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Aluminum Hydrogen Sulfate as a Green Catalyst for the Solvent-Free Synthesis of Pyrazolopyridines[1]

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Abstract—Aluminum hydrogen sulfate turned out to be a mild, convenient, and efficient reagent for the conversion of substituted benzyl alcohols into pyrazolopyridines via condensation with 3-methyl-1*H*-pyrazole-5-amine and CH acid (malononitrile or indan-1,3-dione) at room temperature under solvent-free conditions with high yield, high purity, and short reaction time.

Keywords: pyrazolopyridine, solvent free, aluminum hydrogen sulfate, green catalyst

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The use of solid acids in organic reactions is important since solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal. On the other hand, any reduction in the amount of liquid acid is required for economic and environmental protection. Among solid acids, Al $(HSO_4)_3$ is a useful alternative to nitric acid as oxidant. The pyrazolopyridine ring system represents the core skeleton of a number of pharmaceutically important heterocyclic compounds possessing a broad range of biological activity, in particular potent cyclin kinase 1 (CDK1) inhibitors [1], HIV reverse transcriptase inhibitors [2], CCR1 antagonists [3], protein kinase inhibitors [4], inhibitors of cGMP degradation [5], xanthine oxidase inhibitors [6], and antiviral [7], antimalarial [8], vasodilator [9], antimicrobial [10], anti-inflammatory [11], anxiolytic [12], hypoglycemic [13], and antitumor agents [14].

In continuation of our ongoing studies on the synthesis of heterocyclic and pharmaceutical compounds using mild and practical protocols [15–18], herein we report our experimental results on the synthesis of Al $(HSO_4)_3$ and its application as a green oxidizing catalyst for the synthesis of pyrazolopyridines from different substituted benzyl alcohols, malononitrile or indan-1,3-dione, and 3-methyl-1*H*-pyrazol-5-amine under solvent-free condition (Scheme 1). To the best of our knowledge, there has been no report on the synthesis of pyrazolopyridine based on alcohols.

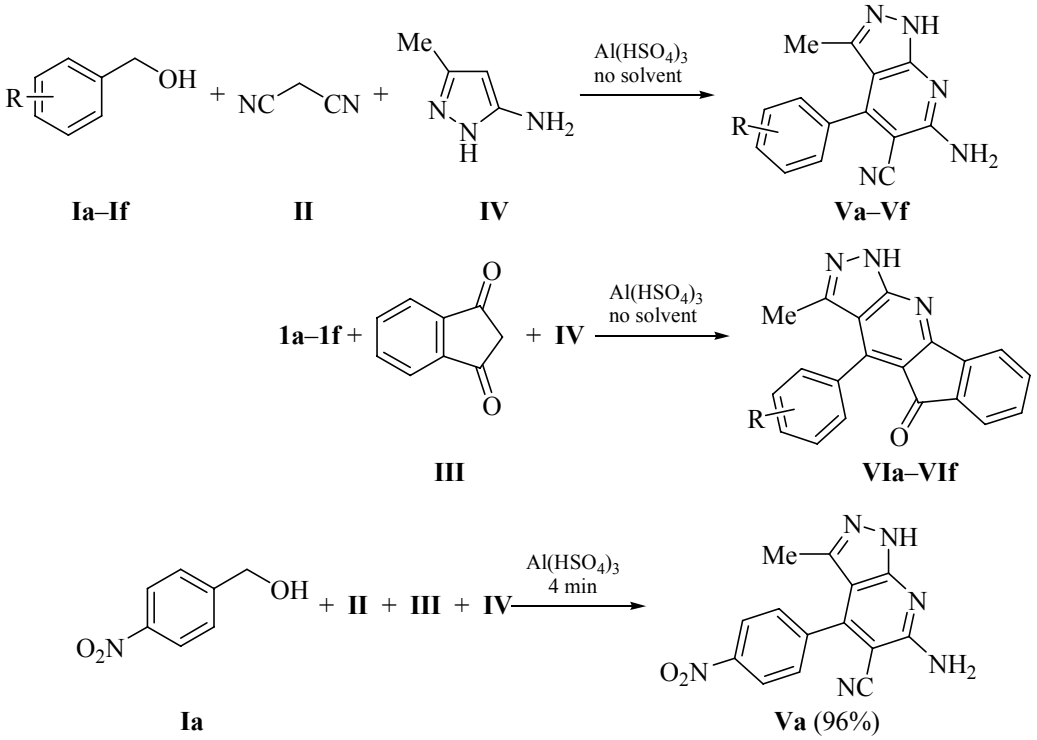
With the catalyst in hand (see Experimental), we moved to study the effect of the catalyst amount on the model reaction of 4-nitrobenzyl alcohol (**Ia**) with malononitrile (**II**) and 3-methyl-1*H*-pyrazol-5-amine (**IV**). No reaction occurred in the absence of $Al(HSO_4)_3$ even after extending the reaction time, whereas 10 mol % of $Al(HSO_4)_3$ was sufficient to push the reaction forward; lower or higher amount of the catalyst did not improve the yield of pyrazolopyridine **Va**. The effect of various solvents on the transformation of **Ia** into **Va** in the presence of $Al(HSO_4)_3$ (10 mol %) was studied. Acetonitrile, *n*-hexane, ethanol, chloroform, and acetone, as well as solvent- free conditions, were tested

Table 1. Yields of pyrazolopyridine **Va** in the condensation of 4-nitrobenzyl alcohol (**Ia**) with malononitrile (**II**) and aminopyrazole **IV** in different solvents and under solvent-free conditions at room temperature

Solvent	Time, min	Yield, %
Acetonitrile	5	57
n-Hexane	10	Traces
Ethanol	5	78
Chloroform	5	64
Acetone	5	37
No solvent	4	97

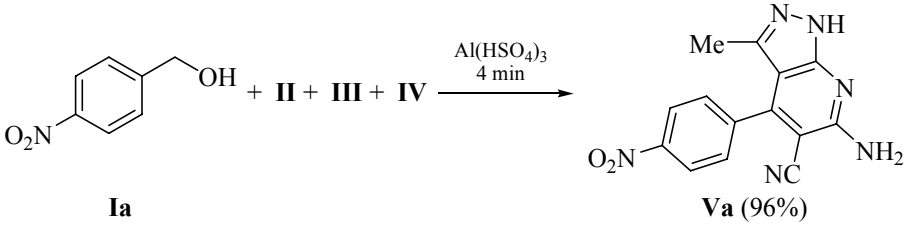
[1] The text was submitted by the authors in English.

Scheme 1.



I, **V**, **VI**, R = 4-O_2N (**a**), 3-O_2N (**b**), 2-O_2N (**c**), 4-Cl (**d**), 4-Br (**e**), 3-Br (**f**).

Scheme 2.



at room temperature. The results are summarized in Table 1.

Thus the best results are attained using 0.1 mmol of $Al(HSO_4)_3$ per mmole of the other components under solvent-free conditions. To investigate the scope of this synthesis, different substituted benzyl alcohols **Ia**–**If** were reacted with malononitrile (**II**) or indanedione (**III**) and 3-methyl-1*H*-pyrazol-5-amine (**IV**) in the presence of 10 mol % of $Al(HSO_4)_3$ in the absence of a solvent at room temperature. The results are listed in Table 2. The reaction proceeded smoothly yielding 91–98% of pyrazolopyridines **Va**–**Vf** or **VIa**–**VIf**.

Following these results, we further investigated the potential of $Al(HSO_4)_3$ for the chemoselective synthesis of pyrazolopyridines from different CH acids. The results showed that $Al(HSO_4)_3$ is able to discriminate between various CH acids including indan-1,3-dione and malononitrile. The reaction of **Ia** with equimolar amounts of CH acids **II** and **III** and pyrazole **IV** (1 mmol each) in the presence of $Al(HSO_4)_3$ gave 96% of **Va**, while no condensation product derived from indandione **III** was formed (Scheme 2).

In continuation of our study, other catalysts such as β-cyclodextrin, ceric ammonium nitrate, ceric ammonium sulfate, tetrabutylammonium hydrogen sulfide, urea–hydrogen peroxide, and copper(II) chloride (0.1 mmol) were used in the synthesis of pyrazolopyridine **VIa** in comparison to aluminum hydrogen sulfate. As

Table 2. Synthesis of pyrazolopyridines **V** and **VI** from benzyl alcohols using $Al(HSO_4)_3$

Benzyl alcohol	R	CH acid	Product	Time, min	Yield,[a, b] %	mp, °C	
						observed	reported
Ia	4-O_2N	**II**	**Va**	4	97	308–310	310–312
Ia	4-O_2N	**III**	**VIa**	5	96	234–235	–
Ib	3-O_2N	**II**	**Vb**	3	91	286–287	285–287
Ib	3-O_2N	**III**	**VIb**	4	94	267–268	–
Ic	2-O_2N	**II**	**Vc**	3	98	288–290	290–292
Ic	2-O_2N	**III**	**VIc**	4	98	302–303	–
Id	4-Cl	**II**	**Vd**	Instant	94	269–271	268–270
Id	4-Cl	**III**	**VId**	Instant	96	271–273	–
Ie	4-Br	**II**	**Ve**	Instant	93	276–278	278–280
Ie	4-Br	**III**	**VIe**	3	95	302–303	–
If	3-Br	**II**	**V f**	3	96	265–266	–
If	3-Br	**III**	**VIf**	Instant	94	267–268	–

[a] The products were identified by comparison of their IR and NMR spectra and physical properties with those of authentic samples [19, 20]. [b] Isolated yield.

Table 3. Synthesis of pyrazolopyridine **VIa** in the presence of different catalysts

Catalyst	Reaction conditions	Time, min	Yield, %
β-Cyclodextrin	100°C	15	89
Ceric ammonium nitrate	100°C	10	85
Ceric ammonium sulfate	100°C	15	91
Tetrabutylammonium hydrogen sulfide	100°C	10	85
Urea–hydrogen peroxide	100°C	20	91
Copper chloride	100°C	15	76
$Al(HSO_4)_3$	100°C	10	92
$Al(HSO_4)_3$	Solvent free	5	96

follows from the data in Table 3, $Al(HSO_4)_3$ ensured higher yield and shorter reaction time.

EXPERIMENTAL

The melting points were measured on an Electrothermal 9100 apparatus. The IR spectra were determined on a Shimadzu IR-470 spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) in DMSO-d_6 or $CDCl_3$ using TMS as internal standard. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures. All yields refer to the isolated products.

General procedure for the preparation of aluminum hydrogen sulfate. A 500-mL suction flask was equipped with a constant pressure dropping funnel and a gas outlet connected to a vacuum system through

an absorbing solution (water) and an alkali trap. The flask was charged with 66.7 g (0.5 mol) of anhydrous aluminum chloride, and 147.1 g (1.5 mol) of concentrated sulfuric acid was added dropwise over a period of 40 min at room temperature. Gaseous hydrogen chloride evolved immediately. When the addition of H_2SO_4 was complete, the mixture was shaken for 30 min while removing the residual HCl by suction. A white solid material was thus obtained. Yield 158.5 g.

General procedure for the preparation of pyrazolopyridines Va–Vf and VIa–VIf. A mixture of 1 mmol of substituted benzyl alcohol **Ia–If**, 1 mmol of malononitrile (**II**) or indan-1,3-dione (**III**), 1 mmol of 3-methyl-1*H*-pyrazol-5-amine (**IV**) and 0.1 mmol of $Al(HSO_4)_3$ was stirred at room temperature until the reaction was complete according to the TLC data (EtOAc–petroleum ether, 1 : 4; see Table 2). The mixture was diluted with 10 mL of acetone and filtered, the filtrate was evaporated under reduced pressure, and the resulting crude material was purified by recrystallization from ethyl acetate. The newly synthesized compounds were characterized by IR and NMR spectra, and the others were identified by comparison of their IR and physical properties with those of authentic samples [19, 20].

3-Methyl-4-(4-nitrophenyl)indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (VIa). mp 234–235°C , IR spectrum (KBr), ν, cm^{-1}: 1537, 1570, 1625, 1678, 3154, 3325. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.77 s (3H), 7.21 d (1H, *J* = 7.2 Hz), 7.29 t (1H, *J* = 7.4 Hz), 7.40 t (1H, *J* = 7.5 Hz), 7.72 d (2H, *J* = 8.5 Hz), 7.76 d (1H, *J* = 7.1 Hz), 8.12 d (2H, *J* = 8.2 Hz), 11.13 s (1H).^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.87, 103.14, 105.03, 120.21, 120.67, 125.68, 129.55, 131.12, 131.60, 133.35, 135.93, 137.09, 137.35, 146.99, 147.64, 154.03, 158.08, 190.23. Found, %: C 67.20; H 3.50; N 15.79. $C_{20}H_{12}N_4O_3$. Calculated, %: C 67.41; H 3.39; N 15.72.

3-Methyl-4-(3-nitrophenyl)indeno[1,2-*b*]pyrazolo-[4,3-*e*]pyridin-5(1*H*)-one (VIb). mp 286–287°C. IR spectrum (KBr), ν, cm^{-1}: 1466, 1546, 1569, 1690, 3067, 3125, 3345. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.78 s (3H), 7.24 d (1H, *J* = 7.2 Hz), 7.30 t (1H, *J* = 7.2 Hz), 7.38 t (1H, *J* = 7.4 Hz), 7.58 t (1H, *J* = 7.8 Hz), 7.72 d (1H, *J* = 7.4 Hz), 7.78 (1H, *J* = 7.8 Hz), 7.92 d.d (1H, *J* = 8.1, 1.8 Hz), 8.09 s (1H), 11.07 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.76, 102.87, 104.76, 120.41, 120.98, 121.87, 122.04, 130.12, 131.10, 131.56, 131.99, 135.62, 135.78, 137.35, 139.74, 147.21, 148.52, 150.13, 158.76, 190.54. Found, %: C 67.21; H 3.67; N 15.65. $C_{20}H_{12}N_4O_3$. Calculated, %: C 67.41; H 3.39; N 15.72.

3-Methyl-4-(3-nitrophenyl)indeno[1,2-*b*]pyrazolo-[4,3-*e*]pyridin-5(1*H*)-one (VIc). mp 302–303°C. IR spectrum (KBr), ν, cm^{-1}: 1535, 1581, 1639, 1682, 3086, 3124. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.78 s (3H), 5.59 s (1H), 7.21 d (1H, *J* = 7.2 Hz), 7.28 t (2H, *J* = 7.7 Hz), 7.30–7.49 m (2H), 7.49–7.76 m (1H), 7.69 d (1H, *J* = 7.2 Hz), 7.76 t (1H, *J* = 7.2 Hz), 11.23 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.98, 103.25, 104.75, 120.21, 122.40, 124.98, 127.62, 130.19, 131.46, 131.97, 132.06, 133.87, 136.22, 138.85, 143.48, 148.22, 149.98, 157.12, 189.26. Found, %: C 67.61; H 3.43; N 15.49. $C_{20}H_{12}N_4O_3$. Calculated, %: C 67.41; H 3.39; N 15.72.

4-(4-Chlorophenyl)-3-methylindeno[1,2-*b*]pyrazolo-[4,3-*e*]pyridin-5(1*H*)-one (VId). mp 271–273°C. IR spectrum (KBr), ν, cm^{-1}: 1072, 1493, 1547, 1628, 1687, 3029, 3152, 3329. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.89 s (3H), 7.19 d (1H, *J* = 7.2 Hz), 7.26 d (2H, *J* = 8.2 Hz), 7.35 d (2H, *J* = 8.2 Hz), 7.24 t (1H, *J* = 76 Hz), 7.35 t (1H, *J* = 7.7 Hz), 7.65 t (1H, *J* = 7.1 Hz), 11.12 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.37, 104.78, 105.87, 119.76, 121.38, 128.90, 130.14, 130.84, 131.87, 131.99, 132.04, 135.70, 137.32, 145.43, 147.87, 157.34, 190.02. Found, %: C 69.28; H 4.01; N 12.21. $C_{20}H_{14}ClN_3O$. Calculated, %: C 69.47; H 3.50; N 12.15.

4-(4-Bromophenyl)-3-methylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (VIe). mp 312–313°C. IR spectrum (KBr), ν, cm^{-1}: 1021, 1490, 1555, 1626, 1677, 3056, 3150, 3312. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.80 s (3H), 7.15 d (1H, *J* = 7.2 Hz), 7.25 d (2H, *J* = 8.4 Hz), 7.29 d (2H, *J* = 8.2 Hz), 7.34 t (1H, *J* = 7.8 Hz), 7.46 t (1H, *J* = 7.4 Hz), 7.65 d (1H, *J* = 7.2 Hz), 11.00 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.97, 103.78, 105.52, 119.47, 120.21, 128.67, 130.34, 130.77, 130.94, 131.67 131.96, 135.42, 137.68, 145.93, 147.63, 157.23, 190.32. Found, %: C 69.78; H 3.75; N 10.51. $C_{20}H_{14}BrN_3O$. Calculated, %: C 61.56; H 3.10; N 10.77.

4-(3-Bromophenyl)-3-methylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (VIf). mp 267–268°C. IR spectrum (KBr), ν, cm^{-1}: 1348, 1557, 1586, 1627, 1677, 3163, 3359. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.77 s (3H), 6.67–7.00 m (2H), 7.09–7.13 m (1H), 7.30 t (1H, *J* = 7.5 Hz), 7.42 d (1H, *J* = 7.3 Hz), 7.56 d (1H,

J = 7.2 Hz), 7.79 d (1H, J = 8.2 Hz), 7.80 s (1H), 10.89 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.99, 105.88, 108.12, 123.14, 124.14, 124.56, 127.57, 129.65, 131.07, 131.39, 132.65, 132.26, 133.92, 136.71, 136.98, 137.85, 138.92, 141.00, 145.61, 192.61. Found, %: C 61.32; H 3.69; N 10.78. $C_{20}H_{14}BrN_3O$. Calculated, %: C 61.56; H 3.10; N 10.77.

6-Amino-4-(3-bromophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (Vf). mp 265–266°C. IR spectrum (KBr), ν, cm^{-1}: 3346, 3267, 3100, 2937, 2256, 1600, 1504, 1558, 1375. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.11 s (3H), 6.93 d (1H, J = 7.5 Hz), 7.64 d (1H, J = 8.0 Hz), 8.01–8.05 m (2H), 8.79 s (1H) 9.19 s (1H), 10.5 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.87, 103.19, 105.23, 120.29, 125.48, 129.88, 131.84, 131.60, 133.43, 137.95, 146.39, 147.35, 155.03, 168.08. Found, %: C 51.10; H 3.00; N 21.45. $C_{14}H_{10}BrN_5$. Calculated, %: C 51.24; H 3.07; N 21.34.

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