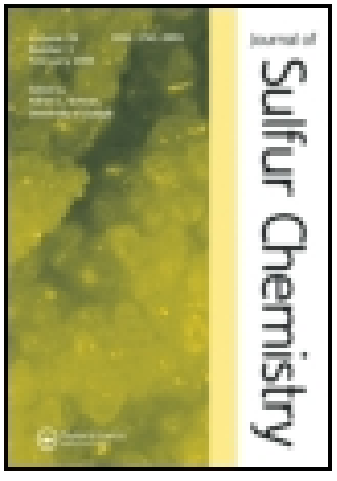


Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

The first general protocol for N-monoalkylation of sulfamate esters: benign synthesis of N-alkyl Topiramate (anticonvulsant drug) derivatives

Hamid Saeidian[a] & Morteza Abdoli[a]
[a] Department of Science, Payame Noor University (PNU), PO Box: 19395-4697, Tehran, Iran
Published online: 29 Jul 2015.

Journal of Sulfur Chemistry, 2015
http://dx.doi.org/10.1080/17415993.2015.1069294

Taylor & Francis
Taylor & Francis Group

SHORT COMMUNICATION

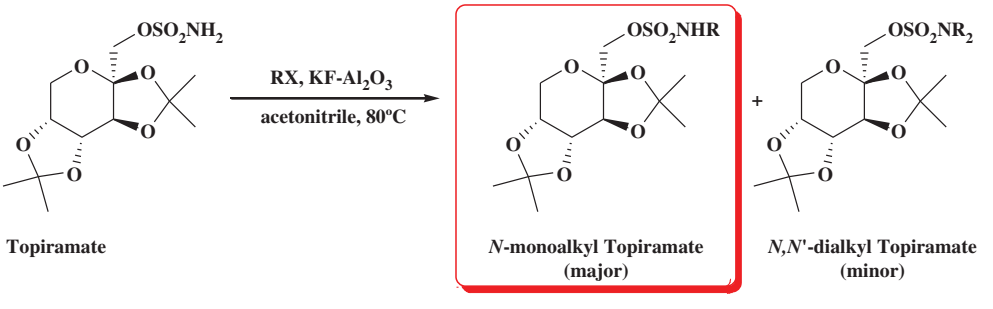
The first general protocol for *N*-monoalkylation of sulfamate esters: benign synthesis of *N*-alkyl Topiramate (anticonvulsant drug) derivatives

Hamid Saeidian* and Morteza Abdoli

Department of Science, Payame Noor University (PNU), PO Box: 19395-4697, Tehran, Iran

(*Received 23 April 2015; accepted 1 July 2015*)

A novel protocol for the highly selective *N*-monoalkylation of the sulfamate ester moiety has been developed. This reaction proceeded efficiently using alkyl halides, benzyl halides and α-halo ketones as the electrophile in the presence of KF-Al_2O_3 as a cost-effective and robust catalyst. This approach provides new access to *N*-monoalkylated Topiramate (anticonvulsant drug) derivatives which are potentially of great importance in medicinal chemistry.



Keywords: sulfamate esters; topiramate; *N*-alkylation; KF-Al_2O_3; alkyl halides

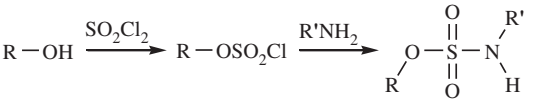
1. Introduction

Sulfamate esters are an important family of compounds in chemistry and biology. They are widely used in the production of pharmaceuticals and sweeteners.[1–3] Among the sulfamates, synthesis and investigation of biological activates of the *N*-monoalkylated sulfamates are absent in the literature, perhaps because their selective synthesis is challenging, due to competitive *N*-*di*-alkylation.

The existing method for the preparation of *N*-monoalkylated sulfamates generally involves the reaction of primary amines with chlorosulfates (Scheme 1).[4] This protocol is associated with some drawbacks such as: (1) very low reaction temperature in the first step and (2) very

*Corresponding author. Email: saeidian1980@gmail.com

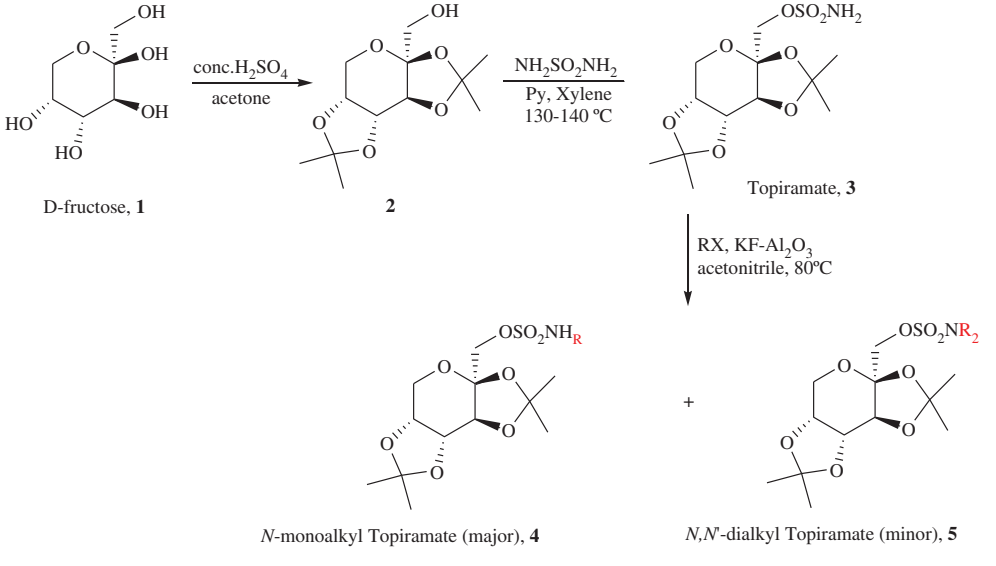
poor selectivity of reaction of amines with chlorosulfates in the presence of aldehyde, ketone, ester, halides and other electrophilic moieties. In addition, many of the needed amines are not commercially available. Therefore, the report of a general protocol for low-cost and highly selective *N*-monoalkylation of sulfamates is very important in organic synthesis and drug discovery programs.



Scheme 1. Existing method for the preparation of *N*-monoalkylated sulfamates.

N-alkylation with alkyl halides is an important reaction in synthetic organic chemistry.[5–7] To the best of our knowledge, there is no method for *N*-alkylation of sulfamates in the literature. It is evident that a novel and flexible protocol with wide substituent tolerance and mild reaction conditions is desirable in the preparation of *N*-substituted sulfamates.

KF-Al_2O_3 was introduced by Clark as a solid base and was applied as a catalyst in a wide variety of organic synthetic procedures.[8,9] The strongly basic nature of KF-Al_2O_3 allows it to replace organic bases in a number of reactions. As a part of our continuing effort to design new routes for the preparation of biologically active organic compounds; herein, we report the synthesis of *N*-substituted Topiramate as an important sulfamate containing drug by the reaction of Topiramate with various alkyl halides in the presence of KF-Al_2O_3 as an efficient solid base (Scheme 2).



Scheme 2. Synthesis of *N*-alkyl Topiramate derivatives from d-fructose.

Topiramate **3** has emerged as a promising anticonvulsant drug marketed worldwide for the treatment of epilepsy and the prophylaxis of migraine.[10] Recently, it is being used

in a growing number of other applications such as treatment of bipolar disorders and post-traumatic stress disorders.[11–13] The search for structural improvement of Topiramate to produce less-toxic and more efficient agents for the treatment of seizure disorders is an ongoing struggle.[14] Derivatization of Topiramate at the sulfamate moiety provides Topiramate analogs that are immunologically similar to Topiramate.[15] Therefore, the synthesis of *N*-substituted Topiramate derivatives is pharmaceutically worthwhile.

2. Results and discussion

The readily available 2,3:4,5-bis-*O*-(1-methylethylidene)-β-d-fructopyranose **2** was synthesized from condensation of d-fructose **1** with acetone in the presence of sulfuric acid.[16] Treatment of **2** with sulfamide in xylene and pyridine yielded Topiramate **3** in good yield (55%).[17]

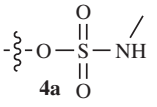
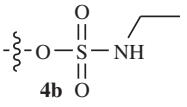
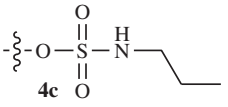
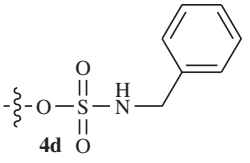
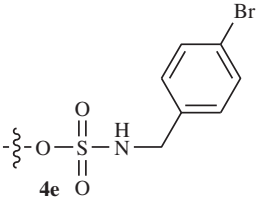
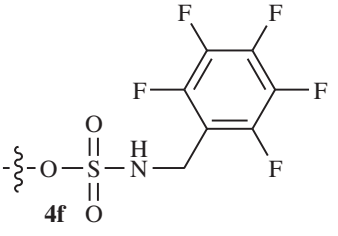
We started our studies with the optimization of the catalytic system and reaction conditions for the model reaction of Topiramate with methyl iodide. Several catalysts were tested in this experiment. As shown in Table 1, the reaction did not work with metal oxides (Entries 1 and 2), iodine (Entry 3) and calcium carbonate (Entry 4). When KF-Al_2O_3 was used as the catalyst, low conversion of **3** was obtained (Entry 5). KF-SiO_2 as a solid-supported catalyst was tested, and did not show better activities than KF-Al_2O_3 (Entry 6), so KF-Al_2O_3 was the suitable catalyst for this reaction. Then the effect of the catalyst amount was examined, and the results showed that the reduction of the amount of the catalyst led to a lower conversion of **3** (Entries 7). The alkyl halide amount is more important in determining the reaction yield (Entries 8 and 9). An acceptable conversion was obtained using 40% mol KF-Al_2O_3 and 2 equiv. of methyl iodide, and the isolated yield of *N*-monomethylated product reached 41% (Entry 10). Disappointedly, when we reduced the amount of the catalyst to 20% mol, lower conversion of **3** was obtained even when the amount of methyl iodide was increased to 4 equiv. (Entry 11). Further screening of reaction time and temperature showed that 48 h and 80°C was the best choice (Entry 15). Therefore, optimal reaction conditions involved KF-Al_2O_3 (40% mol) as the catalyst, acetonitrile as the solvent, and 2 equiv. of alkyl halide as the electrophile at 80°C for 48 h.

To establish the generality of this method, we used a series of alkyl halides to obtain their corresponding *N*-alkylated Topiramates. As shown in Table 2, *N*-monoalkyl Topiramate derivatives

Table 1. Optimization reaction conditions for the model reaction of Topiramate with methyl iodide.

Entry	Catalyst	Time (h)	*T* (°C)	Catalyst amount (mol %)	Methyl iodide amount (equiv.)	Yield (%) of **4**
1	CuO	24	r.t.	5	1	Trace
2	MgO	24	r.t.	5	1	Trace
3	I_2	24	r.t.	5	1	Trace
4	$CaCO_3$	24	r.t.	5	1	Trace
5	KF-Al_2O_3	24	r.t.	40	1	17
6	KF-SiO_2	24	r.t.	40	1	Trace
7	KF-Al_2O_3	24	r.t.	20	1	10
8	KF-Al_2O_3	24	r.t.	40	1.2	21
9	KF-Al_2O_3	24	r.t.	40	1.5	29
10	KF-Al_2O_3	24	r.t.	40	2	41
11	KF-Al_2O_3	24	r.t.	20	4	21
12	KF-Al_2O_3	36	r.t.	40	2	48
13	KF-Al_2O_3	48	r.t.	40	2	57
14	KF-Al_2O_3	48	50	40	2	66
15	KF-Al_2O_3	48	80	40	2	86

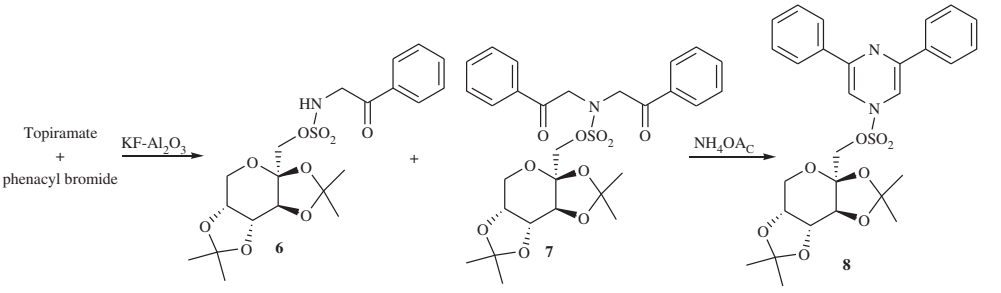
Table 2. Synthesis of *N*-alkyl Topiramate derivatives[a].

Entry	Alkyl halide	*N*-monoalkyl Topiramate	Yield %	Time (h)
1	Methyl iodide	 **4a**	86 (trace)[b]	48
2	Ethyl iodide	 **4b**	88 (trace)	48
3	Propyl iodide	 **4c**	77 (trace)	48
4	Benzyl bromide	 **4d**	77 (7)	36
5	4-Bromo benzyl bromide	 **4e**	68 (11)	36
6	Penta flouro benzyl bromide	 **4f**	64 (28)	36

[a]Reaction conditions: **3** (1 mmol), alkyl halide (2 mmol), KF-Al_2O_3 (40 mol%), ACN (5 mL), at 80°C, 48 h.
[b]Yield of *N,N′-di*-alkyl Topiramate derivatives.

were synthesized in high yields. The reaction proceeds via an S_N2 mechanism. It is worth noting that direct displacement reactions take place rapidly in benzylic systems. The π systems of the benzylic group provide extended conjugation, which stabilizes the TS in the S_N2 mechanism.[18] Therefore, the reaction of Topiramate with benzyl halides affords *N*-monoalkyl Topiramate and *N,N′–di–*alkyl Topiramate derivatives in good to moderate yields in short reaction time (Table 2, Entries 4–6).

The structures of the products were confirmed by C/H/N elemental analysis, electrospray ionization-mass spectrum (ESI-MS), ^{1}H NMR and ^{13}C NMR analysis (see supporting information). The ^{1}H NMR and ^{13}C NMR spectra of the product clearly indicated the formation of **4a**. The ^{1}H NMR spectrum of **4a** consisted of a broad line at $\delta = 4.77$ ppm correlating



Scheme 3. Synthesis of *N*-phenacyl topiramate, *N,N'*-diphenacyl Topiramate and 1,4-dihydro-pyrazines **8**.

to the NH, seven signals at $\delta = 4.65$–3.77 ppm that can be assigned to diastereotopic methylene protons (2 × CH2) and methine protons (3 × CH), a singlet at $\delta = 2.85$ ppm from the *N*-methyl and four singlets to the methyl protons at $\delta = 1.57$–1.36 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances which is in agreement with the proposed structure. ESI-MS of **4a** showed the presence of $[M + H]^+$ at *m/z* 354 and the sodium adduct at *m/z* 376.

The applicability of the present methodology was further extended by performing the reaction of Topiramate with phenacyl bromide in the presence of KF-Al_2O_3 to provide *N*-phenacyl Topiramate **6** and *N,N'*-diphenacyl Topiramate **7** in 54% and 33% yields, respectively (Scheme 3). It is interesting to note that the reaction of **7** with ammonium acetate generates the 1,4-dihydropyrazine **8**, that incorporates the Topiramate moiety. Further studies of the reactions for synthesis of the 1,4-dihydro-pyrazines by this method are in progress.

In conclusion, a novel protocol for the *N*-monoalkylation of sulfamate moiety with alkyl halides has been developed. To the best of our knowledge, this reaction is the first example that uses alkyl halides as electrophiles to perform direct and highly selective *N*-monoalkylation of sulfamates. Further investigation of the expansion of this novel method to a broad spectrum of substrates is underway in our laboratory.

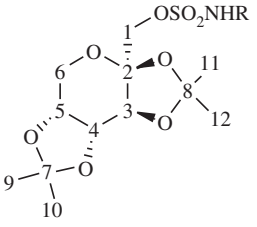
3. Experimental

All the chemicals required for the synthesis of *N*-monoalkyl Topiramate derivatives were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluka (Neu-Ulm, Germany) and Merck (Darmstadt, Germany) companies and were used as received. ^{1}H NMR spectra were recorded on 500, 400 and 300 MHz NMR spec-trometer and ^{13}C NMR spectra were recorded on 125, 100 and 75 MHz NMR spectrometer using $CDCl_3$ as the solvent, chemical shifts have been expressed in ppm. The KF-Al_2O_3 support was prepared according to a previously reported procedure.[19]

3.1. *General procedure*

To a stirred suspension of KF-Al_2O_3 (65 mg) in CH_3CN (5 mL) were added Topiramate (1.0 mmol) and alkyl halide (2.0 mmol). The reaction mixture was stirred at 80°C for 36–48 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the solvent was removed under reduced pressure, and the residue was separated by preparative TLC with petroleum ether/ethyl acetate (3:1) as an eluent to obtain the pure product.

4. Spectral data of the *N*-monoalkyl and *N,N′*-dialkyl Topiramate derivatives



Topiramate: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38, 1.46, 1.52, 1.59 (4 × s, 12H, –C(CH_3)$_2$), 3.81–3.83 (m, 1H, H-6), 3.94 (dd, 1H, *J* 13.0, 1.8 Hz, H-6), 4.26–4.29 (m, 2H, H-1 and H-5), 4.33–4.38 (m, 2H, H-1 and H-3), 4.65 (dd, 1H, *J* 7.9, 2.6 Hz, H-4), 4.91 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 25.4, 26.2, 26.8, 61.7, 70.4, 70.9, 71.0, 71.5, 101.4, 109.7, 109.8.

N-methyl Topiramate (**4a**): ^{1}H NMR (400 MHz, CDC1$_3$): δ 1.37, 1.45, 1.50, 1.57 (4 × s, 12H, –C(CH_3)$_2$), 2.85 (s, 3H, N-CH_3), 3.78 (ABdd, 1H, *J* 12.8, 0.4 Hz, H-6), 3.93 (ABdd, 1H, *J* 12.8, 2.0 Hz, H-6), 4.14 (ABd, 1H, *J* 10.8 Hz, H-1), 4.20 (ABd, 1H, *J* 10.4 Hz, H-1), 4.27 (dd, 1H, *J* 7.6, 1.2 Hz, H-5), 4.36 (d, 1H, *J* 2.8 Hz, H-3), 4.64 (dd, 1H, *J* 7.6, 2.8 Hz, H-4), 4.78 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 25.2, 25.8, 26.5, 29.8, 61.3, 69.9, 70.0, 70.2, 70.6, 100.8, 109.2, 109.3. Anal. Calcd for $C1_3H_{23}NO_8S$: C, 44.18; H, 6.56; N, 3.96. Found: C, 44.27; H, 6.62; N, 3.89.

N-ethyl Topiramate (**4b**): ^{1}H NMR (400 MHz, CDCl3): δ 1.25 (t, 3H, *J* 7.2 Hz, N-CH_2CH_3), 1.36, 1.44, 1.49, 1.57 (4 × s, 12H, –C(CH_3)$_2$), 3.23 (m, 2H, N-CH_2CH_3), 3.78 (ABd, 1H, *J* 12.8, 0.4 Hz, H-6), 3.93 (ABdd, 1H, *J* 12.8, 1.6 Hz, H-6), 4.13 (ABd, 1H, *J* 10.4 Hz, H-1), 4.20 (ABd, 1H, *J* 10.4 Hz, H-1), 4.27 (dd, 1H, *J* 8.0, 1.2 Hz, H-5), 4.36 (d, 1H, *J* 2.4 Hz, H-3), 4.63 (dd, 1H, *J* 8.0, 2.4 Hz, H-4), 4,68 (t, 1H, *J* 6.0 Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 24.0, 25.2, 25.8, 26.5, 38.9, 61.3, 69.7, 69.9, 70.1, 70.6, 100.9, 109.15, 109.22. Anal. Calcd for $C1_4H_{25}NO_8S$: C, 45.77; H, 6.86; N, 3.81. Found: C, 45.71; H, 6.91; N, 3.75.

N-propyl Topiramate (**4c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* 14.8 Hz, N-$CH_2CH_2CH_3$), 1.35, 1.42, 1.48, 1.55 (4 × s, 12H, –C(CH_3)$_2$), 1.60 (m, 2H, N-$CH_2CH_2CH_3$), 3.12 (m, 2H, N-$CH_2CH_2CH_3$), 3.76 (ABd, 1H, *J* 13.2 Hz, H-6), 3.91 (ABdd, 1H, *J* 12.8, 0.8 Hz, H-6), 4.11 (ABd, 1H, *J* 10.4 Hz, H-1), 4.18 (ABd, 1H, *J* 10.4 Hz, H-1), 4.25 (d, 1H, *J* 7.6 Hz, H-5), 4.35 (d, 1H, *J* 2.4 Hz, H-3), 4.62 (dd, 1H, *J* 8.0, 2.4 Hz, H-4), 4.93 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 22.7, 23.9, 25.1, 25.7, 26.4, 45.3, 61.2, 69.4, 69.8, 70.0, 70.6, 100.8, 109.0, 109.1.

N-benzyl Topiramate (**4d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36, 1.42, 1.47, 1.55 (4 × s, 12H, –C(CH_3)$_2$), 3.73 (ABd, 1H, *J* 13.2 Hz, H-6), 3.89 (ABd, 1H, *J* 13.2 Hz, H-6), 4.13 (ABd, 1H, *J* 10.4 Hz, H-1), 4.21 (ABd, 1H, *J* 9.6 Hz, H-1), 4.23 (d, 1H, *J* 7.6 Hz, H-5), 4.31–4.32 (m, 3H, N-CH_2 and H-3), 4.60–4.65 (m, 1H, H-4), 5.33 (br s, 1H, NH), 7.31–7.38 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 25.2, 25.6, 26.5, 47.7, 61.3, 69.86, 69.95, 70.2, 71.6, 109.2, 109.3, 128.15, 128.20, 128.8, 136.2. Anal. Calcd for $C1_9H_{27}NO_8S$: C, 53.13; H, 6.34; N, 3.26. Found: C, 53.23; H, 6.27; N, 3.34.

N,N′-dibenzyl Topiramate (**5d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32, 1.40, 1.51, 1.56 (4 × s, 12H, -C(CH_3)$_2$), 3.78 (ABd, 1H, *J* 12.4 Hz, H-6), 3.94 (ABd, 1H, *J* 12.4 Hz, H-6), 4.18 (ABd, 1H, *J* 10.4 Hz, H-1), 4.22 (ABd, 1H, J 10.0 Hz, H-1), 4.26–4.33 (m, 2H, H-5, H-3), 4.31 (ABd, 2H, *J* 14.8 Hz, N-CH_2), 4.44 (ABd, 2H, *J* 14.8 Hz, N-CH_2), 4.64 (dd, 1H, *J* 7.6, 2.4 Hz, H-4), 7.29–7.4 (m, 10H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 25.2, 26.0, 26.6, 50.9, 61.4, 69.2, 70.0, 70.7, 100.9, 109, 128.2, 128.7, 129.0, 135.0.

N-(4-bromo benzyl) Topiramate (**4e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38, 1.43, 1.49, 1.56 (4 × s, 12H, -C(CH_3)$_2$), 3.77 (ABd, 1H, *J* 12.8 Hz, H-6), 3.92 (ABdd, 1H, *J* 12.8, 1.6 Hz, H-6), 4.16 (ABd, 1H, *J* 10.4 Hz, H-1), 4.26 (ABd, 1H, *J* 10.4 Hz, H-1), 4.26–4.31 (m, 4H, N-CH_2, H-5, H-3), 4.64 (dd, 1H, *J* 7.6, 2.4 Hz, H-4), 5.01 (br s, 1H, NH), 7.27 (d, 2H, *J* 8.4 Hz, Ar), 7.52 (d, 2H, *J* 8.4 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 25.2, 25.9, 26.5, 47.3, 61.4, 69.9, 70.3, 70.59, 70.60, 100.8, 109.2, 109.3, 122.3, 129.9, 132.0, 135.

N,N-di(4-bromo benzyl) Topiramate (**5e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.39, 1.49, 1.56 (4 × s, 12H, -C(CH_3)$_2$), 3.78 (ABd, 1H, *J* 12.8 Hz, H-6), 3.93 (ABd, 1H, *J* 12.0 Hz, H-6), 4.15 (ABd, 1H, *J* 10.0 Hz, H-1), 4.21–4.36 (m, 7H), 4.64 (dd, 1H, *J* 7.6, 2.4 Hz, H-4), 7.16 (d, 4H, *J* 8.2 Hz, Ar), 7.48 (d, 4H, *J* 8.2 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 25.2, 25.9, 26.6, 50.6, 61.4, 69.7, 69.9, 70.1, 70.6, 100.7, 109.15, 109.19, 122.3, 130.6, 131.9, 133.8.

N,N-di(pentaflouro benzyl) Topiramate (**5f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6H, –C(CH_3)$_2$), 1.41, 1.50 (s, 6H, –C(CH_3)$_2$), 3.67 (ABd, 1H, *J* 12.9 Hz, H-6), 3.84 (ABd, 1H, *J* 12.9 Hz, H-6), 3.93 (ABd, 1H, *J* 10.2 Hz, H-1), 3.99–4.04 (m, 2H), 4.19 (d, 1H, *J* 7.9 Hz), 4.54 (dd, 1H, *J* 7.5, 2.3 Hz), 4.59–4.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 24.7, 25.4, 26.2, 41.8, 61.2, 69.7, 70.0, 70.2, 70.4, 100.2, 109.2, 109.4, 135.8–136.0, 139.1–139.8, 143.2–144.0, 147.2–148.0.

Acknowledgements

We are thankful to Mr Biglari for NMR spectral support.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Winum JY, Scozzafava A, Montero JL, Supuran CT. Sulfamates and their therapeutic potential. Med Res Rev. 2005;25:186–228.
[2] Saeidian H, Abdoli M, Mirjafary Z. Synthesis of acyclic and cyclic sulfamates: a review. Synthesis. 2015;47:1057–1075.
[3] Spillane WJ, Rayder CA, Walsh MR, Curran PJ, Concagh DG, Wall SN. Sulfamate sweeteners. Food Chem. 1996;56:255–261.
[4] Maryanoff BEM, Costanzo MJ, Shank RP, Schupsky JJ, Ortegon ME, Vaught JL. Anticonvulsant sugar sulfamates. Potent cyclic sulfate and cyclic sulfite analogues of topiramate. Bioorg Med Chem Lett. 1993;3:2653–2656.
[5] Katritzky AR, Meth-Cohn O, Rees CW. Comprehensive organic functional group transformation. New York(NY): Pergamon; 1995.
[6] Conreaux D, Bossharth E, Monteiro N, Desbordes P, Balme G. A practical procedure for the selective N-alkylation of 4-alkoxy-2-pyridones and its use in a sulfone-mediated synthesis of N-methyl-4-methoxy-2-pyridone. Tetrahedron Lett. 2005;46:7917–7920.
[7] Smith MB, March J. Advanced organic chemistry. 5th ed. New York (NY): Wiley; 2001.
[8] Clark JH, Macquarrie DJ. Heterogeneous catalysis in liquid phase transformations of importance in the industrial preparation of fine chemicals. Org Proc Res Dev. 1997;1:149–162.
[9] Blass BE. KF/Al_2O_3 mediated organic synthesis. Tetrahedron. 2002;58:9301–9320.
[10] Shank RP, Gordoeki JF, Streter AJ. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia. 2000;41:S3–S9.
[11] Mirza N, Marson AG, Pirmohamed MB. Effect of topiramate on acid–base balance: extent, mechanism and effects. J Clin Pharmacol. 2009;68:655–661.
[12] Vasudev K, Macritchie K, Geddes J, Watson S, Young A. Cochrane Database Syst Rev; 2006, Art. No.: CD003384.
[13] Berlin HA. Antiepileptic drugs for the treatment of post-traumatic stress disorder. Curr Psychiat Rep. 2007;9:291–300.
[14] Stefan H, Feuerstein TJ. Novel anticonvulsant drugs. Pharmacol Therapeut. 2007;113:165–183.
[15] Stenglein KJ, Cawlay KD, Maryanoff BE, Sorgi KL. United States patent US 005952187A. 1999.
[16] Brady RF. Cyclic acetals of ketoses: Part III. Re-investigation of the synthesis of the isomeric Di-O-isopropylidene-β-d-fructopyranoses. Carbohydr Res. 1970;15:35–40.

[17] Berkner JE, Duncan S, Mills J. EP patent 1599490. 2009.
[18] Carey FA, Sundberg RJ. Advanced organic chemistry, Part A: structure and mechanisms. 4th ed. Charlottesville, VA: Springer Science Business Media, LLC; 2007.
[19] Saeidian H, Sadeghi A, Mirjafary Z, Moghaddam FM. Solvent-free synthesis of 2-amino-3-aryl-5-substituted Thiophenes as anti-inflammatory agents using KF-Al_2O_3 under microwave irradiation. Synthetic Commun. 2008;38:2043–2053.