines

Introduction

Sulfonyl chlorides are an important class of building blocks widely used in medicinal and combinatorial chemistry [1]. The main application of sulfonyl chlorides is for the preparation of sulfonamides—compounds exhibiting a broad spectrum of biological activities [2,3]. The significant number of bioactive compounds were prepared from the corresponding heteroaromatic sulfonyl chlorides. Antiviral agent Tipranavir, antiglaucoma agent Brinzolamide, fungicide Amisulbrom, and herbicide Pyroxsulam (Fig. 1) are examples of recently approved substances whose syntheses started from heterocyclic sulfonyl chlorides [4–7].

Nowadays, among the various synthetic approaches to sulfonyl chlorides [8–10], the most popular are electrophilic substitution by chlorosulfonic acid [11–13] or Sandmeyer-type chlorosulfonation [14–17]. However, these methods require harsh conditions, which lead to polymerization and/or complex mixtures in many instances. These facts limit the range for using these methods especially in the case of electron-rich heterocycles which are sensitive to both reactions with electrophilic reagents and diazotation where the mentioned side processes are often strongly pronounced.

An alternative method for the preparation of sulfonyl chlorides is the oxidative chlorination of sulfur-containing compounds, such as thiols and sulfides [18–22], thioacetates [23,24], thiocarbamates [25,26], and thioethers [27–29] using mostly aqueous chlorine. Nevertheless, these approaches are rarely used in the synthesis of heterocyclic sulfonyl chlorides since the introduction of sulfur-containing substituents in a particular position of the heterocyclic ring often cannot be easily performed.

This problem can be solved using appropriate sulfur-containing building blocks, such as derivatives of 2-mercapto malonaldehyde of general structure **1** (Scheme 1), to be used as substrates for the corresponding heterocyclization.

Compounds **1** are 1,3-dielectrophiles and can be involved in heterocyclizations with different binucleophiles followed by their transformation to their corresponding sulfonyl chlorides by oxidative chlorination under mild conditions [25–29].

In this report, we present the successful application of intermediates **1** for the synthesis of different pyrazole-4-sulfonyl chlorides.

Electronic supplementary material The online version of this article (doi:10.1007/s11030-015-9633-z) contains supplementary material, which is available to authorized users.

✉ Ivan S. Kondratov
kondratov@mail.enamine.net

[1] Kyiv National Taras Shevchenko University, 64 Volodymirska st., Kyiv, 33 01033, Ukraine

[2] Enamine Ltd., 23 A. Matrosova st., Kyiv 01103, Ukraine

[3] Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Science, Murmanska 1, Kyiv, 94 02660, Ukraine

Published online: 12 September 2015

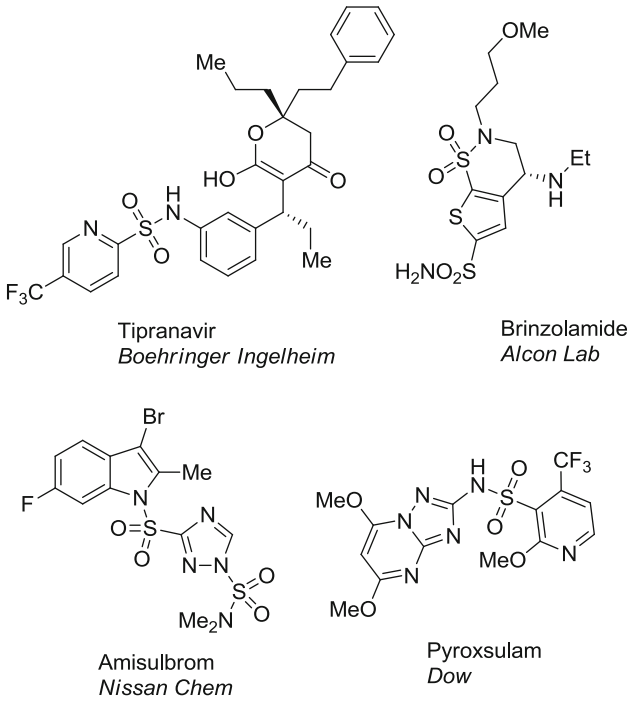


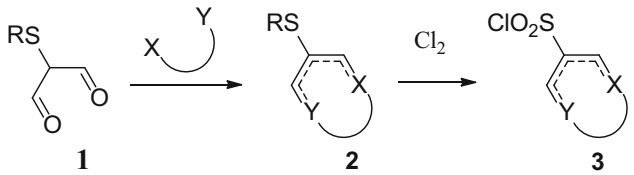
Fig. 1 Examples of sulfonamides used as drugs and pesticides

Results and discussions

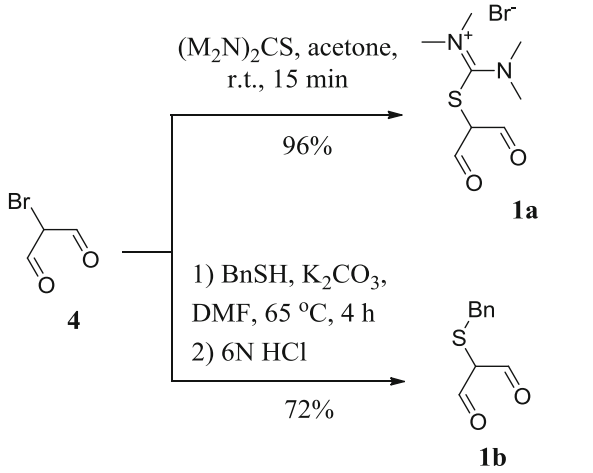
First, we considered two possible reagents of formula **1**: the isothiouronium salt **1a** [26] and hitherto unknown 2-benzylthio malonaldehyde **1b** (Scheme 2).

Both dialdehydes **1a,b** were obtained starting from 2-bromo malonoaldehyde **4** by treatment with *N*,*N*′-tetramethyl thiourea and benzyl mercaptane, respectively. The synthesis of compound **1b** requires heating in DMF in the presence of K_2CO_3 at 65 °C for 4 hours while compound **1a** is easily formed in acetone as it precipitates at r.t. (Scheme 2). Using these 2 methods, compounds **1a,b** can be obtained in 105 and 138 gram scale, respectively.

In order to compare **1a,b** as precursors to the desired sulfonyl chlorides, we studied the synthetic approach to 4-pyrazolyl sulfonyl chlorides **7a,b** using dialdehydes **1a,b** (Scheme 3). The reaction of **1a** with aryl hydrazines **3a,b** took place under reflux in EtOH in the presence of catalytic amounts of hydrochloric acid giving *N*,*N*-



Scheme 1 Synthetic approach to heterocyclic sulfonyl chlorides of general structure **3** starting from 2-(benzylthio)malonaldehyde **1**



Scheme 2 Synthesis of compounds **1a,b**

dimethylthiocarbomates **6a,b**. Thiobenzyl dialdehyde **1b** also underwent a similar heterocyclization to afford the corresponding pyrazoles **8a,b** under reflux in methanol. Both thiocarbamate-containing pyrazoles **6a,b** and thiobenzyl-containing pyrazoles **8a,b** can be transformed to sulfonyl chlorides **7a,b** by chlorination under mild conditions (CH_2Cl_2/H_2O, 0–10 °C).

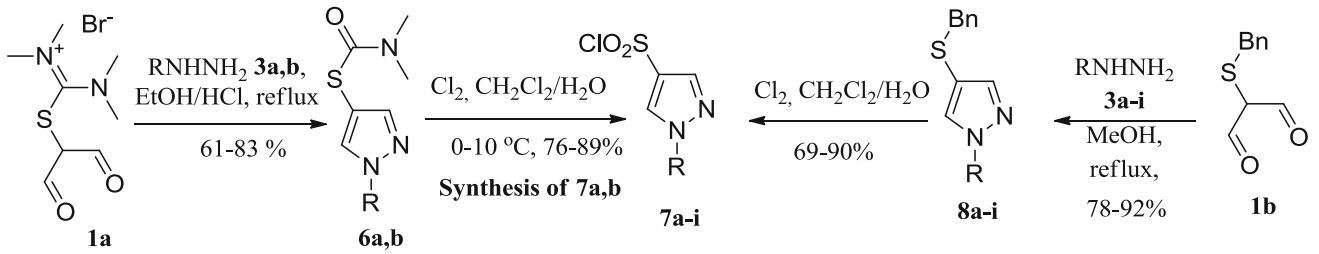
We focused on using compound **1b** as a valuable stable intermediate since compound **1a**, and most of isothiouronium salts, gradually decompose during storing and should be used immediately after the preparation.

A library of 1-substituted pyrazolyl-4-sulfonyl chlorides **7c–i** was readily obtained in two steps through the corresponding benzyl thioethers **8c–i.** Our new process proved to be robust all the way to multi-gram scale, easy to carry out and highly efficient affording products in high yields

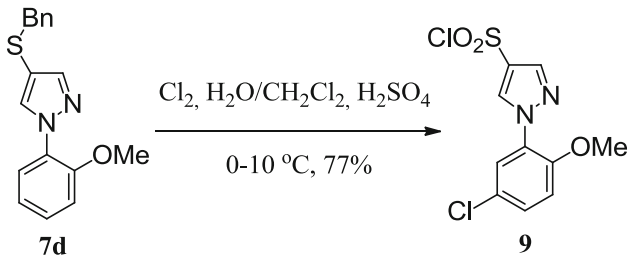
Among the target substances, **7c–i** are compounds that are difficult to obtain by direct chlorosulfonation of the corresponding 1-substituted pyrazoles.

For instance, compounds **7d,e** containing donor aromatic rings are sensitive to electrophilic substitution under common chlorosulfonation conditions. At the same time, mild chlorination conditions of the corresponding intermediates **8d,e** (Cl_2, CH_2Cl_2/H_2O, r.t.) did not afford the expected chlorinated aromatic ring. Nevertheless, the formation of sulfonyl chloride and simultaneous selective chlorination of the benzene ring can be carried out in the presence of sulfuric acid as demonstrated in the synthesis of compound **9** from benzyl thioether **7d** (Scheme 4).

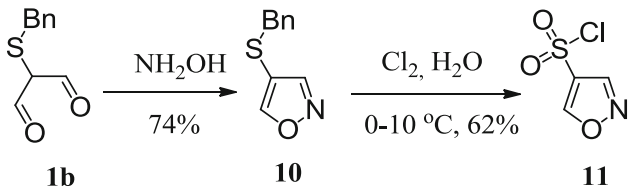
We also applied intermediate **1b** for the multi-gram scale synthesis of isoxazole-4-sulfonyl chloride **11** through the corresponding benzyl thioether **10** (Scheme 5). Good yields were observed on both steps using our methodology while any attempt to synthesize the same compound by direct chlorosulfonation failed.



Scheme 3 Synthetic routes to sulfonyl chlorides **7a–i** starting from dialdehyde **1a** (*left side*) and **1b** (*right side*, see also **Table** 1)



Scheme 4 Synthesis of compound **9**



Scheme 5 Synthesis of isoxazole-4-sulfonyl chloride **11**

In order to introduce diverse substituents in the first position of the pyrazole ring, we studied the alkylation of N-unsubstituted pyrazole **8j** which can be synthesized by reacting reagent **1b** with hydrazine hydrate (Scheme 6). The introduction of N-substitution starting from **8j** is particularly important in cases where the corresponding alkyl hydrazines are not accessible. Thus, compound **8k** can be easily obtained from pyrazole **8j** and used for the synthesis of sulfonyl chloride **7k**. It should be mentioned that for the last stage, chlorine had to be generated in situ from $HCl/KClO_3$ since the cyclopropyl ring is often unstable under harsh chlorination conditions.

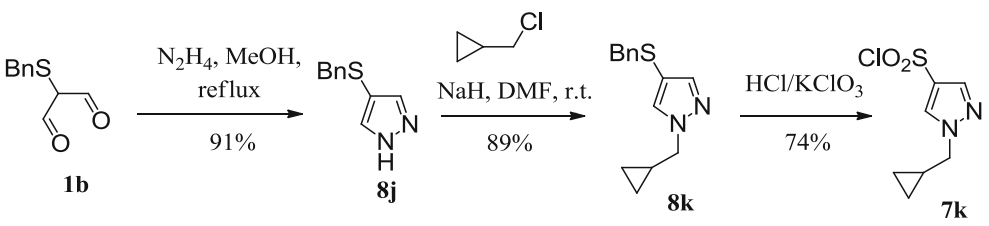
Scheme 7 Synthesis of sulfonamides **12a–e** (for list of substituents see Table 1)

Sulfonyl chlorides **7a–e** were reacted with ammonia affording the corresponding sulfonamides **12a–e** in high yields (Scheme 7).

Conclusions

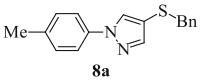
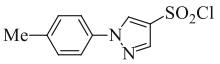
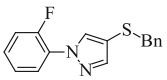
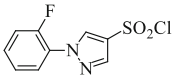
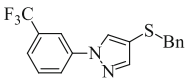
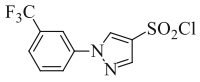
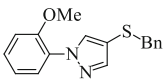
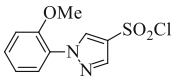
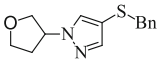
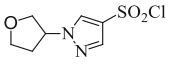
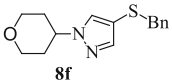
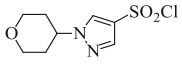
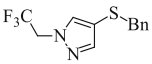
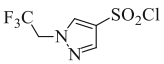
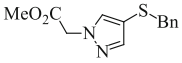
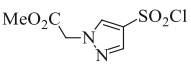
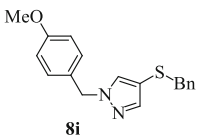
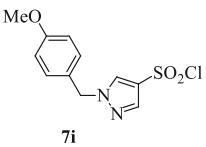
In summary, we developed a new robust two-step methodology for the preparation of diverse pyrazoles containing sulfonyl chlorides based on (2-benzylthio)malonaldehyde. The method is based on the application of (2-benzylthio) malonaldehyde—hitherto unknown stable reagent which can be easily obtained in multi-gram scale starting from 2-bromo malonoaldehyde. Our method includes the heterocyclization of (2-benzylthio)malonaldehyde with hydrazines followed by oxidative chlorination which selectively transforms the thiobenzyl group into a sulfonyl chloride. Both steps proceed under mild conditions and high yields.

Our new method offers a new route to the direct chlorosulfonation of pyrazoles which usually require harsh conditions. Moreover, it was used in the synthesis of isoxazole-4-sulfonyl chloride which can scarcely be obtained by other methods. Sulfonyl chlorides are key building blocks in drug discovery for the formation of new sulfonamides and, in our case, bearing diverse N-substituted pyrazoles.



Scheme 6 Synthetic approach to sulfonyl chloride **7k**

Table 1 Synthesis of sulfonyl chlorides **7a–i** starting from dialdehyde **1b**

Entry	Substituent R	Product **8**	Yield of **8** (%)	Product **7**	Yield of **7** (%)
1	*p*-MeC_6H_4	 **8a**	91	 **7a**	90
2	*o*-F-C_6H_4	 **8b**	79	 **7b**	78
3	*m*-CF_3-C_6H_4	 **8c**	84	 **7c**	76
4	*o*-MeO-C_6H_4	 **8d**	84	 **7d**	77
5	Tetrahydro-furan-3-yl	 **8e**	91	 **7e**	74
6	Tetrahydro-pyran-4-yl	 **8f**	86	 **7f**	71
7	CF_3CH_2	 **8g**	92	 **5g**	82
8	MeO_2CCH_2	 **8h**	78	 **7h**	69
9	*p*-MeO-$C_6H_4CH_2$	 **8i**	84	 **7i**	73

Experimental part

General

Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Merck, Fluka, and Enamine. Melting points are uncorrected. NMR spectra were recorded on Bruker Avance DRX at 500 MHz (^{1}H), 126 MHz (^{13}C), and 470 MHz (^{19}F) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).The progress of reactions was monitored by TLC-plates (silica gel 60 F254, Merck). All starting materials were of the highest commercial quality and were used without further purification.

NMR abbreviations: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

2-(1,3-Dioxopropan-2-yl)-1,1,3,3-tetramethylisothiouronium bromide ***1a***

To a solution of 2-bromomalonaldehyde (75.5 g, 0.5 mol) in acetone (1000 mL) 1,1,3,3-tetramethylthiourea (66 g, 0.5 mol) was added at 25 °C under vigorous stirring. During the addition, the formation of precipitate was observed. Stirring was continued for 2 h at r.t., the precipitate was filtered and washed with acetone to give 105 g (74 %) of compound **1a**.

NMR spectra and properties coincide with the literature data [26].

*2-(Benzylthio)malonaldehyde **1b***

A mixture of K_2CO_3 (145 g, 1.05 mol), 2-bromomalonaldehyde (151 g, 1 mol) and phenylmethanethiol (117.8 g, 0.95 mol) in DMF (1500 mL) was stirred at 55 °C for 4 h. The solution was cooled to r.t. and the resulting precipitate was filtered, washed with water (1500 mL) and then with CH_2Cl_2 (3×500 mL). The water layer was treated with 6N HCl (∼200 mL) until reaching pH = 1. The precipitate obtained was filtered, washed with water and methyl *t*−butyl ether (MTBE), and dried in vacuum giving pure titled compound. Yield: 138 g (71 %). Light gray solid, mp 131–132 °C.

IR (KBr): ν = 861, 884, 1004, 1028, 1175, 1229, 1313, 1355, 1424, 1452, 1552, 1653, 1707, 3061 cm^{-1}.
^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.91 (2H, s, CH_2), 7.18–7.30 (5H, m, Ph), 8.60 (2H, br. s, 2CH) ppm.
^{13}C NMR (125 MHz, DMSO-d_6): δ = 36.7, 113.3, 127.2, 128.6, 129.2, 138.9, 181.2 (br.) ppm.
m/*z* (CI): 190 (M+1, 100 %).
Anal. Calcd. for: $C_{20}H_{18}F_3NO_6$ (425.36): C, 56.47; H, 4.27; N, 3.29. Found C, 56.58; H, 4.20; N, 3.27.

*General procedure for synthesis of pyrazol-4-yl N,N-dimethylcarbamothioates **6a** and **6b***

A mixture of compound **1a** (14.1 g, 0.05 mol), corresponding hydrazine hydrochloride (0.05 mol) and catalytic conc. HCl (0.2 mL) was refluxed in EtOH (200 mL) under stirring for 2 h, then cooled to r.t. and concentrated in vacuum. Water (300 mL) was added and the resulting precipitate was filtered, washed with water (3 × 50 mL), and dried in vacuum giving corresponding products **6a,b** which were used for the next step without purification.

*S-1-p-Tolyl-1H-pyrazol-4-yl N,N-dimethylcarbamothioate **6a*** was obtained using our general procedure starting from 1-*p*-tolylhydrazine hydrochloride (7.9 g, 0,05 mol). Yield: 10.8 g (83 %). Light gray solid, mp 94–95 °C.

IR (KBr): ν = 980, 1032, 1101, 1151, 1192, 1261, 1325, 1367, 1405, 1430, 1523, 1658, 2923, 3038, 3110 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (3H, s, CH_3), 3.05 (3H, s, CH_3N), 3.11 (3H, s, CH_3N), 7.25 (2H, d, *J* = 8.0 Hz, Ar), 7.57 (2H, d, *J* = 8.0 Hz, Ar), 7.73 (1H, s, Ar), 8.01 (1H, s, Ar) ppm.
^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9, 37.1, 106.3, 118.8, 130.4, 133.2, 136.6, 137.6, 146.0, 165.3 ppm.
m/*z* (CI): 262 (M+1, 100 %).
Anal. Calcd. for $C_{13}H_{15}N_3OS$ (261.34): C, 59.74; H, 5.79; N, 16.08. Found: C, 59.61; H, 5.87; N, 16.07.

*4-(Benzylthio)-1-p-tolyl-1H-pyrazole **8a*** was obtained using our general procedure starting from 1-*p*-tolylhydrazine hydrochloride (7.9 g, 0,05 mol) and did not require any purification after isolation. Yield: 12.7 g (91 %).

Colorless solid, mp 69–70 °C.

IR (KBr): ν = 701, 776, 814, 860, 951, 1333, 1374, 1452, 1528, 3031, 3115 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (3H, s, CH_3), 3.85 (2H, s, CH_2), 7.23 (5H, m, Ar), 7.44 (2H, d, *J* = 7.5 Hz, Ar), 7.51 (1H, s, Ar), 7.57 (1H, s, Ar) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 41.5, 111.4, 118.6, 126.8, 128.0, 128.8, 129.6, 130.5, 136.3, 137.1, 137.9, 144.5
m/*z*(CI): 281 (M+1, 100 %).
Anal. Calcd. for $C_{20}H_{18}F_3NO_6$ (425.36): C, 56.47; H, 4.27; N, 3.29. Found C, 56.38; H, 4.33; N, 3.27.

General procedure for the preparation of sulfochlorides 7a–i and 11

Chlorine gas was bubbled into a vigorously stirred solution of corresponding *N,N*-dimethylcarbamothioate **6** (0.02 mol) [Method 1] or benzyl thioether **8** (0.02 mol) [Method 2] in CH_2Cl_2 (200 mL) and water (70 mL) at 0–10 °C. When the reaction completed (no absorption of chlorine and temperature decrease) (also based by TLC monitoring), the organic layer was separated, dried under Na_2SO_4, concentrated in vacuum and the residue was purified by an appropriate method.

*1-p-Tolyl-1H-pyrazole-4-sulfonyl chloride **7a*** was obtained by general procedure by Method 1 starting from compound **6a** (5.2 g, 0.02 mol) and did not require any purification after work-up. Yield: 4.6 g (89 %).

Also compound **7a** was obtained by Method 2 starting from compound **8a** (8.5 g, 0.02 mol) and did not require any purification after work-up. Yield: 4.5 g (90 %).

Light yellow solid, mp 95–96 °C.

IR (CH_2Cl_2): ν = 981, 1029, 1144, 1187, 1378, 1396, 15233141cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (3H, s, CH_3), 7.34 (2H, d, *J* = 7.9 Hz, Ar), 7.95 (2H, d, *J* = 7.9 Hz, Ar), 8.16 (1H, s, Ar), 8.49 (1H, s, Ar) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 119.0, 126.5, 130.3, 132.0, 136.3, 137.6, 138.9 ppm.
m/*z*(CI): 239 [SO_3H] (M+1, 100 %).

Anal. Calcd. for $C_{10}H_9ClN_2O_2S$ (256.71): C, 46.79; H, 3.53; N, 10.91. Found: C, 46.82; H, 3.41; N, 11.02.

4-(Benzylthio)-1-(cyclopropylmethyl)-1H-pyrazole ***8k***

To a solution of DMF (50 mL) 60 % NaH (1.0 g, 25 mmol) was added under vigorous stirring. Then a solution of pyrazole **6j** (3.8 g, 20 mmol) in DMF (15 mL) was added dropwise under r.t. After stirring for 30 min (complete hydrogen release), (bromomethyl)cyclopropane (4.05 g, 30 mmol) was added dropwise. The mixture was left stirring overnight. The resulting precipitate (NaBr) was filtered and the filtrate concentrated in vacuum. The resulting residue was purified by column chromatography (EtOAc/Hex, 1:1 $R_f = 0.7$). Yield: 4.34 g (89 %). Light yellow oil.

IR (ATR): 765, 931, 977, 1023, 1070, 1172, 1236, 1431, 1452, 1494, 1513, 2966, 3027 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.30$ (2H, m, *c*-Pr), 0.61 (2H, m, *c*-Pr), 1.18 (1H, m, c-Pr), 3.78 (2H, s, CH_2), 3.88 (2H, d, $J = 6.5$ Hz, CH_2N), 7.13 (2H, m, Ar), 7.18 (1H, s, Ar), 7.25 (3H, m, Ar), 7.36 (1H, s, Ar) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 3.6$, 10.6, 41.7, 55.6, 108.7, 126.6, 127.9, 128.7, 132.6, 138.2, 143.1 ppm.
m/*z*(CI): 245 (M+1, 100 %).
Anal. Calcd. For $C_{14}H_{16}N_2S$ (244.36): C, 68.81; H, 6.60; N, 11.46. Found: C, 68.73; H, 6.64; N, 11.40.

1-(Cyclopropylmethyl)-1H-pyrazole-4-sulfonyl chloride ***7k***

To a solution of compound **8k** (4.9 g, 0.02 mol) in 35 % HCl (50 mL), $KClO_3$ (2.7 g, 0.022 mol) was added in several portions under vigorous stirring keeping the temperature between 5–10 °C using an ice-water bath (highly exothermic reaction). After 30 min of the addition of $KClO_3$, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over Na_2SO_4, concentrated in vacuum and the residue was purified by column chromatography (EtOAc/Hex, 1:1, $R_f = 0.8$). Yield: 3.26 g (74 %). Colorless liquid.

IR (ATR) 803, 932, 980, 1026, 1110, 1161, 1369, 1393, 1513, 3010, 3133 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.45$ (2H, m, *c*-Pr), 0.77 (2H, m, *c*-Pr), 1.32 (1H, m, *c*−Pr), 4.06 (2H, d, $J = 7.0$ Hz, CH_2), 7.98 (1H, s, Ar), 8.19 (1H, s, Ar) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 3.9$, 10.0, 57.6, 125.9, 130.8, 137.9 ppm.
m/*z* (CI):203 [SO_3H] (M+1, 100 %).
Anal. Calcd. For $C_7H_9ClN_2O_2S$ (220.68): C, 38.10; H, 4.11; N, 12.69; Cl, 16.07. Found: C, 38.01; H, 4.17; N, 12.58; Cl, 16.00.

General procedure for the preparation of sulfonamides 12a–e

Sulfonyl chloride **7a–e** (10 mmol) was added in portions to an aqueous solution of ammonia (20 %, 50 mL) under stirring at 40 °C. The mixture was then stirred at 80 °C for 2 h, cooled, concentrated in vacuum, and treated with water (25 mL). The resulting precipitate was filtered, washed with water (3 × 20 mL), and dried in vacuum giving pure products **12a–e**.

1-(p-Tolyl)-1H-pyrazole-4-sulfonamide ***12a*** was obtained using our general procedure starting from compound **7a** (2.56 g, 10 mmol). Yield: 2.18 g (92 %). Colorless solid, mp 189–191 °C.

IR (KBr) 918, 955, 988, 1136, 1182, 1329, 1351, 1393, 1530, 3040, 3123, 3240, 3328 cm^{-1}
^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.39$ (3H, s), 7.32 (2H, d, $J = 8.0$ Hz), 7.39 (2H, br. s), 7.76 (2H, d $J = 8.0$ Hz), 8.00 (1H, s), 8,87 (1H, s) ppm.
^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.6$, 119.1, 128.0, 128.7, 130.1, 136.7, 137.0 138.6 ppm.
m/*z*(CI): 238 (M+1, 100 %).
Anal. Calcd. For $C_{10}H_{11}N_3O_2S$ (237.28): C, 50.62; H, 4.67; N, 17.71. Found: C, 50.49; H, 4.77; N, 17.60.

See Supporting Information for all the experimental data as well as copies of ^1H and ^{13}C NMR.

Acknowledgments We express our appreciation to Dr. S. I. Vdovenko and O. A. Fedorenko (Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences, Ukraine) for measuring the IR-spectra.

References

1. Patai S, Rapport Z (1991) The chemistry of sulfonic acids, esters and their derivatives (The Chemistry of Functional Groups). New York, Wiley. doi:10.1002/0470034394
2. Shah SSA, Rivera G, Ashfaq M (2013) Recent advances in medicinal chemistry of sulfonamides. Rational design as anti-tumoral, anti-bacterial and anti-inflammatory agents. Mini-Rev Med Chem 13:70–86. doi:10.2174/1389557511307010070
3. Carta FScozzafava A, Supuran CT (2012) Sulfonamides: a patent review (2008–2012). Expert Opin Ther Pat 22:747–758. doi:10.1517/13543776.2012.698264
4. Turner SR, Stohbach JW, Tommasi RA, Aristoff PA, Johnson PD, Skulnick HI, Dolak LA, Seest EP, Tomich PK, Bohanon MJ, Horng M-M, Lynn JC, Chong K-T, Hinshaw RR, Watenpaugh KD, Janakiraman MN, Thaisrivongs S (1998) Tipranavir (PNU-140690): a potent, orally bioavailable nonpeptidic HIV protease inhibitor of the 5,6-dihydro-4-hydroxy-2-pyrone sulfonamide class. J Med Chem 41:3467–3476. doi:10.1021/jm9802158
5. Conrow RE, Dean WD, Zinke PW, Deason ME, Sproull SJ, Dantanarayana AP, DuPriest MT (1999) Enantioselective synthesis of brinzolamide (AL-4862), a new topical carbonic anhydrase

inhibitor. The "DCAT Route" to thiophenesulfonamides. Org Process Res Dev 3:114–120. doi:10.1021/op9802125
6. Kondo Y, Fukuda K, Makabe T, Kondo Y, Fukuda K, Sakurai Y, Utsunomiya T, Tanaka (2007) Processes for production of indole compounds. Patent EP1829872
7. Bell BM, Fanwick PE, Graupner PR, Roth GA (2006) Application of the tisler triazolopyrimidine cyclization to the synthesis of a crop protection agent and an intermediate. Org Process Res Dev 10:1167–1171. doi:10.1021/op0601518
8. Porcs-Makkay M, Lukacs G, Pandur A, Simig G, Volk B (2014) Synthesis of 4-unsubstituted 2H–1,2,3-benzothiadiazine 1,1-dioxides via ortho lithiation of protected benzaldehyde derivatives. Tetrahedron 70:286–293. doi:10.1016/j.tet.2013.11.058
9. De Bergh JR, Niljianskul N, Buchwald SL (2013) Synthesis of aryl sulfonamides via palladium-catalyzed chlorosulfonylation of arylboronic acids. J Am Chem Soc 135:10638–10641. doi:10.1021/ja405949a
10. Pandya R, Murashima T, Tedeschi L, Barrett AGM (2003) Facile one-pot synthesis of aromatic and heteroaromatic sulfonamides. J Org Chem 68:8274–8276. doi:10.1021/jo034643j
11. Ichinose M, Suematsu H, Yasutomi Y, Nishioka Y, Uchida T, Katsuki T (2011) Enantioselective intramolecular benzylic C–H bond amination: efficient synthesis of optically active benzosultams. Angew Chem Int Ed Engl 50:9884–9887. doi:10.1002/anie.201101801
12. Velazquez C, Abdellatif K, Chowdhury M, Jain S, Reisz J, DuMond J, King SB, Knaus E (2010) Acyclic triaryl olefins possessing a sulfohydroxamic acid pharmacophore: synthesis, nitric oxide/nitroxyl release, cyclooxygenase inhibition, and anti-inflammatory studies. Org Biomol Chem 8:4124–4130. doi:10.1039/C005066K
13. Foschi F, Tagliabule A, Mihali V, Pilati T, Pecnikaj I, Penso M (2013) Memory of chirality approach to the enantiodivergent synthesis of chiral benzo[d]sultams. Org Lett 14:3686–3689. doi:10.1021/ol401557v
14. Malet-Sanz L, Madrzak J, Ley SV, Baxendale IR (2010) Preparation of arylsulfonyl chlorides by chlorosulfonylation of in situ generated diazonium salts using a continuous flow reactor. Org Biomol Chem 8:5324–5332. doi:10.1039/C0OB00450B
15. Hogan PJ, Cox BG (2009) Aqueous process chemistry: the preparation of aryl sulfonyl chlorides. Org Proc Res Dev 13:875–879. doi:10.1021/op9000862
16. Yang L, Xue X, Zhang Y (2010) Simple and efficient synthesis of belinostat. Synth Commun 40:2520–2524. doi:10.1080/00397911.2010.510386
17. Tang G, Lin X, Qiu Z, Li W, Zhu L, Wang L, Li S, Li H, Lin W, Yang M, Guo T, Chen L, Lee D, Wu JZ, Yang W (2011) Design and synthesis of benzenesulfonamide derivatives as potent antiinfluenza hemagglutinin inhibitors. ACS Med Chem Lett 2:603–607. doi:10.1021/ml2000627
18. Bahrami K, Khodaei MM, Soheilizad M (2009) Direct conversion of thiols to sulfonyl chlorides and sulfonamides. J Org Chem 74:9287–9291. doi:10.1021/jo901924m
19. Bahrami K, Khodaei MM, Soheilizad M (2009) A novel, practical synthesis of sulfonyl chlorides from thiol and disulfide derivatives. Synlett 17:2773–2776. doi:10.1055/s-0029-1217989
20. Bahrami K, Khodaei MM, Khaledian D (2012) Synthesis of sulfonyl chlorides and thiosulfonates from $H_2O_2-TiCl_4$. Tetrahedron Lett 53:354–358. doi:10.1016/j.tetlet.2011.11.052
21. Veisi H, Ghorbani-Vaghei R, Hemmati S, Mahmoodi J (2011) Convenient one-pot synthesis of sulfonamides and sulfonyl azides from thiols using N-chlorosuccinimide. Synlett 16:2315–2320. doi:10.1055/s-0030-1261232
22. Prakash GKS, Mathew T, Panja C, Olah GA (2007) Chlorotrimethylsilane-nitrate salts as oxidants:? direct oxidative conversion of thiols and disulfides to sulfonyl chlorides. J Org Chem 72:5847–5850. doi:10.1021/jo070907g
23. Nishiguchi A, Maeda K, Miki S (2006) Sulfonyl chloride formation from thiol derivatives by N-chlorosuccinimide mediated oxidation. Synthesis 24:4131–4134. doi:10.1055/s-2006-950353
24. Muesmann TWT, Wickleder MS, Christoffers J (2011) Preparation of linear aromatic disulfonic acids: new linker molecules for metal-organic frameworks. Synthesis 17:2775–2780. doi:10.1055/s-0030-1260123
25. Percec V, Bera TK, De BB, Sanai Y, Smith J, Holerca MN, Barboiu B, Grubbs RB, Frechet JMJ (2001) Synthesis of Functional Aromatic Multisulfonyl Chlorides and Their Masked Precursors. J Org Chem 66:2104–2117. doi:10.1021/jo001694x
26. Wall M, Benkovic SJ (2002) Synthesis and biological evaluation of 9-thia-5,10-dideazafolic acid. J Heterocyclic Chem 39:1097–1099. doi:10.1002/jhet.5570390541
27. Demydchuk BA, Kondratyuk KM, Korniyenko AN, Brovarets VS, Vasylyshyn RY, Tolmachev A, Lukin O (2012) A facile synthesis of 1,3-thiazole-4-sulfonyl chlorides. Synth Commun 42:2866–2875. doi:10.1080/00397911.2011.571356
28. Zhersh S, Lukin O, Matvienko V, Tolmachev A (2010) Synthesis of isomeric fluoronitrobenzene-sulfonyl chlorides. Tetrahedron 66:5982–5986. doi:10.1016/j.tet.2010.06.036
29. Pu YM, Christesen A, Ku Y-Y (2010) A simple and highly effective oxidative chlorination protocol for the preparation of arenesulfonyl chlorides. Tetrahedron Lett 51:418–421. doi:10.1016/j.tetlet.2009.11.047