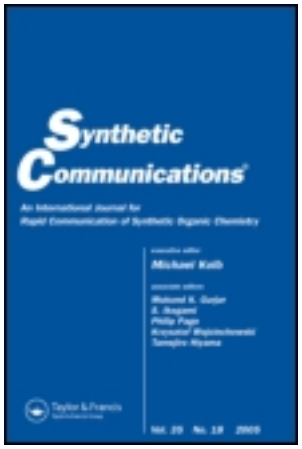


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Ionic Liquid-Mediated One-Pot Synthesis of 5-(Trifluoromethyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine Derivatives

Tuan-Jie Li [a], Chang-Sheng Yao [a], Chen-Xia Yu [a], Xiang-Shan Wang [a] & Shu-Jiang Tu [a]

[a] School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou Jiangsu, P. R. China

Accepted author version posted online: 31 Oct 2011.Version of record first published: 29 May 2012.

To cite this article: Tuan-Jie Li, Chang-Sheng Yao, Chen-Xia Yu, Xiang-Shan Wang & Shu-Jiang Tu (2012): Ionic Liquid-Mediated One-Pot Synthesis of 5-(Trifluoromethyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:18, 2728-2738

To link to this article: http://dx.doi.org/10.1080/00397911.2011.566460

Synthetic Communications®, 42: 2728–2738, 2012

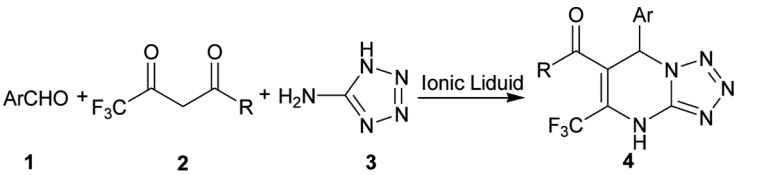
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.566460

IONIC LIQUID–MEDIATED ONE-POT SYNTHESIS OF 5-(TRIFLUOROMETHYL)-4,7-DIHYDROTETRAZOLO-[1,5-*a*]PYRIMIDINE DERIVATIVES

Tuan-Jie Li, Chang-Sheng Yao, Chen-Xia Yu, Xiang-Shan Wang, and Shu-Jiang Tu

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou Jiangsu, P. R. China

GRAPHICAL ABSTRACT



Abstract *A facile one-pot synthesis of 5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine derivatives is described via a three-component reaction of aldehydes with 5-aminotetrazole and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione in ionic liquid. This method has the advantages of short synthetic route, operational simplicities, good yields, ecofriendliness, and recyclability of the solvent.*

Keywords Cyclization; ionic liquid; tetrazolo[1,5-*a*]pyrimidine; trifluoromethylated

INTRODUCTION

In the past, ionic liquids as environmentally benign reaction media have been used in many organic transformations because of their many fascinating properties such as nonvolatility, recyclability, and nonflammability, and they offer homogenous media. On the other hand, multicomponent reactions (MCRs)[1] have been an increasingly valuable approach to drug-like heterocyclic compounds because of their intrinsic convergence, operational simplicity, and energy efficiency. Many procedures for the synthesis of heterocyclic compounds via MCRs in ionic liquids were well documented in the literature.[2]

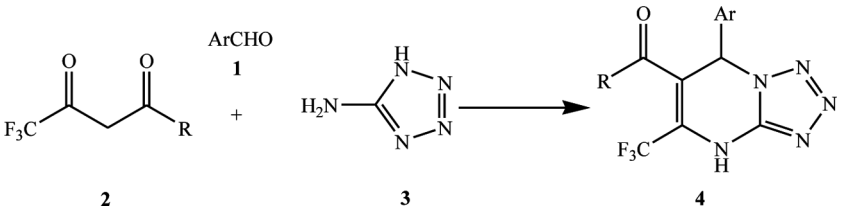
Received August 29, 2010.

Address correspondence to Chang-Sheng Yao, School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou Jiangsu 221116, P. R. China. E-mail: csyao@xznu.edu.cn

Compounds with the tetrazolo[1,5-*a*]pyrimidine core unit are known to exhibit various biological activities, such as antimicrobial activity,[3] anticonvulsant and antidepressant activities,[4] and antituberculosis activity.[5] They are also used as late sodium channel blockers,[6] transforming growth factor-β type I receptor (ALK5) inhibitors,[7] and human neutrophil elastase inhibitors in the treatment of pulmonary and cardiovascular diseases.[8] Hence, the synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives is of considerable interest for both organic chemistry and medicinal chemistry.

The introduction of a trifluoromethyl group into organic molecules often changes their physical, chemical, and physiological properties, which might result in an entirely new complementary biological activity. Subsequently, the interest of the pharmaceutical industry in trifluoromethyl-containing compounds has grown significantly.[9] Although many tetrazolo[1,5-*a*]pyrimidine derivatives were prepared by the Biginelli-like reactions of aromatic aldehyde and 5-aminotetrazole with acetoacetic acid derivatives or cyclic β-diketones,[10] only limited publications have been devoted to the synthesis of trifluoromethylated tetrazolo[1,5-*a*]pyrimidine. Pryadeina et al.[11] and Abelman et al.[12] respectively reported the syntheses of 5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives via the reactions of ethyl 4,4,4-trifluoro-3-oxobutanoate with aldehyde and 5-aminotetrazole. In their procedures, the cyclocondensations were realized by using corrosive hydrochloric acid and *p*-toluenesulfonic acid[11] and Et_3N[12] as catalysts, respectively. Furthermore, these reactions required harmful organic solvents and have some drawbacks such as tedious workup, poor yields, the narrow application scope of substrates, and two-stage routines. Therefore, the development of simple, convenient, and environmentally benign approaches for the synthesis of these compounds is still desirable.

However, to date, the preparation of 5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives by MCRs in ionic liquids was seldom described. With the aim of broadening the diversity of the heterocyclic compound library and in continuation of our recent interest in the synthesis of heterocyclic compounds via MCRs in ionic liquids,[13,2c,2d] herein we report an efficient and simple procedure for the direct synthesis of 5-(trifluoromethyl)-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives from the one-pot reaction of aldehydes with 5-aminotetrazole and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione in ionic liquid (Scheme 1).



Scheme 1. Three-component synthesis of 5-(trifluoromethyl)-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives.

RESULTS AND DISCUSSION

To search for the optimal solvent, the reaction of 4-bromobenzaldehyde (1 mmol) with 5-aminotetrazole (1 mmol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (1 mmol) was examined in different solvents at 100 °C. The results in Table 1 show that the [bmim$^+$][BF$_4^-$] is the best solvent for the synthesis of target product **4aa** among those examined. Thus, to further evaluate the effect of reaction temperature, the same reaction was performed in [bmim$^+$][BF$_4^-$] at temperatures ranging from 80 to 130 °C, with an increment of 10 °C each time. The results are summarized in Table 2. From the results, it can be seen that the yield of product **4aa** was increased, and the reaction time was shortened with the temperature increasing from 80 to 110 °C, whereas the yield was significently decreased when the temperature was further increased to 120 and 130 °C. Therefore, 110 °C was chosen as optimal reaction temperature for all further MCR reactions in ionic liquid.

Under these optimized reaction conditions ([bmim$^+$][BF$_4^-$], 110 °C), various kinds of benzaldehydes were reacted with **2** and **3** to give the corresponding 5-(trifluoromethyl)-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives **4**, and representative examples are shown in Table 3 (**4aa–4al**). To expand the scope of this method, the replacement of ethyl 4,4,4-trifluoro-3-oxobutanoate with 4,4,4-trifluoro-1-phenylbutane-1,3-dione was examined. To our delight, the reactions proceeded steadily to yield a series of new tetrazolo[1,5-*a*]pyrimidine compounds **4ba–4bg** (Table 3) with good yields at 80 °C. The results reveal that all of the benzaldehydes gave expected

Table 1. Solvent effect on the synthesis of **4aa**[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	[byp$^+$][BF$_4^-$]	7	79
2	**[bmim$^+$][BF$_4^-$]**	**7**	**85**
3	CH_3CN	9	75
4	EtOH	7	73
5	HOAc	8	68
6	DMF	8	70

[a][byp$^+$][BF$_4^-$],1-butylpyridinium tetrafluoroborate, [bmim$^+$][BF$_4^-$], 3-butyl-1-methyl-*1H*-imidazol-3-ium tetrafluoroborate.
[b]Isolated yield.

Table 2. Temperature effect on the synthesis of **4aa**[a]

Entry	Temp. (°C)	Time (h)	Yield[b] (%)
1	80	10	73
2	90	9	77
3	100	7	85
4	**110**	**7**	**89**
5	120	6	81
6	130	6	78

[a][bmim$^+$][BF$_4^-$] was used as solvent.
[b]Isolated yield.

Table 3. Synthesis of **4** in ionic liquid ([bmim$^+$][BF_4^-])

Products	Ar	R	Time (h)	Yield[a] (%)
4aa	4-BrC_6H_4	OC_2H_5	7	89
4ab	2,4-$Cl_2C_6H_3$	OC_2H_5	8	85
4ac	3-FC_6H_5	OC_2H_5	8	85
4ad	3-OH-4-$NO_2C_6H_3$	OC_2H_5	7	80
4ae	4-$N(CH_3)_2C_6H_4$	OC_2H_5	8	79
4af	2-FC_6H_4	OC_2H_5	8	86
4ag	3-BrC_6H_4	OC_2H_5	7	85
4ah	4-FC_6H_4	OC_2H_5	8	84
4ai	2-ClC_6H_4	OC_2H_5	7	87
4aj	3-ClC_6H_4	OC_2H_5	8	81
4ak	4-$NO_2C_6H_4$	OC_2H_5	8	88
4ba	4-$NO_2C_6H_4$	C_6H_5	9	85
4bb	3,4-$(OCH_2O)C_6H_3$	C_6H_5	9	82
4bc	3-FC_6H_4	C_6H_5	8	83
4bd	3-BrC_6H_4	C_6H_5	8	86
4be	2-ClC_6H_4	C_6H_5	7	81
4bf	2-FC_6H_4	C_6H_5	7	80
4bg	3-$NO_2C_6H_4$	C_6H_5	8	81
4bh	3,4,5-$(CH_3O)_3C_6H_3$	C_6H_5	9	78

[a]Isolated yield.

products in good yields, either bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group, alkoxyl group) under the same reaction conditions. Therefore we concluded that the electronic nature of the substituents has no significant effects on this reaction. The structure of the products **4aa** was established by x-ray crystallographic analysis, as shown in Fig. 1.

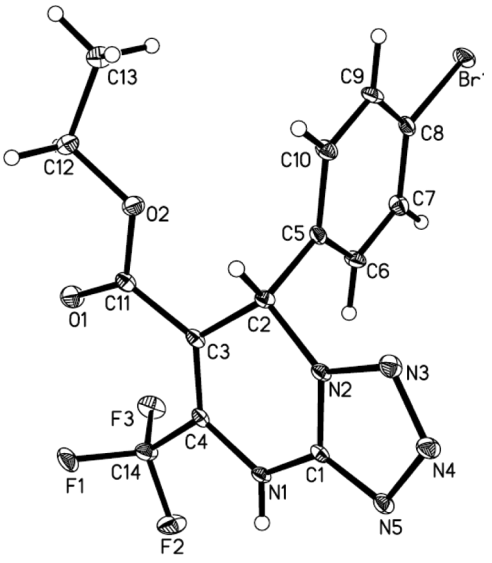


Figure 1. Crystal structure of **4ap**.

Table 4. Study on the reuse of ionic liquid ([bmim$^+$][BF$_4^-$])

Round	**4aa** yield[a] (%)
1	89
2	86
3	84
4	80

[a]Isolated yield.

To test the recyclability of the reaction solvent ([bmim$^+$][BF$_4^-$]), after completion of the model reaction of 4-bromobenzaldehyde, 5-aminotetrazole, and ethyl 4,4,4-trifluoro-3-oxobutanoate, the mixture was cooled to room temperature and poured into water, and precipitated products were separated by filtration. The filtrate was washed with acetic ester, concentrated under reduced pressure, and dried in vacuo at 100 °C for several hours to obtain the reusable solvent. The obtained solvent was used in subsequent reactions with a modest loss in its efficiency (Table 4).

In summary, we report here a facile, one-pot, three-component synthesis of 5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine derivatives from readily available aldhyde, 5-aminotetrazole, and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione in ionic liquid. This method has the advantages of short synthetic route, operational simplicities, good yields, ecofriendliness, and the recyclability of the solvent.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Tensor 27 spectrophotometer in KBr pellets and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on a Bruker DPX 400 instrument; elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument. Melting points were determined in open capillaries and are uncorrected. The single-crystal diffraction data were gathered on a Rigaku Saturn diffractometer.

General Procedure for the Synthesis of Ethyl 5-(Trifluoromethyl)-4,7-dihydro-7-aryltetrazolo[1,5-*a*]pyrimidine-6-carboxylate and (5-(Trifluoromethyl)-4,7-dihydro-7-aryltetrazolo[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone (4)

AryL aldehyde **1** (1.0 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dion **2** (1.0 mmol), and 5-aminotetrazole **3** (1.0 mmol) were mixed in 3 mL[bmim$^+$][BF$_4^-$] and stirred for a certain time (monitored by thin-layer chromatography, TLC) at 110 °C or 80 °C. The mixture was cooled to room temperature and poured into 20 mL of water. The solid product was collected by filtration and recrystallized from ethanol to give the pure compound **4**. The filtrate was washed with acetic ester several times, concentrated under reduced pressure, and dried in vacuo at 100 °C for several hours to give the reusable solvent.

Ethyl 7-(4-Bromophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo [1,5-*a*]pyrimidine-6-carboxylate 4aa

Pale white crystals, mp 230–232 °C. IR (KBr): 3190, 3064, 2979, 2926, 1736, 1650, 1588, 1488, 1440, 1408, 1344, 1283, 1257, 1177, 1101, 1072, 1012, 999, 835, 772, 735, 704, 644 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.83 (s, 1H, CH), 7.35 (d, $J = 8.4$ Hz, 2H, ArH), 7.62 (d, $J = 8.4$ Hz, 2H, ArH), 12.08 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}BrF_3N_5O_2$: C, 40.21; H, 2.65; N, 16.75. Found: C, 40.33; H, 2.77; N, 16.57.

Ethyl 7-(2,4-Dichlorophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo [1,5-*a*]pyrimidine-6-carboxylate 4ab

Pale white crystals, mp 206–207 °C. IR (KBr): 3172, 3064, 2966, 1737, 1709, 1594, 1561, 1475, 1433, 1371, 1342, 1290, 1056, 1194, 1104, 1051, 996, 863, 848, 761, 732, 699, 667, 637 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 7.15 (s, 1H, CH), 7.52 (d, $J = 8.0$ Hz, 1H, ArH), 7.61 (d, $J = 8.0$ Hz, 1H, ArH), 7.72 (s, 1H, ArH), 12.12 (br, 1H, NH). Anal. calcd. for $C_{14}H_{10}Cl_2F_3N_5O_2$: C, 41.20; H, 2.47; N, 17.16. Found: C, 41.11; H, 2.36; N, 17.21.

Ethyl 5-(Trifluoromethyl)-7-(3-fluorophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4ac

Pale white crystals, mp 195–196 °C. IR (KBr): 3173, 3069, 2988, 2931, 1715, 1607, 1558, 1489, 1469, 1454, 1435, 1374, 1339, 1308, 1259, 1232, 1189, 1164, 1084, 1017, 996, 918, 866, 804, 791, 758, 692, 648 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.85 (s, 1H, CH), 7.32–7.29 (m, 2H, ArH), 7.48 (d, $J = 7.2$ Hz, 2H, ArH), 12.06 (br,1H, NH). Anal. calcd. for $C_{14}H_{11}F_4N_5O_2$: C, 47.07; H, 3.10; N, 19.60. Found: C, 47.10; H, 3.17; N, 19.54.

Ethyl 5-(Trifluoromethyl)-4,7-dihydro-7-(3-hydroxy-4-nitrophenyl)tetrazolo [1,5-*a*]pyrimidine-6-carboxylate 4ad

Pale white crystals, mp 211–213 °C. IR (KBr): 3180, 3071, 2963, 1716, 1610, 1543, 1489, 1470, 1452, 1425, 1311, 1256, 1194, 1108, 1086, 1084, 996, 920, 843, 825, 791, 760, 688, 675, 646 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.87 (s, 1H, CH), 7.20 (s, 1H, ArH), 7.52 (s, 1H, ArH), 8.00 (s, 1H, ArH), 9.62 (s, 1H, OH), 12.04 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}F_3N_6O_5$: C, 42.01; H, 2.77; N, 21.00. Found: C, 42.12; H, 2.68; N, 21.10.

Ethyl 7-(4-(Dimethylamino)phenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4ae

Pale white crystals, mp 211–213 °C. IR (KBr): 3173, 3062, 2950, 2021,1721, 1602, 1561, 1532, 1476, 1442, 1425, 1365, 1341, 1292, 1250, 1196, 1105, 1087, 994, 873, 816, 785, 740, 704, 648, 627 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t,

$J = 7.2$ Hz, 3H, CH_3), 2.94 (s, 6H, $N(CH_3)_2$), 4.00 (q, $J = 7.6$ Hz, 2H, CH_2), 6.63 (s, 1H,CH), 7.00 (d, $J = 8.0$ Hz, 2H, ArH), 7.25 (d, $J = 8.0$ Hz, 2H, ArH), 11.52 (br, 1H, NH). Anal. calcd. for $C_{16}H_{17}F_3N_6O_2$: C, 50.26; H, 4.48; N, 21.98. Found: C, 50.31; H, 4.31; N, 21.87.

Ethyl 5-(Trifluoromethyl)-7-(2-fluorophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4af

Pale white crystals, mp 163–164 °C. IR (KBr): 3175, 3072, 2984, 2861, 1717, 1612, 1556, 1494, 1459, 1434, 1371, 1307, 1254, 1235, 1194, 1164, 1098, 1084, 993, 956, 881, 859, 787, 759, 730, 702, 686, 644 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.99 (s, 1H, CH), 7.11–7.17 (m, 2H, ArH), 7.32–7.37 (m, 2H, ArH), 11.96 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}F_4N_5O_2$: C, 47.07; H, 3.10; N, 19.60. Found: C, 47.11; H, 3.21; N, 19.56.

Ethyl 7-(3-Bromophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4ag

Pale white crystals, mp 219–220 °C. IR (KBr): 3176, 3067, 2976, 2936, 1730, 1602, 1562, 1478, 1434, 1366, 1346, 1287, 1252, 1165, 1143, 1105, 1091, 1018, 996, 886, 797, 776, 736, 723, 693, 670, 652 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.84 (s, 1H, CH), 7.35–7.39 (m, 2H, ArH), 7.59–7.64 (m, 1H, ArH), 7.68 (s, 1H, ArH), 11.99 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}BrF_3N_5O_2$: C, 40.21; H, 2.65; N, 16.75. Found: C, 40.18; H, 2.71; N, 16.73.

Ethyl 5-(Trifluoromethyl)-7-(4-fluorophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4ah

Pale white crystals, mp 206–208 °C. IR (KBr): 3217, 3065, 2994, 2934, 1735, 1609, 1561, 1513, 1468, 1433, 1343, 1290, 1239, 1202, 1160, 1102, 1082, 999, 878, 837, 784, 735, 704, 642 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 8.0$ Hz, 3H, CH_3), 4.00 (q, $J = 7.6$ Hz, 2H, CH_2), 6.79 (s, 1H, CH), 7.06–7.10 (m, 2H, ArH), 7.37 (d, $J = 8.0$ Hz, 2H, ArH), 11.78 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}F_4N_5O_2$: C, 47.07; H, 3.10; N, 19.60. Found: C, 47.11; H, 3.07; N, 19.55.

Ethyl 7-(2-Chlorophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate 4ai

Pale white crystals, mp 160–162 °C. IR (KBr): 3195, 3062, 2981, 1740, 1600, 1566, 1476, 1440, 1394, 1343, 1289, 1251, 1168, 1103, 1050, 1021, 995, 869, 797, 754, 734, 707, 680, 651 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 8.0$ Hz, 3H, CH_3), 4.00 (q, $J = 7.6$ Hz, 2H, CH_2), 7.18 (s, 1H, CH), 7.29–7.32 (m, 2H, ArH), 7.74–7.78 (m, 2H, ArH), 11.92 (br, 1H, NH). Anal. calcd. for $C_{14}H_{11}ClF_3N_5O_2$: C, 44.99; H, 2.97; N, 18.74. Found: C, 44.87; H, 2.83; N, 18.85.

Ethyl 7-(3-Chlorophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate 4aj

Pale white crystals, mp 203–204 °C. IR (KBr): 3177, 3068, 2978, 2937, 1731, 1603, 1562, 1480, 1438, 1393, 1368, 1347, 1288, 1253, 1164, 1143, 1105, 1020, 996, 891, 867, 798, 777, 737, 694, 652 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 8.0$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 6.77 (s, 1H, CH), 7.28 (s, 1H, ArH), 7.35–7.38 (m, 3H, ArH), 11.59 (br, 1H, NH). Anal. calcd for $C_{14}H_{11}ClF_3N_5O_2$: C, 44.99; H, 2.97; N, 18.74. Found: C, 44.85; H, 2.81; N, 18.96.

Ethyl 5-(Trifluoromethyl)-4,7-dihydro-7-(4-nitrophenyl)tetrazolo-[1,5-*a*]pyrimidine-6-carboxylate 4ak

Pale white crystals, mp 216–217 °C. IR (KBr): 3189, 3064, 2984, 1735, 1649, 1590, 1530, 1439, 1351, 1286, 1244, 1179, 1145, 1101, 1021, 999, 824, 780, 750, 725, 691, 649 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.00 (t, $J = 7.2$ Hz, 3H, CH_3), 4.00 (q, $J = 6.8$ Hz, 2H, CH_2), 7.03 (s, 1H, CH), 7.72 (d, $J = 8.4$ Hz, 2H, ArH), 8.26 (d, $J = 8.4$ Hz, 2H, ArH), 12.10 (br,1H, NH). Anal. calcd. for $C_{14}H_{11}F_3N_6O_4$: C, 43.76; H, 2.89; N, 21.87. Found: C, 43.63; H, 2.78; N, 21.75.

(5-(Trifluoromethyl)-4,7-dihydro-7-(4-nitrophenyl)tetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4ba

Pale white crystals, mp 215–217 °C. IR (KBr): 3184, 3089, 2849, 1673, 1597, 1531, 1451, 1432, 1400, 1349, 1284, 1255, 1198, 1175, 1146, 1088, 1000, 823, 760, 734, 697, 615 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 6.83 (s, 1H, CH), 7.42–7.39 (m, 5H, ArH), 7.66 (d, $J = 7.6$ Hz, 2H, ArH), 8.16 (d, $J = 7.6$ Hz, 2H, ArH), 12.10 (br, 1H, NH). Anal. calcd. for $C_{18}H_{11}F_3N_6O_3$: C, 51.93; H, 2.66; N, 20.19. Found: C, 51.81; H, 2.71; N, 20.25.

(7-(Benzo[*d*][1,3]dioxol-5-yl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4bb

Pale white crystals, mp 231–232 °C. IR (KBr): 3178, 3065, 2873, 1662, 1622, 1565, 1501, 1449, 1407, 1351, 1312, 1272, 1206, 1125, 1086, 1039, 998, 928, 802, 749, 655, 629 cm^{-1};^1H NMR (DMSO-d_6) (δ, ppm): 5.98 (d, $J = 6.4$ Hz, 2H, OCH_2O), 6.65 (dd, $J = 8.01$, 1.29 Hz, 1H, ArH), 6.70 (s, 1H, CH), 6.79 (d, $J = 8.0$ Hz, 1H, ArH), 6.84 (d, $J = 1.2$ Hz, 1H, ArH), 7.50 (t, $J = 7.6$ Hz, 2H, ArH), 7.67 (t, $J = 7.2$ Hz, 1H, ArH), 7.88 (d, $J = 7.6$ Hz, 2H, ArH), 12.04 (br, 1H, NH). Anal. calcd. for $C_{19}H_{12}F_3N_5O_3$: C, 54.95; H, 2.91; N, 16.86. Found: C, 54.87; H, 2.83; N, 16.95.

(5-(Trifluoromethyl)-7-(3-fluorophenyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4bc

Pale white crystals, mp 246–248 °C. IR (KBr): 3171, 3115, 3060, 2929, 2854, 1678, 1660, 1555, 1500, 1438, 1407, 1354, 1342, 1277, 1265, 1180, 1135, 1041, 991,

791, 694, 616 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 6.84 (s, 1H, CH), 7.21–7.29 (m, 2H, ArH), 7.46–7.55 (m, 4H, ArH), 7.66 (t, $J = 8.0$ Hz, 1H, ArH), 7.89 (d, $J = 7.2$ Hz, 2H, ArH), 12.00 (br, 1H, NH). Anal. calcd. for $C_{18}H_{11}F_4N_5O$: C, 55.53; H, 2.85; N, 17.99. Found: C, 55.47; H, 2.71; N, 18.12.

(7-(3-Bromophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4bd

Pale white crystals, mp 229–230 °C. IR (KBr): 3172, 3062, 2932, 2857, 1662, 1658, 1523, 1487, 1457, 1355, 1326, 1279, 1265, 1219, 1135, 1088, 996, 792, 697, 686, 624 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 6.84 (s, 1H, CH), 7.05 (d, $J = 8.0$ Hz, 1H, ArH), 7.20–7.10 (m, 2H, ArH), 7.31–7.37 (m, 1H, ArH), 7.48 (t, $J = 8.0$ Hz, 2H, ArH), 7.66 (t, $J = 7.2$ Hz, 1H, ArH), 7.87 (d, $J = 7.6$ Hz, 2H, ArH), 12.00 (br, 1H, NH). Anal. calcd. for $C_{18}H_{11}BrF_3N_5O$: C, 48.02; H, 2.46; N, 15.56. Found: C, 48.11; H, 2.32; N, 15.61.

(7-(2-Chlorophenyl)-5-(trifluoromethyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4be

Pale white crystals, mp 198–199 °C. IR (KBr): 3215, 3175, 3018, 2861, 1661, 1608, 1561, 1477, 1449, 1355, 1341, 1315, 1281, 1244, 1201, 1181, 1153, 1088, 995, 921, 846, 814, 769, 757, 719, 703, 687, 634 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 7.10 (s, 1H, CH), 7.28 (s, 2H, ArH), 7.32–7.36(m, 1H, ArH), 7.40 (d, $J = 8.0$ Hz, 1H, ArH), 7.50 (t, $J = 7.6$ Hz, 2H, ArH), 7.67 (t, $J = 7.2$ Hz, 1H, ArH), 7.89 (d, $J = 7.6$ Hz, 2H, ArH), 12.16 (br, 1H, NH). Anal. calcd. for $C_{18}H_{11}ClF_3N_5O$: C, 53.28; H, 2.73; N, 17.26. Found: C, 53.19; H, 2.69; N, 17.35.

(5-(Trifluoromethyl)-7-(2-fluorophenyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4bf

Pale white crystals, mp 192–194 °C. IR (KBr): 3173, 3068, 2856, 1656, 1605, 1558, 1494, 1459, 1450, 1341, 1319, 1234, 1200, 1098, 1086, 890, 846, 762, 694, 635 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 6.98 (s, 1H, CH), 7.11–7.19 (m, 2H, ArH), 7.24–7.28(m, 1H, ArH), 7.36–7.43(m, 1H, ArH), 7.50(t, $J = 7.6$ Hz, 2H, ArH), 7.67 (t, $J = 7.2$ Hz, 1H, ArH), 7.88(d, $J = 7.2$ Hz, 2H, ArH), 12.00(br, 1H, NH). Anal. calcd. for $C_{18}H_{11}F_4N_5O$: C, 55.53; H, 2.85; N, 17.99. Found: C, 55.61; H, 2.77; N, 18.03.

(5-(Trifluoromethyl)-4,7-dihydro-7-(3-nitrophenyl)tetrazolo-[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone 4bg

Pale white crystals, mp 234–236 °C. IR (KBr): 3170, 3069, 2930, 2877, 1683, 1657, 1608, 1539, 1482, 1450, 1422, 1353, 1281, 1264, 1199, 1166, 1085, 999, 932, 908, 931, 821, 809, 754, 733, 696, 684, 625 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 7.08 (s, 1H, CH), 7.48 (t, $J = 8.0$ Hz, 2H, ArH), 7.60–7.68 (m, 2H, ArH), 7.76 (d, $J = 7.6$ Hz, 1H, ArH), 7.90 (d, $J = 7.6$ Hz, 2H, ArH), 8.14–8.17(m, 1H, ArH), 8.20 (t, $J = 1.6$ Hz, 1H, ArH), 11.89 (br, 1H, NH). Anal. calcd. for $C_{18}H_{11}F_3N_6O_3$: C, 51.93; H, 2.66; N, 20.19. Found: C, 51.81; H, 2.59; N, 20.27.

(5-(Trifluoromethyl)-7-(3,4,5-trimethoxyphenyl)-4,7-dihydrotetrazolo-[1,5-a]pyrimidin-6-yl)(phenyl)methanone 4bh

Pale white crystals, mp 231–232 °C. IR (KBr): 3181, 3061, 2938, 2840, 1655, 1618, 1560, 1508, 1466, 1426, 1350, 1330, 1282, 1239, 1186, 1126, 1085, 1010, 820, 753, 653, 632 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.53 (s, 3H, OCH_3), 3.61 (s, 6H, $2 \times OCH_3$), 6.50 (s, 1H, CH), 6.89 (s, 2H, ArH), 7.46 (t, $J = 8.0$ Hz, 2H, ArH), 7.63 (t, $J = 8.0$ Hz, 1H, ArH), 7.87 (d, $J = 8.0$ Hz, 2H, ArH), 11.84 (br, 1H, NH). Anal. calcd. for $C_{21}H_{18}F_3N_5O_4$: C, 54.67; H, 3.93; N, 15.18. Found: C, 54.55; H, 3.84; N, 15.28.

X-Ray Crystallography for 4aa

Empirical formula $C_{14}H_{11}BrF_3N_5O_2$, $F_W = 418.19$, $T = 113(2)$ K, monoclinic, space group P 1 21/c 1, $a = 18.773(2)$ Å, $b = 10.4716(11)$ Å, $c = 7.8700(8)$ (4) Å, $\beta = 92.27(3)°$, $V = 1545.9(3)$ $Å^3$, $Z = 4$, $Dc = 1.797$ Mg/m^3, $\lambda(MoK\alpha) = 0.71073$ Å, $\mu = 2.713$ mm^{-1}, $F(000) = 832$. $2.17° < \theta < 27.86°$, $R = 0.0295$, $wR = 0.0714$. $S = 0.941$, Largest diff. Peak and hole: 0.431 and −0.823 e · $Å^{-3}$.

ACKNOWLEDGMENTS

We are grateful for financial support by the Natural Science Foundation of China (Nos. 20672090 and 200810102050), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (09KJA430003), the Natural Science Foundation of Xuzhou City (XM09B016), the Graduate Foundation of Xuzhou Normal University (09YLB030), and the Qing Lan Project (08QLT001).

REFERENCES

1. (a) Toure, B. B.; Hall, D. G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **2009**, *109*, 4439–4486; (b) Ganem, B. Strategies for innovation in multicomponent reaction design. *Acc. Chem. Res.* **2009**, *42*, 463–472; (c) Tietze, L. F.; Kinzel, T.; Brazel, C. C. The domino multicomponent allylation reaction for the stereoselective synthesis of homoallylic alcohols. *Acc. Chem. Res.* **2009**, *42*, 367–378.
2. (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Ionic liquids in heterocyclic synthesis. *Chem. Rev.* **2008**, *108*, 2015–2050; (b) Lingampalle, D.; Jawale, D.; Waghmare, R.; Mane, R. Ionic liquid–mediated, one-pot synthesis for 4-thiazolidinones. *Synth. Commun.* **2010**, *40*, 2397–2401; (c) Wang, X. S.; Zhang, M. M.; Jiang, H.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. An improved and benign synthesis of 9,10-diarylacridin-1,8-dione and indenoquinoline derivatives from 3-arylamino-5,5-dimethyl cyclohex-2-enone, arylaldehyde, and 1,3-dicarbonyl compound in ionic liquid medium. *Synthesis* **2006**, 4187–4199; (d) Wang, X. S.; Yang, K.; Zhang, M. M.; Yao, C. S. Synthesis of 2-arylquinazolin-4(*3H*)-one derivatives catalyzed by iodine in [$bmim^+$][BF_4^-]. *Synth. Commun.* **2010**, *40*, 2633–2646.
3. (a) Gein, V. L.; Mishunin, V. V.; Tsyplyakova, E. P.; Vinokurova, O. V.; Vakhrin, M. I. Synthesis and antimicrobial activity of methyl-7-aryl(heteryl)-6-(2-thienoyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylates. *Pharm. Chem. J.* **2009**, *43*, 652–654; (b) Bondock, S.; Fadaly, W.; Metwally, M. A. Enaminonitrile in heterocyclic synthesis:

Synthesis and antimicrobial evaluation of some new pyrazole, isoxazole, and pyrimidine derivatives incorporating a benzothiazole moiety. *Eur. J. Med. Chem.* **2009**, *44*, 4813–4818.
4. Wang, H. J.; Wei, C. X.; Deng, X. Q.; Li, F. L.; Quan, Z. S. Synthesis and evaluation on anticonvulsant and antidepressant activities of 5-alkoxy-tetrazolo[1,5-*a*]quinazolines. *Arch. Pharm.* **2009**, *342*, 671–675.
5. Pereyaslavskaya, E. S.; Potemkin, V. A.; Bartashevich, E. V.; Grishina, M. A.; Rusinov, G. L.; Fedorova, O. V.; Zhidovinova, M. S.; Ovchinnikova, I. G. Theoretical investigation of the antituberculosis activity of compounds of the dihydropyrimidine series. *Pharm. Chem. J.* **2008**, *42*, 622–625.
6. Abelman, M.; Jiang, R.; Zablocki, J. Preparation of tetrazolo[1,5-*a*]pyrimidine-6-carboxylate derivatives and analogs as late sodium channel blockers. U.S. Patent 2009181986, 2009.
7. Ren, J. X.; Li, L. L.; Zou, J.; Yang, L.; Yang, J. L.; Yang, S. Y. Pharmacophore modeling and virtual screening for the discovery of new transforming growth factor-type I receptor (ALK5) inhibitors. *Eur. J. Med. Chem.* **2009**, *44*, 4259–4265.
8. Von Nussbaum, F.; Karthaus, D.; Anlauf, S.; Delbeck, M.; Li, V. M. J.; Meibom, D.; Lustig, K. Preparation of tetrazolopyrimidines as human neutrophil elastase inhibitors in treatment of pulmonary and cardiovascular diseases. WO Patent 2010078953, 2010.
9. (a) KirK, K. L. Fluorine in medicinal chemistry: Recent therapeutic applications of fluorinated small molecules. *J. Fluorine Chem.* **2006**, *127*, 1013–1029; (b) Himaya, T. *Organofluorine Compounds*; Springer-Verlag; Berlin, 2001; (c) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society; Washington, DC, 1996; (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier; Amsterdam, 1993; (e) Jiang, B.; Si, Y.-C. Zn(II)-mediated alkynylation–cyclization of o-trifluoroacetyl anilines: One-pot synthesis of 4-trifluoromethyl-substituted quinoline derivatives. *J. Org. Chem.* **2002**, *67*, 9449–9451.
10. (a) Zeng, L. Y.; Cai, C. Iodine-catalyzed one-pot multicomponent synthesis of a library of compounds containing tetrazolo[1,5-*a*]pyrimidine core. *J. Comb. Chem.* **2010**, *12*, 35–40; (b) Gein, V. L.; Zamaraeva, T. M.; Zorina, A. A.; Levandovskaya, E. B.; Nosova, N. V.; Vakhrin, M. I. Synthesis of N,N-dimethyl(diethyl)-7-aryl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides. *Russ. J. Org. Chem.* **2009**, *45*, 942–943; (c) Yao, C. S.; Lei, S.; Wang, C. H.; Yu, C. X.; Tu, S. J. Solvent-free synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters catalyzed by sulfamic acid. *J. Heterocyc. Chem.* **2008**, *45*, 1609–1613; (d) Gein, V. L.; Gein, L. F.; Tsyplyakova, E. P.; Panova, O. S. Synthesis of 6-acyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylic acids and their methyl esters. *Russ. J. Org. Chem.* **2007**, *43*, 1382–1386; (e) Gladkov, E.; Sirko, S.; Khanetskii, B.; Lukinova, E.; Desenko, S. Multicomponent facile synthesis of novel dihydroazolopyrimidinyl carbamides. *Chem. Pap.* **2007**, *61*, 146–149; (f) Chebanov, V. A.; Sakhno, Y. I.; Desenko, S. M.; Shishkina, S. V.; Musatov, V. I.; Shishkin, O. V.; Knyazeva, I. V. Three-component procedure for the synthesis of 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids. *Synthesis* **2005**, 2597–2601.
11. Pryadeina, M. V.; Burgart, Y. V.; Saloutin, V. I.; Kodess, M. I.; Ulomskii, E. N.; Rusinov, V. L. Synthesis of 7-alkyl(aryl)-6-alkoxycarbonyl-5-fluoroalkyl-1,2,4-tri(tetr)azolo [1,5-*a*]pyrimidines. *Russ. J. Org. Chem.* **2004**, *6*, 902–907.
12. Abelman, M.; Jiang, R.; Zablocki, J. Preparation of dihydropyridine derivatives and analogs as late sodium channel blockers. WO Patent 2009006580, 2009.
13. (a) Yao, C. S.; Lei, S.; Wang, C. H.; Li, T. J.; Yu, C. X.; Wang, X. S.; Tu, S. J. Three-component synthesis of 4-aryl-*1H*-pyrimido[1,2-*a*]benzimidazole derivatives in ionic liquid. *J. Heterocycl. Chem.* **2010**, *47*, 26–32; (b) Wang, X. S.; Zhang, M. M.; Jiang, H.; Yao, C. S.; Tu, S. J. Three-component green synthesis of N-arylquinoline derivatives in ionic liquid [$bmim^+$][BF_4^-]: Reactions of arylaldehyde, 3-arylamino-5,5-dimethylcyclohex-2-enone, and active methylene compounds. *Tetrahedron* **2007**, *63*, 4439.