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SYNTHESIS OF 1-(METHYLSULFONYL)-1-PROPENE AND *N,N*-DIMETHYL-1-PROPENE-1-SULFONAMIDE

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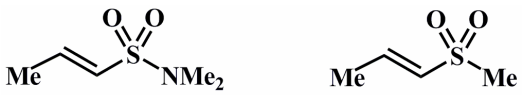
Various vinylsulfones and vinylsulfonamides have a wide range of biological activities (mainly, inhibition of different types of enzymes) and are frequently used in synthetic organic chemistry (as active dienophiles, Michael acceptors and, generally, active agents in 1,4-addition and electrocyclization reactions). However, despite numerous synthesized substances of this type, the synthetic protocols for the obtaining of the low molecular weight representatives of these compounds – 1-(methylsulfonyl)-1-propene and *N*,*N*-dimethyl-1-propene-1-sulfonamide – seem to be still little known. In the present work we report a simple, efficient and general protocol for the dehydrative synthesis of 1-(methylsulfonyl)-1-propene and *N*,*N*-dimethyl-1-propene-1-sulfonamide starting from corresponding 1-(methylsulfonyl)-2-propanol and *N*,*N*-dimethyl-2-hydroxypropanesulfonamide, respectively, using $MeSO_2Cl$/organic base system basing on the preliminary experiment of 2-(4-bromophenyl)-*N*,*N*-dimethylethenesulfonamide synthesis from 2-(4-bromophenyl)-2-hydroxy-*N*,*N*-dimethylethanesulfonamide. The latter in its turn has been obtained starting from *N*,*N*-dimethylmethanesulfonamide by lithiation with *n*-BuLi, subsequent action of 4-bromobenzaldehyde and further workup. The applied protocol of vinyl derivatives synthesis allows to avoid isolation of intermediate mesyl derivatives, consisting of one-pot formation of leaving group and its elimination. Accordingly to coupling constants in ^{1}H NMR spectra, synthesized *N*,*N*-dimethyl-1-propene-1-sulfonamide exists as mixture of *E*- and Z-isomers (in the ratio 88:12), while isolated 1-(methylsulfonyl)-1-propene and 2-(4-bromophenyl)-*N*,*N*-dimethylethenesulfonamide are the most stable *E*-isomers. The structures of the synthesized compounds are confirmed by the methods of ^{1}H NMR-spectroscopy and mass-spectrometry.

Keywords: vinylsulfones, vinylsulfonamides, 1-(methylsulfonyl)-1-propene, *N,N*-dimethyl-1-propene-1-sulfonamide, dehydration.

Introduction

Vinylsulfones and vinylsulfonamides possess a variety of biological activities and this fact causes their wide application in medical chemistry [1–3]. Moreover, these compounds are active Michael acceptors, being intensively explored for the syntheses of *β*-functionalized sulfones and sulfonamides and in Diels-Alder reaction [4–7]

Nevertheless, the low molecular weight representatives of vinylsulfones and vinylsulfonamides – *N*,*N*-dimethyl-1-propene-1-sulfonamide **1** and 1-(methylsulfonyl)-1-propene **2** – are still little known, and their synthetic preparation is not well-studied [8–10] (Figure 1).



1 **2**

Figure 1. Structure of the target *N*,*N*-dimethyl-1-propene-1-sulfonamide **1** and 1-(methylsulfonyl)-1-propene **2**.

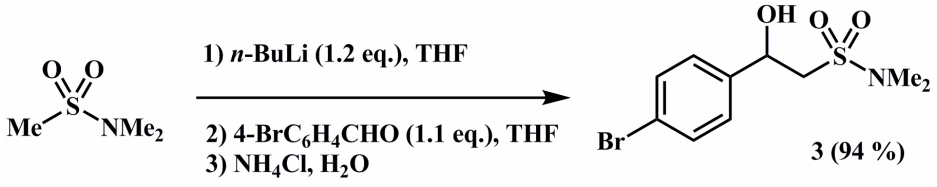
The purpose of the present work is to work up simple and preparative protocols for the synthesis of compounds **1** and **2**.

Results and discussion

First we tested ability of vinylsulfonamides' synthesis starting from corresponding *β*-hydroxy-SO_2-derivatives using $MeSO_2Cl$/organic base system on the example of transformation of bromoalcohol **3**

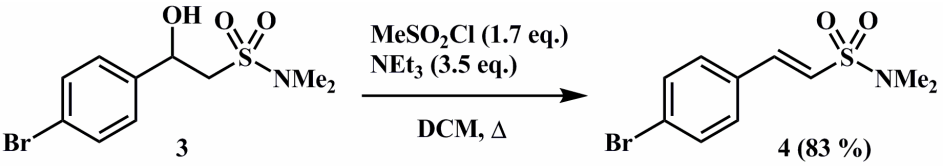
to corresponding vinylsulfonamide **4**. Bromoderivatives **3** and **4** were chosen because of their relatively low solubility in most organic solvents (that was expected comparing with target compounds **1** and **2**) and due to our ability to fix characteristic bromo-containing ions by MS-techniques.

Alcohol **3** was synthesized similarly to been reported [11, 12]. Initial *N,N*-dimethylmethanesulfonamide was metallated with *n*-BuLi in THF at the temperature below 0ºC and formed salt was then treated with 4-bromobenzaldehyde in the same conditions, giving the product after appropriate workup (Scheme 1).



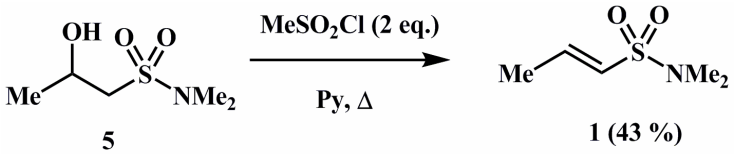
Scheme 1. Synthesis of alcohol **3**.

Noteworthy, that all the preliminary experiments on the syntheses of tosylates and mesylates of *β*-hydroxy-SO_2-derivatives **3**, **5** and **6** anyway led (accordingly to ^{1}H NMR spectra of the probes of reaction mixtures) to formation of some amount of corresponding vinyl derivatives. That is why we undertook dehydration of secondary alcohol **3** according to the synthesis of the similar vinyl sulfonamides in the presence of excess $MeSO_2Cl$ and NEt_3 in DCM at reflux, that allowed to avoid isolation of intermediate mesylate [13]. The reaction proceeded smoothly and gave model vinylsulfonamide **4** with 83 % yield. The existence of the only set of signals in ^{1}H NMR spectrum of the obtained compound **4** and observed coupling constants of 15.8 Hz, which belonged to vinyl protons, testified the formation of the most stable *E*-isomer of compound **4** (Scheme 2).



Scheme 2. Synthesis of model *E*-2-(4-bromophenyl)-*N,N*-dimethylethenesulfonamide **4**.

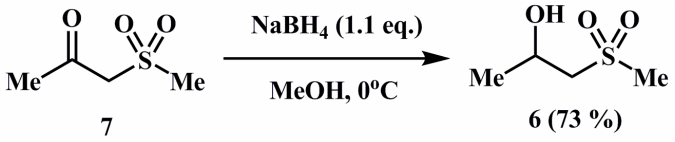
Inspired by successful synthesis of compound **4**, we tried to transfer applied conditions to the synthesis of vinyl derivative **1**. In contrast, it turned out that the best choice for the synthesis of the target vinyl sulfone **1** was the use of higher excess of $MeSO_2Cl$ (2 eq.) and pyridine as solvent under heating. This difference may be attributed to the fact that elimination process for the molecule of compound **3** is influenced as by SO_2NMe_2-substituent, as by aromatic ring, and in the case of compound **5** only the effect of SO_2NMe_2-group is present (Scheme 3).



Scheme 3. Synthesis of the target *N,N*-dimethyl-1-propene-1-sulfonamide **1**.

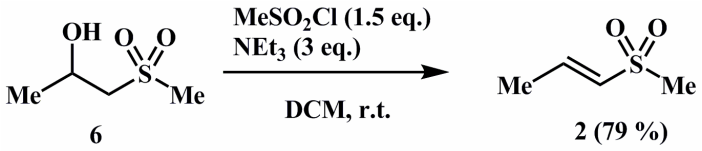
Compound **1** was isolated as a mixture of major *E*- and minor *Z*-isomer. The assignment of the signals and the ratio between two isomers (*E* : *Z* = 88 : 12) was established basing on their ^{1}H NMR-data. Namely, the coupling constant of C=C*H*SO_2-atom equals in the case of *E*-isomer to 15.1 Hz, and for *Z*-isomer it equals to 11.2 Hz.

Interestingly, that 1-(methylsulfonyl)-2-propanol **6**, the simplest secondary *β*-hydroxysulfone and the initial substance for the synthesis of the target compound **2**, was unknown to the moment. It was synthesized starting from 1-(methylsulfonyl)-2-propanone **7** by reduction with $NaBH_4$ in MeOH (Scheme 4).



Scheme 4. Synthesis of 1-(methylsulfonyl)-2-propanol **6**.

Expectedly, that compound **6**, having more electron-withdrawing $MeSO_2$-substituent (comparing with SO_2NMe_2-group in molecules of compounds **3** and **5**) should form corresponding vinyl derivative under relatively milder conditions. Really, the formation of the target product **2** occurred in DCM under the action of 1.5 eq. of $MeSO_2Cl$ on compound **6** in the presence of 3 eq. of NEt_3 at room temperature with good yield (Scheme 5).



Scheme 5. Synthesis of the target *E*-1-(methylsulfonyl)-1-propene **2**.

As well as for compound **4**, formation of only *E*-isomer of the product **2** was detected using ^{1}H NMR spectrum, which showed the only HC=C*H*SO_2-coupling constant equal to 15.3 Hz.

Synthesized compounds **1**–**4** are stable in time and in air for at least several months, that was also confirmed by the permanence of their spectral data.

Conclusion

Basing on the successful preliminary synthesis of *E*-2-(4-bromophenyl)-*N*,*N*-dimethylethenesulfonamide, we worked up the simple and convenient protocols of the synthesis of (*E*/*Z*)-*N*,*N*-dimethyl-1-propene-1-sulfonamide and *E*-1-(methylsulfonyl)-1-propene, being, together with obtained 1-(methylsulfonyl)-2-propanol, among the most low molecular weight and little-known compounds in their series.

Experimental

^{1}H NMR spectra were registered in $(CD_3)_2SO$ (δ_H = 2.50 ppm) at 400 MHz using Varian MR-400 spectrometer with $Si(CH_3)_4$ as an internal standard. Chemical shifts are given in ppm, coupling constants are given in Hz. Resonance multiplicity is described as s (singlet), doublet (d), m (multiplet) and br (broad signal). EI mass spectra were obtained with a Shimadzu GCMS-QP2020 instrument (70 eV ionizing energy) using direct inlet method. Argon of 99.993 % purity was used for the syntheses with *n*-BuLi and $MeSO_2Cl$. Starting *n*-BuLi (2.5 M in hexanes), $MeSO_2Cl$, 4-bromobenzaldehyde, triethylamine, inorganic reagents and solvents were commercially available. THF was dried over KOH and distilled over molten potassium before use. Dichloromethane (DCM) was dried over K_2CO_3. Triethylamine and pyridine were dried over KOH. *N,N*-Dimethylmethanesulfonamide and 2-hydroxy-*N*,*N*-dimethyl-1-propanesulfonamide **5** were synthesized, as reported [12]. 1-(Methylsulfonyl)-2-propanone **7** was obtained, as shown elsewhere [14, 15].

***N*,*N*-Dimethyl-1-propene-1-sulfonamide 1, mixture of *E*- and *Z*-isomers (*E*:*Z* = 88:12).** $MeSO_2Cl$ (27.5 g, 0.240 mol) was added dropwise to a solution of 2-hydroxy-*N*,*N*-dimethyl-1-propanesulfonamide (20.0 g, 0.120 mol) in anhydrous pyridine (100 ml) at r.t. Resulting mixture was than heated for 48 h. at 90ºC, cooled and poured into water (800 ml) and extracted with $CHCl_3$ (7×40 ml). The obtained extract was washed with brine (2×40 ml), conc. HCl (3×45 ml), brine (40 ml), saturated aqueous $NaHCO_3$ (2×40 ml), brine (2×40 ml) and dried over K_2CO_3. After filtering the drying agent and evaporating the solvent 7.74 g (43 %) of the target product were obtained. Dark-orange liquid. ^{1}H NMR ($(CD_3)_2SO$), δ, ppm (*J*, Hz): 6.54–6.65 (1H, m, *E*-C*H*CH_3), 6.40–6.54 (1H, m, *Z*-C*H*CH_3), 6.43 (1H, d, *J* = 15.1, *E*-C=CHS), 6.22 (1H, d, *J* = 11.2, *Z*-C=CHS), 2.65 (6H, s, *Z*-N$(CH_3)_2$), 2.60 (3H, s, *E*-N$(CH_3)_2$), 1.98 (3H, d, *J* = 7.2, *Z*-C*H*$_3$CH), 1.87 (3H, d, *J* = 6.7, *E*-C*H*$_3$CH). m/z (EI, 70 eV): 149 (M^+, 27), 105 (15), 44 (100), 41 (63).

***E*-1-(Methylsulfonyl)-1-propene 2.** $MeSO_2Cl$ (72.3 g, 0.631 mol) was added dropwise to a solution of 1-(methylsulfonyl)-2-propanol **6** (58.0 g, 0.420 mol) and NEt_3 (175 ml, 1.26 mol) in 1 l of dry DCM at temperature below 0ºC. The resulting mixture was stirred for 72 h. at r.t., washed with saturated aqueous NaCl (2×300 ml), aqueous 10 % HCl (3×200 ml), brine (200 ml), saturated aqueous $NaHCO_3$ (2×200 ml), dried over K_2CO_3. After filtering the drying agent and evaporating the solvent 39.6 g (79 %) of the product were obtained. Pale-yellow crystals after washing with mixture hexane/MTBE (2:1) and air drying. M.p. 38–9ºC. ^{1}H NMR ($(CD_3)_2SO$), δ, ppm (*J*, Hz): 6.68–6.77 (1H, m, C*H*CH_3), 6.65 (1H, d, *J* = 15.3, C=CHS), 2.93 (3H, s, SO_2Me), 1.86 (3H, d, *J* = 5.5, C*H*$_3$CH). m/z (EI, 70 eV): 120 (M^+, 6), 105 (17), 91 (28), 64 (22), 57 (37), 45 (53), 41 (100).

2-(4-Bromophenyl)-2-hydroxy-*N*,*N*-dimethylethanesulfonamide 3. *n*-BuLi (2.5 M in hexanes, 27 ml, 68 mmol) was added dropwise to a solution of *N*,*N*-dimethylmethanesulfonamide (7.0 g, 57 mmol) in 45 ml of THF at temperatures below –5ºC. The mixture was stirred under cooling for 1.5 h and a solution of 4-bromobenzaldehyde (11.6 g, 63 mmol) in 20 ml of THF was added dropwise at temperatures below –5ºC. The resulting mixture was stirred for 12 h. A conc. aqueous solution of NH_4Cl (18 ml) and 750 ml of water were added in turn. The mixture was extracted with EtOAc (5×100 ml), the extract was dried over K_2CO_3. After filtration of drying agent and evaporation of a solvent 16.5 g (94 %) of the product were obtained. M. p. 76–8ºC. ^{1}H NMR ($(CD_3)_2SO$), δ, ppm (*J*, Hz): 7.50 (2H, d, *J* = 8.3, ArH), 7.33 (2H, d, *J* = 8.3, ArH), 5.83 (1H, br. s, OH), 4.93 (1H, dd, *J* = 8.7, *J* = 3.5, C*H*OH), 3.35 (1H, dd, *J* = 14.5, *J* = 8.7, CH_AH$_B$), 3.17 (1H, dd, *J* = 14.5, *J* = 3.5, CH$_A$*H*$_B$), 2.72 (6H, s, $N(CH_3)_2$). m/z (EI, 70 eV): 308 (M^+, 1), 198 (80), 185 (57), 120 (36), 92 (67), 77 (48), 44 (100).

***E*-2-(4-Bromophenyl)-*N*,*N*-dimethylethenesulfonamide 4.** $MeSO_2Cl$ (50.8 g, 0.44 mol) was added dropwise to a solution of 2-(4-bromophenyl)-2-hydroxy-*N*,*N*-dimethylethanesulfonamide **3** (80.2 g, 0.26 mol) and NEt_3 (126 ml, 0.91 mol) in 710 ml of dry DCM at temperatures below 0ºC. The resulting mixture was heated to reflux for 24 h., cooled, washed with water (3×400 ml), aqueous 20 % HCl (3×60 ml), saturated aqueous $NaHCO_3$ (4×100 ml), water (400 ml), dried over K_2CO_3. After filtering the drying agent and evaporating the solvent 63.0 g (83 %) of the product were obtained. Pale-yellow crystals. M. p. 128-9ºC (EtOAc). ^{1}H NMR ($(CD_3)_2SO$), δ, ppm (*J*, Hz): 7.70 (2H, d, *J* = 8.0, ArH), 7.61 (2H, d, *J* = 8.0, ArH), 7.36 (1H, d, *J* = 15.8, C=CHAr), 7.31 (1H, d, *J* = 15.8, SCH=C), 2.69 (6H, s, $N(CH_3)_2$). m/z (EI, 70 eV): 291 (M(^{81}Br)$^+$, 21), 289 (M(^{79}Br)$^+$, 20), 225 (70), 181 (31), 102 (100), 75 (20), 44 (23).

1-(Methylsulfonyl)-2-propanol 6. $NaBH_4$ (30.8 g, 0.81 mol) was added portionwise to a solution of 1-(methylsulfonyl)-2-propanone **7** (100 g, 0.73 mol) in MeOH (800 ml) under bubbler at temperatures below 0ºC. The resulting mixture was stirred for 24 h. at r.t., the solvent was removed under reduced pressure. $CHCl_3$ (600 ml) and saturated aqueous Na_2CO_3 (150 ml) were added to the residue and the resulting mixture was allowed to stir for 1.5 h. Organic phase was collected, dried over K_2CO_3. After filtering the drying agent and evaporating the solvent 74.5 g (73 %) of the product were obtained. Pale-yellow crystals. M. p. 61–3ºC ^{1}H NMR ($(CD_3)_2SO$), δ, ppm (*J*, Hz): 5.10 (1H, br. s, OH), 4.01–4.13 (1H, m, CH), 3.19 (1H, dd, *J* = 14.6, *J* = 8.6, CH_AH$_B$), 3.00 (1H, dd, *J* = 14.6, *J* = 3.0, CH$_A$*H*$_B$), 2.94 (3H, s, SO_2CH_3), 1.14 (3H, d, *J* = 6.3, C*H*$_3$CH). m/z (EI, 70 eV): 139 (52), 123 (66), 121 (48), 94 (100), 79 (66), 59 (41), 45 (33), 41 (43), 31 (56), 15 (32).

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І.Д. Гужва, О.Г. Швець, М.О. Колосов. Синтез 1-(метилсульфоніл)-1-пропену та *N,N*-диметил-1-пропен-1-сульфонаміду.

Харківський національний університет імені В.Н. Каразіна, хімічний факультет, майдан Свободи, 4, Харків, 61022, Україна

Різноманітні вінілсульфони та вінілсульфонаміди мають широкий спектр біологічної активності (це, в основному, інгібування різних типів ферментів) і часто використовуються в синтетичній органічної хімії (як активні дієнофіли, акцептори Міхаеля і, в цілому, активні агенти в реакціях 1,4-приєднання та електроциклізації). Однак, незважаючи на популярність великої кількості подібних сполук, препаративні методики одержання низькомолекулярних представників цього класу – 1-(метилсульфоніл)-1-пропену і *N,N*-диметил-1-пропен-1-сульфонаміду – до теперішнього часу вивчені мало. У цій роботі ми повідомляємо про простий, ефективний і загальний спосіб синтезу 1-(метилсульфоніл)-1-пропену і *N,N*-диметил-1-пропен-1-сульфонаміду шляхом дегідратації, відповідно, 1-(метилсульфоніл)-2-пропанолу та *N,N*-диметил-2-гідроксіпропансульфонаміду в системі $MeSO_2Cl$/органічна основа, спираючись на попередній експеримент з синтезу 2-(4-бромфеніл)-*N,N*-диметилвінілсульфонаміду виходячи з 2-(4-бромфеніл)-2-гідрокси-*N,N*-диметилетансульфонаміду. Останній, у свою чергу, було отримано, виходячи з *N,N*-диметилметансульфонаміду шляхом літіювання за допомогою *н*-BuLi, подальшої дії

4-бромбензальдегіду і наступної обробки. Використана методика синтезу вінілпохідних дозволяє уникнути виділення проміжних мезилатів і полягає в однореакторному формуванні відхідної групи та її відщеплення. Згідно констант спін-спінового розщеплення у спектрах ^{1}H ЯМР, отриманий *N*,*N*-диметил-1-пропен-1-сульфонамід існує у вигляді суміші *E*- і *Z*-ізомерів (у співвідношенні 88:12), у той час як виділені 1-(метилсульфоніл)-1-пропен і 2-(4-бромфеніл)-*N*,*N*-диметилвінілсульфонамід є найбільш стабільними *E*-изомерами. Будову синтезованих сполук підтверджено методами ^{1}H ЯМР-спектроскопії та мас-спектрометрії.

Ключові слова: вінілсульфони, вінілсульфонаміди, 1-(метилсульфоніл)-1-пропен, *N,N*-диметил-1-пропен-1-сульфонамід, дегідратація.

И.Д.Гужва, Е.Г.Швец, М.А.Колосов. Синтез 1-(метилсульфонил)-1-пропена и *N,N*-диметил-1-пропен-1-сульфонамида.

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Различные винилсульфоны и винилсульфонамиды обладают широким спектром биологической активности (это, в основном, ингибирование различных типов ферментов) и часто используются в синтетической органической химии (в качестве активных диенофилов, акцепторов Михаэля и, в целом, активных агентов в реакциях 1,4-присоединения и электроциклизации). Однако, несмотря на известность большого количества подобных соединений, препаративные методики получения низкомолекулярных представителей этого класса – 1-(метилсульфонил)-1-пропена и *N*,*N*-диметил-1-пропен-1-сульфонамида – до настоящего времени изучены мало. В настоящей работе мы сообщаем о простом, эффективном и общем способе синтеза 1-(метилсульфонил)-1-пропена и *N*,*N*-диметил-1-пропен-1-сульфонамида путём дегидратации, соответственно, 1-(метилсульфонил)-2-пропанола и *N*,*N*-диметил-2-гидроксипропансульфонамида в системе $MeSO_2Cl$/органическое основание, опираясь на предварительный эксперимент по синтезу 2-(4-бромфенил)-*N*,*N*-диметилвинилсульфонамида исходя из 2-(4-бромфенил)-2-гидрокси-*N*,*N*-диметилэтансульфонамида. Последний, в свою очередь, был получен исходя из *N*,*N*-диметилметансульфонамида путем литирования с помощью *н*-BuLi, последующего действия 4-бромбензальдегида и дальнейшей обработки. Использованная методика синтеза винилпроизводных позволяет избежать выделения промежуточных мезилатов и состоит из однореакторного формирования уходящей группы и ее отщепления. Согласно константам спин-спинового расщепления в спектрах ^{1}H ЯМР, полученный *N*,*N*-диметил-1-пропен-1-сульфонамид существует в виде смеси *E*- и *Z*-изомеров (в соотношении 88:12), в то время как выделенные 1-(метилсульфонил)-1-пропен и 2-(4-бромфенил)-*N*,*N*-диметилвинилсульфонамид являются наиболее стабильными *E*-изомерами. Строение синтезированных соединений подтверждено методами ^{1}H ЯМР-спектроскопии и масс-спектрометрии.

Ключевые слова: винилсульфоны, винилсульфонамиды, 1-(метилсульфонил)-1-пропен, N,N-диметил-1-пропен-1-сульфонамид, дегидратация.