A Facile Synthesis of 1-Substituted Cyclopropylsulfonamides

Jianqing Li,* Daniel Smith, Henry S. Wong, Jeffrey A. Campbell, Nicholas A. Meanwell, Paul M. Scola

Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA
Fax +1(203)6777702; E-mail: Jianqing.Li@bms.com

Received 28 November 2005

Abstract: A practical, convenient, and high-yielding three-step synthesis of cyclopropanesulfonamide and 1-substituted cyclopropanesulfonamides, starting from 3-chloropropanesulfonyl chloride, is described.

Key words: sulfonamides, lithiation, cyclizations, cyclopropanesulfonamides, alkylations

The cyclopropylsulfonamide moiety (Figure 1) has recently emerged as an interesting structural element in many biologically active compounds.[1] Examples of molecules incorporating this functionality include antagonists of neuropeptide Y Y5,[1a] CCR5[1b] and NK1[1c] receptors, inhibitors of dipeptidylpeptidase IV (DPP IV),[1d] HCV NS3 protease,[1e] factor VIIa,[1f] leiomyosarcoma SK-UT-1B cell proliferation,[1g] farnesyl protein transferase[1h] and phosphodiesterase,[1i] and antiinflammatory[1j] and antiarrhythmic[1k] agents.

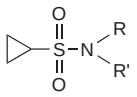


Figure 1

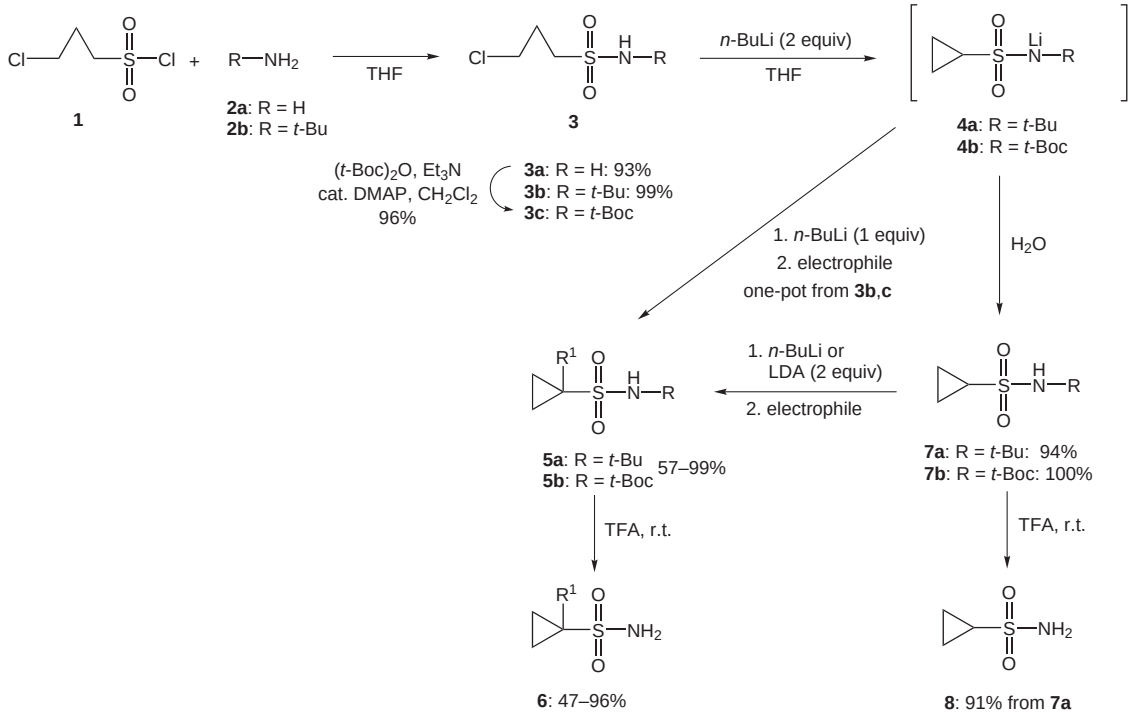
A number of methods have been reported in the literature for the synthesis of cyclopropylsulfonamide derivatives. The reaction of dimethylsulfonium methylide with α,β-unsaturated sulfonamides represents a general route to *N*,*N*-dialkyl cyclopropylsulfonamides.[2] However, this method failed to provide N- or N,N-unsubstituted derivatives. *N*,*N*-Dialkyl cyclopropylsulfonamides have also been prepared by the reaction of α-metalated *N*,*N*-dialkyl chloromethanesulfonamides with activated olefins[3] or from the reaction of N,N-disubstituted methanesulfonamides with a 1,2-dihaloethane in the presence of a base.[4] Base-promoted α,γ-dehydrohalogenation of 3-halopropylsulfonamide yields *N*-alkyl or *N*,*N*-dialkyl cyclopropylsulfonamides.[5] Although cyclopropylsulfonyl chloride is commercially available and can readily be coupled with amines to afford sulfonamides, it is expensive, the consequence of a multistep synthesis.[6]

In the course of a structure–activity survey, we required convenient and reliable access to cyclopropylsulfonamide **8** and a variety of 1-substituted cyclopropylsulfonamides **6**, which are not easily accessible using the existing methods. Herein, we wish to report a practical and convenient synthesis of **8** that is amenable to large scale and its conversion to a series of substituted derivatives **6** as depicted in Scheme 1.

Two different protecting groups for the sulfonamide NH_2 moiety were examined. *tert*-Butylamine was selected as the source of NH_2 based on Thompson's[7] findings that the *tert*-butyl group can be readily removed in acidic medium and that its steric bulk minimizes N-alkylation or acylation. The *t*-Boc moiety behaves in a similar fashion, providing a protecting element that is readily installed,[8] easily removed under acidic[9] or thermal[10] conditions and which is not prone to N-alkylation.[9] Thus, 3-chloropropanesulfonyl chloride **1** reacted smoothly with excess ammonia (**2a**) at 0 °C to room temperature or two equivalents of *tert*-butylamine (**2b**) in THF from –20 °C to room temperature to give the 3-chloropropylsulfonamides **3a** and **3b** in 93% and 99% yield, respectively.[11–14] Both procedures are readily conducted on large scale. Conversion of **3a** to the *t*-Boc derivative **3c** was accomplished by exposure to $(t\text{-Boc})_2O$ in CH_2Cl_2 using Et_3N as the base in the presence of a catalytic amount of DMAP.[8] Dilithiation of **3b** and **3c** with two equivalents of *n*-butyllithium at –78 °C in THF effected metallation at the sulfonamide nitrogen and the α-carbon atom to provide a dianion that subsequently cyclized to form the lithiated cyclopropylsulfonamides **4a** and **4b**, respectively, upon warming to room temperature. Aqueous workup afforded **7a** and **7b** in isolated yields of 94% and 100%, respectively. Treatment of **7a** with TFA at room temperature afforded cyclopropylsulfonamide **8** in good yield.[12] This three-step procedure afforded cyclopropylsulfonamide **8** in a very simple operation without resort to column chromatography for purification, and in an economical fashion.

Treating **7a** and **7b** with 2 equivalents of a strong base (*n*-BuLi for **7a** and either *n*-BuLi or LDA for **7b**) effected formation of the *N*,*C*-dianion which reacted with a range of electrophiles on carbon to provide a series of 1-substituted cyclopropylsulfonamides **6** after deprotection of the sulfonamide nitrogen atom. Moreover, this process could be telescoped into a simple and convenient one-pot operation by treating the intermediate anions **4a** and **4b** with an equivalent of *n*-BuLi to generate the dianion in situ.[11–14] The results compiled in Table 1 demonstrate the scope of the electrophiles that successfully participate in this process. The dianions reacted readily with both activated and unactivated alkyl halides (entries 1–15),

SYNLETT 2006, No. 5, pp 0725–0728
Advanced online publication: 09.03.2006
DOI: 10.1055/s-2006-933130; Art ID: S11805ST



Scheme 1

aldehydes and ketones (entries 16–19), an ester (entry 20), isocyanates (entries 21 and 22), trimethylsilyl chloride (entry 23) and halogenating agents (entries 24 and 25) to produce α-substituted cyclopropylsulfonamides **5** in good to excellent isolated yields.[11–14] The examples shown are reactions performed a single time, many using the one-pot process and the yields are unoptimized.

As indicated in Table 1, in most cases the *t*-Bu and *t*-Boc groups of the intermediates **5** can be removed by exposure to trifluoroacetic acid at room temperature for 16 hours to give the corresponding sulfonamides **6** in good yields. The adducts derived from aldehydes and ketones provided for complications with the cyclohexanone and acetone adducts (entries 18 and 19) suffering dehydration under the conditions for deprotection. The benzaldehyde adduct (entry 17) provided a complex mixture when exposed to trifluoroacetic acid and attempts to moderate this reaction by diluting with CH_2Cl_2 merely produced an equally complicated mixture at a slower rate, over four to five days. However, heating the benzyl alcohol at reflux in xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid for five hours, cooling and collecting the precipitate afforded product that could be further purified by trituration with methanol to give product in 68% yield.

In summary, we have described a convenient and efficient methodology for the synthesis of cyclopropylsulfonamide **8** and 1-substituted cyclopropylsulfonamides **6** that takes advantage of two N-protecting moieties. The three-step procedure using readily available starting materials is convenient and readily conducted on large scale and allows the facile introduction of a wide array of substituents at the 1-position of the cyclopropyl ring. The application of this methodology in the synthesis of bioactive compounds will be reported in due course.

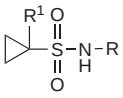
Acknowledgment

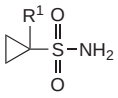
The authors thank Dr. Balu Balasubramanian and Dr. Bang-Chi Chen for comments and suggestions on the manuscript.

References and Notes

(1) A Scifinder search based on substructure A revealed more than 90 patents claiming bioactivities of cyclosulfonamide derivatives. See: (a) Greenlee, W. J.; Huang, Y.; Kelly, J. M.; McCombie, S. W.; Stamford, A. W.; Wu, Y. US Patent Appl. 2003/114517, **2003**. (b) Miller, M. W.; Scott, J. D. PCT Int. Appl. WO 2004/056770, **2004**. (c) Paliwal, S.; Reichard, G. A.; Wang, C.; Xiao, D.; Tsui, H.-C.; Shih, N.-Y.; Arredondo, J. D.; Wrobleski, M. L.; Palani, A. PCT Int. Appl. WO 2003/051840, **2003**. (d) De Nanteuil, G.; Portevin, B.; Benoist, A.; Levens, N.; Nosjean, O.; Husson-Robert, B. Eur. Pat. Appl. 1245568, **2002**. (e) Llinas-Brunet, M.; Bailey, M. D. PCT Int. Appl. WO 2004/037855, **2004**. (f) Glunz, P. W.; Bisacchi, G. S.; Morton, G. C.; Holubec, A. A.; Priestley, E. S.; Zhang, X.; Treuner, U. D. PCT Int. Appl. WO 2004/072101, **2004**. (g) Walter, R.; Heckel, A.; Roth, G. J.; Kley, J.; Schnapp, G.; Lenter, M.; Van Meel, J. C. A.; Spevak, W.; Weyer-Czernilofsky, U. PCT Int. Appl. WO 2002/36564, **2002**. (h) Zhu, H. Y.; Njoroge, F. G.; Cooper, A. B.; Guzi, T.; Dinanath, F. R.; Minor, K. P.; Doll, R. J.; Girijavallabhan, V. M.; Santhanam, B.; Pinto, P. A.; Vibulbhan, B.; Keertikar, K. M.;

Table 1 Synthesis of α-Substituted Cyclopropylsulfonamides **5** and **6**





Entry	Electrophile	**5**[a]	Yield (%)[b]	**6**[a]	Yield (%)[b]
1	CH_3I	R = *t*-Bu; $R^1 = CH_3$	81	$R^1 = CH_3$	96
2	*n*-C_4H_9I	R = *t*-Boc; R^1 = *n*-C_4H_9	89	R^1 = *n*-C_4H_9	90
3	*i*-PrI	R = *t*-Boc; R^1 = *i*-Pr	69[c]	R^1 = *i*-Pr	69
4	*c*-$C_4H_7CH_2I$	R = *t*-Boc; $R^1 = CH_2$(*c*-C_4H_7)	55[c]	$R^1 = CH_2$(*c*-C_4H_7)	99
5	*c*-$C_3H_5CH_2I$	R = *t*-Boc; $R^1 = CH_2$(*c*-C_3H_5)	92	$R^1 = CH_2$(*c*-C_3H_5)	65
6	CH_3OCH_2Cl	R = *t*-Boc; $R^1 = CH_2OCH_3$		$R^1 = CH_2OCH_3$	77 (2 steps)
7	*i*-$PrOCH_2Br$	R = *t*-Boc; $R^1 = CH_2O$*i*-Pr	79	$R^1 = CH_2O$*i*-Pr	98
8	$CH_3OCH_2CH_2Br$	R = *t*-Boc; $R^1 = CH_2CH_2OCH_3$	96	$R^1 = CH_2CH_2OCH_3$	45
9	$PhCH_2OCH_2CH_2Br$	R = *t*-Boc; $R^1 = CH_2CH_2OCH_2Ph$	47	$R^1 = CH_2CH_2OCH_2Ph$	85
10	$PhCH_2Br$	R = *t*-Bu; $R^1 = CH_2Ph$	69	$R^1 = CH_2Ph$	66
11	4-$CH_3OC_6H_4CH_2Cl$	R = *t*-Boc; $R^1 = CH_2$(4-$CH_3OC_6H_4$)	78	$R^1 = CH_2$(4-$CH_3OC_6H_4$)	89
12	4-$FC_6H_4CH_2Br$	R = *t*-Boc; $R^1 = CH_2$(4-FC_6H_4)		$R^1 = CH_2$(4-FC_6H_4)	25 (2 steps)
13	2-$FC_6H_4CH_2Cl$	R = *t*-Boc; $R^1 = CH_2$(2-FC_6H_4)		$R^1 = CH_2$(2-FC_6H_4)	36 (2 steps)
14	CH_2=$CHCH_2Br$	R = *t*-Bu; $R^1 = CH_2CH{=}CH_2$	97	$R^1 = CH_2CH{=}CH_2$	74
15	$C_2H_5CvCCH_2Br$	R = *t*-Bu; $R^1 = CH_2C{\equiv}CC_2H_5$	79	$R^1 = CH_2C{\equiv}CC_2H_5$	100
16	CH_3CH_2CHO	R = *t*-Bu; $R^1 = CH(OH)CH_2CH_3$	61	$R^1 = CH(OH)CH_2CH_3$	47
17	PhCHO	R = *t*-Bu; R^1 = CH(OH)Ph	78	R^1 = CH(OH)Ph	68[d]
18	Cyclohexanone	R = *t*-Bu; R^1 = 	84	R^1 = 1-Cyclohexenyl	85
19	Acetone	R = *t*-Boc; $R^1 = C(OH)(CH_3)_2$	49	2-Isopropenyl	94
20	$PhCO_2CH_3$	R = *t*-Bu; R^1 = COPh	66	R^1 = COPh	87
21	PhN=C=O	R = *t*-Bu; R^1 = CONHPh	57	R^1 = CONHPh	75
22	*n*-C_3H_7N=C=O	R = *t*-Boc; R^1 = CONH*n*-C_3H_7	100	R^1 = CONH*n*-C_3H_7	50
23	$(CH_3)_3SiCl$	R = *t*-Bu; $R^1 = Si(CH_3)_3$	99	$R^1 = Si(CH_3)_3$	73
24	*N*-Chlorosuccinimide	R = *t*-Boc; R^1 = Cl	67	R^1 = Cl	100
25	I_2	R = *t*-Boc; R^1 = I		R^1 = I	78 (2 steps)

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis or HRMS.
[b] All yields are unoptimized and isolated yields are after purification by crystallization or column chromatography.
[c] LDA used as the base.
[d] PTSA monohydrate was used to remove the *tert*-butyl group.

Alvarez, C. S.; Baldwin, J. J.; Li, G.; Huang, C.-Y.; James, R. A.; Bishop, W. R.; Wang, J. J.-S.; Desai, J. A. US Patent Appl. 2004/122018, **2004**. (i) Allen, D. G.; Coe, D. M.; Cook, C. M.; Cooper, A. W. J.; Dowle, M. D.; Edlin, C. D.; Hamblin, J. N.; Johnson, M. R.; Jones, P. S.; Lindvall, M. K.; Mitchell, C. J.; Redgrave, A. J. PCT Int. Appl. WO 2004/056823, **2004**. (j) Breitfelder, S.; Cirillo, P. F.; Regan, J. R. PCT Int. Appl. WO 2002/083642, **2002**. (k) Brendel, J.; Pirard, B.; Peukert, S.; Kleemann, H.-W.; Hemmerle, H. PCT Int. Appl. WO 2002/088073, **2002**.

(2) (a) Truce, W. E.; Goralski, C. T. *J. Org. Chem.* **1968**, *33*, 3849. (b) Brienne, M.-J.; Varech, D.; Leclercq, M.; Jacques, J.; Radembino, N.; Dessalles, M.-C.; Mahuzier, G.; Gueyouche, C.; Bories, C.; Loiseau, P.; Gayral, P. *J. Med. Chem.* **1987**, *30*, 2232.

(3) (a) Christensen, L. W.; Seaman, J. M.; Truce, W. E. *J. Org. Chem.* **1973**, *38*, 2243. (b) Makosza, M.; Golinski, J.; Ostrowski, S.; Rykowski, A.; Sahasrabudhe, A. B. *Chem. Ber.* **1991**, *124*, 577.

(4) (a) Kosinski, S.; Wojciechowski, K. *Eur. J. Org. Chem.* **2000**, 1263. (b) Meyle, E.; Schwenkkraus, P.; Zsigmondy, M.; Otto, H.-H. *Arch. Pharm.* **1989**, *322*, 17.

(5) (a) Truce, W. E.; Goralski, C. T. *J. Org. Chem.* **1969**, *34*, 3324. (b) Neale, R. S.; Marcus, N. L. *J. Org. Chem.* **1969**, *34*, 1808.

(6) (a) Block, E.; Schwan, A.; Dixon, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 3492. (b) King, J. F.; Lam, J. Y. L.; Ferrazzi, G. *J. Org. Chem.* **1993**, *58*, 1128.

(7) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.

(8) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379.

(9) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900.

(10) (a) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141. (b) Reuter, D. C.; McIntosh, J. E.; Guinn, A. C.; Madera, A. M. *Synthesis* **2003**, 2321.

(11) White, E. H.; Lim, H. M. *J. Org. Chem.* **1987**, *52*, 2162.

(12) **Procedure for the Synthesis of 8.**
tert-Butylamine (**2a**, 3.0 mol, 315.3 mL) was dissolved in THF (2.5 L). The solution was cooled to –20 °C and 3-chloropropanesulfonyl chloride (**1**, 1.5 mol, 182.4 mL) was added slowly. The reaction mixture was allowed to warm to r.t. and stirred for 24 h. The mixture was filtered, and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2.0 L), washed with 1 N HCl (1.0 L), H_2O (1.0 L) and brine (1.0 L) before being dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give a slightly yellow solid, which was crystallized from hexane to afford the product **3b** as a white solid (316.0 g, 99%). Mp 70–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 3 × CH_3), 2.25–2.30 (m, 2 H, CH_2), 3.21 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.67 (t, *J* = 7.5 Hz, 2 H, CH_2), 4.36 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 30.4, 42.9, 53.4, 54.9. Anal. Calcd for $C_7H_{16}NO_2S$: C, 39.33; H, 7.54; N, 6.55. Found: C, 39.37; H, 7.33; N, 6.49.
To a stirred solution of compound **3b** (0.75 mol, 160 g) in dry THF (2 L) at –78 °C under N_2 was added slowly a solution of *n*-BuLi (2.5 M in hexane, 2.1 equiv, 1.575 mol, 630 mL). After addition, the dry ice bath was removed and the reaction mixture was allowed to warm to r.t. over a period of 2 h. The reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl solution (500 mL). The THF was removed in vacuo and the residue partitioned between EtOAc (1.5 L) and H_2O (1 L). The organic phase was separated, washed with brine (1 L) and dried over $MgSO_4$ before being filtered and concentrated in vacuo to give a white solid which was recrystallized from hexane to give the product **7a** as white needles (125.0 g, 94%). Mp 81–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96–1.00 (m, 2 H, CH_2), 1.16–1.19 (m, 2 H, CH_2), 1.38 (s, 9 H, 3 × CH_3), 2.43–2.47 (m, CH), 4.23 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.5, 30.7, 33.6, 54.3. Anal. Calcd for $C_7H_{15}NO_2S$: C, 47.43; H, 8.52; N, 7.90. Found: C, 47.53; H, 8.49; N, 7.74.
A solution of compound **7a** (0.62 mol, 110.0 g) in TFA (500 mL) was stirred at r.t. under N_2 for 16 h. The TFA was removed in vacuo to give a yellow oil which was crystallized from EtOAc–hexane (1:3, 300 mL) to afford product **8** as white needles (68.5 g, 91%). Mp 106–107 °C. ^{1}H NMR (500 MHz, DMSO): δ = 0.87–0.93 (m, 4 H, 2 × CH_2), 2.49–2.54 (m, 1 H, CH), 6.76 (br s, 2 H, NH_2). ^{13}C NMR (125 MHz, DMSO): δ = 4.90, 32.0. Anal. Calcd for $C_3H_7NO_2S$: C, 29.74; H, 5.82; N, 11.56. Found: C, 30.02; H, 5.61; N, 11.37.

(13) **Typical Procedure Exemplified by the Preparation of 1-Methylcyclopropylsulfonamide (Table, Entry 1).**
To a solution of **3b** (20 mmol, 4.3 g) in dry THF (100 mL) under N_2 was added a solution of *n*-BuLi (2.5 M in hexane, 2.1 equiv, 44 mmol, 17.6 mL) at –78 °C. The reaction mixture was allowed to warm to r.t. over a period of 1.5 h and then was cooled to –78 °C. Another equivalent of *n*-BuLi (8 mL) was added, the mixture warmed to r.t. over a period of 1.5 h and then recooled to –78 °C. The MeI (2 equiv, 40 mmol, 2.5 mL) was added and the reaction mixture was allowed to warm to r.t. over a period of 12 h. The mixture was quenched with a solution of sat. NH_4Cl (100 mL) and extracted with EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil which was crystallized from hexane to afford the product as slightly yellow needles (3.1 g, 81%). Mp 77–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77–0.80 (m, 2 H, CH_2), 1.38–1.41 (m, 2 H, CH_2), 1.36 (s, 9 H, 3 × CH_3), 1.51 (s, 3 H, CH_3), 4.07 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.0, 30.9, 37.3, 54.4. Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.23; H, 8.95; N, 7.32. Found: C, 50.05; H, 8.80; N, 7.32.
Treatment of this material (10 mmol, 1.91 g) with TFA (30 mL) using the same procedure described above for **8** gave the product as a white solid (1.25 g, 96%). Mp 103–104 °C. ^{1}H NMR (500 MHz, DMSO): δ = 0.74 (dd, *J* = 6.1, 4.0, 2 H, CH_2), 1.13 (dd, *J* = 6.1, 4.0, 2 H, CH_2), 1.44 (s, 3 H, CH_3), 6.72 (br s, 2 H, NH_2). ^{13}C NMR (125 MHz, DMSO): δ = 12.1, 17.6, 36.4. Anal. Calcd for $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36. Found: C, 35.67; H, 6.80; N, 10.40.

(14) For procedures on synthesis of **3a**,**c**, **4b**, **5b** and removal of *t*-Boc group, see: Campbell, J. A.; D'Andrea, S.; Good, A.; Li, J.; McPhee, F.; Ripka, A.; Scola, P. M.; Tu, Y. US Patent Appl. 2004/0077551, **2004**.