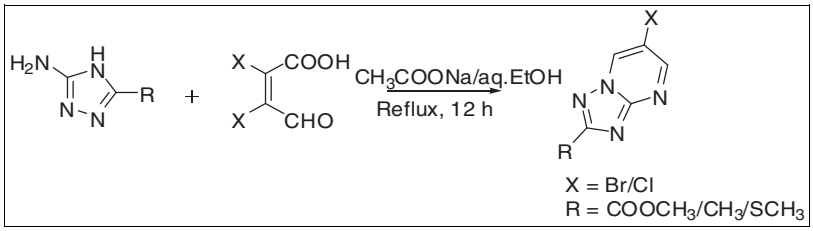
A New Route for the Synthesis of 6-Substituted [1,2,4]Triazolo[4,3-*a*]pyrimidines

Thulasiraman Krishnaraj and Shanmugam Muthusubramanian*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India
*E-mail: muthumanian2001@yahoo.com

Received May 5, 2012
DOI 10.1002/jhet.1806
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



A new method of generating the fused heterocyclic system with bridgehead nitrogen, triazolo[4,3-*a*] pyrimidine, from 3-amino-1,2,4-triazole and unsaturated halo acids has been described.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

A number of heterocyclic systems incorporating 1,2,4-triazole nucleus fused with other heterocycles possess a broad spectrum of biological activities [1]. A survey of literature also revealed that substituted 1,2,4-triazoles and their N-bridged heterocyclic derivatives have received considerable attention during the last two decades as they are endowed with variety of biological activities and have a wide range of therapeutic properties [2]. Fusion of 1,2,4-triazole ring with pyrimidine ring gives rise to the formation of bicyclic heterocycles known as 1,2,4-triazolopyrimidines, where the nitrogen common to the triazole and the pyrimidine occupies the ring junction. These triazole fused pyrimidines exhibit good antimicrobial activity, antitumor activity, analgesic, anti-inflammatory, and ulcerogenic behavior [3]. Khera *et al.* have synthesized a new series of triazolopyrimidines with oxazolidinone and evaluated the antibacterial activities of the target compounds [4]. The synthesis and the studies on the biological activities of tricyclic pyrido-triazolo-pyrimidine have been recently carried out [5]. A set of pyridotriazolopyrimidines has been reported, and their potent antitumor activity has been evaluated [6].

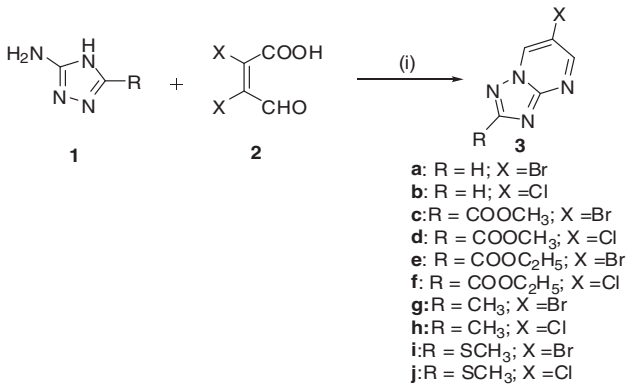
RESULTS AND DISCUSSION

In an attempt to generate fused heterocycle over the triazole, the 3-aminotriazole and its 5-substituted derivatives **1** were allowed to react with unsaturated acid, 2,3-dibromo/dichloro-4-oxobut-2-enoic acid **2**. As anticipated, the reaction proceeded smoothly generating triazolopyrimidines **3**. Ten such fused systems have been generated by this protocol (Scheme 1). All the compounds are adequately characterized by one and two-dimensional NMR spectral data.

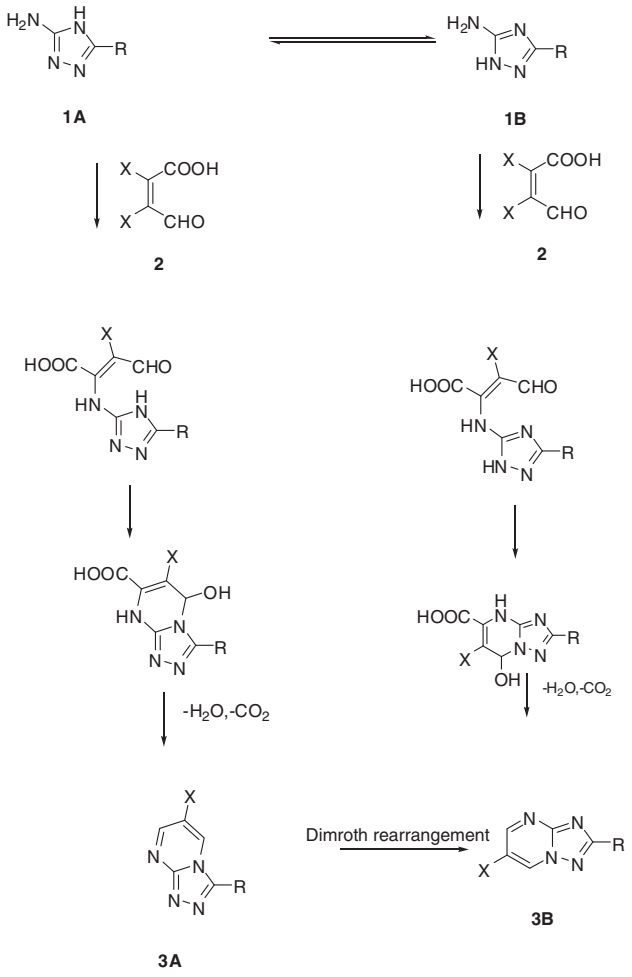
It is to be realized that the reaction would have expected to yield either **3A** or **3B** based on the fact that the reaction would have taken place on either of the two tautomeric forms of the aminotriazole. The mechanism of the formation of the product(s) is given in Scheme 2. But it is commonly expected that 1,2,4-triazolo[4,3-*a*]pyrimidine **3A** is formed first, which isomerizes to more stable **1**,**5a** isomer **3B** [7]. This can happen either thermally or by the treatment of acid/base. This process is known as Dimroth rearrangement. The thermodynamic stability of **3B** may be due to the *peri* interaction between lone pair and hydrogen, whereas in **3A**, the corresponding *peri* interaction is between hydrogen and hydrogen (sometimes between hydrogen and the substituent methyl/carbethoxy/methylthio). Thus, it is safely arrived at that the reaction between **1** and **3** has ended up with **3B** and not **3A**. Hence, the compounds formed are all given the structure **3B**. There is support for this conclusion. Compound **3a** has been prepared by a different route, by the reaction of aminotriazole and dialdehyde $CHBr(CHO)_2$, whose structure has been unambiguously confirmed by ^{15}N–^{1}H HMBC spectrum of this compound [7]. The ^{1}H and ^{13}C NMR spectral data for **3a** as reported by Salgado *et al*. [7] is given in Table 1. The spectral data for the same compound **3a** obtained by us are also given in Table 1. It can be seen that the ^{13}C NMR spectrum matches very well, whereas one of the hydrogens (H-5) in the ^{1}H NMR spectrum has suffered quite a deshielding. This may be due to the change in the solvent polarity. The spectra by Salgado *et al*. [7] were recorded in $CDCl_3$/MeOD, whereas in our case, they have been recorded in DMSO-d_6. When recorded in $CDCl_3$, although the solubility is poor, the reported values are nearly matching.

The assignment of carbons and hydrogens are made for **3h** based on the two-dimensional NMR data. However, it is not possible to unambiguously assign between H-5 and H-7. This is because both these hydrogens can have HMBC connection

Scheme 1



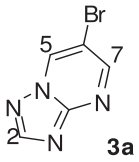
Scheme 2



with the same set of carbons. However, on the basis of the reported values for **3a** [7], the assignment of different hydrogens and carbons are tentatively made as shown in Figure 1. Unambiguous assignment can be made with ^{15}N–^{1}H HMBC spectrum.

Table 1

Comparison of the chemical shifts of **3a**.



Nuclei of **3a**	Salgado *et al.*[7] ($CDCl_3$/MeOD)	Our case (DMSO-d_6)
H-2	8.46 (s)	8.69 (s, 1H)
H-5	8.98 (s)	9.91 (d, J = 2.4 Hz, 1H)
H-7	8.81 (s)	8.99 (d, J = 2.4 Hz, 1H)
C-2	156.3	156.8
C-5	138.1	138.1
C-6	111.3	106.3
C-7	156.0	156.5
C-8a	155.1	153.8

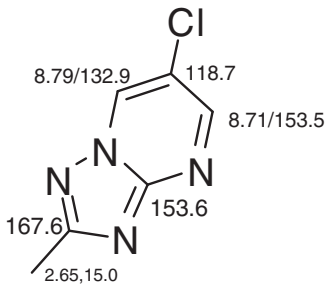


Figure 1. NMR assignment for **3h**.

The mechanism of the reaction is shown in Scheme 2. It is formulated from both the tautomeric forms. **3B** is ultimately obtained, either solely from **1B** or after the initial formation of **3A** and then undergoing Dimroth rearrangement. The initial attack is by the amino group on the vinyl carbon by a nucleophilic attack, displacing the halogen.

The antibacterial activity of the synthesized compounds have been tested against *Staphylococcus aureus*, *Bacillus* polymyxa, *Escherichia coli*, and Paratyphi-A. The compounds (**3a–3j**) were dissolved in DMSO to prepare chemical stock solution of 20 mg/mL. Gentamicin was used as the standard drug. Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37°C for 18 h. The agar plates of the aforementioned media were prepared, and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 µL, 10^{-4} cfu) and spread evenly on the plate. After 20 min, the wells were filled with compound at different concentrations. The control wells with gentamicin were also prepared. All the plates were incubated at 37°C for 24 h, and the diameter of inhibition zone were noted.

Only the halo substituted triazolopyrimidines (**3b** and **3g**) showed appreciable activity against *E. coli* (MIC 2 mg), although they are not active against other organisms.

EXPERIMENTAL

All chemicals used in this investigation were of reagent grade quality and used without further purification. All melting points were recorded in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (Bruker, Fallanden, Switzerland) at 400 MHz and 100 MHz, respectively, in $CDCl_3$/DMSO-d_6 using TMS as internal standard. The chemical shifts are presented in δ scale. Microanalyses were carried out on a Perkin-Elmer instrument (PerkinElmer, Lu Vento, The Netherlands). All chromatographic separations were performed on 60–120 mesh silica gel using petroleum ether ethyl acetate as eluent, unless mentioned otherwise.

6-Substituted-[1,2,4]triazolo[4,3-a]pyrimidine (3). 4H-3-Amino-1,2,4-triazole **1** was heated with unsaturated acid 2 and sodium acetate in equimolar amount in ethanol-water mixture at 95 °C for 12 h and the reaction mass was worked out to give **3**, which was purified by crystallization.

6-Bromo-[1,2,4]triazolo[4,3-*a*]pyrimidine (3a). This compound was obtained as yellow solid, mp 176°C; yield 72%; ^{1}H NMR (400 MHz, DMSO-d_6) 8.69 (s, 1H), 8.99 (d, J = 2.6 Hz, 1H), 9.91 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 106.3, 138.1, 153.8, 156.5, 156.8. ESI-Mass (*m*/*z*) Calcd $[C_5H_3BrN_4 + H]^+$197.95, found 198.7.

6-Chloro-[1,2,4]triazolo[4,3-*a*]pyrimidine (3b). This compound was obtained as yellow solid, mp 134°C; yield 71%; ^{1}H NMR (400 MHz, DMSO-d_6) 8.72 (s, 1H), 8.97 (d, J = 2.4 Hz, 1H), 9.86 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 119.2, 136.2, 153.7, 155.0, 157.0. ESI-Mass (*m*/*z*) Calcd $[C_5H_3ClN_4 + H]^+$154.00, found 156.8. *Anal*. Calcd For $C_5H_3ClN_4$: C, 38.86; H, 1.96; N, 36.25. Found: C, 38.93; H, 2.01; N, 36.42%.

Methyl 6-bromo-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (3c). This compound was obtained as yellow solid, mp 169°C; yield 63%; ^{1}H NMR (400 MHz, DMSO-d_6) 3.95 (s, 3H), 9.11 (d, J = 2.3 Hz, 1H), 9.99 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 53.3, 108.2, 138.7, 153.9, 156.8, 158.3, 160.4. *Anal*. Calcd For $C_7H_5BrN_4O_2$: C, 32.71; H, 1.96; N, 21.80. Found: C, 32.83; H, 2.07; N, 21.63%.

Methyl 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (3d). This compound was obtained as yellow solid, mp 145°C; yield 61%; ^{1}H NMR (400 MHz, DMSO-d_6) 3.95 (s, 3H), 9.09 (d, J = 2.0 Hz, 1H), 9.95 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 53.3, 120.9, 136.7, 153.9, 156.7, 157.1, 160.4. *Anal*. Calcd For $C_7H_5ClN_4O_2$: C, 39.55; H, 2.37; N, 26.35. Found: C, 39.43; H, 2.30; N, 26.48%.

Ethyl 6-bromo-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (3e). This compound was obtained as yellow solid, mp 164°C; yield 64%; ^{1}H NMR (400 MHz, DMSO-d_6) 1.36 (t, 3H), 4.42 (q, 2H), 9.12 (d, J = 2.3 Hz, 1H), 10.00 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 14.4, 62.3, 108.1, 138.6, 153.9, 157.0, 158.2, 159.9. *Anal*. Calcd For $C_8H_7BrN_4O_2$: C, 35.45; H, 2.60; N, 20.67. Found: C, 35.55; H, 2.58; N, 20.73%; ESI-Mass (*m*/*z*) Calcd $[C_8H_7BrN_4O_2 + H]^+$ 269.98, found 273.0.

Ethyl 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (3f). This compound was obtained as yellow solid, mp 128°C; yield 63%; ^{1}H NMR (400 MHz, DMSO-d_6) 1.34 (t, 3H), 4.41 (q, 2H), 9.08 (d, J = 2.5 Hz, 1H), 9.95 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 14.0, 61.9, 120.4, 136.3, 153.4, 156.3, 156.8, 159.5. *Anal*. Calcd For $C_8H_7ClN_4O_2$: C, 42.40; H, 3.11; N, 24.72. Found: C, 42.18; H, 3.26; N, 24.59%; ESI-Mass (*m*/*z*) Calcd $[C_8H_7ClN_4O_2 + H]^+$ 226.03, found 227.2.

6-Bromo-3-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidine (3g). This compound was obtained as yellow solid, mp 172°C; yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) 2.64 (s, 3H), 8.76 (d, J = 2.4 Hz, 1H), 8.89 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 15.0, 105.1, 135.1, 154.2, 155.0, 167.5. *Anal*. Calcd For $C_6H_5BrN_4$: C, 33.83; H, 2.37; N, 26.30. Found: C, 33.92; H, 2.18; N, 26.35%; ESI-Mass (*m*/*z*) Calcd $[C_6H_5BrN_4 + H]^+$ 211.97, found 215.2.

6-Chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidine (3h). This compound was obtained as yellow solid, mp 159°C; yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$) 2.65 (s, 3H), 8.71 (d, J = 2.5 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 15.0, 118.7, 132.9, 153.5, 153.6, 167.6. *Anal*. Calcd For $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.58; H, 3.07; N, 33.16%; ESI-Mass (*m*/*z*) Calcd $[C_6H_5ClN_4]^+$ 168.02, found 168.8.

6-Bromo-3-(methylthio)-[1,2,4]triazolo[4,3-*a*]pyrimidine (3i). This compound was obtained as yellow solid, mp 145°C; yield 86%; ^{1}H NMR (400 MHz, DMSO-d_6) 2.65 (s, 3H), 8.89 (d, J = 2.3 Hz, 1H), 9.78(d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 13.7, 105.4, 137.1, 154.5, 155.8, 168.8. *Anal*. Calcd For $C_6H_5BrN_4S$: C, 29.40; H, 2.06; N, 22.86. Found: C, 29.90; H, 2.18; N, 22.63%; ESI-Mass (*m*/*z*) Calcd $[C_6H_5BrN_4S + H]^+$ 243.94, found 245.7.

6-Chloro-3-(methylthio)-[1,2,4]triazolo[4,3-*a*] pyrimidine (3j). This compound was obtained as yellow solid, mp 131°C; yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) 2.71 (s, 3H), 8.67 (d, J = 2.4 Hz, 1H), 8.76 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 118.4, 132.3, 153.1, 154.2, 170.7. *Anal*. Calcd For $C_6H_5ClN_4S$: C, 35.92; H, 2.51; N, 27.92. Found: C, 36.08; H, 2.63; N, 28.12%; ESI-Mass (*m*/*z*) Calcd $[C_6H_5ClN_4S + H]^+$ 199.99, found 201.4.

Acknowledgments. The authors thank DST, New Delhi, for assistance under the IRHPA program for the NMR facility.

REFERENCES AND NOTES

[1] Udupi, R. H.; Kulkarni, V. M.; Srinivasulu, N.; Purushottamachar, P. J Indian Chem Soc 2002, 79, 381.

[2] Udupi, R. H.; Rao, P. S.; Sudheendra, G. Indian J Heterocycl Chem 2006, 15, 291.

[3] Hend, N. H.; Hebat-allah, S. A.; Abdel-rahman, B. A. E. Acta Pharm 2008, 58, 359.

[4] Khera, M. K.; Cliffe, I. A.; Mathur, T.; Prakash, O. Bioorg Med Chem Lett 2011, 21, 2887.

[5] El-Gazzar, A. B. A.; Hafez, H. N.; Nawwar, G. A. M. Eur J Med Chem 2009, 44, 1427.

[6] El-Nassan, H. B. Eur J Med Chem 2011, 46, 2031.

[7] Salgado, A.; Varela, C.; Collazo, A. M. G.; Pavarello, P. Magn Reson Chem 2010, 48, 614 and the references cited therein.