Facile and convenient strategy towards synthesis of 4-substituted 2-aminothiazolo[4,5-d]pyridazinones

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ABSTRACT

Convenient synthesis of 4-substituted 2-aminothiazolo[4,5-d]pyridazinones has been achieved in 12 steps with overall yield of 19% by employing Grignard reaction as the key step. The route utilizes well established thiazole ring formation followed by Grignard reaction to introduce substitution at 4-position effectively. In addition to the use of inexpensive chemicals, the present route first time gave access to the 4-substituted 2-aminothiazolo [4,5-d]pyridazinones with free amino group at C-2 position.

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Sulfur-containing fused pyridazinones have drawn much attention due to their potential biological activities.[1] Recently, heterocyclic-fused pyridazinones have been synthesized as potential *anti*-asthmatic and *anti*-inflammatory agents devoid of CNS and cardiovascular side effects.[2] Heterocyclic-fused 3(2H)-pyridazinones have been synthesized as potent and selective phosphodiesterase (PDE)IV inhibitors for the treatment of asthma, inflammation and several CNS pathologies (Fig. 1).[3,4] 2-aminothiazolo[4,5-d]pyridazinones, which possess analgesic and *anti*-inflammatory activities were first synthesized by Takaya et al. by cyclization of 5-amino-6-chloropyridazinones with carbon disulfide, followed by *S*-methylation and then amination.[5] Furukawa and co-workers reported the synthesis of 2-arylaminothiazolo[4,5-d]pyridazinones by reacting 5(4)-amino-4(5)-chloropyridazin-3(2H)-ones with methyl dithiocarbamates and isothiocynates[6,7] but failed to introduce free amino group at the C-2 position. Free amino group at this position may serve as powerful handle for further functional group transformations. Additionally, these literature methods have used properly substituted pyridazinones as one of the building blocks, which may restrict the incorporation of substituent at 4-position in [4,5-d]pyridazinone ring. For our drug discovery programme and in continuation of our interest,[8] we needed substitution at 4-position as well as free amino group at 2-position in thiazolo[4,5-d]pyridazin-7(6H)-one ring system.

To the best of our knowledge, there is no report describing synthesis of 4-substituted 2-aminothiazolo [4,5-d]pyridazin-7(6H)-ones. Herein, we would like to report convenient and general strategy towards the synthesis of 4-substituted 2-aminothiazolo [4,5-d]pyridazinones.

We envisioned the synthesis of desired heterocycle as a hybridization approach, viz formation of 2-aminothiazole subsequently followed by formation of pyridazinone ring (Fig. 2). According to the notion, we first constructed substituted thiazole ring 7 followed by functional group transformations to obtain aldehyde 9. Addition of Grignard reagent to aldehyde 9 subsequently followed by cyclization with hydrazine hydrate furnished desired heterocycle 13.

The synthesis of desired heterocycle began with commercially available 4-chloroethylacetoacetate 5, (Scheme 1) which was treated with suspension of sodium hydride and potassium *tert*-butox-
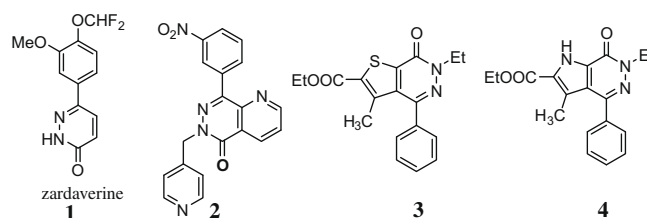

Figure 1. Recently reported heterocyclic-fused pyridazinones as potent PDE (IV) inhibitors.

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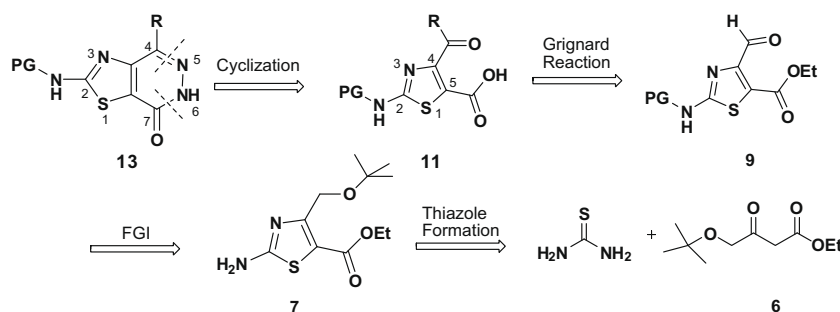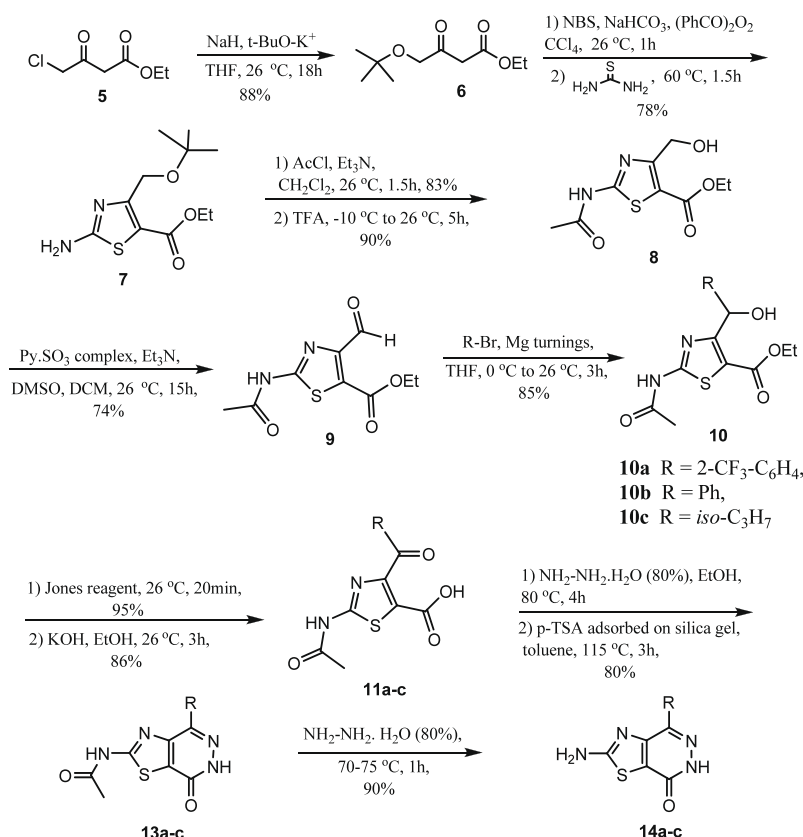*E-mail address:* rajendrakharul@zyduscadila.com (R.K. Kharul).

Figure 2. Retrosynthetic analysis.

Scheme 1. Synthesis of 4-substituted 2-aminothiazolo[4,5-d]-pyridazinones.

ide in dry tetrahydrofuran to obtain 6.[9,10] Bromination using *N*-bromosuccinimide followed by reaction with thiourea of compound 6 yielded thiazole derivative 7.[11,12] The amino group was protected as acetamide followed by deprotection of *tert*-butoxide with TFA to furnish thiazole alcohol 8. In our opinion, thiazole alcohol 8 was suitable candidate for introduction of aryl or alkyl substituent at 4-position in the pyridazinone ring. To achieve this, thiazole alcohol 8 was oxidized to the corresponding aldehyde 9.

The oxidation was attempted with different oxidizing agents including pyridinium dichromate (PDC),[13a] pyridinium chlorochromate (PCC),[13b] Jones reagent[13c] and Swern oxidation.[13d] To insure complete oxidation, excess of the reagent was used. Isolation of aldehyde in pure state with good yield was also a problem. However, by using Parikh–Doering oxidation[14a,14b] the above problems were circumvented and aldehyde 9 was obtained in good yield after purifying as its bisulfite adduct.[14c]

Once, aldehyde 9 was in hand, we were set to introduce alkyl, aryl substituent at 4-position in thiazolo[4,5-d]pyridazinone ring
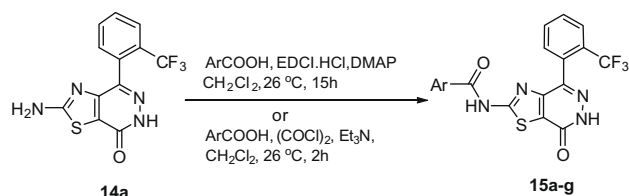
system. To achieve this, under optimized reaction conditions, aldehyde 9 was subjected to the Grignard reaction to furnish corresponding secondary alcohol 10. Initially, when Grignard reaction was carried out under unoptimized reaction parameters, reduction of aldehyde 9 to the primary alcohol 8 was preferred over addition of Grignard reagent to the aldehyde. This observation was in accordance with the literature.[15] Although presence of β-hydrogen is necessary in Grignard reaction for reduction,[15] the Grignard reaction still led to reduction. This is confirmed by ^{1}H NMR and mass spectrometric analysis. After Grignard reaction, the alcohol 10 was oxidized with Jones reagent followed by basic hydrolysis and acidic treatment to yield ketoacid 11. Ketoacid 11a was subjected to cyclization using hydrazine hydrate[16a,16b] (1.7 equiv, 80%) in ethanol to furnish 12a, 13a and 14a in ratio of 3:2:1. When the cyclization of ketoacid 11a (1 mmol) was assayed for molar ratio of hydrazine hydrate (80%) from 1.3 to 1.9 mmol, we have observed that, lower molar ratio of hydrazine hydrate (80%) led to incomplete cyclization while higher molar ratio did not improve
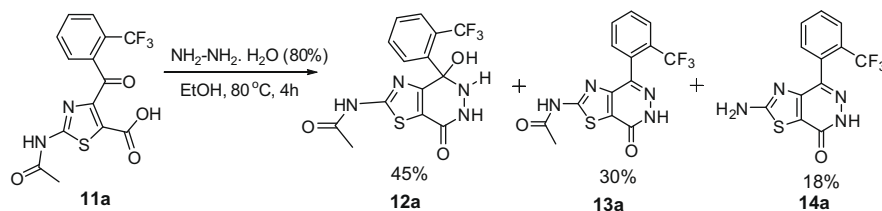
Scheme 2. One-pot synthesis of three derivatives of 2-aminothiazolo[4,5-d]pyridazinones.

the above mentioned ratio of **12a**, **13a** and **14a**. The conversion ratio was unaltered throughout the series **11a–c** (Scheme 2). To obtain target molecule **14**, the mixture of **12**, **13** and **14** was treated with *p*-TSA adsorbed on silica gel to insure complete dehydration followed by deprotection of acetamide with hydrazine hydrate.[17]

As mentioned earlier, free amino group at 2-position may give a proper handle for further functional group transformations. To exemplify, 2-aminothiazolo[4,5-d]pyridazin-7(6H)-one **14** when treated with different aryl carboxylic acids by using 3-ethyl-1(N,N-dimethyl)amino propylcarbodiimide (EDCI) as coupling agent, gave carboxamides **15a–e**[18] in low yield. Alternatively, carboxamides **15f–g**[19] were synthesized by converting carboxylic acid to corresponding acid chloride followed by treatment with 2-aminothiazolo[4,5-d]pyridazin-7(6H)-one **14** (Scheme 3, Table 1). The low yield could be attributed to the weaker nucleophilicity of the amino group imparting low reactivity of the substrate.

In summary, new convenient synthetic methodology towards 4-substituted 2-aminothiazolo[4,5-d]pyridazinones was established by using simple organic functional group transformations as well as inexpensive chemicals. Although, the synthetic sequence was multi-step, it provides free amino group at C-2 position with substitution at C-4 position with impressive overall yield. Presently, we are working to improve the overall yield. Further, its conversion to the corresponding aryl carboxamides was demonstrated. The developed methodology may prove suitable for alternative, rapid synthesis of thiazolopyridazinone libraries, which are of interest as promising structural analogues of biologically active pyridazinones.

Acknowledgements

Supplementary data

Supplementary data (additional experimental procedures, compound characterization data, copies of spectra and chromatograms) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.105.

Scheme 3. Synthesis of aryl carboxamides **15a–g**.

Table 1
A series of arylcarboxamides prepared **15a–g**

Entry	Compound	Ar	Isolated yield (%)
1	**15a**	phenyl	48
2	**15b**	4-F-phenyl	36
3	**15c**	2-OMe-phenyl	18
4	**15d**	2-Cl-phenyl	21
5	**15e**	2,4-diCl-phenyl	20
6	**15f**	phenyl-SO2-N-piperidine	38
7	**15g**	phenyl-SO2-N-piperidine	35

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12. *Preparation of substituted thiazole*: Ethyl-2-amino-4-(*tert*-butoxymethyl)-thiazole-5-carboxylate (**7**): *N*-bromosuccinimide (28.0 g, 157.37 mmol, 1.1 equiv), benzoyl peroxide (589 mg, 2.43 mmol, 1.7 mol%), sodium bicarbonate (14.4 g, 50%w/w) were added successively at 26 °C with stirring to

the solution of ethyl 4-*tert*-butoxy-3-oxobutanoate (**6**) (28.9 g, 143.06 mmol, 1 equiv) in CCl$_4$ (75 mL). The reaction mixture was stirred for 1 h at 26 °C. After 1 h, the white solid of succinamide was filtered off and the filtrate was evaporated in vacuo. The thick liquid thus obtained was used for further reaction without purification. Thiourea (14.7 g, 193.13 mmol, 1.35 equiv) was added to crude ethyl 2-bromo-4-*tert*-butoxy-3-oxobutanoate (30.2 g) at 26 °C. The neat reaction mixture was then heated to 60–65 °C for 1.5 h. After completion of the reaction, it was cooled to 26 °C and water was added to it. The aqueous layer was extracted with DCM (3 × 150 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and distilled in vacuo. The crude product was purified by column chromatography using silica gel (100–200 mesh size) as stationary phase and ethyl acetate:petroleum ether (1:1) as a mobile phase. (28.79 g, 78% yield): mp 108–110 °C; IR (KBr cm^{-1}) 3163, 1701, 1512, 1288, 759; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 5.88 (s, 2H) 4.73 (s, 2H) 4.27 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H) 1.29 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 170.8, 162.1, 159.5, 111.5, 74.2, 61.1, 58.8, 27.7, 14.4; UPLC purity: 97.1%, t_R 3.12 min; *m/z* (Relative intensities) (+ve mode) 258.9 (M+H)$^+$, (100%); 280.9 (M+Na)$^+$, (60%). Anal. Calcd for C$_{11}$H$_{18}$N$_2$O$_3$S: C, 51.14; H, 7.02; N, 10.84; S, 12.41. Found: C, 50.97; H, 6.95; N 10.57; S, 12.79.

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18. *General procedure for preparation of aryl carboxamides* (**15a–e**): To the stirring solution of acid (1.5 equiv) in DCM, EDCI, HCl (2.4 equiv) and 4-*N,N*-dimethylamino pyridine (1 equiv) were added simultaneously under nitrogen atmosphere at 26 °C. The amine (**14a**) (1 equiv) was added portion-

wise to the reaction mixture at 0–5 °C. The reaction mixture was stirred for 10 min at 0–5 °C and then at 26 °C for 15 h. After completion, the reaction mixture was diluted with DCM (50 mL), washed with water (15 mL), brine (10 mL), dried over anhydrous sodium sulfate and filtered. The organic layer was then concentrated in vacuo to furnish crude product. The crude product was purified by column chromatography using silica gel (100–200 mesh size) as stationary phase and ethyl acetate:petroleum ether (2:3) as a mobile phase. Compound **15b** (0.128 g, 36% yield): IR (KBr cm^{-1}) 2928, 2854, 1651, 1508, 1280, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.41 (s, 1H), 13.25 (s, 1H), 8.18 (dd, J_1 = 5.6 Hz, J_2 = 8.8 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.75–7.67 (m, 2H), 7.36 (t, *J* = 8.8 Hz, 2H); HPLC purity 99.7%, t_R 18.36 min.; ESI-MS *m/z* (Relative intensities) (+ve mode) 434.9 (M+H)$^+$, (100%), 466.9 (M+Na)$^+$, (30%).

19. *General procedure for preparation of aryl carboxamides* (**15f–g**): Acid (1 equiv) was dissolved in DCM (3 mL) under N$_2$ atmosphere. Oxalyl chloride (1.5 equiv) was added dropwise in the reaction mixture at 0 °C. The reaction mixture was then stirred for 1.5 h at 26 °C. Upon completion, DCM and excess oxalyl chloride were removed in vacuo. The acid chloride thus prepared was dissolved in DCM (5 mL) under nitrogen atmosphere. In another round-bottomed flask amine (**14a**) (1 equiv) dissolved in DCM (3 mL) was taken and Et$_3$N (2.5 equiv) was added at 26 °C, stirred for 10 min at the same temperature. The acid chloride dissolved in DCM (5 mL) was added in drops to the above mixture at 0 °C. The whole reaction mixture was stirred for 2 h at 26 °C. After 2 h, the reaction mixture was diluted with DCM (50 mL), washed with water (15 mL), brine (10 mL), dried over anhydrous sodium sulfate and filtered. The organic layer was concentrated in vacuo to obtain crude product. The crude product was purified by column chromatography using silica gel (100–200 mesh size) as stationary phase and ethyl acetate: petroleum ether (2:3) as a mobile phase. Compound **15f** (0.138 g, 38% yield): IR (KBr cm^{-1}) 3173, 2926, 1649, 1537, 1171, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.26 (s, 1H), 13.15 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.74–7.70 (m, 4H), 7.65–7.62 (t, *J* = 7.2 Hz, 3H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 1H), 2.39 (t, *J* = 11.2 Hz, 1H), 2.24 (t, *J* = 11.2 Hz, 1H), 1.85–1.82 (m, 1H), 1.43–1.28 (m, 3H), 0.98–0.85 (m, 1H); HPLC purity 95.7%, t_R 4.16 min.; ESI-MS *m/z* (Relative intensities) (+ve mode) 564.1 (M+H)$^+$, (90%), 585.9 (M+Na)$^+$, (100%).