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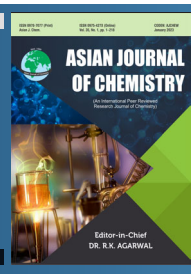

Synthesis of Novel Biaryl Fused Thiazolo[3,2-*b*][1,2,4]triazol-2-amines from Thiazole Amine Involving Suzuki Coupling Reaction under Microwave Irradiation

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Novel series of fused heterocycles in which amino triazole fused to biphenyl thiazole were synthesized in a multistep reaction starting from 2-aminothiazole. The amino compound with ethoxy carbonyl isothiocyanate afforded the ethyl carbamate thiomide derivative of thiazole, which further underwent intramolecular cyclization with hydroxyl amine hydrochloride in presence of DIPEA to furnish the fused thiazolotriazole amine. Haloaryl group in the fused heterocycle under Suzuki coupling condition afforded biphenyl derivatives of fused thiazolotriazole amines. All the synthesized compounds were confirmed based on their spectral data.

Keywords: Biaryl, Fused thiazolo 1,2,4-triazole, Suzuki coupling, Microwave irradiation.

INTRODUCTION

1,2,4-Triazole and its derivatives belong to an important class of compounds, which attracted the attention of many chemists and biologists in organic synthesis, medicinal and pharmaceutical fields [1]. These compounds exhibited diverse biological activities such as anticancer [2], antimicrobial, anticonvulsant [3], anti-inflammatory [4], antitubercular [5], analgesic [6], antibacterial [7] and anti-HIV [8]. 1,2,4-Triazole moiety found in many chemotherapeutic drugs such as fluconazole [9], itraconazole [10] are the potent antifungal drugs, prothioconazole [11] active against plant-pathogenic fungal infections, alprazolam [12] is used for treatment of anxiety disorders and anastrozole [13], letrozole are used to treat anticancer disease [14]. Furthermore, 1,2,4-triazoles have several applications in organocatalysts, medicines and pesticides [15-22]. In addition, thiazole derivatives are important bioactive nucleus in medicinal chemistry due to their wide range of pharmacological applications. Many of the synthesized thiazole derivatives exemplified for various biological activities including antifungal, anticancer, antimalarial, antioxidant, analgesic, anti-inflammatory, antibacterial, antiallergic, antihypertensive and antipsychotic and also the thiazole scaffold is present in more than 18 FDA-approved drugs [23-28].

On the other hand, fused thiazolo-triazole nucleus has been the subject of intense interest because of its remarkable biological properties such as anticancer, anti-inflammatory, antimicrobial, antioxidant and antidiabetic activities [29-32]. Biphenyl derivatives have wide range of activities such as antimicrobial, antifungal, antiproliferative, antidiabetic, immunosuppressant, analgesic, anti-inflammatory, *etc*. [33-35]. Recent literature on pharmacological study reveals that considerable improvement in biological activity, when two or more pharmacophore units were combined together in one molecule. In view of the above aspect, we taken up the synthesis of a series of bioactive molecules with three active pharmacophore units such as biphenyl substituted fused thiazolotriazole.

EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. The Bruker AV instrument was used to record ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra.

$CDCl_3$, DMSO-d_6 solvents were used to record NMR spectra of samples. ESI-MS spectra were recorded Agilent 1100 LC-Q TOF instrument. TLC plates coated with Merck silica gel 60 F_{254} were used to monitor the reactions.

Synthesis of ethyl(4-(4-bromophenyl)thiazol-2-yl-amino)carbonothioylcarbamate (2): To a stirred solution of compound **1** (39 mmol, 1.0 equiv.) in 1,4-dioxane (40 mL) was added ethoxycarbonyl isothiocyanate (43 mmol, 1.1 equiv.) and then stirred the reaction mixture at 25 ºC. After 18 h, reaction mixture was concentrated under reduced pressure to obtain the crude compound, which was on trituration with methanol afforded compound **2** (yield: 90%) as white solid (**Scheme-I**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (brs, 1H), 11.92 (brs, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 4.27 (q, *J* = 14.4 Hz, 2H), 1.29 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 175.90, 158.99, 154.32, 148.27, 133.45, 132.15, 128.22, 121.63, 110.01, 66.82, 14.51. Mass ESI *m/z*: 385.9 $[M+H]^+$, 388.0 $[M+H+2]^+$.

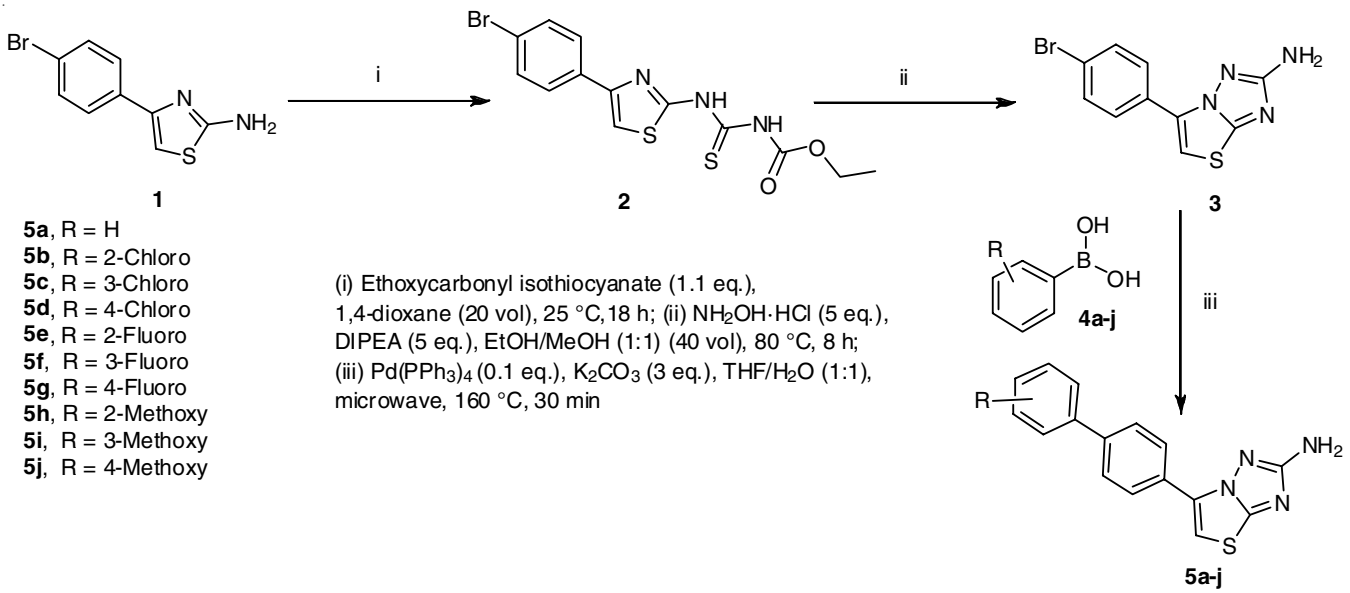
Synthesis of 6-(4-bromophenyl)thiazolo[3,2-*b*][1,2,4]-triazol-2-amine (3): Hydroxylamine hydrochloride (185 mmol, 5.13 equiv.) was dried under vacuum at 70 ºC for 30 min. Then cool to 25 ºC was added EtOH/MeOH (1:1) (40 vol.) followed by compound **2** (36 mmol, 1.0 equiv.) and DIPEA (185 mmol, 5.13 equiv.) and then stirred the reaction mixture at 80 ºC for 8 h. Progress of the reaction monitored by TLC (50% EtOAc/hexane, R_f: 0.3). Reaction mixture was concentrated under reduced pressure to obtain the residue, which was taken in water (5 vol.) stirred for 1 h and the resulted solid was filtered and recrystalized from methanol to give compound **3** (yield: 85%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 168.80, 155.85, 132.21, 130.98, 128.43, 127.80, 123.00, 106.22. ESI-Mass *m/z*: 295.0 $[M+H]^+$, 297.0 $[M+H+2]^+$.

General procedure for the synthesis of 6-(substituted-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*][1,2,4]triazol-2-amine (5a-i): To a stirred solution of compound **3** (0.68 mmol, 1.0 equiv.) in THF/H_2O (1:1) (10 vol) was added compound **4a-j** (1.02 mmol, 1.5 equiv.) and K_2CO_3 (2.04 mmol, 3.0 equiv.) degassed for 10 min with N_2 followed by $Pd(PPh_3)_4$ (0.068 mmol, 0.1 equiv.) again degassed for 10 min. Then the reaction was carried out under microwave conditions at 160 ºC for 30 min. After completion of the reaction, the content of the reaction mixture was filtered through celite pad, which was washed with THF (5 vol.) (**Scheme-I**). The filtrate was concentrated to obtain crude residue, which was purified by silica gel column chromatography using gradient elution with 5-10% MeOH/DCM to furnish the corresponding 6-(substituted-[1,1′-biphenyl]-4-yl)-thiazolo[3,2-*b*][1,2,4]triazol-2-amine (**5a-j**).

6-([1,1′-Biphenyl]-4-yl)thiazolo[3,2-*b*][1,2,4]triazol-2-amine (5a): White solid, yield: 67%, m.p.: 169-172 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.30 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.55-7.51 (m, 3H), 6.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 166.93, 153.73, 147.91, 140.81, 138.35, 133.16, 129.53, 129.24, 128.74, 127.69, 127.12, 127.09, 124.7, 105.47. ESI-Mass *m/z*: 293.5 $[M+H]^+$.

6-(2′-Chloro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5b): White solid, yield: 65%, m.p.: 171-174 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm: 8.08 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.51-7.48 (m, 1H), 7.37-7.31 (m, 3H), 6.88 (s, 1H), 4.38 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ ppm: 167.47, 156.52, 156.12, 140.76, 139.77, 133.16, 132.57, 131.36, 130.20, 129.09, 127.65, 127.13, 126.43, 104.42. Mass ESI *m/z*: 326.9 $[M+H]^+$.

6-(3′-Chloro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5c): White solid, yield: 68%, m.p.: 190-193 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.32 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.94, 155.90, 141.82, 139.53, 134.33, 131.60, 131.30, 128.25, 128.18, 127.60, 127.08, 126.89, 125.91, 105.72. Mass ESI *m/z*: 326.9 $[M+H]^+$.



Scheme-I: Synthesis of 6-(substituted-[1,1'-biphenyl]-4-yl)thiazolo[3,2-*b*][1,2,4]triazol-2-amines (**5a-j**)

6-(4′-Chloro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5d): White solid, yield: 63%, m.p.: 245-248 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.31 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.62 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 6.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.93, 155.90, 139.76, 138.45, 133.26, 131.64, 129.43, 128.94, 127.97, 127.34, 127.10, 105.57. Mass ESI *m/z*: 326.9 $[M+H]^+$.

6-(2′-Fluoro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5e): Off-white solid, yield: 65%, m.p.: 178-181 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.31 (d, *J* = 8.4 Hz, 2H), 7.72 (dd, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.62-7.58 (m, 1H), 7.48-7.44 (m, 1H), 7.37-7.32 (m, 2H), 6.00 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.94, 160.84, 158.39, 155.89, 136.25, 131.67, 131.23, 130.50, 130.41, 129.61, 128.04, 126.75, 125.53, 125.50, 116.79, 116.57, 105.76. Mass ESI *m/z*: 311.0 $[M+H]^+$.

6-(3′-Fluoro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5f): Off-white solid, yield: 69%, m.p.: 208-211 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.32 (d, *J* = 8.4 Hz, 2H), 7.89 (dd, *J* = 8.4 Hz, 2H), 7.66-7.60 (m, 3H), 7.54 (q, *J* = 14.4 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.94, 164.44, 162.02, 155.89, 142.13, 142.05, 139.67, 131.61, 131.46, 131.38, 128.22, 127.55, 127.07, 123.25, 115.17, 114.96, 114.00, 113.78, 105.68. Mass ESI *m/z*: 311.0 $[M+H]^+$.

6-(4′-Fluoro-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5g): Off-white solid, yield: 67%, m.p.: 231-234 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.29 (d, *J* = 8.4 Hz, 2H), 7.84-7.79 (m, 4H), 7.61 (s, 1H), 7.33 (t, *J* = 8.8 Hz, 2H), 5.98 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6), δ ppm: 167.45, 163.85, 161.40, 156.23, 141.06, 136.22, 132.73, 128.63, 128.55, 127.26, 127.16, 126.96, 115.85, 115.64, 103.94. Mass ESI *m/z*: 311.0 $[M+H]^+$.

6-(2′-Methoxy-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5h): Off-white solid, yield: 61%, m.p.: 168-171 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.30 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.37-7.32 (m, 2H), 7.12-7.08 (m, 2H), 6.01 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 167.40, 156.50, 156.08, 153.3, 139.63, 133.12, 132.53, 131.30, 130.23, 129.09, 127.65, 126.43,114.7, 104.42, 56.5. Mass ESI *m/z*: 323.1 $[M+H]^+$.

6-(3′-Methoxy-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5i): Off-white solid, yield: 63%, m.p.: 165-168 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.29 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.29-7.26 (m, 2H), 7.08-7.05 (m, 1H), 6.98 (s, 1H), 6.01 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.87, 155.74, 153.23, 141.12, 139.50, 134.25, 130.04, 128.13, 127.41, 126.55, 125.42, 122.3, 118.5, 104.72, 55.92. Mass ESI *m/z*: 323.1 $[M+H]^+$.

6-(4′-Methoxy-[1,1′-biphenyl]-4-yl)thiazolo[3,2-*b*]-[1,2,4]triazol-2-amine (5j): Off-white solid, yield: 62%, m.p.: 162-165 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm: 8.30 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.00 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm: 168.77, 155.81, 153.2, 139.65, 138.20, 133.13, 131.44, 129.12, 128.65, 127.97, 127.05, 117.3, 105.57, 55.83. Mass ESI *m/z*: 323.1 $[M+H]^+$.

RESULTS AND DISCUSSION

Compound ethyl(4-(4-bromophenyl)thiazol-2-ylamino)-carbonothioylcarbamate (**2**) was synthesized by the reaction of 4-(4-bromophenyl)thiazol-2-amine (**1**) with ethoxycarbonyl isothiocyanate in 1,4-dioxane at 25 ºC for 18 h to afford the desired compound **2** with 90% yield. The formation of carbamate **2** was confirmed by spectral data. The ^{1}H NMR spectrum of compound **2** showed two characteristic broad singlet peaks at δ 13.12 and 11.92 ppm integrated each for one proton are assigned to two NH protons, a singlet signal at δ 7.77 ppm integrated for one proton was corresponded to thiazole ring proton and also the spectrum showed two more characteristics peaks at δ 4.27 ppm as quartet and 1.29 ppm as triplet integrated each for two and three protons are assigned to ester ethyl group protons, respectively. The remaining four phenyl ring protons signals are appeared at δ 7.87 and 7.62 ppm as a doublet integrated each for two protons. In ^{13}C NMR spectrum, compound **2** showed characteristic thiocarbonyl carbon and carbonyl carbon peaks at δ 175.9 and 158.98 ppm, respectively. Other characteristic ethyl group carbon signals are appeared at δ 66.82 and 14.51 ppm. The ESI-mass spectrum of **2** showed the molecular ion peak at *m/z* 388 $[M+H]^+$ corresponds to the molecular formula $C_{13}H_{12}N_3O_2S_2Br$. The reaction of carbamate (**2**) with hydroxylamine hydrochloride in the presence of DIPEA in EtOH/MeOH (1:1) at 80 ºC for 8 h furnished compound **3** (yield: 85%) as white solid. The structure of the compound **3** was deduced from ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of compound **3** showed a characteristic singlet peak at δ 7.63 ppm integrated for one proton was assigned to thiazole ring proton and two doublet peaks at δ 8.17 & 7.35 ppm for four phenyl ring protons. In the ^{13}C NMR spectrum, it indicates the absence of signals δ 175.9, 158.98 ppm due to thiocarbonyl and carbonyl carbons and the presence of fused thiazolotriazole ring by showing the signal at δ 168.80 ppm due to the amine attached carbon of triazole ring. The ESI mass spectrum of compound **3** showed the molecular ion peak appeared at *m/z* 295 $[M+H]^+$, 297 $[M+H+2]^+$ corresponds to the molecular formula $C_{10}H_7N_4SBr$. The target compounds biaryl fused thiazolotriazole amines **5a-j** were synthesized from the C-C coupling reaction of compound **3** with different aryl boronic acids **4a-j** in the presence of $Pd(PPh_3)_4$ as catalyst, K_2CO_3 as base in THF/H_2O (1:1) medium under microwave conditions at 160 ºC for 30 min (**Scheme-I**). All the synthesized 6-(substituted-[1,1′-biphenyl]-4-yl)thiazolo-[3,2-*b*][1,2,4]triazol-2-amine (**5a-j**) were confirmed by the spectral analysis data. As a representative case, compound **5d** is discussed. The ^{1}H NMR spectrum of **5d** showed four doublet signals at δ 8.31, 7.84, 7.79 and 7.55 ppm each integrated for two protons corresponds to biphenyl protons along with a singlet signal at δ 7.62 ppm corresponds to thiazole ring proton. A broad singlet signal at δ 6.01 ppm integrated for two protons corresponds to amine group. The ^{13}C NMR spectrum of compound **5d** showed the characteristic carbon signal at δ 168.93 due to amino attached thiazolofused triazole carbon,

while remaining carbons of fused thiazolotriazole carbons resonated at δ 155.90, 127.10 and 105.57 ppm. The ESI mass spectrum of copound **5d** showed the protonated molecular ion peak at *m/z* 326.9, which corresponds to the molecular formula $C_{16}H_{11}N_4SCl$. The structures of the remaining all the target compounds were also confirmed on the basis on the spectral analysis data.

Conclusion

In summary, a new series of biaryl fused thiazolotriazoles starting from 4-bromophenylthiazol-2-amine (**1**) *via* three steps were synthesized. Amine **1** on reaction with ethoxycarbonyl isothiocyanate gave carbamate derivative **2**, which further underwent cyclization reaction with hydroxyl amine in the presence of DIEPA to furnish the fused thiazolotriazole **3**. The bromo fused compound **3** on palladium catalyzed Suzuki aryl coupling reaction with aryl boronic acids **4a-j** under microwave condition yielded the corresponding target biaryl fused thiazolotriazoles **5a-j** in excellent yields.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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