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One-Pot Synthesis Of 1,3-Benzo[*d*]thiazolederivatives Promoted By $Al(HSO_4)_3$ Under Solvent Free Conditions

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Heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimization of chemical wastes as compared to the liquid phase counterparts. $Al(HSO_4)_3$ as an heterogeneous, efficient, readily available, and cheap catalyst was synthesized and applied for the synthesis of 1,3-benzo[*d*]thiazole derivatives by condensation protocol of 2-aminothiophenol and aldehydes under solvent free conditions. Short reaction times, high yields, a clean process, simple methodology, easy work-up and green conditions are some advantages of this protocol.

Keywords: 1,3-Benzo[*d*]thiazole, Benzothiazoles, $Al(HSO_4)_3$, Aluminium hydrogen sulfate

INTRODUCTION

The presence of a benzothiazole ring in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles. Benzothiazole derivatives have many biological and pharmaceutical applications such as probes for the 5HT1A receptor, serotonin transporter (SERT) [1], antitumor [2], histone deacetylase inhibitor [3] anticancer activity [4-7], anti-tubercular [8], antimicrobial [9-10], antibacterial [11], anti-inflammatory and anti-nociceptive [12], fungicidal neurotoxicity [13] and anticonvulsant [14] cytotoxic [15], analgesic [16], cyclin-dependent kinases (CDK2) inhibitors [17], potent S1P1 agonists with *in vivo* lymphocyte-depleting activity [18] inhibitors of thrombin and trypsin IV [19], adenosine A2B receptor antagonists [20], for imaging of amyloids [21] and inhibitors of beta-glucuronidase [22]. Optical properties such as dye sensitized solar cells [23], fluorescent probe for thiol bioimaging [24], fluorescent DNA intercalators for studying Alzheimer Abeta1-42 and prion amyloid peptides [25] as potential radiotracers for β-amyloid plaques in Alzheimer's disease [26], photosensitizing agents [27] and alkyne fluorescent sensor for Cu detection in living cell [28] have been found for some benzothiazole derivatives. Some benzothiazoles have liquid crystalline [29,30] and ionic liquid [31] properties. Benzothiazoles have been synthesized *via* a two-component coupling of 2-aminothiophenol with gem-dibromomethyl-arenes [32], carboxylic acids [33] or aldehydes. Previously, many catalysts have been applied for the latter protocol such as ZnO-beta zeolite [34], molecular iodine [35], $NaHSO_4.SiO_2$ [36], SiO_2 in microwave [37], *p*-toluene-sulfonic acid [38], $Co(NO_3)_3/H_2O_2$ [39], montmorillonite K10 [40], acetic acid [41], ceric ammonium nitrate (CAN) [42] and oxalic acid, silica sulfuric acid or $AlCl_3$ [43].

Very recently, we among many others have demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimization of chemical wastes as compared to the liquid phase counterparts. Thus, inorganic acidic salts such as $Al(HSO_4)_3$, $Mg(HSO_4)_2$ and $Zr(HSO_4)_4$ could be recommended for above mentioned purposes.

$Al(HSO_4)_3$ is prepared *via* reaction of aluminium chloride with concentrated sulfuric acid. Previously, this catalyst was used for promotion of friedlecrafts acylation

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[44], xanthene synthesis and acetylation [45], formylation, and oxidation of alcohols [46-48].

EXPERIMENTAL

General

The chemicals were used without any additional purification. The products were characterized by FT-IR, ^{1}H NMR, and a comparison of their physical properties with those reported in the literature was made. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the ^{1}H NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus.BANDELIN Sonopuls HD 3200 ultrasonic apparatus (20 kHz, 150 W) was used for sonication. The microwave oven Kenwood, 1300 W and Mixer Mill(MM 400) in 25 Hz frequency were used for running the described reactions.

General Procedure for the Synthesis of 1,3-Benzo[d]thiazole Derivatives under Solvent Gree Conditions

A mixture containing of 2-aminothiophenol (1 mmol), aldehyde (1 mmol) and $Al(HSO_4)_3$ (0.02 g) was heated at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the obtained solid dissolved in acetone followed by addition of water. The obtained solid product was re-crystallized in hot ethanol. All the products were known and identified by comparison of their physical and spectral data with those of authentic samples.

Selected Spectroscopic Data

2-(4-Nitrophenyl)benzo[d]thiazole (Table 2, Entry 1). FT-IR (ATR, neat), ῡ = 1605, 1518, 1341, 1311, 1250, 1107, 968, 851, 765,751, 729, 685 cm^{-1}. ^{1}H NMR (400 MHz, Acetone-d_6), δ (ppm): 8.44 (sbr, 4H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H).

2-(4-Isopropyl)-1,3-benzo[d]thiazole (Table 2, Entry 2). FT-IR (ATR, neat), ῡ = 1589, 1484, 1434, 1312, 967, 838, 755, 726. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.12 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.4 (d, *J* = 8.3 Hz, 2H), 3.03 (sept, *J* = 7.1 Hz, 1H), 1.35 (d, *J* = 7 Hz, 6H. Elemental analysis, Found, %: C, 75.40; H, 6.22; N, 5.73; $C_{16}H_{15}NS$. Calcd., %: C, 75.85; H, 5.97; N, 5.53.

2-(4-Dimethylamino phenyl)-1,3-benzo[d]thiazole (Table 2, Entry 5). FT-IR (ATR, neat), ῡ = 1606, 1476, 1430, 1368, 1227, 1186, 943, 816, 750, 720. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8 (d, *J* = 8 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8 Hz, 2H), 3.07 (s, 6H).

Benzo[d]thiazole (Table 2, Entry 6). FT-IR (ATR, neat) ῡ = 1615, 1471, 1445, 1300, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), ä (ppm): 5.1 (s, 1H) 6.49 (t, *J* = 8 Hz, 1H), 6.8 (d, *J* = 8 Hz, 1H), 7.1 (t, *J* = 8 Hz, 1H), 7.12 (brs, 1H) ppm. Elemental analysis. Found, %: C, 62.50; H, 3.83; N, 10.57; C_7H_5NS. Calcd., %: C, 62.19; H, 3.73; N, 10.36.

2-(3-Nitrophenyl)-1,3-benzo[d]thiazole (Table 2, Entry 7). FT-IR (ATR, neat), ῡ = 1617, 1527, 1344, 988, 888, 842, 760, 729, 670. ^{1}H NMR (500 MHz,$CDCl_3$), δ (ppm): 8.98 (dd, *J* = 1.9 and 1.5 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.39 (dd, *J* = 7.9 and 1.5 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8 (d, *J* = 8Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.59 (t, *J* = 10 Hz, 1H), 7.5 (t, *J* = 8 Hz, 1H).

2-(2-Furyl)-1,3-benzo[d]thiazole (Table 2, Entry 10). FT-IR (ATR, neat), ῡ = 1580, 1503, 1434, 1312, 1285, 1245, 1219, 1011, 896, 744. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.15 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 8.01 (s, 1H), 7.56 (td, *J* = 7.6 and 0.9 Hz,1H), 7.46 (td, *J* = 7.5 and 0.85 Hz, 1H), 7.37 (d, *J* = 3.4 Hz, 1H), 6.8 (m, 1H).

2-(3-Pyridyl)-1,3-benzo[d]thiazole (Table 2, Entry 12). FT-IR (ATR, neat), ῡ = 1573, 1503, 1428, 1310, 963, 763, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 9.35 (s, 1H), 8.7 (d, *J* = 8.1, 1H), 8.38 (d, *J* = 8.1, 1H), 8.1 (d, *J* = 8.1, 1H), 7.95 (d, *J* = 7.9, 1H), 7.5 (t, *J* = 7.2, 1H), 7.45 (t, *J* = 7.4, 2H).

RESULTS AND DISCUSSION

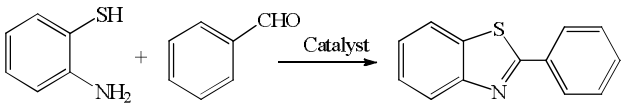
In continuation of our investigations on the applications of solid acids in organic synthesis, we investigated the synthesis of benzothiazoles *via* the condensation of different aldehydes and 2-aminothiophenol in the presence of $Al(HSO_4)_3$ as catalyst. The reaction of benzaldehyde (1 mmol) with 2-aminothiophenol (1.2 mmol) was investigated

for optimization of the reaction conditions (Table 1). We found that solvent free conditions at 80 °C and a molar ratio of benzaldehyde:2-aminothiophenol: $Al(HSO_4)_3$ equal to1:1:0.06 would be the best conditions. The reusability of the $Al(HSO_4)_3$ catalyst was also examined and no reusability was observed. The applicability of the present method to a large scale process was examined with 10 mmol of benzaldehyde and 12 mmol of 2-aminothiophenol under solvent free conditions at 80 °C which gave 2-phenyl-benzothiazole in 89% yield.

2-Aminothiophenol and various aldehydes were used as substrates for the synthesis of benzothiazoles under sonication conditions in ethylacetate (Scheme 1 and Table 2).

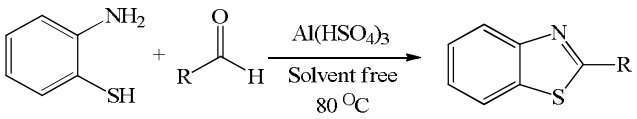
For synthesis of benzo[*d*]thiazole, we used trioxane as formaldehyde source (Table 2, Entry 6). The aromatic aldehydes containing electron releasing or electron withdrawing groups have reacted in this protocol with high yields. In this protocol, many aliphatic aldehydes were examined but oily liquids with difficult purification method

Table 1. Synthesis of 2-Phenyl, 1,3-Benzo[*d*]thiazole under Various Conditions[a]



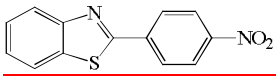
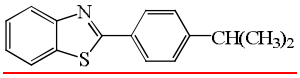
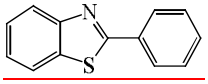
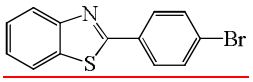
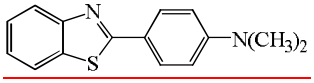
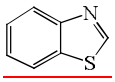
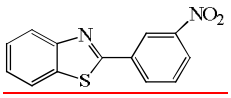
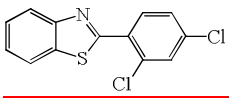
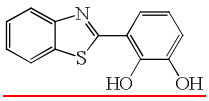
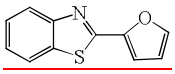
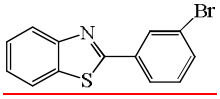
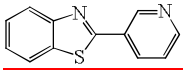
Entry	Catalyst (g)	Solvent	Condition	Time (min)	Yield (%)	Ref.
1	$Al(HSO_4)_3$ (0.01)	-	r.t	20	50	-
2	$Al(HSO_4)_3$ (0.02)	-	r.t	20	57	-
3	$Al(HSO_4)_3$ (.03)	-	r.t	20	60	-
4	$Al(HSO_4)_3$ (0.01)	-	60 °C	10	63	-
5	$Al(HSO_4)_3$ (0.01)	-	80 °C	10	74	
6	$Al(HSO_4)_3$ (0.02)	-	60 °C	10	80	-
7	$Al(HSO_4)_3$ (0.02)	-	80 °C	10	91	-
8	$Al(HSO_4)_3$ (0.02)	EtOAc	Sonication	20	83	
9	$Al(HSO_4)_3$ (0.02)	EtOH	Reflux	180	20	-
10	$Al(HSO_4)_3$ (0.02)	EtOAc	Reflux	120	55	-
11	$Al(HSO_4)_3$ (0.02)	*n*-Hexane	Reflux	240	35	-
12	$Al(HSO_4)_3$ (0.02)	MeOH	Reflux	360	40	-
13	$Al(HSO_4)_3$ (0.02)	CH_3Cl	Reflux	90	45	-
14	$Al(HSO_4)_3$ (0.02)	-	M.W.	5	60	-
15	$Al(HSO_4)_3$ (0.02)	-	Mixer mill	60	54	-
16	PTSA (10 mol%)	H_2O	70 °C	60	97	[38]
17	$Co(NO_3)_2.6H_2O$	DMF	80 °C	35	88	[39]
18	CAN	MeOH	r.t.	Overnight	75	[42]
19	Silica sulfuric acid	-	M.W.	12	90	[49]
20	Silica sulfuric acid	CH_3CN	80 °C	25	82	[43]
21	Oxalic acid	$EtOH/H_2O$	80 °C	30	80	[43]
22	$AlCl_3.6H_2O$	MeOH:H_2O (20:1)	r.t.	30	90	[43]
23	Montmorillonite K10	$PhNO_2$	M.W.	5	92	[40]
24	Acetic acid	Acetic acid	Reflux	300	76	[41]

[a]The molar ratio of 2-aminothiophenol : benzaldehyde is 1.2:1.



Scheme 1

Table 2. Synthesis of 2-Substituted Benzothiazoles in the Presence of $Al(HSO_4)_3$ under Solvent Free Conditions at 80 °C[a]

Entry	Product	Yield (%)	M.P. (°C)	Reported Ref.
1		97	227-228	224-225 [42]
2		89	65-67	-
3		91	112-113	111-112 [43]
4		94	132-134	133-134 [43]
5		85	169-171	173 [52]
6		82	80-81	-
7		96	181-183	184-186 [42]
8		95	133-134	- [50]
9		82	179-181	- [50]
10		87	102-103	103 [51]
11		92	81-83	82-83 [43]
12		87	113-115	- [50]

[a]A mixture of 2-aminothiophenol (1.2 mmol), aldehyde (1 mmol), $Al(HSO_4)_3$ (0.02 g) was heated at 80 °C under solvent free conditions for 10 min.

were obtained.

CONCLUSIONS

We have demonstrated a simple method for the synthesis of 1,3-benzo[*d*]thiazoles using $Al(HSO_4)_3$ as eco-friendly and efficient catalyst under solvent free conditions. Short reaction times, high yields, a clean process, simple methodology, easy work-up and green conditions are some advantages of this protocol.

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