Three-Component Uncatalyzed Eco-Friendly Reactions for One-Pot Synthesis of 4,7-Dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine Derivatives

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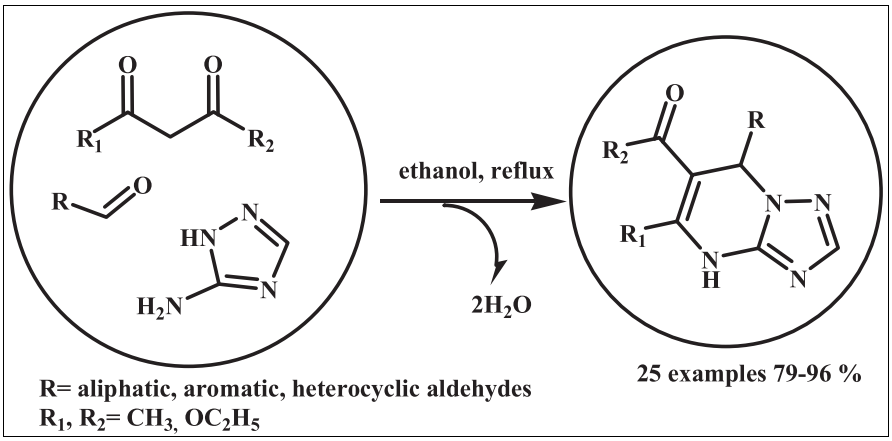

A three-component system of one-pot synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives using condensation of 1,3-dicarbonyl compounds, aldehydes, and 5-amino[1,2,4]triazole in ethanol without any catalyst was reported in high yields via simple, efficient, and environmentally friendly process. The method reported herein considered a green process; this method has significant advantages of simple workup procedure, excellent yield, minimal environmental pollution, and short reaction time over classical reported methods.

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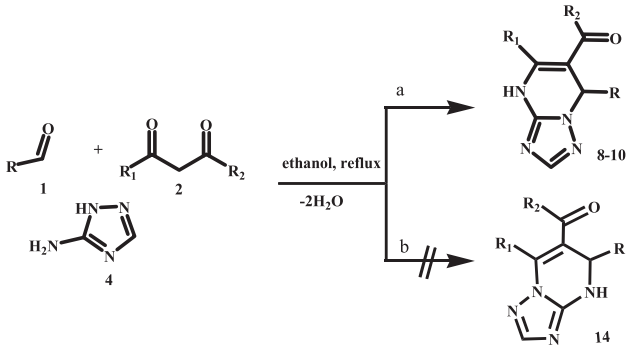
INTRODUCTION

Green chemistry has become a subject of intensive research and important focuses within organic synthesis; thus, it attracts more scientists and researchers to work in this area. Also, green chemistry and its applications [1–7] in synthetic organic chemistry are to reduce the use of hazardous chemicals and formation of waste products that concern the environment [8–11]. In recent years, most researchers have been focusing on developing environmentally benign reactions. The various methodologies and routes have been developed for these purposes, from the requirements of a green synthesis methodology is the use of eco-friendly solvents, catalyst, and nontoxic chemicals [12–17]. The environmentally benign synthetic methods have received considerable attention, and some uncatalyzed reactions have been developed [18]. In the green chemistry, it is the marriage of economic and environmental aspects for the new reactions. Thus, many researchers tend to use multicomponent reaction strategy. It has been found that the three-component condensation constitutes an especially attractive synthetic strategy for rapid efficient route because the products are formed in single step without isolation of any intermediate, thus reducing reaction time, energy, and material use [19–39]. The Biginelli reaction [40,41] is one of the most important examples of multicomponent reaction for the synthesis of dihydropyrimidinone due to its wide range of biological activities [42–45]. The reactions described herein are comparable intrinsically with the Biginelli reaction type, using analogous amino azoles as alternative to urea/thiourea in classical Biginelli reaction [38,39,46–48]. However, work in this field has not lost current interest because of varying reagents, catalysts, and conditions used in similar reactions. Recently, the Biginelli reaction was developed for the synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine and its derivatives because of their remarkable diverse therapeutic and pharmacological activities such as analgesic, anticonvulsant, anti-inflammatory, antimalarials, antimicrobial, and antifungal effects [49–52]. Owing to the demand for an environmentally benign, green methodologies and continuing the interest for the synthesis of heterocyclic compounds [53–58], the synthesis of [1,2,4] triazolo[1,5-*a*]pyrimidine via a three-component system under reflux without any catalyst have been reported herein (Scheme 1).

RESULTS AND DISCUSSION

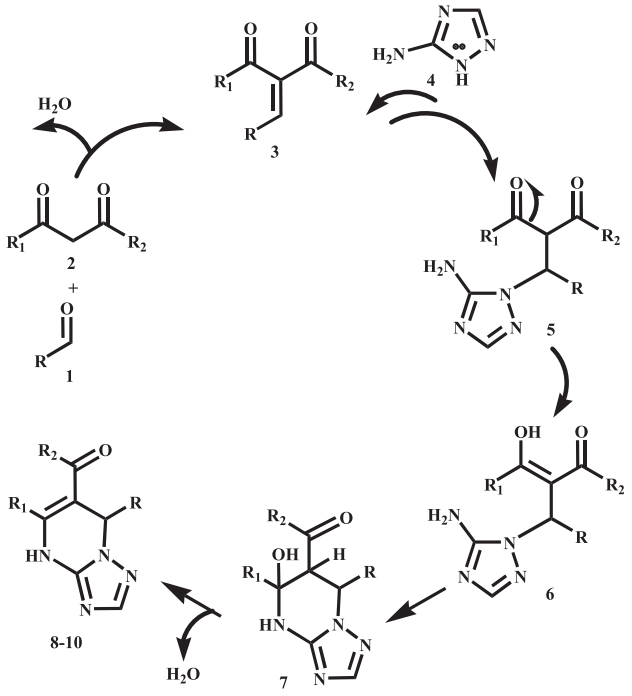
The general method for the synthesis of [1,2,4]triazolo [1,5-*a*]pyrimidine involves cyclocondensation of aminotriazole with α,β-unsaturated carbonyl compounds [59,60]. As a part of our interest in using the simple methods for

Scheme 1. Synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives.

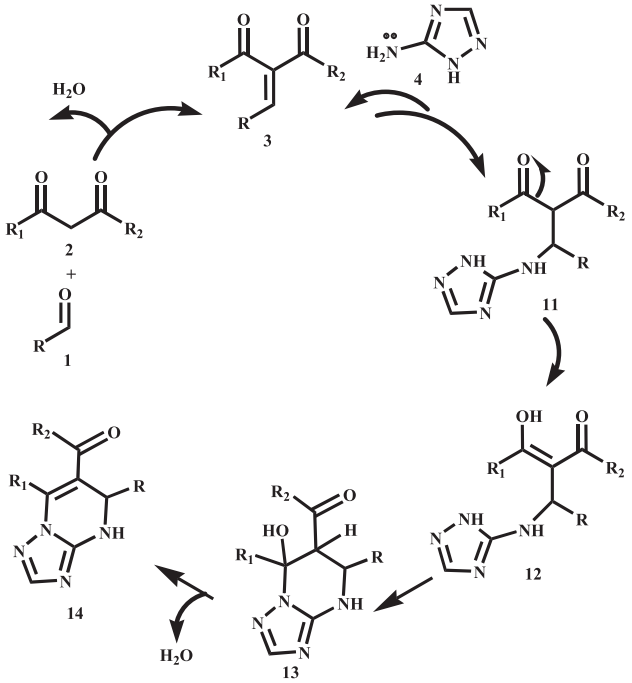


the synthesis of various heterocyclic compounds [61–64], a very simple, green, and efficient method for the development of a one-pot synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives by three-component condensation of aliphatic, various aromatic, and heterocyclic aldehydes with 1,3-dicarbonyl compounds (ethyl acetoacetate, acetyl acetone, and diethyl malonate) and 5-amino[1,2,4]triazole have been reported. The reaction was carried out under reflux in ethanol without any catalyst. The progress of the reaction was monitored by TLC; after completion, the reaction mixture was cooled at room temperature, and the solvent was concentrated under vacuum. The obtained solid was filtered off, dried, and recrystallized from proper solvent (see Experimental section). The structure of the products was confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS spectroscopy, and elemental analysis. The previous method was examined by the use of several aldehydes with different 1,3-dicarbonyl compounds under the same reaction conditions. It has been found that the reaction proceeds very easy to give [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives in excellent high yields. A proposed mechanism to account for the formation of [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives is shown in Schemes 2 and 3. Two possible isomeric structures of 7-aryl/alkyl-4,7-dihydro[1,2,4]triazolo [1,5-*a*]pyrimidine [8–10] and 5-aryl/alkyl-4,5-dihydro [1,2,4]triazolo[1,5-*a*]pyrimidine [14] could be obtained theoretically according to the plausible mechanism for the synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine. A pyrimidine ring could be formed with participation of NH or NH_2 of 3-amino[1,2,4]triazole with arylidene dicarbonyl compounds **3** to form two expected isomers **8–10** and/or **14**. As a start, the aldehyde is condensed with active methylene of 1,3-dicarbonyl compounds forming α,β-unsaturated carbonyl compounds **3** *in situ* via Knoevenagel reaction; this is followed by Michael reaction of NH of 5-amino[1,2,4]-triazole **4** with α, β-unsaturated carbonyl compounds **3** forming the intermediates **5–7** (Scheme 2) or by addition of NH_2 of 5-amino[1,2,4]triazole **4** with α,β-unsaturated carbonyl compounds **3** to form the intermediates **11–13** (Scheme 3). Finally, after intramolecular cyclization, the expected isomeric products **8–10** or **14** are formed.

Scheme 2. (Route a) Plausible mechanism for the formation of 7-aryl/alkyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine derivatives.



Scheme 3. (Route b) Plausible mechanism for the formation of 5-aryl/alkyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine derivatives.



Regioselectivity of the reaction with participation of NH is the subject of studies, and the preference was to produce the isomers **8–10** referring to [36–39,46–48].

CONCLUSION

In summary, the one-pot synthesis of three-component reaction of aldehydes, 5-amino[1,2,4]triazole, and 1,3-dicarbonyl compounds that were refluxed in ethanol for appropriate time afforded [1,2,4]triazolo [1,5-*a*]pyrimidine derivatives in good to excellent yields as well as an improved Biginelli reaction via Knoevenagel and Michael reactions.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected, IR spectra were recorded as potassium bromide pellets using an FTIR unit Bruker Vector 22 spectrophotometer, ^{1}H NMR spectra were obtained in deuterated dimethyl sulfoxide as solvent at 300 MHz and 75 MHz, respectively, on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Microanalytical Center of Cairo University, Egypt.

General procedure for the synthesis of ethyl 4,7-dihydro-7-substituted-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate 8a–i. A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), and 5-amino[1,2,4]triazole (1 mmol) in 10-mL ethanol was refluxed; after 3 h, a precipitate was separated during reflux. After completion of the reaction, the precipitate was collected by filtration and recrystallized from a proper solvent (Table 1).

Ethyl 4,7-dihydro-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate 8a. mp 145–147°C (150–152°C ref. [36]); Yield: 0.70 g, 80% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3277 (NH), 1710 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.19 (t, 3H, CH_3), 1.43 (d, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.99 (q, 2H, CH_2), 5.46 (q, 1H, $C_{(7)}H$), 7.77 (s, 1H, $C_{(2)}H$), 10.59 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 21.62, 31.49, 47.77, 111.43, 150.11, 150.42, 151.23, 199.12. MS (*m/z* %) = 222 (M^+, 40%). *Anal*. Calcd for $C_{10}H_{14}N_4O_2$ (222.24): C, 54.04%; H, 6.35%; N, 25.21%. Found: C, 54.44%; H, 6.39%; N, 25.32%.

Ethyl 4,7-dihydro-5-methyl-7-phenyl-[1,2,4]triazolo[1,5-a] pyrimidine-6-carboxylate 8b. mp 190–192°C (190–192°C ref. [36]); Yield: 0.84 g, 96% (dioxane/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3289 (NH), 1713 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.12 (t, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.88 (q, 2H, CH_2), 6.36 (s, 1H, $C_{(7)}H$), 7.44 (m, 5H, Ph), 7.87 (s, 1H, $C_{(2)}H$), 10.89 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 11.76, 31.49, 47.79, 112.55, 125.70, 128.34, 129.11, 137.32, 150.12, 150.21, 155.32, 199.86. MS (*m/z* %) = 284 (M^+, 45%). *Anal*. Calcd for $C_{15}H_{16}N_4O_2$ (284.31): C, 63.37%; H, 5.67%; N, 19.71%. Found: C, 63.47%; H, 5.53%; N, 19.80%.

Ethyl 7-(4-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 8c. mp 260–262°C; Yield: 0.76 g, 87% (dioxane/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3299 (NH), 1710 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.31(t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.19 (q, 2H, CH_2), 5.88 (s, 1H, $C_{(7)}H$), 7.44 (m, 4H, Ph), 8.22 (s, 1H, $C_{(2)}H$), 9.56 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.43, 11.78, 31.46, 47.88, 112.54, 128.34, 129.11, 131.22, 137.32, 150.11, 150.21, 155.33, 199.84. MS (*m/z* %) = 318 (M^+, 55%). *Anal*. Calcd for $C_{15}H_{15}ClN_4O_2$ (318.76): C, 56.52%; H, 4.74%; N, 17.58%. Found: C, 56.59%; H, 4.80%; N, 17.63%.

Ethyl 4,7-dihydro-7-(4-methoxyphenyl)-5-methyl-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 8d. mp 240–242°C; Yield: 0.84 g, 96% (dioxane). IR (KBr): ν_{max} (in cm^{-1}) 3287 (NH), 1705 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.33 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.36 (s, 3H, OCH_3), 4.17 (q, 2H, CH_2), 5.86 (s, 1H, $C_{(7)}H$), 7.43 (m, 4H, Ph), 8.20 (s, 1H, $C_{(2)}H$), 9.58 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 11.76, 31.49, 47.79, 55.32, 112.55, 114.21, 130.34, 130.55, 150.12, 150.21, 155.32, 157.32, 199.86. MS (*m/z* %) = 314 (M^+, 50%). *Anal*. Calcd for $C_{16}H_{18}N_4O_3$ (314.34): C, 61.13%; H, 5.77%; N, 17.82%. Found: C, 61.18%; H, 5.67%; N, 17.89%.

Ethyl 4,7-dihydro-7-(4-methylphenyl)-5-methyl-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 8e. mp 235–237°C; Yield: 0.67 g, 77% (dioxane/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3290 (NH), 1709 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.25 (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.19 (q, 2H, CH_2), 5.88 (s, 1H, $C_{(7)}H$), 7.49 (m, 4H, Ph), 8.29 (s, 1H, $C_{(2)}H$), 9.68 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 11.78, 25.33, 31.49, 47.84, 112.54, 128.34, 129.11, 131.22, 137.36, 150.12,

Table 1

Ethyl acetoacetate as 1,3-dicarbonyl compounds with 3-amino triazole and aldehydes[a] for the synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine **8a–i** in refluxing ethanol.[b]

Entry	Product[c]	R	R_1	R_2	Time (h)	mp (°C)	Yield (%)[d]
1	**8a**	CH_3	CH_3	OC_2H_5	4	142	80
2	**8b**	C_6H_5	CH_3	OC_2H_5	4	190	96
3	**8c**	4-Cl-C_6H_4	CH_3	OC_2H_5	3	260	87
4	**8d**	4-CH_3-C_6H_4	CH_3	OC_2H_5	3	235	96
5	**8e**	4-CH_3O-C_6H_4	CH_3	OC_2H_5	3	240	77
6	**8f**	4-N$(CH_3)_2C_6H_4$	CH_3	OC_2H_5	4	225	95
7	**8g**	4-NO_2-C_6H_4	CH_3	OC_2H_5	4	195	88
8	**8h**	2-$NO_2C_6H_4$	CH_3	OC_2H_5	3	220	76
9	**8i**	2-Thienyl	CH_3	OC_2H_5	4	195	88

[a]Various aldehydes (aliphatic, aromatic, and heterocyclic).
[b]The reaction occurred in ethanol without any catalyst.
[c]Structural assignments of the products were based on their IR, ^{1}HNMR, and MS.
[d]Isolated yields.

150.21, 155.32, 199.86. MS (*m/z* %) = 298 (M^+, 55%). *Anal*. Calcd for $C_{16}H_{18}N_4O_2$ (298.34): C, 64.41%; H, 6.08%; N, 18.78%. Found: C, 64.49%; H, 6.78%; N, 18.85%.

Ethyl 7-(4-(dimethylamino)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate 8f. mp 225–227°C; Yield: 0.83 g, 95% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3298 (NH), 1710 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.31 (t, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.38 (s, 6H, $2CH_3$), 4.13 (q, 2H, CH_2), 5.80 (s, 1H, $C_{(7)}$H), 7.42 (m, 4H, Ph), 8.24 (s, 1H, $C_{(2)}$H), 9.66 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 11.76, 31.49, 47.75, 55.37, 40.21, 112.55, 114.21, 130.37, 130.57, 150.12, 150.21, 155.32, 157.32, 199.86. MS (*m/z* %) = 327 (M^+, 59%). *Anal*. Calcd for $C_{17}H_{21}N_5O_2$ (327.38): C, 62.37%; H, 6.47%; N, 21.39%. Found: C, 62.27%; H, 6.55%; N, 21.47%.

Ethyl 4,7-dihydro-5-methyl-7-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate 8g. mp 195–197°C; Yield: 0.77 g, 88% (dioxane/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3298 (NH), 1707 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.34 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.84 (s, 1H, $C_{(7)}$H), 7.40 (m, 4H, Ph), 8.25 (s, 1H, $C_{(2)}$H), 9.67 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 11.78, 31.49, 47.79, 112.55, 114.22, 130.32, 130.57, 150.13, 150.21, 155.32, 157.32, 199.86. MS (*m/z* %) = 329 (M^+, 50%). *Anal*. Calcd for $C_{15}H_{15}N_5O_4$ (329.11): C, 54.71%; H, 4.59%; N, 21.27%. Found: C, 54.78%; H, 4.65%; N, 21.35%.

Ethyl 4,7-dihydro-5-methyl-7-(2-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate 8h. mp 220–222°C; Yield: 0.66 g, 76% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3289 (NH), 1705 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.37 (t, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.85 (s, 1H, $C_{(7)}$H), 7.42 (m, 4H, Ph), 8.25 (s, 1H, $C_{(2)}$H), 9.68 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.43, 11.77, 31.49, 47.79, 112.55, 114.22, 130.32, 130.59, 150.13, 150.21, 155.32, 157.37, 199.89. MS (*m/z* %) = 329 (M^+, 50%). *Anal*. Calcd for $C_{15}H_{15}N_5O_4$ (329.11): C, 54.71%; H, 4.59%; N, 21.27%. Found: C, 54.77%; H, 4.66%; N, 21.34%.

Ethyl 4,7-dihydro-5-methyl-7-(thiophene-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate 8i. mp 195–197°C; Yield: 0.77 g, 88% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3269 (NH), 1708 (CO); ^{1}H NMR (δ ppm, DMSO-d_6): 1.34 (s, 6H, $2CH_3$), 5.83 (s, 1H, $C_{(7)}$H), 6.11 (d, 1H, $C_{(3)}$H thienyl), 6.32 (d, 1H, $C_{(4)}$H thienyl), 6.45 (d, 1H, $C_{(5)}$H thienyl), 8.21 (s, 1H,$C_{(2)}$H), 9.76 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.42, 11.73, 31.49, 47.75, 55.37, 40.21, 112.55, 122.21, 125.37, 125.57, 150.21, 155.32, 157.32, 199.86. MS (*m/z* %) = 291 (M + 1, 45%). *Anal*. Calcd for $C_{13}H_{14}N_4O_2S$ (290.34): C, 53.78%; H, 4.86%; N, 19.30%. Found: C, 53.89%; H, 4.99%; N, 19.45%.

General procedure for the synthesis of 1-(4,7-dihydro-5-methyl-7-substituted[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)ethanone 9a–h. Aldehyde (1 mmol), aectylacetone (1 mmol) and 5-amino [1,2,4]triazole (1 mmol) in 10 ml ethanol was heated at 90°C for the appropriate time as mentioned in Table 2. After the completion of reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure, the resulting solid product was triturated with methanol and filtered, recrystallized from proper solvent.

1-(5,7-Dimethyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)ethanone 9a. mp 170–172°C; Yield: 0.70 g, 80% (EtOH/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3267 (NH); ^{1}H NMR (δ ppm, DMSO-d_6): 1.43 (s, 3H, CH_3), 1.63 (d, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.40 (q, 1H, $C_{(7)}$H), 7.79 (s, 1H, $C_{(2)}$H), 10.57 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.43, 15.22, 21.62, 56.77, 106.32, 138.21, 150.11, 151.23. MS (*m/z* %) = 164 (M^+, 66%). *Anal*. Calcd for $C_8H_{12}N_4$ (164.21): C, 58.51%; H, 7.37%; N, 34.12%. Found: C, 58.55%; H, 7.27%; N, 34.22%.

1-(4,7-Dihydro-5-methyl-7-phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)ethanone 9b. mp 265–267°C; Yield: 0.83 g, 95% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3280 (NH); ^{1}H NMR (δ ppm, DMSO-d_6): 1.40 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 5.43 (s, 1H, $C_{(7)}$H), 7.27 (s, 1H, $C_{(2)}$H), 7.44 (m, 4H, Ph), 10.09 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 56.77, 106.50, 125.70, 128.77, 129.11, 137.32, 138.32, 150.21, 151.54. MS (*m/z* %) = 226 (M^+, 49%). *Anal*. Calcd for $C_{13}H_{14}N_4$ (226.12): C, 69.00%; H, 6.24%; N, 24.76%. Found: C, 69.09%; H, 6.34%; N, 24.65%.

1-(7-(4-Chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)ethanone 9c. mp 230–232°C; Yield: 0.83 g, 95% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3298 (NH); ^{1}H NMR (δ ppm, DMSO-d_6): 1.28 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 5.87 (s, 1H, $C_{(7)}$H), 7.42 (m, 4H, Ph), 8.21 (s, 1H, $C_{(2)}$H), 9.56 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 56.77, 106.50, 114.43, 129.11, 137.32, 138.32, 141.55, 150.21, 151.54. MS (*m/z* %) = 260 (M^+, 67%). *Anal*. Calcd for

Table 2

Acetylacetone as 1,3-dicarbonyl compounds with 3-amino triazole and aldehyde[a] for the synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine **9a–h** in refluxing ethanol.[b]

Entry	Product[c]	R	R_1	R_2	Time (h)	mp (°C)	Yield (%)[d]
1	**9a**	CH_3	CH_3	CH_3	5	170	80
2	**9b**	C_6H_5	CH_3	CH_3	4	265	95
3	**9c**	4-Cl-C_6H_4	CH_3	CH_3	3	230	95
4	**9d**	4-CH_3-C_6H_4	CH_3	CH_3	4	255	79
5	**9e**	4-CH_3O-C_6H_4	CH_3	CH_3	4	260	81
6	**9f**	4-$N(CH_3)_2C_6H_4$	CH_3	CH_3	5	285	80
7	**9g**	2-$NO_2C_6H_4$	CH_3	CH_3	5	280	79
8	**9h**	2-Thienyl	CH_3	CH_3	5	215	78

[a]Various aldehydes (aliphatic, aromatic, and heterocyclic).
[b]The reaction occurred in ethanol without any catalyst.
[c]Structural assignments of the products were based on their IR, ^{1}HNMR, and MS.
[d]Isolated yields.

$C_{13}H_{13}ClN_4$ (260.72): C, 59.89%; H, 5.03%; N, 21.49%. Found: C, 59.77%; H, 5.12%; N, 21.37%.

1-(4,7-Dihydro-7-(4-methoxyphenyl)-5-methyl-[1,2,4]triazolo [1,5-a]pyrimidin-6-yl)ethanone 9d. mp 260–267°C; Yield: 0.69 g, 79% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3286 (NH); ^1H NMR (δ ppm, DMSO-d_6): 1.33(s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.37 (s, 3H, OCH_3), 5.82 (s, 1H, $C_{(7)}H$), 7.43 (m, 4H, Ph), 8.23 (s, 1H, $C_{(2)}H$), 9.50 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 32.22, 56.77, 106.50, 114.43, 129.12, 137.32, 138.32, 139.55, 150.21, 151.55. MS (*m/z* %) = 256 (M^+, 62%). *Anal*. Calcd for $C_{14}H_{16}N_4O$ (256.30): C, 65.61%; H, 6.29%; N, 21.86%. Found: C, 65.55%; H, 6.34%; N, 21.98%.

1-(4,7-Dihydro-5-methyl-7-(p-tolyl)-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)ethanone 9e. mp 255–257°C; Yield: 0.71 g, 81% (dioxane). IR (KBr): ν_{max} (in cm^{-1}) 3290 (NH); ^1H NMR (δ ppm, DMSO-d_6): 1.25 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 5.86 (s, 1H, $C_{(7)}H$), 7.42 (m, 4H, Ph), 8.25 (s, 1H, $C_{(2)}H$), 9.67 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 23.11, 56.73, 106.56, 114.43, 129.11, 137.32, 138.39, 141.55, 150.21, 151.59. MS (*m/z* %) = 240 (M^+, 55%). *Anal*. Calcd for $C_{14}H_{16}N_4$ (240.30): C, 69.97%; H, 6.71%; N, 23.32%. Found: C, 69.85%; H, 6.65%; N, 23.44%.

1-(7-(4-(Dimethylamino)phenyl)-4,7-dihydro-5-methyl-[1,2,4] triazolo[1,5-a]pyrimidin-6-yl)ethanone 9f. mp 285–287°C; Yield: 0.70 g, 80% (dioxane). IR (KBr): ν_{max} (in cm^{-1}) 3287 (NH); ^1H NMR (δ ppm, DMSO-d_6): 1.31 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 5.82 (s, 1H, $C_{(7)}H$), 7.43 (m, 4H, Ph), 8.22 (s, 1H, $C_{(2)}H$), 9.69 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 40.12, 56.77, 106.58, 114.43, 129.11, 137.33, 138.32, 141.59, 150.21, 151.86. MS (*m/z* %) = 269 (M^+, 60%). *Anal*. Calcd for $C_{15}H_{19}N_5$ (269.16): C, 66.89%; H, 7.11%; N, 26.00%. Found: C, 66.78%; H, 7.24%; N, 26.21%.

1-(4,7-Dihydro-5-methyl-7-(2-nitrophenyl)-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)ethanone 9g. mp 280–282°C; Yield: 0.69 g, 79% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3279 (NH); ^1H NMR (δ ppm, DMSO-d_6): 1.86 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.87 (s, 1H, $C_{(7)}H$), 7.42 (m, 4H, Ph), 8.23 (s, 1H, $C_{(2)}H$), 9.67 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 47.77, 106.51, 128.43, 129.11, 137.32, 138.33, 141.55, 150.21, 151.57. MS (*m/z* %) = 271 (M^+, 49%). *Anal*. Calcd for $C_{13}H_{13}N_5$ (271.27): C, 57.56%; H, 4.83%; N, 25.82%. Found: C, 57.64%; H, 4.99%; N, 25.96%.

1-(4,7-Dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)ethanone 9h. mp 215–217°C; Yield: 0.68 g, 78% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3269 (NH), 1708 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.34 (s, 6H, $2CH_3$), 5.83 (s, 1H, $C_{(7)}H$), 6.11 (d, 1H, $C_{(3)}H$ thienyl), 6.32 (d, 1H, $C_{(4)}H$ thienyl), 6.45 (d, 1H, $C_{(5)}H$ thienyl), 8.21 (s, 1H,$C_{(2)}H$), 9.76 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.44, 15.90, 56.77, 106.50, 125.70, 126.77, 126.11, 137.32, 150.21, 151.54. MS (*m/z* %) = 232 (M^+, 45%). *Anal*. Calcd for $C_{11}H_{12}N_4S$ (232.30): C, 56.87%; H, 5.21%; N, 24.12%. Found: C, 56.95%; H, 5.42%; N, 24.42%.

General procedure for the synthesis of ethyl 5-ethoxy-4,7-dihydro-7-substituted-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate 10a–h. Aldehyde (1 mmol), diethyl malonate (1 mmol), and 5-amino[1,2,4]triazole (1 mmol) in ethanol were heated at 90°C for the appropriate time as mentioned in Table 3. After the completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure, and the resulting solid product was triturated with methanol and filtered, and recrystallized from proper solvent.

Ethyl 5-ethoxy-4,7-dihydro-7-methyl-[1,2,4]triazolo[1,5-a] pyrimidine-6-carboxylate 10a. mp 160–162°C; Yield: 0.68 g, 78% (MeOH/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3267 (NH), 1713 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.34 (t, 6H, $2CH_3$), 2.15 (d, 3H, CH_3), 4.10 (q, 4H, $2CH_2$), 5.40 (q, 1H, $C_{(7)}H$), 7.79 (s, 1H, $C_{(2)}H$), 10.57 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 21.62, 23.11, 31.49, 47.77, 112.43, 150.42, 150.90, 151.23, 155.23, 199.12. MS (*m/z* %) = 280 (M^+, 64%). *Anal*. Calcd for $C_{12}H_{16}N_4O_4$ (280.28): C, 51.42%; H, 5.75%; N, 19.99%. Found: C, 51.49%; H, 5.88%; N, 19.87%.

Ethyl 5-ethoxy-4,7-dihydro-7-phenyl-[1,2,4]triazolo[1,5-a] pyrimidine-6-carboxylate 10b. mp 230–235°C; Yield: 0.84 g, 96% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3280 (NH), 1707 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.36 (t, 6H, $2CH_3$), 4.15 (q, 4H, $2CH_2$), 5.48 (s, 1H, $C_{(7)}H$), 7.78 (s, 1H, $C_{(2)}H$), 7.99 (m, 5H, Ph), 9.99 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.11, 31.49, 47.77, 112.43, 125.23, 128.23, 129.13, 137.11, 150.42, 150.90, 151.21, 155.27, 199.12. MS (*m/z* %) = 342 (M^+, 45%). *Anal*. Calcd for $C_{17}H_{18}N_4O_4$ (342.13): C, 59.64%; H, 5.30%; N, 16.37%. Found: C, 59.77%; H, 5.45%; N, 16.45%.

Table 3

Diethyl malonate as 1,3-dicarbonyl compounds with 3-amino triazole and aldehyde[a] for the synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine **10a–h** in refluxing ethanol.[b]

Entry	Product[c]	R	R_1	R_2	Time (h)	mp(°C)	Yield (%)[d]
1	**10a**	CH_3	OC_2H_5	OC_2H_5	5	160	78
2	**10b**	C_6H_4	OC_2H_5	OC_2H_5	4	237	94
3	**10c**	4-Cl-C_6H_4	OC_2H_5	OC_2H_5	3	220	89
4	**10d**	4-CH_3-C_6H_4	OC_2H_5	OC_2H_5	4	210	87
5	**10e**	4-CH_3O-C_6H_4	OC_2H_5	OC_2H_5	5	217	85
6	**10f**	4-$N(CH_3)_2C_6H_4$	OC_2H_5	OC_2H_5	5	240	87
7	**10g**	2-$NO_2C_6H_4$	OC_2H_5	OC_2H_5	5	190	79
8	**10h**	2-Thienyl	OC_2H_5	OC_2H_5	5	230	78

[a]Various aldehydes (aliphatic, aromatic, and heterocyclic).
[b]The reaction occurred in ethanol without any catalyst.
[c]Structural assignments of the products were based on their IR, ^{1}HNMR, and MS.
[d]Isolated yields.

Ethyl 5-ethoxy-(4-chlorophenyl)-4,7-dihydro-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 10c. mp 220–222°C; Yield: 0.78 g, 89% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3288 (NH), 1712 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.34 (t, 6H, $2CH_3$), 4.16 (q, 4H, $2CH_2$), 5.47 (s, 1H, $C_{(7)}H$), 7.77 (s, 1H, $C_{(2)}H$), 7.94 (m, 4H, Ph), 10.33 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.11, 31.49, 47.77, 112.43, 114.23, 129.13, 138.11, 144.23, 150.44, 150.90, 151.21, 155.27, 199.14. MS (*m/z* %) = 376 (M^+, 66%). *Anal*. Calcd for $C_{17}H_{17}ClN_4O_4$ (376.79): C, 54.19%; H, 4.55%; N, 14.87%. Found: C, 54.27%; H, 4.76%; N, 14.97%.

Ethyl 5-ethoxy-4,7-dihydro-7-(4-methoxyphenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 10d. mp 217–219°C; Yield: 0.76 g, 87% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3285 (NH), 1709 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.32 (s, 6H, $2CH_3$), 2.37 (s, 3H, OCH_3), 4.17 (q, 4H, $2CH_2$), 5.80 (s, 1H, $C_{(7)}H$), 7.43 (m, 4H, Ph), 8.23 (s, 1H,$C_{(2)}H$), 9.55 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.11, 31.49, 40.12, 47.77, 112.43, 114.28, 129.11, 138.11, 144.23, 150.44, 150.88, 151.21, 155.27, 199.10. MS (*m/z* %) = 372 (M^+, 64%). *Anal*. Calcd for $C_{18}H_{20}N_4O_5$ (372.38): C, 58.06%; H, 5.41%; N, 15.05%. Found: C, 58.26%; H, 5.61%; N, 15.25%.

Ethyl 5-ethoxy-4,7-dihydro-7-(4-methylphenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 10e. mp 210–212°C; Yield: 0.74 g, 85% (dioxane/H_2O). IR (KBr): ν_{max} (in cm^{-1}) 3290 (NH), 1709 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.35 (t, 6H, $2CH_3$), 2.30 (s, 3H, CH_3), 4.12 (q, 4H, $2CH_2$), 5.83 (s, 1H, $C_{(7)}$ H), 7.45 (m, 4H, Ph), 8.24 (s, 1H,$C_{(2)}H$), 9.56 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 30.11, 31.49, 40.12, 47.77, 112.43, 115.28, 129.11, 139.11, 144.23, 150.44, 150.88, 151.21, 155.27, 199.13. MS (*m/z* %) = 356 (M^+, 50%). *Anal*. Calcd for $C_{18}H_{20}N_4O_4$ (356.38): C, 60.66%; H, 5.66%; N, 15.72%. Found: C, 60.56%; H, 5.77%; N, 15.84%.

Ethyl 5-ethoxy-7-(4-(dimethylamino)phenyl)-4,7-dihydro-[1,2,4] triazolo[1,5-a] pyrimidine-6-carboxylate 10f. mp 240–242°C; Yield: 0.76 g, 87% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3287 (NH), 1707 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.31 (t, 6H, $2CH_3$), 2.35 (s, 6H, $2CH_3$), 4.12 (q, 4H, $2CH_2$), 5.82 (s, 1H, $C_{(7)}H$), 7.43 (m, 4H, Ph), 8.22 (s, 1H, $C_{(2)}H$), 9.69 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.11, 31.49, 40.56, 47.77, 112.43, 114.23, 128.13, 140.11, 144.23, 150.44, 150.90, 151.21, 155.27, 199.19. MS (*m/z* %) = 385 (M^+, 60%). *Anal*. Calcd for $C_{15}H_{19}N_5$ (385.42): C, 59.21%; H, 6.01%; N, 18.17%. Found: C, 65.21%; H, 6.21%; N, 18.31%.

Ethyl 5-ethoxy-4,7-dihydro-7-(2-nitrophenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 10g. mp 190–192°C; Yield: 0.69 g, 79% (EtOH). IR (KBr): ν_{max} (in cm^{-1}) 3279 (NH), 1709 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.81 (t, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 5.87 (s, 1H, $C_{(7)}H$), 7.42 (m, 4H, Ph), 8.23 (s, 1H, $C_{(2)}H$), 9.67 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.13, 31.49, 47.70, 112.43, 114.23, 129.13, 138.19, 144.22, 150.44, 150.90, 151.11, 155.27, 199.21. MS (*m/z* %) = 387 (M^+, 48%). *Anal*. Calcd for $C_{17}H_{17}N_5O_6$ (387.35): C, 52.71%; H, 4.42%; N, 18.08%. Found: C, 52.66%; H, 4.56%; N, 18.24%.

Ethyl 5-ethoxy-4,7-dihydro-7-(thiophen-2-yl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxylate 10h. mp 230–232°C; Yield: 0.68 g, 78% (MeOH). IR (KBr): ν_{max} (in cm^{-1}) 3279 (NH), 1709 (CO); ^1H NMR (δ ppm, DMSO-d_6): 1.34 (t, 6H, $2CH_3$), 4.16 (q, 4H, $2CH_2$), 5.87 (s, 1H, $C_{(7)}H$), 6.23 (d, 1H, $C_{(3)}H$ thienyl), 6.45 (d, 1H, $C_{(4)}H$ thienyl), 6.89 (d, 1H, $C_{(5)}H$ thienyl), 8.11 (s, 1H,$C_{(2)}H$), 9.69 (s, 1H, NH). ^{13}C NMR (δ ppm, DMSO-d_6): 8.21, 11.22, 23.11, 31.49, 47.77, 112.43, 123.23, 126.13, 126.22, 139.11, 150.44, 150.90, 151.21, 155.27, 199.14. MS (*m/z* %) = 348 (M^+, 41%). *Anal*. Calcd for $C_{15}H_{16}N_4O_4S$ (348.09): C, 51.71%; H, 4.63%; N, 16.08%. Found: C, 51.88%; H, 4.76%; N, 16.22%.

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