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Heteropolyacid as an Efficient Catalyst for Synthesis of 3,4-Dihydro-1H-2,3benzothiazine-2,2-dioxides

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Heteropolyacid as an Efficient Catalyst for Synthesis of 3,4-Dihydro-1H-2,3-benzothiazine 2,2-dioxides

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Abstract: A facile and efficient method for the formation of 3,4-dihydro-1H-2,3benzothiazine 2,2-dioxides 2, compounds from benzylsulfonamides and formaldehyde is described using heteropolyacids $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ supported on silica as catalysts.

Keywords: Benzothiazines, catalyst, intramolecular cyclization, keggin heteropolyacid, sulfonylamidomethylation

The sulfonylamidomethylation of aromatic sulfonamides is an example of electrophilic aromatic substitution and has been studied in the preparation of 3,4-dihydro-1H-2,3-benzothiazine-2,2-dioxides, **2**, compounds with unexplored potential biological activity.

The reaction occurs by interaction of benzylsulfonamide **1** and formaldehyde in the presence of an acid catalyst followed by intramolecular cyclization of imine intermediate via electrophilic aromatic substitution.^[1]

For this procedure, homogeneous and heterogeneous catalysts are used. By using homogeneous catalysts, such as methanesulfonic acid (MSA), trifluoromethanesulfonic anhydride (TFMSA), and trifluoroacetic acid (TFA), the final products are obtained in good yield.^[1]

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Scheme 1. 1a, R = H; R' = H; 1b, R = 3-Me; R' = H; 1c, R = 3-AcNH; R' = H; 1d, R = 3-Cl; R' = H; 1e, R = H; R' = Me; 1f, R = H; R' = Et; 1g, R = H, R' = i-Pr; 1h, R = H; R' = p-ClC₆H₄; and 1i, R = H; R' = p-NO₂C₆H₄.

As reported, short reaction times or low acid strength led to 1,3,5-tris-(benzylsulfonyl)-hexahydro-1,3,5-triazines **3** ($\mathbf{R'} = \mathbf{H}$) and N,N'-methylene-bis-benzylsulfonamides **4** ($\mathbf{R} = \mathbf{H}$, $\mathbf{R'} \neq \mathbf{H}$) as kinetic products, whereas under strong acid catalysis, the thermodynamic products were obtained in good yield.^[1] (Scheme 1).

Similar compounds are obtained, alternatively, in good yield by another route, the intramolecular vicarious nucleophilic substitution of hydrogen of m-nitrochloromethylsulfonamides.^[2–4]

The problems associated with the handling and disposal of strong acids, and their environmental and potential hazards, have directed our attention to the development of alternative procedures using solid acid catalysts, which are safer and more environmentally friendly. Hetero-geneous catalysts are used in a great number of developed processes, and in view of the increasingly strict environmental legislation, the application of these catalysts has become attractive.^[5–8] In addition, solid acid catalysts can be regenerated and reused after the reactions.

More recently, we used ion exchange resins Amberlyst 15 and Amberlyst XN 1010 in the synthesis of 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide, which had important advantages over the previously reported method. The workup is an easy process, and highly pure products are obtained, in most cases with excellent yield.^[9,10]

Heteropolyacids (HPAs) are another type of promising acid catalysts used in electrophilic substitutions. They are typical strong Brønsted acids such as perchloric and sulfuric acids, and they have attracted much attention, particularly in the past two decades. Until now, most of fundamental investigations and all practical applications employed Keggin-type HPAs, with the general formula $H_3M_{12}O_{40}P$.^[11,12]

The HPAs have been supported on different materials possessing high surface area in order to increase their activity in the heterogeneous reactions. The equilibrium impregnation of tungstophosphoric acid

3,4-Dihydro-1H-2,3-benzothiazine 2,2-dioxides

(TPA) or molybdophosphoric acid (MPA) on silica, among other supports, was studied and showed higher catalytic activity in different reactions.^[13,14] Many typical acid-catalyzed reactions such as alkene hydratation, ether cleavage, esterification, hydrolysis, transesterification, and acetalization are effective in the presence of these catalysts.^[15–17]

In continuation of our program to develop reactions with ecofriendly conditions, and given our interest in the synthesis of 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxides **2**, in the present work we report an efficient and convenient procedure for the cyclization of benzylsulfonamides using Keggin-type HPAs $H_3PW_{12}O_{40}$ (TPA) and $H_3PMO_{12}O_{40}$ (MPA) supported on silica as catalysts.

The reaction was performed by stirring a solution of benzylsulfonamide 1 (1.0 mmol) and trioxane (0.33 mmol) in 1,2-dichloroethane or toluene under reflux (80 °C or 110 °C, respectively) with the catalyst for the specified time. The catalyst was then removed by filtration, and the solvent was evaporated. The crude products were purified by crystallization or column chromatography on silica gel. All products are known compounds and were characterized by melting points and ¹H NMR spectra.

Cyclization experiments were conducted using different TPA and MPA ratios (5–50 wt%). By-product formation increased as the catalyst quantity increased. The yield of the final product has been invariable when either TPA or MPA were used.

The best results were obtained with 25% of catalyst. The reactions were completed in 4.5 h, with the exception of substrate 1i with an electron-withdrawing group on the aromatic ring. In this case, greater reaction time (8 h) and catalyst quantity (50%) were used.

The effect of temperature on the yield and rate of the reaction was studied in the range of 80-110 °C. With an increase in the temperature from 80 °C to 110 °C, the rate of the reaction increased significantly. However, there was almost no change in the yield of final products.

Good yields with high selectivity of final products 2 were obtained under the reaction conditions used. Compounds 3 (R = R' = H) were obtained when either lower catalyst quantities or shorter reaction times are used. The yields of 2 are comparable with the reported method using homogeneous catalyst (Table 1).

In summary, a simple and attractive catalytic process for the synthesis of 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxides 2 has been demonstrated. The mild conditions, good yields, high selectivity, operational simplicity, and easy availability make this process a useful and practical alternative to the existing methods for the preparation of these compounds. The waste disposal of the process is greatly diminished compared with the use of homogeneous catalysts.

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			Temnerature	Time	TPA/MPA	Yield (9	‰) (2)	Mp	(°C)
Entry	R	\mathbf{R}'	(°C)	(h)	(%, p/p)	Found	Lit. ^[1]	Found	Lit. ^[1]
1a	Н	Н	80	9	25	60	68	142–143	142-143
			110	4.5	25	62		142 - 143	142 - 143
1 b	Η	Me	80	9	25	68	78	75-76	74-75
			110	4.5	25	68		74-75	74-75
1c	Η	Et	80	9	25	86	88	71–72	71–72
			110	4.5	25	88		71–71.5	71–72
1d	Η	i-Pr	80	9	25	84	90	89–90	90 - 91
			110	4.5	25	87		89 - 90	90-91
le	Η	4-CIC ₆ H ₄	80	9	25	59	75	142 - 143	142–143
			110	4.5	25	58		142 - 143	142 - 143
1f	Η	$4-NO_2C_6H_4$	80	9	25	36	48	155 - 156	154-155
			110	4.5	25	39		154-155	154 - 155
1g	3-Me	Н	80	9	25	43	4	118 - 118	118-119
		110	4.5	25	43			117 - 118	118-119
1h	3-AcNH ₂	Н	80	9	25	65	62	200 - 201	201 - 202
			110	4.5	25	65		201 - 202	201 - 202
li	3-CI	Н	80	12	50	53	49	118 - 119	119-120
			110	8	50	54		119 - 120	119-120

Table 1. Cvclization of henzylsulfonamides 1 catalyzed with H. PW. O. (SiO. (TPA) and H. PM. O. (SiO. (MPA)

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3,4-Dihydro-1H-2,3-benzothiazine 2,2-dioxides

It is noteworthy to mention that the catalyst is reusable. The catalyst was reused up to three times without affecting the yield.

EXPERIMENTAL

Melting points were determined with a Buchi apparatus. ¹H NMR spectra were obtained on a Brucker AC-F (250-MHz) spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel sheets 60 F_{254} (Merck). Reagent-grade s-trioxane was used. Reagent grade solvents were used; 1,2-dichloroethane was distilled over phosphorous pentoxide and stored over 4 Å molecular sieves. Toluene was dried with CaSO₄, filtered, and distilled over sodium. The purity of the isolated compounds was checked by comparison with authentic samples prepared according to known procedures (¹H NMR spectra, mp, TLC).^[1]

The benzylsulfonamides **1** were prepared from the corresponding benzyl halides via sodium benzylsulfonates and benzylsulfonyl chlorides.

The silica-supported catalysts were prepared by impregnation techniques according to a well-established procedure with solutions of MPA ($H_3PMO_{12}O_{40} \cdot nH_2O$, Merck) or TPA ($H_3PW_{12}O_{40} \cdot nH_2O$, Fluka) in H2O–EtOH (1:1) and were physically and chemically characterized.^[18] The support was SiO₂ (Grace) with a surface area of 311 m²/g and a mean pore diameter of 3.4 nm. These catalysts were washed with the reaction solvent, dried, and calcined at 200 °C. The catalyst was dried at 150 °C for 1 h prior to use for the reactions.

The catalyst could be recycled after removing the reaction product by filtration, washing with solvent, and drying at 200 °C for 2 h. The results of the first experiment and subsequent experiment were almost consistent in yields.

General Procedure for Cyclization of Benzylsulphonamides 1 to 3,4-Dihydro-1H-2,3-benzothiazine 2,2-dioxides 2

A flask equipped with a reflux condenser and magnetic bar was charged with benzylsulfonamide 1 (1.0 mmol) and s-trioxane (0.33 mmol) in 1,2-dichloroethane or toluene (4 mL) and the catalyst. Stirring was continued at 80 °C (using 1,2-dichloroethane) or 110 °C (using toluene) 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 benzothiazines. 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.

Procedure for Preparation of 1,3,5-Tris-(benzylsulfonyl)-hexahydro-1,3,5-triazine (3a)

A mixture of 0.171 g (1 mmol) of benzylsulfonamide (1a), s-trioxane (0.33 mmol) in 1,2-dichloroethane (4 mL), and the catalyst (25% p/p) was stirred at 80 °C for 2 h with formation of a white precipitate. The solid was dissolved with dimethylsulfoxide, and the catalyst was filtered off. The solvent was evaporated at reduced pressure. The crude product was purified by crystallization from nitromethane to give 1,3,5-tris-(benzylsulfonyl)-hexahydro-1,3,5-triazine (3a) (yield 51%), mp 277–278 °C (lit.^[19] 276–278 °C).

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3,4-Dihydro-1H-2,3-benzothiazine 2,2-dioxides

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