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Triethylaminium-*N*-sulfonic Acid Tetrachloroaluminate (TSAT) as a New Ionic Liquid Catalyst for the Synthesis of [1,2,4]Triazolo[1,5-a]pyrimidines

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Triethylaminium-*N*-sulfonic acid tetrachloroaluminate (TSAT) as a new ionic liquid was synthesized and characterized by FT-IR, ^{1}H, ^{13}C NMR and mass spectra as well as TG and DTG diagrams. This ionic liquid was employed as a catalyst for the synthesis of [1,2,4]triazolo[1,5-a]pyrimidines-6-carboxamides *via* one-pot three-component reaction of aromatic aldehydes, acetoacetanilide and 3-amino-1,2,4-triazole under solvent-free conditions at 60 °C .The salient features of the present protocol are mild reaction condition, easy isolation of products and clean reaction profiles.

Keywords: Ionic liquid, Triethylaminium-*N*-sulfonic acid tetrachloroaluminate (TSAT), [1,2,4]Triazolo[1,5-a] pyrimidines-6-carboxamide, Acetoacetanilide, 3-Amino-1,2,4-triazole

INTRODUCTION

Fused triazole and pyrimidine ring systems have been studied for several years because of their medicinal and agricultural significance [1-3]. Among their important effects, triazolopyrimidine derivatives are used as blood pressure regulators [4], antibacterial agents [5], selective serotonin 5-HT6 receptor antagonists [6] and cardiovascular vasoditors [7]. In addition, several triazolopyrimidie-2-sulfonumide derivatives with herbicidal activity such as florasulam, flumetsulam and metosulam, are produced commercially [8]. Moreover, some important structures containing fused triazole and pyrimidine scaffolds have biological activities including antiappetite, anticonvulsant and anticancer [9-11]. Recently, new class of triazolopyrimidine derivatives was synthesized in the presence of maltose catalyst [12]. However, considering the properties of these heterocyclic compounds, their synthesis is still demanded.

Ionic liquids (ILs) have attracted rising interest in the last decades for chemists because of their unique properties such as high thermal and chemical stability, non-flammability, easy operation, etc. Therefore, Bronsted acidic ionic liquids were used instead of solid acids and traditional mineral liquid acids to catalyze a large number of chemical reactions. In this respect, more recently some Bronted acidic ionic liquids in which a SO_3H group has bonded with positive nitrogen in organic compound were synthesis, and successfully applied as catalysts and regents in organic transformations [13-18]. Here, triethylaminium-*N*-sulfonic acid tetrachloroaluminate (TSAT) was synthesized as a new, homogeneous and green ionic liquid catalyst and utilized for the preparation of [1,2,4]triazolo[1,5-a]pyrimidines-6-carboxamides 4 (Scheme 1).

EXPERIMENTAL

General

All materials were obtained from Fluka and Merck and were used without further purification. The melting points were recorded on a Buchi B-545 apparatus in open capillary tubes. A Bruker DRX-400 AVANCE spectrometer was used

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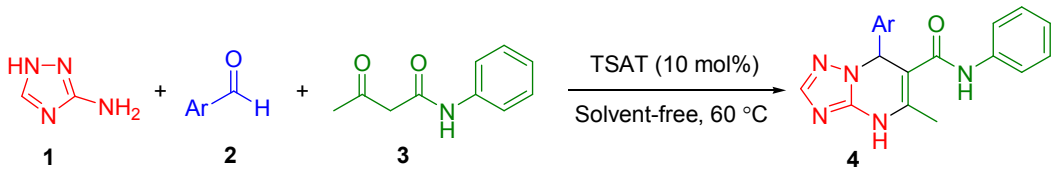
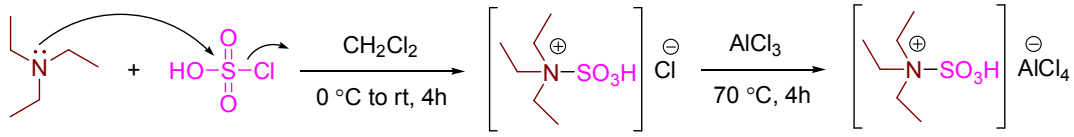


Scheme 1. The synthesis of [1,2,4]triazolo[1,5-a]pyrimidines-6-carboxamides 4



Scheme 2. The preparation of TSAT

at 400 and 100 MHz for ^{1}H NMR and ^{13}C NMR, respectively. IR spectra were obtained on a JASCO FT-IR-600 plus spectrometer. Mass spectra were obtained with Shimadzu GC-MS-QP 1100 EX model.

Preparation of Catalyst TSAT

First, triethylamine (0.506 g, 5 mmol, in 20 ml CH_2Cl_2) was added slowly to chlorosulfonic acid (0.583 g, 5 mmol, in 20 ml CH_2Cl_2) over a period of 10 min at 0 ºC and then the mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored through TLC. After completion of the reaction, solvent was evaporated and triethylamine-bonded sulfonic acid was obtained as a white viscose oil. Next, aluminum chloride (0.667 g, 5 mmol,) was added slowly to triethylamine-bonded sulfonic acid over 5 minutes and was stirred at 70 ºC for another 4 h. After completion, TSAT was obtained as a white solid in 98% yield.

Characterization Data of TSAT

White solid; m.p.: 97-98 °C; FT-IR (KBr): 3600-2400 (OH), 2362, 1653, 1103, 613 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.18 (t, J = 5.8 Hz, 9H, 3CH$_3$), 3.01-3.07 (m, 6H, 3CH$_2$), 10.17 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 8.8, 45.8; MS (EI, 70 eV): *m/z*, (%): 353 (M+2, 10), 313 (35), 284 (30), 256 (30), 236 (36), 213 (25), 185 (25), 173 (27), 129 (50), 97 (52), 86 (100), 69 (65), 57 (76), 43 (74).

General Procedure for the Synthesis of [1,2,4]Triazolo[1,5-a] Pyrimidines-6-carboxamide 4

A mixture of 3-amino-1,2,4-triazole 1 (0.084 g, 1.0 mmol), aromatic aldehyde 2 (1.0 mmol) and acetoacetanilide 3 (0.177 g, 1.0 mmol) in the presence of TSAT (10 mol%) was stirred at 60 °C. The progress of the reaction was monitored by TLC. After completion, EtOH was added to the reaction mixture and stirred at ambient temperature. The resulting precipitate was filtered and recrystallized from EtOH (95%) to give the pure product 4.

Selected spectral data of the products

7-(2,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (Table 2, product 4b). ^{1}H NMR (400 MHz, DMSO-*d6*): δ (ppm) 2.18 (s, 3H, CH$_3$), 6.93 (s, 1H, H-benzylic), 7.01 (t, J = 7.5 Hz, 1H, ArH), 7.25 (t, J = 7.8 Hz, 1H, ArH), 7.32 (d, J = 7.5Hz, 1H, ArH), 7.42 (dd, J = 8.5 Hz, J = 1.7 Hz, 1H, ArH), 7.51 (d, J = 8.2 Hz, 2H, ArH),7.57 (d, J = 1.7 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 9.87 (s, 1H, NH), 10.49 (s, 1H, NH).

4,7-Dihydro-5-methyl-7-(4-nitrophenyl)-*N*-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (Table 2, product 4g). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.21 (s, 3H, CH$_3$), 6.70 (s, 1H, H-benzylic), 7.01 (t, J = 7.5 Hz, 1H, ArH), 7.25 (t, J = 7.8 Hz, 1H, ArH), 7.51 (d, J = 8.6 Hz, 4H, ArH), 7.72 (s, 1H, ArH), 8.21 (d, J = 8.7 Hz, 2H, ArH), 9.80 (s, 1H, NH), 10.01 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.1, 41.2, 121.0, 121.6, 124.4, 129.0, 130.0, 138.3, 143.9, 146.9, 147.2, 150.5, 151.3, 165.5

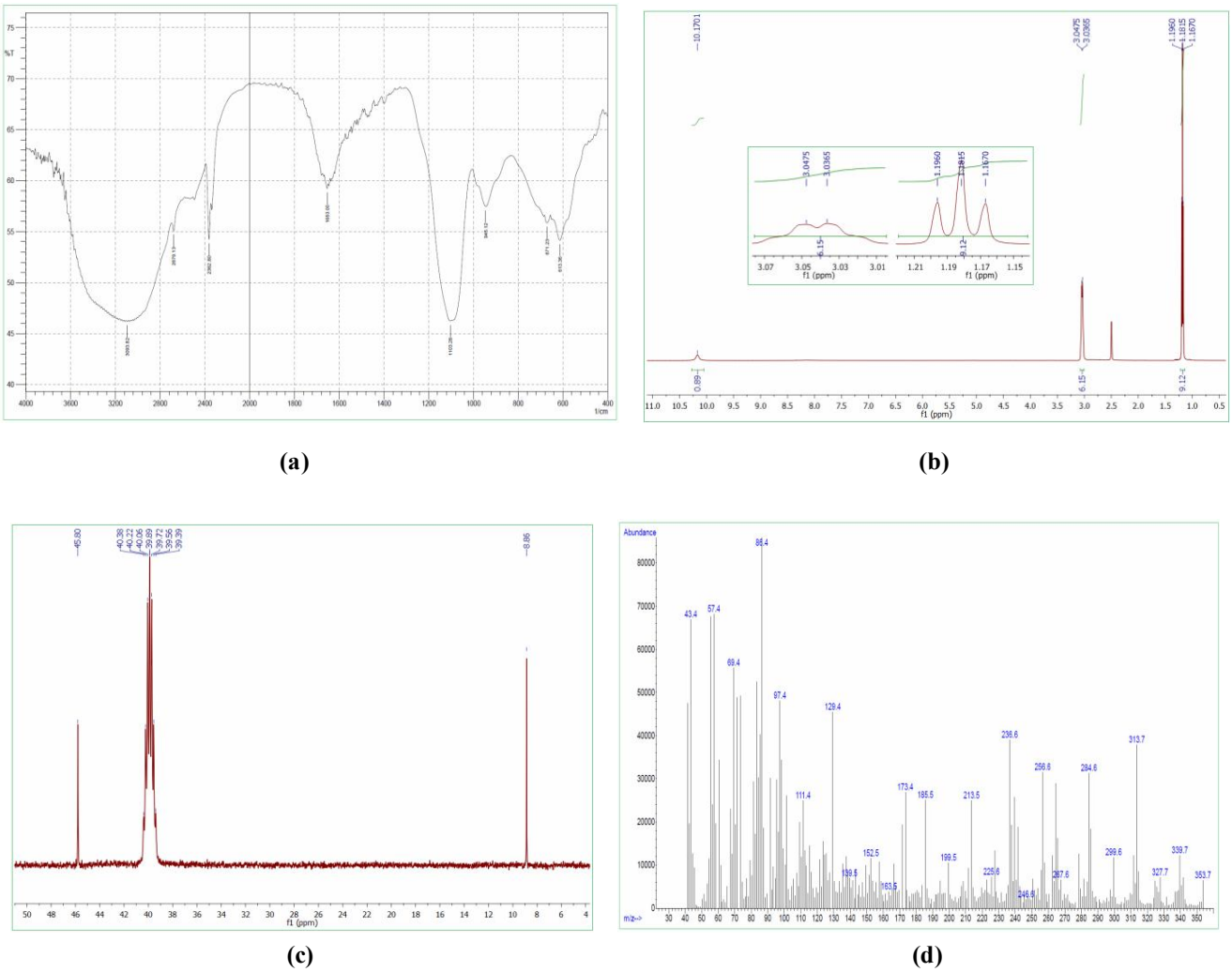


Fig. 1. (a) FT-IR, (b) ^{1}H NMR, (c) ^{13}C NMR, and (d) mass spectra of TSAT

RESULTS AND DISCUSSION

Triethylaminium-*N*-sulfonic acid tetrachloroaluminate was prepared by the reaction of triethylamine, chlorosulfonic acid and aluminum chloride (Scheme 2). The FT-IR spectrum of TSAT exhibited a characteristic absorption at 3600-2400 cm^{-1} for SO_3H group. In ^{1}H NMR spectrum of the catalyst, three methyl groups were observed as a triplet at 1.18 ppm (J = 5.8 Hz). Due to the presence of nitrogen, the methylene groups were appeared as a broad multiplet at 3.01-3.07 ppm. ^{13}C NMR of TSAT showed two distinct singles at 8.8 and 45.8 ppm in agreement with the proposed structure. Additionally, the mass spectrum of catalyst displayed the molecular ion peak (M^+) and M^{2+} at m/z = 351 and 353, respectively (Fig. 1).

The thermal gravimetric (TG) and differential thermal gravimetric (DTG) diagrams of the catalyst showed weight losses in four steps: (i) about 100 ºC (a small weight loss), (ii) 100-170 ºC, (iii) 170-300 ºC, and (iv) 300-700 ºC. The first weight loss can be attributed to evaporation of adsorbed water and other solvents in $[Et_3N\text{-}SO_3H][AlCl_4]$, and the three others are related to decomposition of organic functional groups (Fig. 2).

The catalytic activity of TSAT was tested in the reaction

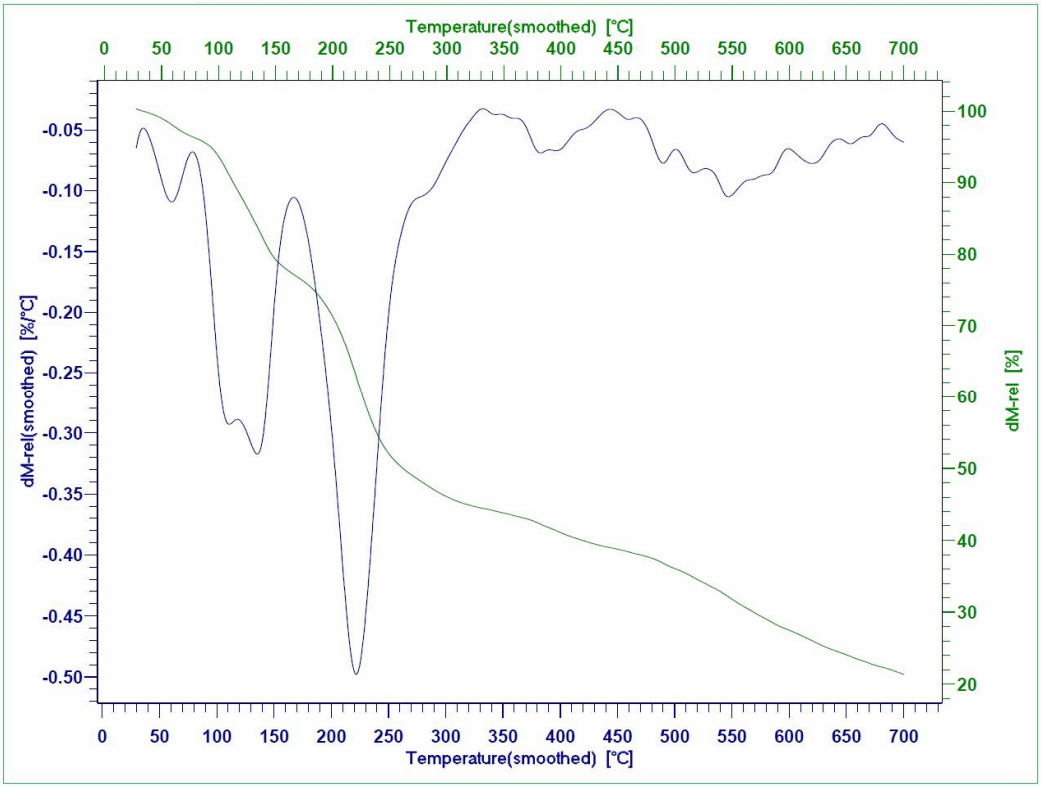
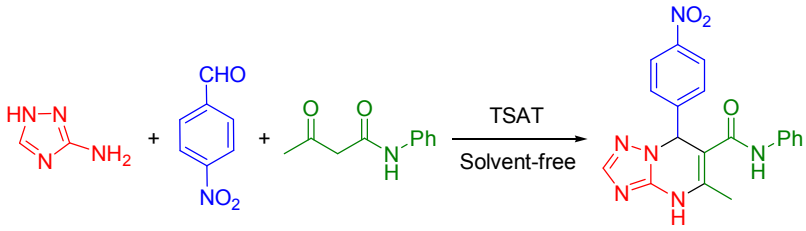


Fig. 2. TG and DTG diagrams of TSAT.

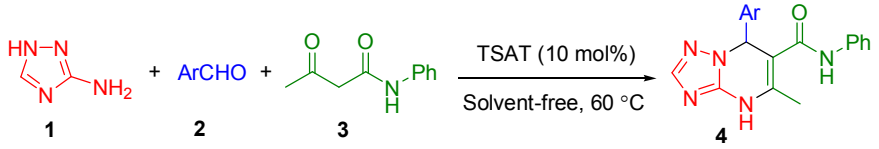
Table 1. Optimization of Reaction Conditions[a]



Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[b]
1	10	50	20	75
2	10	60	10	90
3	5	60	30	61
4	10	80	10	91
5	20	80	10	93
6	10	25	120	trace
7	-	80	120	-

[a]Reaction conditions: 3-amino-1,2,4-triazole (1 mmol), 4-nitrobenzaldehyde (1 mmol) and acetoacetanilide (1 mmol). [b]Isolated yield.

Table 2. Synthesis of [1,2,4]Triazolo[1,5-a]pyrimidine-6-carboxamide 4



Product	Ar	Time (min)	Yield (%)[a]	M.p. (ºC) (Lit.)[12]
4a	Ph	10	85	248-249 (251-253)
4b	2,4-$Cl_2C_6H_3$	15	87	245-247 (246-248)
4c	2-ClC_6H_4	12	90	250-252 (252-254)
4d	3-$MeOC_6H_4$	5	85	240-242 (244-246)
4e	4-$MeOC_6H_4$	5	80	243-245 (245-247)
4f	4-FC_6H_4	5	85	283-285 (277-279)
4g	4-$O_2NC_6H_4$	10	90	255-257 (258-260)
4h	2-BrC_6H_4	5	89	242-244 (241-243)
4i	4-BrC_6H_4	10	90	231-233 (238-240)

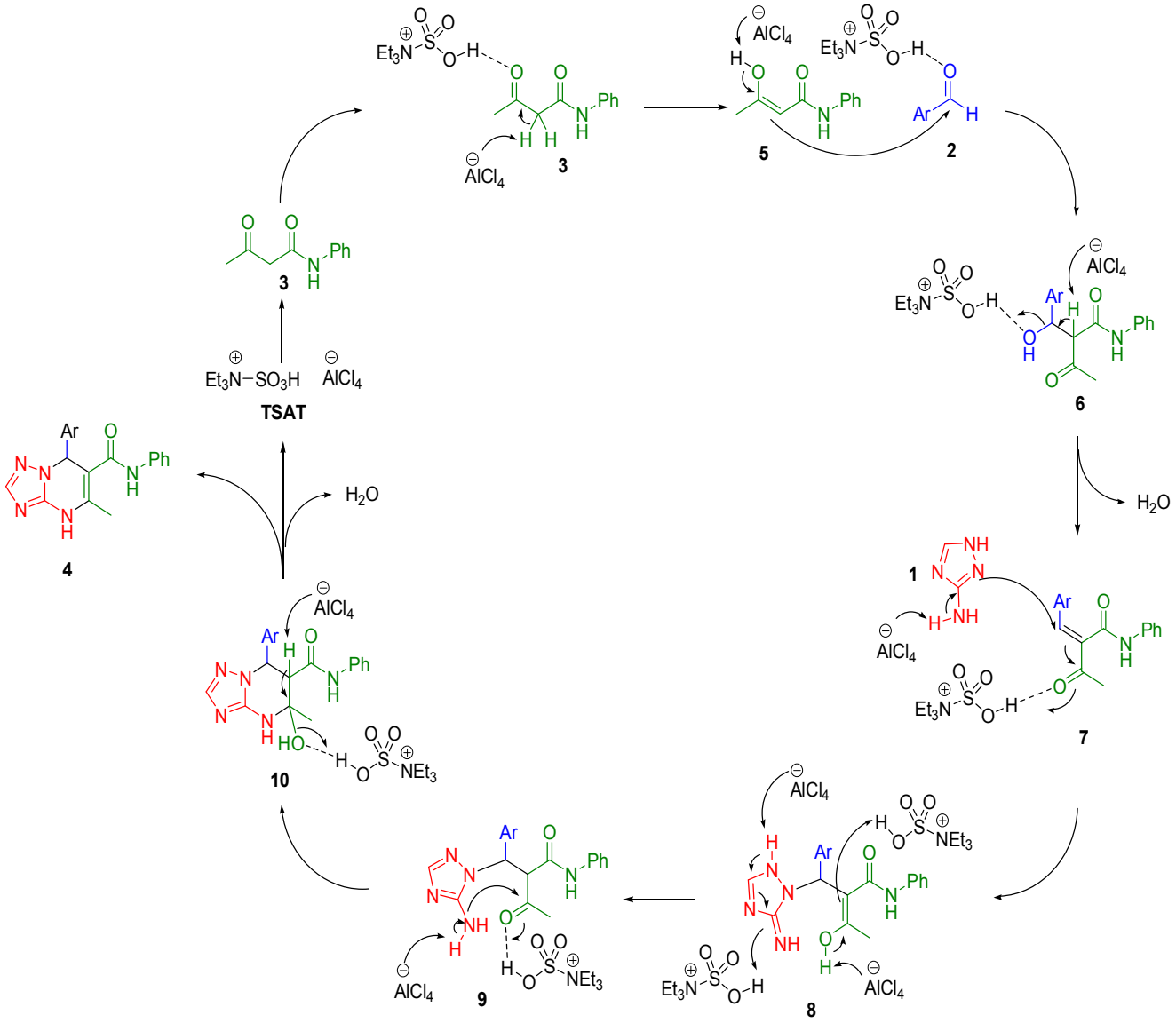
[a]Isolated yield.

of 3-amino-1,2,4-triazole, 4-nitrobenzaldehyde and acetoacetanilide. The corresponding [1,2,4]triazolo[1,5-a]pyrimidines-6-carboxamide was obtained in 75% yield at 50 ºC in the presence of 10 mol% of TSAT. After this success, the reaction condensations were optimized in terms of the catalyst amount and temperature under solvent-free conditions. As shown in Table 1, the best result was achieved in the presence of 10 mol% catalyst at 60 ºC. Increasing the catalyst amount and temperature to 20 mol% and 80 ºC, did not significantly affect the reaction efficiency. Therefore, 60 ºC was selected as the optimal reaction temperature, because one aim of this work was performing the reaction in milder reaction conditions with respect to the reported work, and this was more logical.

The efficiency and the generality of the catalyst were examined by the reaction of a different aromatic aldehyde 2 cantainig electron-withdrawing substituents, electron-donating substituents as well as halogens. The results are shown in Table 1. All reactions were performed efficiently, and afforded the corresponding [1,2,4]triazolo[1,5-a] pyrimidine-6-carboxamide 4 in good to excellent yields and in short reaction times. However, electron-deficient aldehydes gave higher yields. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature [12].

The proposed mechanism for the synthesis of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4 is illustrated in Scheme 3. Initially, enolamide 5 was formed *in situ* from acetoacetanilide 3 in the presence of TSAT. Nucleophilic attack of enolamide 5 on the activated aldehyde 2 gave intermediate 6 which converted to intermediate 7 by H_2O elimination. Reaction between 3-amino-1,2,4-triazole 1 and intermediate 7 led to intermediate 8, which transformed to intermediate 9 in the presence of the catalyst. Next, intermediate 9 gave tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 10 through cyclization reaction. Finally, intermediate 10 converted to [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4 by TSAT-catalyzed elimination of H_2O.

The results of this work are compared with those of the previously reported method in Table 3. Considering the reaction time and amount of catalyst, the presente work can be useful for preparation of these heterocyclic compounds.



Scheme 3. The proposed mechanism for the synthesis of product 4

CONCLUSIONS

In summary, we have introduced triethylaminium-*N*-sulfonic acid tetrachloroaluminate as a novel, highly efficient and homogeneous catalyst for the synthesis of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide *via* one-pot three-component reaction of 3-amino-1,2,4-triazole, arylaldehydes and acetoacetanilide under solvent-free conditions. The advantages of the presented work are high efficiency at relatively short reaction times, synthesis of the catalyst using available and inexpensive reactants, mild and environmentally benign conditions, easy work-up and no need to column chromatography.

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Table 3. Comparison Results of TSAT with Maltose [12]

Compound	Catalyst (mol%)	Conditions	Time (min)	Yield (%)
4a	Maltos (25)	Solvent-free, 80 ºC	25	91
	Maltos (25)	Solvent-free, 60 ºC	40	45
	TSAT (10)	Solvent-free, 60 ºC	10	85
4c	Maltos (25)	Solvent-free, 80 ºC	22	91
	TSAT (10)	Solvent-free, 60 ºC	12	90
4g	Maltos (25)	Solvent-free, 80 ºC	25	90
	TSAT (10)	Solvent-free, 60 ºC	10	90

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