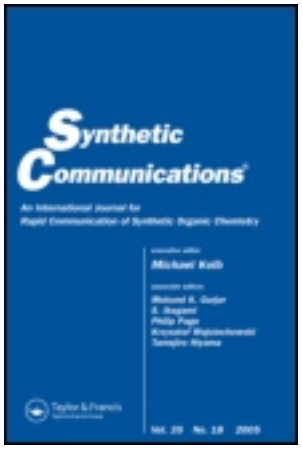

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Synthesis of 1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-Dioxides Using Amberlyst-15

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SYNTHESIS OF 1,2,4,5-TETRAHYDRO-3,2-BENZOTHIAZEPINE 3,3-DIOXIDES USING AMBERLYST-15

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A convenient method for the synthesis of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides from 2-phenylethanesulfonamides and formaldehyde using Amberlyst resin as catalyst is described.

Keywords: Amberlyst-15; 3,2-benzothiazepine 3,3-dioxides; 2-phenylethanesulfonamides; sulfonylamidomethylation

Benzothiazepines are an important class of compounds because of their diverse therapeutic and pharmacological applications. For example, 1,2-, 1,4-, and 1,5-benzothiazepines have shown activity as endogenous natriuretic factors, enzyme inhibitors, anticonvulsants, sedatives, and hypnotics.[1–3]

The biological activity of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides **2** has not been investigated yet.

Until now, only one method for the synthesis of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides is known. These compounds were obtained by sulfonylamidomethylation of 2-phenylethanesulfonamides **1** with formaldehyde in the presence of an acid catalyst followed by intramolecular cyclization of the imine intermediate by means of electrophilic aromatic substitution.[4] For this procedure, homogeneous catalysts have been used such as methanesulfonic acid (MSA) and trifluoroacetic acid (TFA) with good yield of products (Scheme 1).

A series of *N*-mono-substituted 2-phenylethanesulfonamides was employed in this work where R^1 consists of mainly alkyl groups. The cyclization was also studied when functional groups were employed in R^1 such as ester ($R^1 = EtO_2C$), ketone ($R^1 = PhCOCH_2$), or alcohol ($R^1 = HOCH_2CH_2$), although with minor yield of products. Besides, one example with a nuclear substituent ($R^2 = 3$-MeO;

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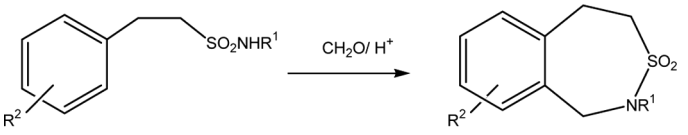


Scheme 1.

$R^1 = PhCH_2CH_2$) was used with a moderate yield. This substituent at the *para* position to ring closure is necessary to avoid the formation of *N*-(2-phenylethanesulfonil)1,2,3,4-tetrahydroisoquinoline as a result of favorable 6-*endo-trig* process.

Until now, only the 1-ethoxy-2,4,5-trihydro-3,2-benzothiazepine 3,3-dioxide, which was obtained in poor yield (17%) with several steps by an alternative synthetic route, was reported.[5]

The use of strong acids has several disadvantages, such as tedious workup procedure, environmental pollution by their disposal, and their corrosive nature.

The intramolecular sulfonylamidomethylation reaction has been previously applied to benzylsulfonamides **3** to obtain the homologous cyclic compounds, 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxides **4**. First, we studied the cyclization using a homogeneous catalyst, such as MSA, TFA, and trifluoromethanesulfonic acid (TFMSA), with good yield for various substituents R^1 and R^2[6] (Scheme 2).

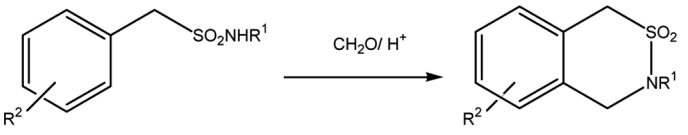
The heterogeneous catalysts offer ideal alternatives to convert polluting processes into greener processes with advantages over homogeneous catalysts, such as ease of isolation, waste minimization, and mild reaction conditions.

More recently, macroporous Amberlyst resin and heteropolyacids H_3PWO_{40} and H_3PMoO_{40} supported on silica as heterogeneous catalysts in the synthesis of 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxides **4** have been employed with very good yields to obtain these products and have advantages compared to homogeneous acid catalysts.[7,8]

Continuing with our work on the use of heterogeneous catalysts for development of useful synthetic methodologies, the cyclization of 2-phenylethanesulfonamides **1** with aldehydes using a macroporous resin, Amberlyst-15, for the synthesis of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides **2** was examined.

The resin Amberlyst-15 was chosen because it presents several advantages. It catalyzes a wide variety of reactions in a heterogeneous phase, offering a strong option for efficient and cleaner processing compared to conventional mineral acids.[9–12]

The reaction was performed by heating a solution of 2-phenylethanesulfonamide **1** (1.0 mmol) and trioxane (0.33 mmol) in 1,2-dichloroethane under reflux



Scheme 2.

Table 1. Cyclization of 2-phenylthanesulfonamides **1** catalyzed with Amberlyst-15

Compound	R^1	Time (h)	Yield (%) **2**	Yield (%) of **2** (lit.)[4]	Mp (°C) found/lit.[4]
1a	H	18	92	89	163–164/163–164
1b	Et	20	92	—	95–96 (cyclohexane)
1c	*i*-Pr	20	42	—	91–92 (hex/EtOAc)
1d	*n*-Bu	18	84	—	78–79 (cyclohexane)
1e	C_6H_{11}	72	—	82	159–160
1f	$CH_2C_6H_4$	12	85	73	136–137/138–139
1g	4-BrC_6H_4	12	60	—	153–154 (hex/EtOAc)
1h	p-$CH_3C_6H_4SO_2$	24	39	79	196–197/195–196
1i	4-ClC_6H_4	12	58	—	141–142 (hex/EtOAc)

(82 °C) with the resin for the specified time, followed by filtration and evaporation of the solvent.

Thus, a series of *N*-substituted 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides **2** ($R^2 = H$) were prepared by this method. The results are summarized in Table 1.

The best yield of the final product was obtained when *N*-alkyl derivatives were used, with the exception of *N*-cyclohexyl-2-phenylethanesulfonamide **1e**, probably because of its steric hindrance. In this case, the reaction was unsuccessful, providing the reactive majority after 72 h.

The best results were obtained with 6 meq. of Amberlyst-15 (calculated with exchange capacity, 4.7 meq/g; Sigma Chemical Company catalog). The crude product was purified by crystallization or preparative column chromatography. The new compounds **2b, 2c, 2d, 2g,** and **2i** were identified by mp, ^{1}H NMR and ^{13}C NMR spectra and elemental analysis. Well-known compounds **2a, 2f,** and **2h** were characterized by mp and ^{1}H NMR spectra.[4]

The recovered catalyst, after activation, was consecutively reused three times with minimum variation in the yield. For example, with fresh catalyst, 92% yield of **2b** compound was obtained; subsequently, with the recovered catalyst in two cycles, the yields of **2b** were 89 and 90%.

In conclusion, the use of Amberlyst-15 provides a simple and attractive catalytic process for the synthesis of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides **2**. The advantages of the present procedure are convenient manipulation, mild conditions, good yields, reusability, and readly availability. The waste disposal of the process was greatly diminished compared with the use of homogeneous catalysts.

EXPERIMENTAL

Melting points were determined with a Buchi apparatus. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian-Mercury (200-MHz) spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel 60 F_{254} sheets (Merck). Reagent-grade s-trioxane was used. Reagent-grade solvents were used; 1,2-dichloroethane was distilled over phosphorous pentoxide and stored over 4-A° molecular sieves. The resin was dried prior to use for 2 h under vacuum at 45 °C.

The purity of the isolated compounds was checked by comparison with authentic samples prepared according to known procedures (^{1}H NMR spectra, mp, TLC).[4]

The 2-phenylethanesulfonamides **1** were prepared from the corresponding 2-phenylethyl halides following the general method.[2]

The catalyst could be recycled. After the reaction, the catalyst was filtered and then refluxed with 1,2-dichloroethane to remove any adsorbed material from the catalyst surface and pores and then dried at 80 °C.

General Procedure for Cyclization of 2-Phenylethanesulfonamides 1 to 1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-Dioxides 2

A flask equipped with a reflux condenser and magnetic bar was charged with 2-phenylethanesulfonamides **1** (1.0 mmol), s-trioxane (0.33 mmol) in 1,2-dichloroethane (4 mL), and the catalyst (6 meq.). Stirring continued at 82 °C for the specified time (Table 1). The progress of the reaction was monitored by TLC. The catalyst was filtered off and washed with fresh solvent, and the organic solution was evaporated at reduced pressure to give the crude benzothiazepines **2**. They were purified by crystallization or by column chromatography on silica gel 60 (70–230 mesh, Merck) with hexane–ethyl acetate (90:10 or 70:30) as eluent in most cases.

Characterization Data of 1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-Dioxides 2

1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-dioxide 2a. ^{13}C NMR (62.9 MHz): δ 30.0 (C-5), 47.8 (C-4), 53.8 (C-1), 128.0, 129.1, 129.4; 130.7 (C-6, C-7, C-8, C-9), 138.9 (C-10), 139.2 (C-11).

N-Ethyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2b. ^{1}H NMR (200 MHz): δ 1.15 (t, 3H, $J = 7.3$ Hz, CH_2-$C\underline{H_3}$), 3.17 (brs, 6H, N-CH_2 exo, $C\underline{H_2}C\underline{H_2}S$), 4.39 (brs, 2H, NCH_2 endo), 7.20–7.35 (m, 4H, Ph); ^{13}C NMR (62.9 MHz): δ 13.6 ($NCH_2\underline{C}H_3$), 30.4 (C-5), 41.1 (C-1), 49.9 (CH_2 exo), 50.4 (C-4), 127.6, 129.1, 130.5, 130.8 (C-6, C-7, C-8, C-9), 136.6 (C-10), 139.0 (C-11). Anal. calcd. for $C_{11}H_{15}NO_2S$ (255.08): C, 58.64; H, 6.71; N, 6.22; O, 14.20; S, 14.23. Found: C, 58.56; H, 6.71; N, 6.16; O, 14.24; S, 14.33.

N-*i*-Propyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2c. ^{1}H NMR (200 MHz): δ 1.01 (d, 6H, $J = 6.8$ Hz, $(C\underline{H_3})_2CH$), 3.21 (s, 4H, $C\underline{H_2}C\underline{H_2}S$), 4.07 (sep, 1H, $J = 6.8$ Hz, $(CH_3)_2C\underline{H}$), 4.40 (s, 2H, NCH_2 endo), 7.25 (s, 4H, Ph); ^{13}C NMR (62.9 MHz): δ 21.5 ($N\underline{C}H(\underline{C}H_3)_2$), 30.8 (C-5), 48.0 (C-1), 51.0 (CH exo), 54.5 (C-4), 127.6, 128.7, 129.4, 130.7 (C-6, C-7, C-8, C-9), 138.9 (C-10), 139.9 (C-11). Anal. calcd. for $C_{12}H_{17}NO_2S$ (239.10): C, 60.22; H, 7.16; N, 5.85; O, 13.37; S, 13.40. Found: C, 60.22; H, 7.27; N, 5.71; O, 13.37; S, 13.41.

N-Butyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2d. ^{1}H NMR (200 MHz): δ 0.87 (t, 3H, $J = 7.3$ Hz, $N(CH_2)_3C\underline{H_3}$), 1.35 (sex, 2H, $J = 7.6$ Hz, $N(CH_2)_2C\underline{H_2}CH_3$), 1.48 (m, 2H, $NCH_2C\underline{H_2}CH_2CH_3$), 3.17 (brs, 6H, N-$CH_2$ exo, $C\underline{H_2}C\underline{H_2}S$), 4.45 (brs, 2H, NCH_2 endo), 7.26 (m, 4H, Ph); ^{13}C NMR (62.9 MHz): δ 13.9 ($N(CH_2)_3\underline{C}H_3$), 19.8 ($N(CH_2)_2\underline{C}H_2CH_3$), 29.7 ($NCH_2\underline{C}H_2CH_2CH_3$), 30.5

(C-5), 45.6 (C-1), 50.2 (NCH_2 exo), 50.3 (C-4), 127.6, 129.1, 130.7, 130.8 (C-6, C-7, C-8, C-9), 136.5 (C-10), 139.0 (C-11). Anal. calcd. for $C_{13}H_{19}NO_2S$ (253.11): C, 61.63; H, 7.56; N, 5.53; O, 12.63; S, 12.66. Found: C, 61.60; H, 7.62; N, 5.47; O, 12.63; S, 12.65.

N-Benzyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2f. ^{13}C NMR (62.9 MHz): δ 30.5 (C-5), 49.5 (C-1), 49.7 (CH_2Ph), 50.9 (C-4), 127.5, 128.1, 128.7, 128.9, 129.2, 130.9, 131.1, 135.5, 136.1, 139.1 (C-6, 7, 8, 9, 10, 11, and Ph).

N-*p*-Bromophenyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2g. ^1H NMR (200 MHz): δ 3.11 (brs, 2H, CH_2CH_2S), 3.63–3.79 (m, 4H, NCH_2; CH_2CH_2S), 6.82 (t, 2H, $J = 6.8$ Hz, Ph), 7.05–7.21 (m, 6H, Ph); ^{13}C NMR (62.9 MHz): δ 29.4 (C-5), 46.3 (C-1), 56.9 (C-4), 125.2, 127.5, 128.7, 128.9, 129.0, 129.4, 129.6, 132.8, 133.1, 136.9 (C-6, 7, 8, 9, 10, 11, and Ph). Anal. calcd. for $C_{15}H_{14}BrNO_2S$ (350.99): C, 51.15; H, 4.01; Br, 22.68; N, 3.98; O, 9.08; S, 9.10. Found: C, 51.05; H, 4.00; Br, 22.60; N, 3.96; O, 9.08; S, 9.23.

N-4-Methylbencensulfonil-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2h. ^{13}C NMR (62.9 MHz): δ 21.8 (CH_3Ph), 30.0 (C-5), 43.7 (C-1), 53.1 (C-4), 128.0, 129.4, 129.04, 129.5, 130.4, 131.8, 136.3, 136.7, 138.0, 145.1 (C-6, 7, 8, 9, 10, 11, and Ph).

N-*p*-Chlorophenyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide 2i. ^1H NMR (200 MHz): δ 2.99 (brs, 2H, CH_2CH_2S), 3.18–3.32 (m, 4H, NCH_2; CH_2CH_2S), 6.59 (t, 2H, $J = 6.8$ Hz, Ph); 6.90 (t, 2H, $J = 6.9$ Hz, Ph), 7.05–7.29 (m, 6H, Ph); ^{13}C NMR (62.9 MHz): δ 30.68 (C-5), 52.62 (C-1), 55.46 (C-4), 127.9, 128.3, 129.5, 130.3, 130.4, 130.9, 134.3, 138.2, 138.4, 138.6 (C-6, 7, 8, 9, 10, 11, and Ph). Anal. calcd. for $C_{15}H_{14}ClNO_2S$ (307.04): C, 58.53; H, 4.58; Cl, 11.52; N, 4.55; O, 10.40; S, 10.42. Found: C, 58.50; H, 4.55; Cl, 11.42; N, 4.60; O, 10.45; S, 10.42.

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