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SILICA SULFURIC ACID PROMOTED ONE-POT SYNTHESIS OF BENZO[4,5]IMIDAZO[1,2-*a*]PYRIMIDINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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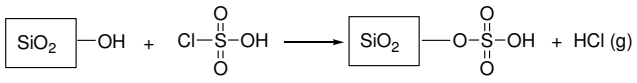
ABSTRACT. A simple and efficient synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives has been accomplished by the reaction of 2-aminobenzimidazole, aldehydes and β-dicarbonyl compounds under solvent-free conditions in the presence of silica sulfuric acid.

KEY WORDS: Benzo[4,5]imidazo[1,2-*a*]pyrimidine, Silica sulfuric acid, 2-Aminobenzimidazole, Aromatic aldehydes, β-Dicarbonyl compounds, Solvent-free

INTRODUCTION

The synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives has been considered of great interest to organic chemists because of their pharmacological and therapeutic properties such as antineoplastic [1], protein kinase inhibitor [2], T cell activation [3], TIE-2 and/or VEGFR2 inhibitory activities [4]. The most common methods for the preparation of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives is the one-pot three-component condensation reactions of β-dicarbonyl compounds, aldehydes and 2-aminobenzimidazole in the presence of, 1,1,3,3,N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT) [5], sulfamic acid [6], microwave [7-9]. Other methods involve the reaction of β-ketoester with aldehyde followed by condensation with 2-aminobenzimidazole to give the target products [10-12].

In recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. They are advantageous over their homogeneous counterparts due to the prime advantage that in most of the cases the catalyst can be recovered easily and reused [13]. Silica sulfuric acid (SSA) have been used as efficient heterogeneous catalysts for many organic transformations because of their low cost, ease of preparation (Scheme 1), catalyst recycling, and ease of handling [14-18].



Scheme 1

We now report a simple and efficient procedure for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives by one-pot three-compounent condensation of 2-aminobenzimidazole with aromatic aldehydes and β-dicarbonyl compounds using SSA as an environmentally benign catalyst under solvent-free conditions (see Scheme 2).

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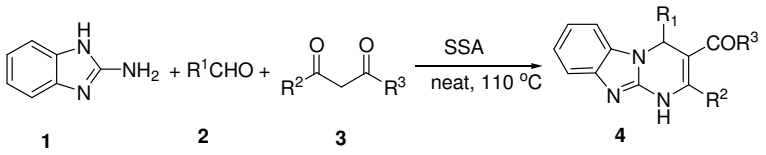


Scheme 2

RESULTS AND DISCUSSION

First, to optimize the amount of catalyst and the reaction temperature, the reaction of 2-aminobenzimidazole (1 mmol), benzaldehyde (1 mmol) and ethyl 3-oxobutanoate (1 mmol) under thermal solvent-free conditions was selected as a model. The best result was obtained by carrying out the reaction using 8 mol% SSA at 110 °C under solvent-free conditions (Table 1).

Table 1**.** Optimization one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives[a].

Entry	SSA mol %	Temp. (°C)	Yield (%)
1	6	110	82
2	6	120	84
3	8	100	90
4	8	110	94
5	8	120	92
6	10	110	93
7	10	120	91

[a]2-Aminobenzimidazole : benzaldehyde : ethyl 3-oxobutanoate = 1 : 1 : 1; reaction time: 6 h.

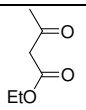
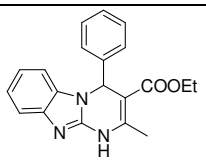
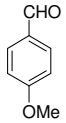
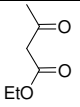
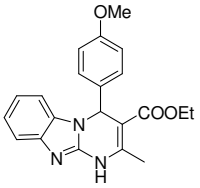
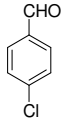
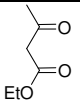
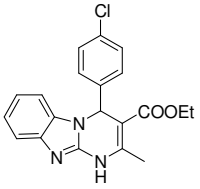
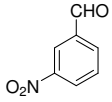
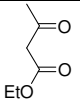
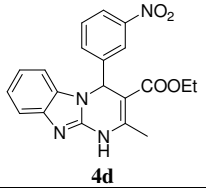
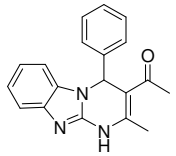
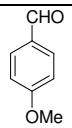
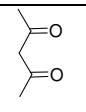
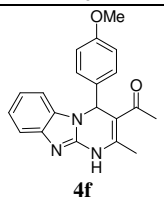
Based on the optimized reaction conditions, a range of benzo[4,5]imidazo[1,2-*a*] pyrimidine derivatives was synthesized by the reaction of 2-aminobenzimidazole (**1**, 1 mmol), aldehydes (**2**, 1 mmol) and β-dicarbonyl compounds (**3**, 1 mmol). The reaction proceeded at 110 °C within 6 hour in excellent yields after the addition of the acid catalyst SSA (see Table 2). In these experiments the catalyst was isolated by filteration and could be reloaded with fresh reagents for further runs, thus, recyclization of catalyst is possible without significant loss of activity (Table 2, entry 1).

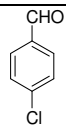
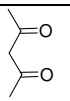
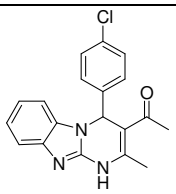
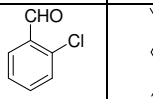
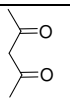
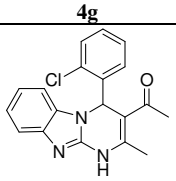
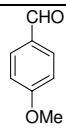
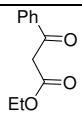
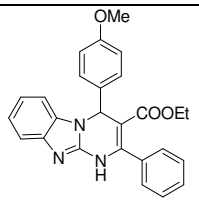
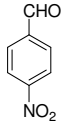
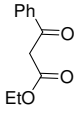
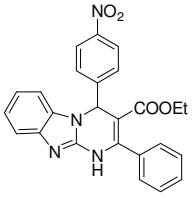
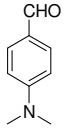
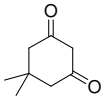
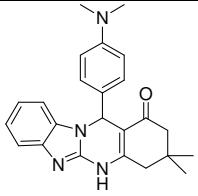
To emphasize the effect of the catalyst, the model reaction 2-aminobenzimidazole, benzaldehyde and ethyl 3-oxobutanoate was described, and different catalysts were subjected to the reaction. All the reactions were run in the same conditions, and similar amounts of catalysts (8 mol%) were used. As shown in Table 3, more satisfactory results were obtained only with silica sulfuric acid.

CONCLUSIONS

We have developed a simple and highly efficient practical method for synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives using SSA under solvent-free conditions. The notable features of this procedure are mild reaction conditions, simple experimental procedure and excellent yields (86-94%), which make it a useful and attractive process for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives. We believe that this methodology will be a valuable addition to the existing methods in the field of synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives.

Table 2. Preparation of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives catalyzed by SSA.[a].

Entry	Alde-hydes	β-Dicarbonyl compounds	Products	Time (h)	Yield (%)	M.p. (°C) (lit. m.p.) [ref.]
1			 **4a**	6	94 (92,93,91)[b]	289-291 (294-296) [6]
2			 **4b**	6	92	266-268 (272-273) [6]
3			 **4c**	6	90	>300 (>300) [6]
4			 **4d**	5	88	288-290 (294-296) [6]
5			 **4e**	6	92	>300 (>300) [6]
6			 **4f**	6	86	275-277 (279-281) [6]

7			 **4g**	5	93	>300 (>300) [6]
8			 **4h**	6	94	>300 (>300) [6]
9			 **4i**	6	87	122-123 (117-120) [5]
10			 **4j**	5	89	246 dec (248 dec) [5]
11			 **4k**	6	91	>300

[a]All the products were characterized from their spectral (IR, ^{1}H NMR) and element analysis. [b]Isolated yields after recycling of catalyst.

Table 3. Comparison of the effect of catalysts in synthesis of benzo[4,5]imidazo[1,2-*a*] pyrimidine derivatives[a].

Entry	Catalyst	Yield (%)
1	H_2SO_4	78
2	$NaHSO_4$	72
3	NH_2SO_3H	83
4	$AlCl_3$	60
5	I_2	42
6	SSA	94

[a]2-Aminobenzimidazole : benzaldehyde : ethyl 3-oxobutanoate = 1 : 1 : 1; reactions executed at 110 ^{o}C for 6 h.

EXPERIMENTAL

General experimental methods

NMR spectra were determined on Bruker AV-300 spectrometer (Switzerland) at room temperature using TMS as internal standard, coupling constants (*J*) were measured in Hz. IR spectra were recorded on a Bruker IFS-55 spectrometer (Switzerland). Elemental analyses were performed by a Vario-III elemental analyzer (Germany). Melting points were determined on a XT-4 binocular microscope (China) and were uncorrected. SSA was prepared according to literature [14]. Commercially available reagents were used throughout without further purification unless otherwise stated. Products **4** are known compounds and their physical data, IR, and NMR spectra were essentially identical with those of the authentic samples. However, their structures were further established using elemental analysis.

*General procedure for the preparation of **4***

To a mixture of 2-aminobenzimidazole (1 mmol) with aldehydes (1 mmol) and β-dicarbonyl compounds (1 mmol), SSA (31 mg, 8 mol%) was added. The mixture was stirred at 110 ^{o}C for an appropriate time (Table 2). After completion of the reaction (TLC), 10 mL EtOAc was added to the reaction mixture and the catalyst was recovered by filteration. The organic layer was dried over $MgSO_4$, the solvent was evaporated and purified by recrystallization from ethanol to afford pure product **4** in 86-94% yields.

*2-Methyl-4-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4a**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.42 (s, 1H, NH), 7.32 (t, *J* = 7.6 Hz, 3H, ArH), 7.24 (t, *J* = 7.8 Hz, 3H, ArH), 7.18-7.12 (m, 1H, ArH), 6.99 (t, *J* = 7.8 Hz, 1H, ArH), 6.92 (t, *J* = 7.5 Hz, 1H, ArH), 6.32 (s, 1H, CH), 4.06 (q, *J* = 7.0 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.20 (t, *J* = 7.0 Hz, 3H, CH_3); IR (KBr) *v*: 3266, 3098, 3012, 2920, 2840, 1720, 1599, 1560, 1360, 1280, 1077, 861, 802, 701 cm^{-1}; anal. calcd. for $C_{20}H_{19}N_3O_2$: C 72.05, H 5.74, N 12.60; found: C 72.25, H 5.58, N 12.44.

*4-(4-Methoxy-phenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4b**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.62 (s, 1H, NH), 7.30-7.20 (m, 6H, ArH), 6.98 (t, *J* = 7.3 Hz, 1H, ArH), 6.90 (t, *J* = 7.5 Hz, 1H, ArH), 6.38 (s, 1H, CH), 4.08 (q, *J* = 7.8 Hz, 2H, CH_2), 3.42 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 1.22 (t, *J* = 7.0 Hz, 3H, CH_3); IR (KBr) *v*: 3250, 3040, 2924, 2846, 1712, 1615, 1550, 1311, 1182, 1043, 930, 829, 724 cm^{-1}; anal. calcd. for $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56; found: C 69.67, H 5.62, N 11.42..

*4-(4-Chloro-phenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4c**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.74 (s, 1H, NH), 7.45-7.30 (m, 6H, ArH), 7.01 (t, *J* = 7.4 Hz, 1H, ArH), 6.92 (t, *J* = 7.2 Hz, 1H, ArH), 6.52 (s, 1H, CH), 4.00 (q, *J* = 7.8 Hz, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3); IR (KBr) *v*: 3255, 3090, 2995, 2842, 1720, 1620, 1550, 1360, 1242, 1172, 902, 829, 740 cm^{-1}; anal. calcd. for $C_{20}H_{18}ClN_3O_2$: C 69.31, H 4.93, N 11.42; found: C 69.62, H 4.70, N 11.54.

*4-(3-Nitro-phenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4d**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.86 (s, 1H, NH), 8.09 (m, 1H, ArH), 7.80 (d, *J* = 7.9 Hz, 2H, ArH), 7.62 (t, *J* = 7.9 Hz, 1H, ArH), 7.35 (d, *J* = 7.9 Hz, 1H, ArH), 7.28 (d, *J* = 7.9 Hz, 1H, ArH), 7.05 (t, *J* = 7.5 Hz, 1H, ArH), 6.92 (t, *J* = 7.0 Hz, 1H, ArH), 6.55 (s, 1H, CH), 4.00 (q, *J* = 7.0 Hz, 2H, CH_2), 2.52 (s, 3H, CH_3), 1.18 (t, *J* = 7.0 Hz, 3H, CH_3); IR (KBr) *v*: 3261, 3088, 3010, 2960, 2830, 1733, 1625, 1560, 1423, 1360, 1182, 905,

820, 732 cm^{-1}; anal. calcd. for $C_{20}H_{18}N_4O_4$: C 69.48, H 4.79, N 14.81; found: C 69.55, H 4.61, N 14.89.

*1-(1,4-Dihydro-2-methyl-4-phenylpyrimido[1,2-a]benzimidazol-3-yl)-ethanone (**4e**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.72 (s, 1H, NH), 7.40 (d, J = 7.8 Hz, 3H, ArH), 7.32-7.25 (m, 3H, ArH), 7.18-7.12 (m, 1H, ArH), 7.04-6.92 ((m, 2H, ArH)), 6.54 (s, 1H, CH), 2.40 (s, 3H, CH_3), 2.18 (s, 3H, CH_3); IR (KBr) v: 3251, 3092, 3014, 2840, 1715, 1600, 1565, 1450, 1261, 1012, 874, 802, 721 cm^{-1}; anal. calcd. for $C_{19}H_{17}N_3O$: C 75.23, H 5.65, N 13.85; found: C 75.28, H 5.50, N 13.59.

*1-[4,10-Dihydro-4-(4-methoxyphenyl)-2-methylpyrimido[1,2-a]benzimidazol-3-yl]-ethanone (**4f**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.68 (s, 1H, NH), 7.32-7.18 (m, 6H, ArH), 6.98-6.95 (m, 2H, ArH), 6.54 (s, 1H, CH), 3.45 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 2.18 (s, 3H, CH_3); IR (KBr) v: 3237, 3090, 3000, 2845, 1690, 1600, 1542, 1450, 1320, 1254, 975, 812, 742 cm^{-1}; anal. calcd. for $C_{20}H_{19}N_3O_2$: C 72.05, H 5.74, N 12.60; found: C 72.09, H 5.58, N 12.43.

*1-[4,10-Dihydro-4-(4-chlorophenyl)-2-methylpyrimido[1,2-a]benzimidazol-3-yl]-ethanone (**4g**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.72 (s, 1H, NH), 7.45-7.30 (m, 6 H, ArH), 7.05-6.95 (m, 2H, ArH), 6.58 (s, 1H, CH), 2.45 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); IR (KBr) v: 3245, 3094, 3008, 2852, 1674, 1602, 1556, 1512, 1442, 1355, 1272, 869, 738 cm^{-1}; anal. calcd. for $C_{19}H_{16}ClN_3O$: C 67.56, H 4.77, N 12.44; found: C 67.60, H 4.82, N 12.40.

*1-[4,10-Dihydro-4-(2-chlorophenyl)-2-methylpyrimido[1,2-a]benzimidazol-3-yl]-ethanone (**4h**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.88 (s, 1H, NH), 7.50 (d, J = 7.0 Hz, 1H, ArH), 7.35-7.22 (m, 3H, ArH), 7.06 (t, J = 7.2 Hz, 1H, ArH), 6.96 (t, J = 7.8 Hz, 3H, ArH), 6.76 (s, 1H, CH), 2.42 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); IR (KBr) v: 3220, 3102, 30048, 2840, 1640, 1608, 1572, 1458, 1420, 1325, 1278, 980, 862, 730 cm^{-1}; anal. calcd. for $C_{19}H_{16}ClN_3O$: C 67.56, H 4.77, N 12.44; found: C 67.68, H 4.70, N 12.42.

*4-(4-Methoxy-phenyl)-2-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4i**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.66 (s, 1H, NH), 7.36-6.82 (m, 13H, ArH), 6.32 (s, 1H, CH), 4.02 (q, J = 8.0 Hz, 2H, CH_2), 3.40 (s, 3H, OCH_3), 1.12 (t, J = 7.0 Hz, 3H, CH_3); IR (KBr) v: 3243, 3072, 2920, 2832, 1698, 1605, 1552, 1420, 1302, 1165, 1028, 912, 820, 736 cm^{-1}; anal. calcd. for $C_{26}H_{23}N_3O_3$: C 73.39, H 5.45, N 9.88; found: C 73.25, H 5.67, N 9.80.

*4-(4-Nitro-phenyl)-2-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (**4j**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.72 (s, 1H, NH), 8.20-6.78 (m, 13H, ArH), 6.12 (s, 1H, CH), 3.96 (q, J = 7.8 Hz, 2H, CH_2), 1.16 (t, J = 6.4 Hz, 3H, CH_3); IR (KBr) v: 3278, 3092, 3010, 2942, 2810, 1692, 1612, 1558, 1420, 1352, 1204, 9025, 814, 748 cm^{-1}; anal. calcd for $C_{25}H_{20}N_5O_5$: C 68.17, H 4.58, N 12.72; found: C 68.20, H 4.50, N 12.53.

*12-(4-Dimethylamino-phenyl)-3,3-dimethyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-b]-quinazolin-1-one (**4k**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.76 (s, 1H, NH), 7.38-7.25 (m, 6H, ArH), 6.98 (t, J = 7.3 Hz, 1H, ArH), 6.90 (t, J = 5.2 Hz, 1H, ArH), 6.35 (s, 1H, CH), 3.16 (s, 6H, NCH_3), 2.60-2.49 (m, 2H, CH_2), 2.28 (d, J = 16.5 Hz, 1H, CH), 2.02 (d, J = 16.5 Hz, 1H, CH), 1.10 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); IR (KBr) v: 3462, 3047, 2934, 2858, 1722, 1642, 1610, 1588, 1560 cm^{-1}; anal. calcd. for $C_{24}H_{26}N_4O$: C 74.58, H 6.78, N 14.50; found: C 74.67, H 6.62, N 14.42.

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