A Convenient Synthesis of New Substituted 1,2,4-Triazolo[4,3-c]Pyrimidines by Oxidative Cyclisation using 1,3-Dibromo-5,5-Dimethyl Hydantoin as Oxidant

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ABSTRACT: A series of new 1,2,4-triazolo[4,3-c]pyrimidines 3(a-h) have been synthesized by oxidative intramolecular cyclisation of heterocyclic hydrazones using 0.51 eq of 1,3-dibromo-5,5-dimethyl hydantoin as oxidant in chloroform with good yield. The purity of novel compounds was confirmed by elemental analyses. The chemical structures of the synthesized compounds were confirmed by FT-IR, 1H NMR and mass spectral studies. The reaction is extremely fast and the reagent utilizes a commercially inexpensive and easily handled oxidant.

KEYWORDS: 2-Chloro-5-fluro-4-hydrazinopyrimidine; Triazolopyrimidine; Oxidative cyclisation.

Introduction

Triazolopyrimidines represent an important class of heterocyclic compounds having wide range of pharmaceutical and biological activities[1-3]. Therefore, versatile and widely applicable methods for the synthesis of triazolopyrimidines are of considerable interest. The existing methods for the preparation of triazolopyrimidines are based on heterocyclic hydrazones or hydrazine precursors. However, the present methods have some restrictions for their applicability as they involve the use of toxic reagents such as phosphorous oxychloride[4], lead tetraacetate[5] and with nitrobenzene at reflux temperature[6]. Recently, synthetic methodologies have been developed under microwave heating[7], iodobenzene diacetate[8,9] bis(trifluoroacetoxy)iodobenzene[10], chloramine-T[11], copper dichloride[12], calcium hypochlorite[13], NBS[14] and as well as electrochemical methods[15]. However, these methods have some limitations such as moisture sensitivity of the reagent, use of hazardous chemicals, difficulty of handling reagent, reaction time and high temperature. Therefore, alternative approach avoiding these reagents is always preferred. We found 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is a versatile reagent for the oxidative heterocyclisation. This reagent is relatively non-toxic, commercially available and stable to moisture. DBDMH is a good and useful reagent for bromination[16] and oxidation[17]. In the present paper, we are reporting a simple, cheap and convenient method for the effective conversion of pyrimidinyl hydrazones to triazolopyrimidines 3(a-h), and characterized by different spectral studies.

Results and Discussion

The synthesised compounds were confirmed by their FT-IR, 1H NMR, LCMS and elemental analytical data. The general procedure involves the addition of 0.51 eq of DBDMH to a stirred solution of aryl-(2-chloro-5-fluropyrimidine-4-yl)hydrazine 2(a-h) in chloroform at 5 to 10 °C for 10 to 30 min. The completion of the reaction was confirmed by thin layer chromatography (TLC). After completion, the reaction mass was washed with water and the solvent was removed under pressure to get the crude product (Scheme 1). During the reaction, dimethyl-hydantoin is the by product, soluble in water and can be easily removed during workup. Since both bromine atoms of hydantoin are utilized for the oxidation, 0.51 eq DBDMH is enough to drive the reaction to completion. Hydrazones of aromatic aldehydes with both electron withdrawing and electron-donating substituents were oxidized to give the corresponding 1,2,4-triazolo[4,3-c]pyrimidines. The chemical structures and physical data of all the synthesized compounds are tabulated in Table 1.
The absorptions around 3000 cm\(^{-1}\) in synthesized compounds confirm the aromatic stretching vibrations, and the appearance of a medium to strong absorption bands above 1600 cm\(^{-1}\) due to a stretching vibration of the azomethine (C=N) bond formation in synthesized compounds. The characterization of 5-chloro-8-fluoro-3-phenyl-[1,2,4]triazolo[4,3-c]pyrimidines \(3(a-h)\) was based upon a careful comparison of \(^1\)H NMR spectra with those of \(2(a-h)\). An important characteristic feature in the \(^1\)H NMR spectra of \(3(a-h)\) was the disappearance of the singlet due to N=CH proton around 8.10 to 8.30 and NH proton around 11.5 to 11.8 which was present in the spectra of \(2(a-h)\). The \(^1\)H NMR spectra of \(3c\) and \(3h\) showed singlet of pyrimidine ring in the region of \(\delta\), 7.90 and 7.88, respectively. Similarly a singlet appeared at \(\delta\), 3.97 are due to the three protons of the methoxy groups in \(3c\). The mass spectra of \(3h\) showed molecular ion peak at m/z 326.0, which is in agreement with the molecular formula \(C_{11}H_{12}BrClF_4N_4\). The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ± 0.4 %.

**Table 1** The chemical structures and physical data of the synthesized compounds \(3(a-h)\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\text{Ar})</th>
<th>Structure</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
<th>Melting Range (°C)</th>
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<td>Cl</td>
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<td>88</td>
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<td>91</td>
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<td>CH(_3)</td>
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*Table 1 Contd…*
### Conclusions

In conclusion, the oxidative intramolecular cyclisation of aryl-(2-chloro-5-fluoropyrimidine-4-yl)hydrazine leads to the formation of 5-chloro-8-fluoro-3-aryl-[1,2,4]triazolo[4,3-c]pyrimidines with high yield using 1,3-dibromo-5,5-dimethylhydantoin under mild conditions. The synthesized compounds were characterized by different spectral studies. The main advantage to this approach is that the reagent used is commercially inexpensive and safe to handle. This approach is especially applicable to large scale synthesis of 1,2,4-triazolo[4,3-c]pyrimidines.

### Experimental

All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt. Ltd. Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. $^1$H NMR spectra were recorded on Bruker DRX -500 spectrometer at 400 MHz using DMSO-d$_6$/CDCl$_3$ as solvent and TMS as an internal standard. The mass spectra of the samples were recorded using the instrument LC-MSD-Trap-XCT. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

**General procedure for the synthesis of aryl-(2-chloro-5-fluoropyrimidine-4-yl)hydrazines (2a-h)**

2-Chloro-5-fluoro-4-hydrazinopyrimidine (0.1 mmol) was dissolved in ethanol (10 ml) and different benzaldehydes (0.1 mmol) were added to the solution. Reaction mixture was heated to reflux for 2 hr. The completion of the reaction was confirmed by the thin layer chromatography (TLC). After completion, the reaction mass was cooled to 5 to 10 °C for 1 hr. The reaction mass was filtered and washed with chilled ethanol and dried to afford 2(a-h).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>Structure</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
<th>Melting Range (°C)</th>
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<td>Br</td>
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<td>18</td>
<td>93</td>
<td>184-187</td>
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</table>
4-Chloro-2-fluorobenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2a)
Yield 91%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.54 (s, 1H, Ar-H), 7.67 (d, 2H, Ar-H), 8.18 (s, 1H, CH), 8.30 (s, 1H, Py-H), 11.72 (s, 1H, NH).

4-Propylbenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2b)
Yield 87%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.49-7.41 (m, 3H, Ar-H), 7.67-7.64 (d, 2H, Ar-H), 8.18 (s, 1H, CH), 8.33 (s, 1H, Py-H), 11.69 (s, 1H, NH).

4-Chloro-2-fluorobenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2c)
Yield 89%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.23-7.21 (t, 2H, Ar-H), 7.36-7.33 (dd, 2H, Ar-H), 2.73-2.66 (t, 2H, CH$_2$), 8.10 (s, 1H, CH), 8.26 (s, 1H, Py-H), 11.74 (s, 1H, NH).

2-Chlorobenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2d)
Yield 88%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.94 (d, 2H, Ar-H), 7.70 (d, 2H, Ar-H), 8.25 (s, 1H, CH), 8.29 (s, 1H, Py-H), 11.70 (s, 1H, NH).

2-Fluoro-3-methoxybenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2e)
Yield 86%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.40-7.37 (m, 3H, Ar-H), 7.52 (d, 1H, Ar-H), 8.02 (d, 1H, Ar-H), 8.26 (s, 1H, CH), 8.26 (s, 1H, Py-H), 11.76 (s, 1H, NH).

Benzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2f)
Yield 89%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.45-7.37 (m, 3H, Ar-H), 7.69-7.66 (d, 2H, Ar-H), 8.25 (s, 1H, CH), 8.28 (s, 1H, Py-H), 11.74 (s, 1H, NH).

4-Bromobenzaldehyde-(2-chloro-5-fluoropyrimidine-4-yl)hydrazone (2g)
Yield 91%; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.61 (s, 4H, Ar-H), 8.27 (s, 1H, CH), 8.30 (s, 1H, Py-H), 11.73 (s, 1H, NH).

General procedure for the synthesis of 5-chloro-8-fluoro-3-phenyl-[1,2,4]triazolo[4,3-c]pyrimidines 3(a-h)
Aryl-(2-chloro-5-fluoropyrimidine-4-yl)hydrazines, 2(a-h) (1 mmol) was dissolved in chloroform (10 ml), triethylamine (3.0 mmol) was added, and DBDMH (0.51 mmol) was added and the reaction mixture was stirred at 5-10 °C. The completion of the reaction was confirmed by TLC. After completion, the reaction mixture was washed with water and the organic layer was dried with anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude product. The compounds were recrystallized from diethyl ether to get the pure products.

5-Chloro-3-(4-chloro-2-fluoro-phenyl)-8-fluoro-[1,2,4]triazolo[4,3-c]pyrimidine (3a)
FT-IR (KBr, cm$^{-1}$): 3056 (C-H), 1610 (C=C), 1312 (C-N), 1229 (C-F), 704 (C-Cl); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.94-7.92 (d, 1H, Ar-H), 7.86-7.84 (d, 1H, Ar-H), 7.72 (s, 1H, Ar-H); MS (ESI) m/z: 302.1; Anal. calcd. for C$_{11}$H$_7$ClFN$_4$ (in %): C-43.88, H-1.34, N-18.61. Found C- 43.76, H-1.44, N-18.82.

5-Chloro-8-fluoro-3-(4-propyl-phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine (3b)
FT-IR (KBr, cm$^{-1}$): 3055 (C-H), 1613 (C=C), 1306 (C-N), 706 (C-Cl); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.95 (s, 1H, Py-H), 7.54-7.51 (dd, 2H, Ar-H), 7.36-7.33 (dd, 2H, Ar-H), 7.73-2.66 (t, 2H, CH$_3$), 1.74-1.67 (m, 2H, CH$_2$), 1.01-0.96 (t, 3H, CH$_3$); MS (ESI) m/z: 292.0; Anal. calcd. for C$_{14}$H$_{12}$ClFN$_4$ (in %): C-57.84, H-4.16, N-19.27. Found C- 57.64, H-4.14, N-19.25.

5-Chloro-8-fluoro-3-(3-chloro-phenyl)-8-fluoro-[1,2,4]triazolo[4,3-c]pyrimidine (3c)
FT-IR (KBr, cm$^{-1}$): 3047 (C-H), 1610 (C=C), 1300 (C-N), 1222 (C-F), 706 (C-Cl); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.90 (s, 1H, Py-H), 7.37-7.35 (d, 2H, Ar-H), 7.30 (m, 1H, Ar-H), 7.28-7.22 (t, 1H, Ar-H), 3.97 (s, 3H, CH$_3$); MS (ESI) m/z: 297.0; Anal. calcd. for C$_{14}$H$_{12}$ClFN$_4$ (in %): C-54.87, H-3.38, N-18.89. Found C- 48.58, H-3.30, N-18.23.

5-Chloro-8-fluoro-3-o-tolyl-[1,2,4]triazolo[4,3-c]pyrimidine (3d)
FT-IR (KBr, cm$^{-1}$): 3050 (C-H), 1617 (C=C), 1300 (C-N), 1220 (C-F), 700 (C-Cl); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.85 (s, 1H, Py-H), 7.50-7.45 (d, 2H, Ar-H), 7.37-7.26 (t, 2H, Ar-H), 2.18 (s, 3H, CH$_3$); MS (ESI) m/z: 268.3; Anal. calcd. for C$_{11}$H$_7$BrN$_2$O (in %): C-54.87, H-3.07, N-21.33. Found C- 54.52, H-2.90, N-21.23.

5-Chloro-3-(3-chloro-phenyl)-8-fluoro-[1,2,4]triazolo[4,3-c]pyrimidine (3e)
FT-IR (KBr, cm$^{-1}$): 3050 (C-H), 1617 (C=C), 1300 (C-N), 1220 (C-F), 700 (C-Cl); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.85 (s, 1H, Py-H), 7.50-7.45 (d, 2H, Ar-H), 7.37-7.26 (t, 2H, Ar-H), 2.18 (s, 3H, CH$_3$); MS (ESI) m/z: 250.1; Anal. calcd. for C$_{14}$H$_{12}$ClFN$_4$ (in %): C-46.67, H-1.78, N-19.79. Found C- 46.62, H-1.76, N-19.83.
5-Chloro-3-(2-chloro-phenyl)-8-fluoro-\[1,2,4\]triazolo[4,3-c]pyrimidine (3f)

FT-IR (KBr, cm\(^{-1}\)) \(\nu\): 3060 (C-H), 1618 (C=N), 1475 (C=C), 1309 (C-N), 1217 (C-F), 704 (C-Cl); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.89 (s, 1H, Py-H), 7.74-7.69 (t, 2H, Ar-H), 7.58-7.47 (d, 2H, Ar-H); MS (ESI) \(m/z\): 284.0; Anal. calcd. for C\(_{11}\)H\(_5\)Cl\(_2\)FN\(_4\) (in %): C-46.67, H-1.78, N-19.79. Found C-46.65, H-1.75, N-19.80.

5-Chloro-8-fluoro-3-phenyl-[1,2,4]triazolo[4,3-c]pyrimidine (3g)

FT-IR (KBr, cm\(^{-1}\)) \(\nu\): 3056 (C-H), 1615 (C=N), 1470 (C=C), 1310 (C-N), 709 (C-Cl); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.87 (s, 1H, Py-H), 7.73-7.71 (m, 3H, Ar-H), 7.60-7.52 (d, 2H, Ar-H); MS (ESI) \(m/z\): 247.7; Anal. calcd. for C\(_{11}\)H\(_6\)ClFN\(_4\) (in %): C-53.14, H-2.43, N-22.53. Found C-53.12, H-2.40, N-22.57.

3-(4-Bromo-phenyl)-5-chloro-8-fluoro-[1,2,4]triazolo[4,3-c]pyrimidine (3h)

FT-IR (KBr, cm\(^{-1}\)) \(\nu\): 3061 (C-H), 1617 (C=N), 1480 (C=C), 1295 (C-N), 1202 (C-F), 697 (C-Cl), 521 (C-Br); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.88 (s, 1H, Py-H), 7.71-7.68 (dd, 2H, Ar-H), 7.63-7.61 (dd, 2H, Ar-H); MS (ESI) \(m/z\): 326.0; Anal. calcd. for C\(_{11}\)H\(_5\)BrClFN\(_4\) (in %): C-40.34, H-1.54, N-17.11. Found C-40.31, H-1.52, N-17.18.

Acknowledgments

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References