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Oxidative Cyclisation Based One-Pot Synthesis of 3-Substituted[1,2,4]triazolo[4,3-*b*]pyridazines Using Me_4NBr/Oxone

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ABSTRACT. A facile one-pot syhthesis of 3-substituted triazolopyridazine and thieno-triazolopyridazine derivatives is described. This protocol involves the preparation of heteroaryl hydrazone from the aldehyde and pyridazinohydrazine derivative followed by subjecting the intermediate directly to oxidative cyclization to assemble the desired 1,2,4-triazloe moiety by employing the mixture of Me_4NBr and oxone. This condition is efficient and is able to tolerate wide range of functional groups.

Key words: 1,2,4-Triazolopyridazine, Tetramethylammonium bromide, Oxone, Aromatic aldehyde

INTRODUCTION

1,2,4-Triazole is an important class of heterocyclic unit which found to have extensive use in organocatalysis and material science. Moreover, 1,2,4-triazole embedded systems display a broad spectrum of biological properties such as antimicrobial, antitubercular, serotonergic, anti-allergy, CNS depressant, anti-inflammatory, anticonvulsants and anti-cancer activities.[1] Recent studies reveal that 1,2,4-triazoles based derivatives are found to be inhibitor of HIV integrase and methionine aminopeptidase-2.[2] Owing to their diverse applications, it gained a great deal of interest among the synthetic chemist. Most common and widely used method to construct 1,2,4-triazole system is the oxidative cyclization of hydrazone. In order to set up the such cyclization reagents such as $POCl_3$, Br_2, $PhI(OAc)_2$, Chloramine –T, $Pb(OAc)_4$, and $CuCl_2$ have been successfully employed on heteroaryl hydrazone.[3] However this protocol suffer by the disadvantages such as the requirement of stiochiometric amount of reagents and the employment of hazardous materials or metal reagents. Further the intermediate hydrazone needs to be isolated and then purified prior to oxidative cyclization. Thus, it is highly desirable to find a new reagent which should be non-toxic and metal-free. Furthermore, one-pot protocol is more convenient since it avoids the unnecessary work up and purification of the intermediate.

In addition, pyridazine represents another important class of heterocyclic compound found to display a variety of biological activities such as antimicrobial, antifungal, antiviral, antitumor, antihypertensive, antitubercular and anticancer agents.[4] Besides, pyridazines and heterocyclic-fused pyridazines are considered to be an important pharmacorein biological research[5] and in particular, thieno skeleton embedded core was found to further enhance the physiological and pharmacological activity.[6] Evidently, triazolopyridazine, a hybrid of pyridazine and 1,2,4-triazole, is a structurally interesting and biologically important unit. Representative examples of this kind are depicted in *Fig.* 1, wherein

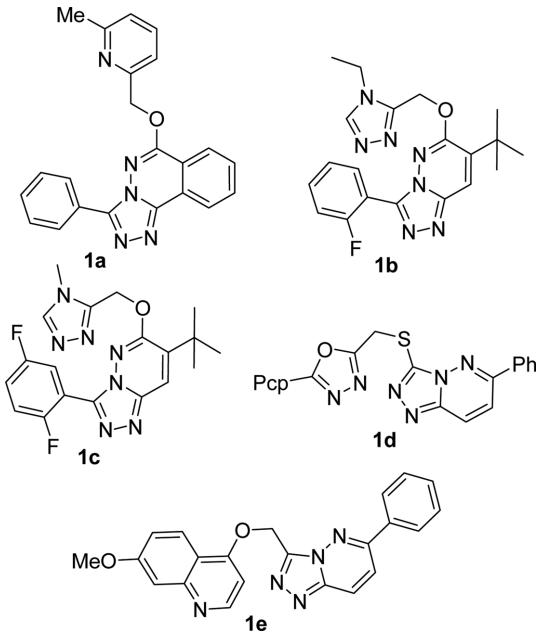


***Figure* 1.** Some biologically active [1,2,4] triazolo [4,3-*b*] pyridazine derivatives.

analogs **1a**–**1c** act as ligand for $GABA_A$ receptor whereas **1d** displayed anti-HIV activity and **1e** was found to act as c-Met kinase inhibitor.[7]

Bearing the biological activities in mind, we planned to devise a viable synthetic route for the triazolopyridazine derivative and thieno-triazolopyridazine derivative. To realize this task, it was decided to construct 1,2,4-triazole unit by keeping the pyridazine moiety as the starting point.

EXPERIMENTAL

All reagents were purchased from commercial suppliers and were used without purification. Melting points were determined in Buchi B-545melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance-400 & 300 NMR MHZ spectrometer in DMSO-d_6 & $CDCl_3$ solution using TMS as an internal reference and ^{13}C NMR were recorded at 100 & 75 MHz. Mass spectra were recorded on LC-MS-Agilent 1200 series, Carbon, Hydrogen, Nitrogen and Sulphur were analyzed on Elementor instrument. All these compounds were purified by flash column Chromatography using 230–400 mesh silica gel.

Typical Procedure for the Synthesis of 3-Substituted Triazolopyridazine

A mixture of corresponding hydrazinylpyridazine **1** or **5** (1 mmol) and aldehyde **2** (1.1 mmol) in ethanol (5 mL) was heated at 60 ºC for 0.5 h. The formation of hydrazone was checked by TLC and the reaction mixture was cooled to rt. Oxone (1.5 mmol) was added to the mixture at rt followed by tetramethyl ammonium bromide (0.2 mmol) and the resulting mixture was heated at 60 ºC for another 5 h. The mixture was cooled to rt and extracted with dichloromethane (2 × 25 mL), dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by column chromatography using hexane/ethyl acetate as eluent to furnish the desired triazolopyridazines **4** and **7**.

Data: 1(4a–4o)

3-(3-Bromophenyl)-6-methyl[1,2,4]triazolo[4,3-*b*]pyridazine: 4a

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1H), 8.47 (d, *J* = 7.89 Hz, 1H), 8.06 (d, *J* = 9.48 Hz, 1H), 7.63–7.60 (m,1H), 7.43–7.38 (m, 1H), 7.06 (d, *J* = 7.98 Hz, 1H) 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 146.2, 144.4, 132.8, 130.9, 130.2, 128.2, 125.9, 124.6, 122.6, 121.8, 21.9.

MS: m/z 290 (M^++1).

3-(2-Bromo-6-chlorophenyl)-6-methyl[1,2,4]triazolo [4,3-*b*] pyridazine: 4b

White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.5 Hz, 1H), 7.69–7.66 (m, 1H), 7.56–7.53 (m,1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.08–7.05 (d, *J* = 9.5 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 146.2, 143.3, 137.1, 132.4, 131.1, 128.5, 127.5, 126.4, 124.2, 122.5, 21.6.

MS: m/z324 (M^++1).

3-(2,6-Dichlorophenyl)-6-methyl[1,2,4]triazolo[4,3-*b*]pyridazine: 4c

White solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 9.6 Hz, 1H), 7.53–7.48 (m, 3H), 7.08 (d, *J* = 9.6 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 144.8, 143.5, 137.1, 132.1, 128.0, 125.5, 124.2, 122.5, 21.6.

MS: m/z 282(M^++2).

3-(4-Bromo-2-fluorophenyl)-6-methyl[1,2,4]triazolo [4,3-*b*]pyridazine: 4d

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 9.5 Hz, 1H), 7.85–7.81 (m, 1H), 7.53–7.50 (m, 2H), 7.08 (d, *J* = 9.5 Hz), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 158.9, 154.8, 144.1, 132.7, 127.8, 125.5, 124.4, 122.5, 120.3, 113.7, 21.8.

MS: m/z 308(M^++1).

3-[2-Chloro-3-(1,1,1-trifluoromethyl)phenyl]-6-methyl [1,2,4]triazolo[4,3-*b*]pyridazine: 4e

Off white solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.5 Hz, 1H), 7.94 (dd, *J* = 1.08, 1.08 Hz, 1H), 7.85 (dd, *J* = 1.10, 1.14 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 9.5 Hz), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 146.4, 143.8, 135.9, 133.4, 129.5, 128.4, 128.3, 126.6, 124.3, 122.6, 120.7, 21.6.

MS: m/z 327(M^++1).

Methyl 4-(6-methyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)benzoate: 4f

White solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 8.5 Hz, 2H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 9.5 Hz, 1H), 7.05 (d, *J* = 9.5 Hz, 1H), 3.95 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 154.8, 146.7, 144.5, 131.0, 130.4, 129.7, 127.2, 124.6, 121.9, 52.2, 21.9.

MS: m/z 269(M^++1).

4-(6-Methyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)benzoic acid: 4g

Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.1 (br, 1H), 8.51 (d, *J* = 8.3 Hz, 2H), 8.3 (d, *J* = 9.5 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 9.5 Hz), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 156.1, 146.1, 145.0, 132.0, 130.6, 130.1, 127.3, 124.9, 123.6, 22.0.

MS: m/z 235(M^++1).

4-(6-Methyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)benzonitrile: 4h

Plae yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 9.5 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.1 (d, *J* = 9.5 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 145.9, 144.7, 132.3, 130.5, 127.7, 124.7, 122.2, 118.4, 113.1, 21.9.

MS: m/z 236 (M^++1).

6-Methyl-3-(3-nitrophenyl)[1,2,4]triazolo[4,3-*b*]pyridazine: 4i

Yellow solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 8.92–8.88 (m, 1H), 8.39–8.83 (s, 1H), 8.16 (d, *J* = 9.5 Hz, 1H), 7.78–7.72 (m, 1H), 7.11 (d, *J* = 9.5 Hz, 1H), 3.8 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 156.2, 148.3, 145.5, 137.3, 133.1, 130.1, 129.7, 127.9, 124.7, 122.1, 22.0.

MS: m/z 256 (M^++1).

3-(4-Ethynylphenyl)-6-methyl[1,2,4]triazolo[4,3-*b*]pyridazine: 4j

Yellow solid; yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 9.4 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 9.4 Hz), 3.22 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 132.3, 127.3, 126.6, 124.7, 123.6, 121.8, 83.2, 78.9, 22.0.

MS: m/z 2365 (M^++1).

6-Methyl-3-[(*E*)-2-phenylethenyl][1,2,4]triazolo[4,3-*b*]pyridazine: 4k

White solid; yield; ^{1}H NMR (300 MHz, DMSO-d_6): 8.27 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 16.6 Hz, 1H), 7.76–7.73 (m, 2H), 7.53–7.33 (m, 4H), 7.30 (d, *J* = 9.5 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.9, 146.7, 144.1, 136.2, 134.6, 129.4, 127.6, 127.1, 124.7, 123.4, 111.5, 21.8.

MS: m/z 237(M^++1).

6-Methyl-3-(thiophen-3-yl)[1,2,4]triazolo[4,3-*b*]pyridazine: 4l

White solid; yield; ^{1}H NMR (400 MHz, $CDCl_3$): 8.64–8.63 (m, 1H), 8.13–8.11 (m, 1H), 8.06 (d, *J* = 9.5 Hz, 1H), 7.50–7.48 (m, 1H), 7.03 (d, *J* = 9.5 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 145.0, 143.5, 126.9, 126.8, 125.8, 125.5, 124.4, 121.5, 21.9.

MS: m/z201(M^++1).

6-Methyl-3-(pyridin-4-yl)[1,2,4]triazolo[4,3-*b*]pyridazine: 4m

White solid; yield; ^{1}H NMR (300 MHz,$CDCl_3$): 8.78 (d, *J* = 5.3 Hz, 2H), 8.44–8.42 (m, 2H), 8.08 (d, *J* = 9.5 Hz, 1H), 7.08 (d, *J* = 9.5 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 150.2, 145.3, 144.8, 133.5, 124.6, 122.3, 120.8, 21.9.

MS: m/z212(M^++1).

3-Cyclopropyl-6-methyl[1,2,4]triazolo[4,3-*b*]pyridazine: 4n

White solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): 7.90 (d, *J* = 9.5 Hz, 1H), 6.91 (d, *J* = 9.5 Hz, 1H), 2.58 (s, 3H), 2.50–2.47 (m, 1H), 1.35–1.31 (m, 2H), 1.28–1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 151.5, 143.3, 124.0, 121.4, 21.6, 7.5, 4.9.

MS: m/z 175(M^++1).

3-Cyclohexyl-6-methyl[1,2,4]triazolo[4,3-*b*]pyridazine: 4o

White solid; yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.96 (d, *J* = 9.6 Hz, 1H), 6.93 (d, *J* = 9.4 Hz, 1H), 3.39–3.32 (m, 1H), 2.60 (s, 3H), 2.15–2.12 (d, *J* = 9.5 Hz, 2H), 2.19–2.17 (m, 6H), 1.56–1.52 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 143.2, 124.2, 121.4, 34.0, 29.9, 25.9, 25.8, 21.6.

MS: m/z 217(M^++1).

Data: 2 (Selected compounds)

3-(3-Bromophenyl)-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7a

Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.7 (s, 1H), 8.5 (s, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (m, 1H), (s, 1H), 7.22.95–2.89 (m, 4H). 1.98–1.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 146.7, 143.1, 142.3, 139.5, 132.8, 130.8, 130.3, 130.1, 130.0, 128.4, 126.1, 122.5, 25.3, 23.4, 22.9, 21.6.

MS: m/z 386(M^++1).

3-(4-Bromophenyl)-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7b

Yellow solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.40 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 2.95–2.89 (m, 4H), 1.98–195 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 147.3, 143.0, 142.4, 139.5, 131.9, 130.8, 130.3, 129.1, 125.4, 124.4, 25.3, 23.4, 22.9, 21.6.

MS: m/z 386(M^++1).

3-(4-Bromo-2-methoxyphenyl)-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7e

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.65–7.62 (m, 1H), 7.51–7.48 (m, 1H), 7.72 (s, 1H), 6.99–6,96 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 2.99–2.97 (m, 2H), 2.91–2.89 (m, 2H), 1.99–1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 157.4, 156.4, 146.4, 141.9, 139.3, 134.7, 134.4, 130.5, 129.8, 117.5, 113.2, 112.7, 56.0, 25.3, 23.4, 22.9, 21.7.

MS: m/z 415(M^++1).

3-(2,4,6-Trimethoxyphenyl)-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7f

Yellow solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 6.25 (s, 2H), 3.88 (s, 3H), 3.70 (s, 6H), 3.95

(s, 3H), 2.96–2.86 (m, 4H), 1.96–1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 160.7, 144.6, 142.3, 141.2, 139.0, 130.5, 130.2, 130.3, 96.8, 90.7, 55.8, 55.3, 25.3, 23.4, 23.0, 21.7.

MS: m/z 397(M^++1).

3-[4(4-Fluorophenoxy)phenyl]-7,8,9,10-tetrahydrobenzo [4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7g

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.8 Hz, 1H), 7.52–7.48 (m, 1H), 7.30–7.27 (m, 1H), 7.04–6.95 (m, 5H), 3.95 (s, 3H), 2.97–2,95 (m, 2H), 2.89–2.87 (m, 2H), 2.00–1.98 (m, Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 152.0, 147.3, 142.6, 141.9, 139.2, 132.4, 131.9, 130.7, 130.4, 130.0, 123.0, 121.1,117.6,117.4, 116.2, 115.9, 25.3, 23.4, 22.9, 21.7.

MS: m/z 447(M^++1).

Methyl 4-(7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*] [1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)benzoate: 7h

Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.59 (d, *J* = 6.7 Hz, 2H), 8.19 (d, *J* = 8.3 Hz, 2H), 3.95 (s, 3H), 2.95–2.89 (m, 4H), 1.98–1.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 147.2, 143.2, 142.4, 139.6, 131.0, 130.8, 130.5, 130.2, 129.7, 127.3, 52.2, 25.3, 23.4, 22.9, 21.6.

MS: m/z 365(M^++1).

3-(4-Allyloxy)phenyl)-7,8,9,10-tetrahydrobenzo[4,5] thieno[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine: 7i

White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (s, 1H), 8.42 (d, *J* = 11.7Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.14–6.03 (m, 1H), 5.49 (d, *J* = 1.2Hz, 2H), 5.34–5.29 (m, 1H), 4.62 (d, *J* = 5.2 Hz, 2H), 2.93–2.86 (m, 4H), 1.96–194 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 148.1, 142.6, 141.6, 139.1, 132.8, 130.7, 130.3, 129.8, 119.2, 117.8, 114.7, 68.7, 25.3, 23.4, 22.9, 21.6.

MS: m/z 363(M^++1).

(*E*)-3-Styryl-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*] [1,2,4]triazolo[4,3-*b*]pyridazine: 7j

Yellow solid; yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.14 (d, *J* = 16.5 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 16.6 Hz, 1H), 7.44–7.39 (m, 2H), 7.36–7.32 (m, 1H), 2.93–2.87 (m, 4H), 1.97–1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 142.5, 142.0, 139.3, 136.2, 135.2, 130.8, 130.2, 128.9, 128.8, 127.2, 111.1, 25.4, 23.5, 23.0, 21.7.

MS: m/z 333(M^++1).

3-Cyclopropyl-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*] [1,2,4]triazolo[4,3-*b*]pyridazine: 7k

White solid; yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 2.96–2.95 (m, 2H), 2.93–2.88 (m,2H), 2.54–2.05 (m, 1H), 1.99–1.97 (m, 4H), 1.41–1.36 (m, 2H), 1.32–1.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 142.1, 141.2, 139.0, 130.6, 130.0, 128.9, 25.2, 23.4, 23.9, 21.6, 7.4, 5.4.

MS: m/z 271(M^++1).

3-Hexyl-7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*d*][1,2,4] triazolo[4,3-*b*]pyridazine: 7l

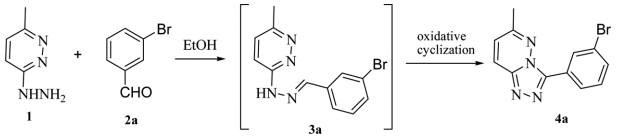
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1H), 3.21–3.31 (m, 2H), 2.91–2.89 (m, 2H), 2.85–2.84 (m, 2H), 1.95–1.85 (m, 8H), 1.48–1.43 (m, 2H), 1.41–139 (m, 6H), 1.12–1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150, 142.0, 141.4, 139.1, 130.7, 130.1, 130.0, 31.4, 28.9, 26.7, 25.3, 24.6, 23.5, 23.0, 22.5, 21.7, 14.0.

MS: m/z 315(M^++1).

RESULTS AND DISCUSSION

Scheme 1 illustrates our plan for the synthesis of triazolopyridazine derivative **4a**. At first, 3-hydrazinyl-6-methylpyridazine **1** was treated with the model substrate, 3-bromobenzaldehyde **2a** in EtOH at 60 ºC for 0.5 h to obtainthe heteroaryl hydrazones **3a** which was subjected directly to oxidative cyclization to acquire the triazolopyridazine **4a**. To perform the oxidative cyclization, various conditions were screened as shown in the *Table* 1. Molecular iodine, potassium iodide and sodium iodide furnished **4a** in poor yield whereas in association with oxidant such as TBHP, DMP, H_2O_2 and *m*CPBA did not improve the yield, however, oxone showed improvement in the yield. Similarly, the reaction was unclean with NBS alone whereas in the presence oxone, **4a** was obtained in moderate yield. Combination of stiochiomentric amount of ^{n}Bu_4NBr/oxone and Me_4NBr/oxone worked well. The mixture of Me_4NBr (20 mol%) and oxone (1.5 equiv.) was found to be the best condition (92%).

Having the optimized condition in hand, various aldehydes were subjected to the one-pot condition to afford the corresponding triazolopyridazine **4** as shown in *Table* 2. Halo substituted aryl aldehydes delivered **4b**–**4f** in good yield. Both, electron donating and electron withdrawing group containing aryl aldehydes worked well. Interestingly, alkyne substituted aldehyde gave **4k** and cinnamaldehyde provided **4l** without affecting C–C multiple bond present in the substituent demonstrates that this oxidative condition is mild and highly efficient. Similarly, hetero aromatic aldehydes and aliphatic aldehydes such as cyclo-



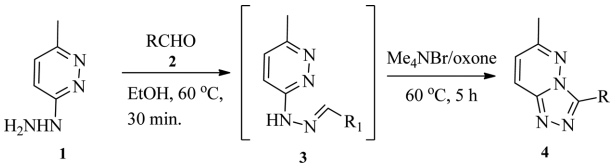
***Scheme* 1.** Synthesis of triazolopyridazine derivative **4a**.

***Table* 1.** Optimization of oxidative cyclization of **1** and **2a**

Entry	Reagent[a]	Oxidant[b]	Temp	Time (h)	Yield (%)[c]
1	I_2	–	rt	12	10
2	KI	–	60 °C	12	12
3	NaI	–	60 °C	12	14
4	I_2	TBHP	rt	12	25
5	KI	TBHP	60 °C	12	20
6	NaI	TBHP	60 °C	12	20
7	I_2	DMP	rt	12	15
8	KI	DMP	60 °C	12	18
9	KI	H_2O_2	60 °C	12	5
10	KI	m-CPBA	60 °C	12	5
11	KI	Oxone	60 °C	12	32
12	NBS	–	60 °C	5	10
13	NBS	Oxone	60 °C	5	42
14	$^nBu_4NBr$	Oxone	60 °C	5	75
15	Me_4NBr	Oxone	60 °C	5	89
16[d]	Me_4NBr	Oxone	60 °C	5	92

[a]1 equiv. of reagent was used.
[b]1.5 equiv. of oxidant was used.
[c]Isolated yield.
[d]20 mol% of reagent and 1.5 equiv. of oxidant were used.

***Table* 2.** One-pot oxidative cyclization of various aldehydes with 4-methylhydrazinopyridazine

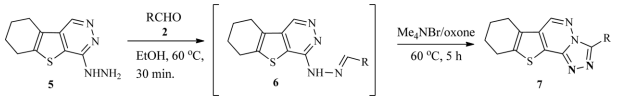


Entry	Product	R	Yield (%)	Mp (°C)
1	**4b**	2-Bromo-6-chlorophenyl	80	220–222
2	**4c**	2,6-Dichlorophenyl	78	235–236
3	**4d**	2-Fluoro-4-bromophenyl	83	152–153
5	**4e**	2-Chloro-3-trifluoromethylphenyl	76	240–243
6	**4f**	4-Methylbenzoate	88	198–200
7	**4g**	4-Phenyl carboxylic acid	84	320–325
8	**4h**	4-Cyanophenyl	90	225–227
9	**4i**	3-Nitrophenyl	89	230–232
10	**4j**	4-Ethynylphenyl	75	176–168
11	**4k**	(*E*)-Styryl	72	189–190
12	**4l**	Thiophen-3-yl	83	155–158
13	**4m**	4-Pyridyl	80	236–238
14	**4n**	Cyclopropyl	88	83–84
15	**4o**	Cyclohexyl	88	90–92

propyl and cyclohexylcarboxaldehydes smoothly underwent oxidative cyclization in good yield.[8]

In order to further build complexity in the triazolopyridazine framework especially with hetereocyclic unit, thieno

***Table* 3.** One-pot oxidative cyclization of various aldehydes with 4-hydrazinyl-6,7,8,9-tetrahydro[1]benzothieno[2,3-*d*]pyridazine



Entry	Product	R	Yield (%)	Mp (°C)
1	**7a**	3-Bromophenyl	90	263–265
2	**7b**	4-Bromophenyl	82	285–286
3	**7c**	2-Fluorophenyl	88	251–252
4	**7d**	2,6-Dichlorophenyl	80	293–295
5	**7e**	2-Methoxy-4-bromophenyl	81	195–197
6	**7f**	2,4,6-Trimethoxyphenyl	78	285–288
7	**7g**	4-(4-Fluorophenoxy)-phenyl	86	175–178
8	**7h**	4-Methylbenzoate	83	268–273
9	**7i**	4-(Allyloxy)phenyl	81	190–192
10	**7j**	(*E*)-Styryl	85	183–185
11	**7k**	Cyclopropyl	82	158–162
12	**7l**	*n*-hexyl	80	170–172

substituted pyridazine derivative **5** was prepared[9] and then subjected to this one-pot process. Accordingly, treatment of **5** with aldehydes **2** furnished the heteroaryl hydrazones **6** and then in situ oxidative cyclization under the optimized condition afforded the thieno-triazolopyridazines **7** (*Table* 3). Halo, electron donating and electron withdrawing group containing aryl aldehydes smoothly underwent to this one-pot process. Towards the end, aliphatic alde-

hydes led to **7** in high yield.[8]

CONCLUSION

In conclusion, one-pot synthesis of 3-substituted triazolopyridazine derivatives was developed from the readily available aldehydes and hydrazinopyridazine derivatives. Similarly, the thieno analogs were obtained from the corresponding thienohydrazinopyridazine derivatives. Our method to construct 1,2,4-triazole moiety is based on oxidative cyclization which was successfully executed by Me_4NBr and oxone, a non-toxic, metal-free and environmentally benign condition. Also, this condition is mild and thus displayed a wide functional group tolerance. Halo, nitro and related functional groups present in the triazolopyridazine derivative can be used for further elaboration.

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8. Thieno-pyridazine derivative **5** was synthesized from 3-formyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic acid in four steps.