A Convenient Route for the Synthesis of Novel 2-Substituted [1,2,4]Triazolo[1,5-*c*]pyrimidine Derivatives

Chao Li, Zhiming Li, Quanrui Wang*

Department of Chemistry, Fudan University, Shanghai 200433, P. R. of China
Fax +86(21)65641740; E-mail: qrwang@fudan.edu.cn

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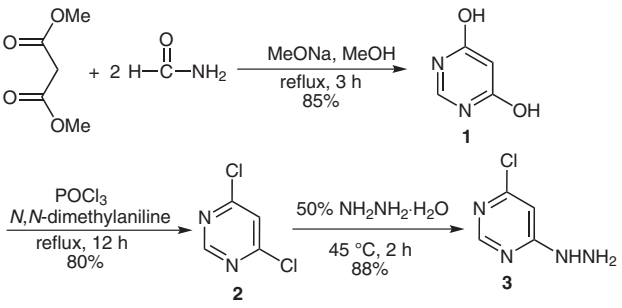
Abstract: Reactions of easily accessible chloropyrimidinyl hydrazones with bromine were investigated. Oxidative cyclization followed by concomitant bromination led to the formation of [1,2,4]triazolo[4,3-*c*]pyrimidines, which then underwent the Dimroth rearrangement to afford highly functionalized 2-substituted [1,2,4]triazolo[1,5-*c*]pyrimidines.

Key words: 4,6-dichloropyrimidine, hydrazones, bromine, Dimroth rearrangement, [1,2,4]triazolo[1,5-*c*]pyrimidine

Pyrimidines and fused bi- or tricyclic analogues are privileged heterocycles that are of immense importance in the design and discovery of new compounds for pharmaceutical and herbicide applications.[1] In particular, compounds carrying a [1,2,4]triazolo[1,5-*c*]pyrimidine nucleus have received considerable attention due to their remarkable adenosine and benzodiazepine receptor affinity.[2] For example, 3- and/or 5-substituted 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines have been reported to be potent xanthine oxidase (XO) inhibitors.[3] Many 1,2,4-triazolo[1,5-*c*]pyrimidines as well as pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines have recently been prepared and investigated for use as selective antagonists at the A2a receptor, which offers great promise in the treatment of Parkinson's disease.[4] A recent paper by Clarkson and co-workers also predicted the potential use of triazolopyrimidines as inhibitors of Shiga toxin trafficking.[5] In addition, various triazolopyrimidines have been used as the new pharmacological tool for the characterization of human A_3 adenosine receptor.[6]

In contrast to the significance of this class of heterocycles, a literature survey revealed that methods available for the construction of the [1,2,4]triazolo[1,5-*c*]pyrimidine moiety are not plentiful. The frequently employed route involves the preformation of 1-amino-6-imino-substituted pyrimidines, from which [1,2,4]triazolo[1,5-*c*]pyrimidine can be assembled by reaction with carboxylic acids or derivatives as the one-carbon cyclizing agent.[4] Alternatively, dehydrative cyclization of the 4-acyl-hydrazinopyrimidines was reported to afford, after ring rearrangement, [1,2,4]triazolo[1,5-*c*]pyrimidines instead of the isomeric [1,2,4]triazolo[4,3-*c*]pyrimidines.[7] Each of the existing methods has its own merits, while sometimes they are plagued by the limitations of complex pathways, harsh conditions, difficult workup aside from the formation of side products. In view of the emerging importance of [1,2,4]triazolo[1,5-*c*]pyrimidine nucleus as a fertile source of biologically important molecules we wish to report our recent findings in this connection.

The required starting material, 4,6-dichloropyrimidine (**2**) was easily prepared using a two-step patent method as depicted in Scheme 1.[8] Thus, dimethyl malonate and two equivalents of formamide, both commercially available, reacted in the presence of sodium methoxide in methanol under reflux to give the intermediate 4,6-dihydroxypyrimidine (**1**) in 85% yield. The transformation into **2** was achieved in 80% yield by chlorination with $POCl_3$ under catalysis by *N*,*N*-dimethylaniline at refluxing temperature for 12 hours. Compound **2** was employed for the synthesis of 1-(6-chloropyrimidin-4-yl)hydrazine (**3**). After screening a set of conditions, an optimal condition could be determined. Thus, **2** was allowed to react with two-mole amount of 50% hydrazine in ethanol at 45 °C for two hours and stirred overnight at room temperature to furnish **3** in 88% yield (Scheme 1).



Scheme 1 Synthesis of the chloropyrimidinyl hydrazine **3**

With compound **3** in hand, we started out the preparation of the corresponding hydrazones of various aldehydes. Thus, the chloropyrimidinyl hydrazone **4a** was firstly prepared by condensation of hydrazine **3** with slightly excessive benzaldehyde at room temperature in about half an hour as an off-white solid in 73% yield. Analogously, a set of different aldehyde hydrazones **4b–l** was prepared under the same conditions except that appropriate recrystallization solvent has to be selected to achieve an optimal purification. The yields ranged from good to excellent (Table 1).[9]

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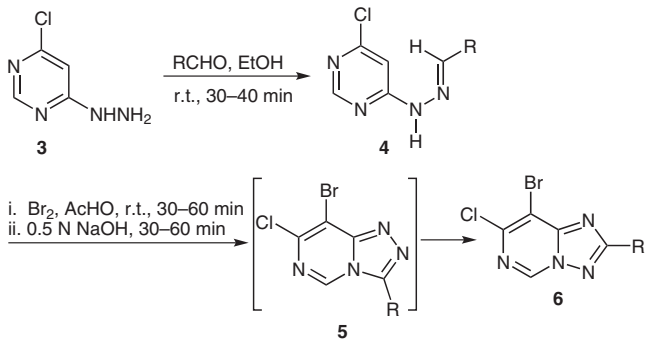


Scheme 2 Synthesis of the [1,2,4]triazolo[1,5-*c*]pyrimidines **6**

As can be seem from Table 1, aromatic aldehydes generally afforded satisfactory isolated yields of the corresponding hydrazones **4**, while aliphatic ones gave inferior results (Table 1, entries 1–9 vs. 10–12). For unsaturated aliphatic aldehydes, the hydrazone preparation failed completely under the same and variable conditions (Table 1, entries 13 and 14).

Since most of the attained chloro-substituted pyrimidinyl hydrazones **4** have not been reported hitherto,[10] they were characterized by means of spectral (MS, IR and NMR) tools (see supporting information). For example, the ^{1}H NMR spectra of all such hydrazones showed a characteristic signal in the downfield region, $\delta = 8.32–9.85$, assignable to the C-2 pyrimidine proton. The absorptions around 3400 cm^{-1} can be attributed to the N–H stretching vibrations of the hydrazone group.

Our initial oxidative cyclization study was attempted using **4a** as the model substrate. Thus, **4a** was treated with 2.2 equivalents of bromine in glacial acetic acid containing a small amount of anhydrous sodium acetate at ambient conditions for one hour. After stirring with 0.5 N aqueous NaOH for 30 minutes, a single off-white solid product was isolated. Based on NMR spectroscopy and mass spectroscopy analysis, this was assigned to be the 2-phenyl-substituted [1,2,4]triazolo[1,5-*c*]pyrimidine **6a** bearing an additional bromo substituent at the pyrimidine ring (Scheme 2). Thus, the mass spectrum revealed that the product has two hydrogen atoms less than the starting hydrazone **4a**. The proton NMR spectrum indicated also the absence of the signals from the N=CH and the NH protons on the hydrazone moiety along with the disappearance of the pyrimidine C(5)-H of **4a**.

The formation of **6a** can be accounted for by the initial oxidative cyclization with concomitant monobromination of the pyrimidine ring at the position next to the chloro-bearing carbon followed by ring isomerization.

This result deviated somewhat from our original expectation that the product was the isomeric [1,2,4]triazolo[4,3-*c*]pyrimidine **5a**. To unambiguously confirm the structural establishment, an X-ray crystallography analysis was performed, providing unequivocal evidence for the structure **6a** (Figure 1).[11]

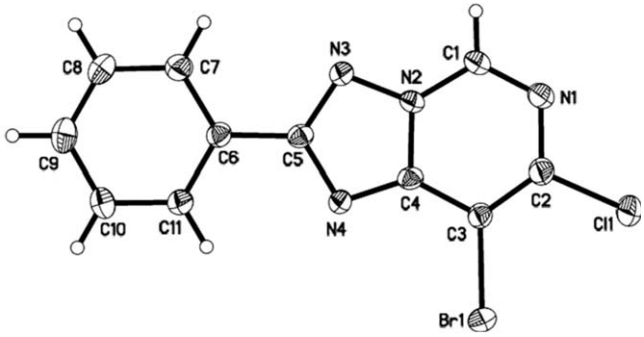
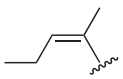
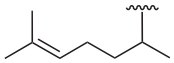


Figure 1 Perspective view and atom labeling of the X-ray crystal structure of **6a**. The bond lengths in the bicyclic system are the following: N(1)–C(2) 1.354, C(2)–C(3) 1.358, C(3)–C(4) 1.417, N(2)–C(4) 1.373, N(2)–C(1) 1.366, N(1)–C(1) 1.289, N(2)–N(3) 1.360, N(3)–C(5) 1.345, N(4)–C(5) 1.368, N(4)–C(4) 1.325, C(5)–C(6) 1.461, Cl(1)–C(2) 1.729, Br(1)–C(3) 1.864 Å. The dihedral angles: C(1)–N(2)–N(3)–C(5), C(4)–N(2)–N(3)–C(5), C(2)–C(3)–C(4)–N(4) and N(2)–N(3)–C(5)–C(6) are –179.6°, –0.7°, 179.2° and –179.9°, respectively.

Table 1 Synthesis of the Chloropyrimidinyl Hydrazones **4**[a]

Entry	R	Product[b]	Solvent[c]	Yield (%)[d]
1	Ph	**4a**	EtOH	73
2	2-ClC_6H_4	**4b**	EtOH	80
3	4-ClC_6H_4	**4c**	DMF	63
4	2,4-$Cl_2C_6H_3$	**4d**	DMF–H_2O (2:8)	85
5	2-BrC_6H_4	**4e**	EtOH	74
6	4-BrC_6H_4	**4f**	EtOH–DMF (2:1)	66
7	2-Br-4,5-$(MeO)_2C_6H_2$	**4g**	DMF	85
8	4-MeOC_6H_4	**4h**	EtOH	84
9	2-MeC_6H_4	**4i**	EtOH	74
10	Et	**4j**	PE	65
11	*i*-Pr	**4k**	EtOH–PE (1:19)	68
12	Me(Ph)CH	**4l**	– (1:19)	78
13		**4m**	–	–[e]
14		**4n**	–	–[e]

[a] Reaction performed using the chloropyrimidinyl hydrazine **2** (0.30 g, 2.08 mmol, 1 equiv), absolute EtOH (15 mL), aldehyde (2.29 mmol, 1.1 equiv), at r.t. for 30–40 min.
[b] For general procedure and selected characterization data, see ref. 9.
[c] Used for recrystallization.
[d] Yields refer to isolated product by recrystallization.
[e] Complex mixture of products.

This result was quite promising to us and drew our attention considerably in view of the significance of this class of heterocyclic compounds. Therefore, the generality of

this facile transformation was established by converting all of the prepared hydrazones **4b–l** into the corresponding [1,2,4]triazolo[1,5-*c*]pyrimidines **6b–l**.[12] As indicated in Table 2, the reactions were all successful leading to the formation of **6** without detection of any intermediates **5**. The protocol showed a good substrate scope. The reaction of substrates **4a–i** derived from aromatic aldehydes went to completion in one hour to provide the corresponding product **6** in moderate to high yields, except with the trisubstituted **4g** which required slightly longer reaction time. Substrates bearing electron-withdrawing group(s) seemed to be beneficial in achieving a better yield (Table 2, entries 2–7) than those bearing electron-releasing groups (Table 2, entries 9–12). Similarly, substrates from aliphatic aldehydes such as isobutyraldehyde and 2-phenylpropanal (**4k**, **4l**) worked smoothly to furnish **6k** and **6l**, respectively, with the latter one more promising in terms of yield and reaction rate. All the new products were fully characterized by IR, NMR and mass spectra.

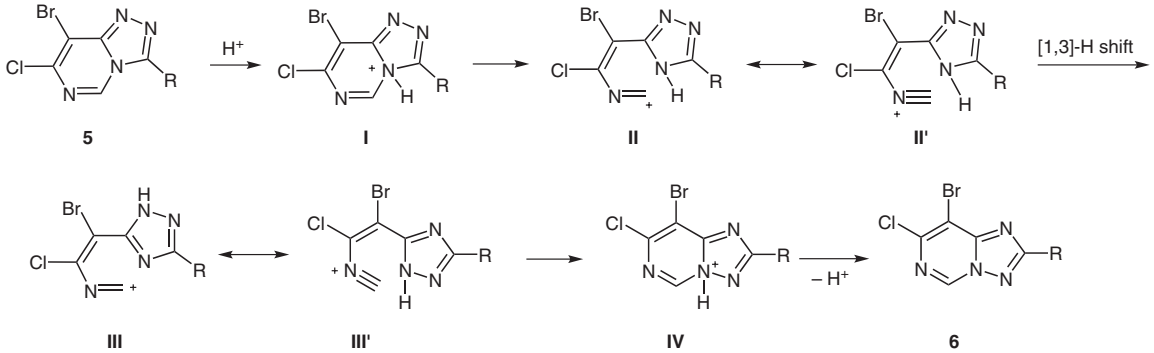
Although we were unable to elucidate the mechanism in detail, the reactions investigated above allow a convenient methodology to access specific triazolopyrimidine isomers from readily accessible precursors by simple oxidation.

The presence of acidic species was assumed to catalyze the Dimroth-type rearrangement of the intermediate 1,2,4-triazolo[4,3-*c*]pyrimidines **5** to the isomeric 1,2,4-triazolo[1,5-*c*]pyrimidines **6** in a similar manner to other acid-catalyzed Dimroth rearrangements (Scheme 3).[13] In the first step, the hydrazones undergo oxidative ring closure and concurrent bromination by reaction with Br_2 to produce 1,2,4-triazolo[4,3-*c*]pyrimidines **5**, which have been reported to be unstable under both acidic and basic conditions.[4d] In our case, compounds **5** are assumed to be

Table 2 Synthesis of the Triazolopyrimidines **6**[a]

Entry	R	Product[b]	Time (min)	Solvent[c]	Yield (%)[d]
1	Ph	**6a**	60	EtOH–H_2O (8:2)	83
2	2-ClC_6H_4	**6b**	60	EtOH	75
3	4-ClC_6H_4	**6c**	60	EtOH	73
4	2,4-$Cl_2C_6H_3$	**6d**	60	EtOH	74
5	2-BrC_6H_4	**6e**	60	EtOH	68
6	4-BrC_6H_4	**6f**	60	EtOH	56
7	2-Br-4,5-$(MeO)_2C_6H_2$	**6g**	80	EtOH	53
8	4-$MeOC_6H_4$	**6h**	60	EtOH	45
9	2-MeC_6H_4	**6i**	60	EtOH	70
10	Et	**6j**	80	EtOH–PE (2:3)	65
11	*i*-Pr	**6k**	120	–[e]	40
12	Me(Ph)CH	**6l**	60	EtOH–PE (1:19)	73

[a] Reaction performed using hydrazone **4** (0.6 mmol), Br_2 (2.2 equiv), AcOH (1.9 mL), at r.t.; then NaOH (0.5 N, 10 mL), 0 °C, 30–60 min.
[b] For general procedure and selected characterization data, see ref. 12.
[c] Used for recrystallization.
[d] Yields refer to isolated product by recrystallization.
[e] Separated by chromatography with PE–EtOAc as eluent (2:1).



Scheme 3 Postulated mechanism for the Dimroth rearrangement **5** → **6**

protonated to generate ammonium salts **I**, which facilitate the ring opening to give the iminium salts **II** (in resonance with the nitrilium salts **II′**). Subsequently, hydrogen shift results in the formation of the triazole-tethered vinyliminium salts **III**. Recyclization by intramolecular nucleophilic attack at another nitrogen atom of the triazole ring affords, after deprotonation of **IV**, the isolated [1,2,4]triazolo[1,5-*c*]pyrimidines **6**. The driving force for the observed rearrangement relies on the fact that [1,2,4]triazolo[1,5-*c*]pyrimidine ring system is thermodynamically more stable than its isomer, namely, [1,2,4]triazolo[4,3-*c*]pyrimidine.[14]

In conclusion, a mild and simple condition has been discovered to induce the conversion of the aldehyde chloropyrimidinyl hydrazones **4** into 1,2,4-triazolo[1,5-*c*]pyrimidines **6** simply by treating with bromine followed by a basic workup. The condition allows concurrent ring-bromination and Dimroth rearrangement taking place via temporary ring opening of the pyrimidine moiety followed by a repeated ring closure. The present methodology carries very attractive features such as good yields, simple reaction conditions and easy workup. Moreover, the two halogen atoms in the products offer great promise for easy elaboration by, for example, nucleophilic displacement and coupling reactions. This investigation is underway in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **General Procedure for the Preparation of the Aldehyde Chloropyrimidinyl Hydrazones 4a–l**: To the suspension of 1-(6-chloropyridin-4-yl)hydrazine (**3**) (0.289 g, 2.00 mmol) in EtOH (15 mL) was added dropwise with vigorous stirring an aldehyde (2.20 mmol, 1.1 equiv) at r.t. over 30–40 min. During this period, a white precipitate was produced. The mixture was stirred further for a couple of hours and then filtrated. The crude products were recrystallized from an appropriate solvent (Table 1) to furnish pure hydrazones **4** as white powders or crystals. The yields ranged from 63% to 85%. **Data for Benzaldehyde (6-Chloro-4-pyrimidinyl)-hydrazone (4a)**: Yield: 0.339 g (73%); off-white powder; mp 208–210 °C. IR (KBr): 3456, 3203, 1608, 1589, 685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 8.46 (s, 1 H), 7.86 (s, 1 H), 7.68–7.70 (m, 2 H), 7.42–7.44 (m, 3 H), 7.30 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 160.9, 158.1, 144.1, 133.6, 130.4, 129.0, 127.2, 103.4. GC–MS (EI): *m*/*z* = 232 $[M]^+$ (100.00), 234 (37.10), 233 (8.23). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_9ClN_4$: 232.0516; found: 232.0528.

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(11) A single crystal of **6a** suitable for X-ray diffraction analysis was obtained by recrystallization from CH_2Cl_2–*n*-hexane. CCDC 768081 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033.

(12) **General Procedure for the Preparation of 2-Substituted 8-Bromo-7-chloro[1,2,4]triazolo[1,5-*c*]pyrimidine 6a–l**: A soln of Br_2 (0.71 g, 4.4 mmol, 2.2 equiv) in glacial AcOH (0.57 mL) was slowly added to a suspension of anhyd NaOAc (1.53 g) and the appropriate hydrazone **4** (2.00 mmol, 1.0 equiv) in glacial AcOH (6.33 mL), and the mixture was stirred at r.t. for additional 30–60 min. The progress of the reaction was monitored by TLC. The reaction was quenched by pouring into ice-cooled 0.5 N aq NaOH soln (25–33 mL). With vigorous stirring, the mixture was agitated for 30–60 min. The product was collected by filtration, washed several times with H_2O, and dried. The product was recrystallized from an appropriate solvent (Table 2). Pure products **6** were obtained as off-white powders or crystals in yields ranging from 40% to 83%. All are previously unknown products and were fully characterized by IR, NMR and mass spectra. **Selected Data for 8-Bromo-7-chloro-2–phenyl[1,2,4]triazolo[1,5-*c*]-pyrimidine (6a)**: Yield: 0.52 g (83%); off-white powder; mp 240–242 °C. IR (KBr): 3404, 1606, 1486, 1364, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.32–8.34 (m, 2 H), 7.52–7.54 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =

166.1, 153.8, 146.7, 140.1, 131.9, 130.4, 129.5, 127.9, 106.3. GC–MS (EI): *m*/*z* = 311 $[M + H]^+$ (100.00), 309 (78.21), 274 (38.13). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_7BrClN_4$: 310.9522; found: 310.9519.

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