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Synthesis of Novel 2-diethylamino-4H-7-(Het) aryl pyrido[1,2-a][1,3,5]triazin-4-ones via a Suzuki Cross-Coupling Reaction of 2-Diethylamino-4H-7-iodopyrido[1,2a][1,3,5]triazin-4-one with (Het) arylboronic Acids in Water

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Abstract

Suzuki cross coupling reaction is one of the most famous organic reactions of the 20th century's chemistry. It is deemed of as one of the most famous reaction in the field of chemistry. It is a very effective method for making carbon–carbon bonds. It has been extensively utilized in the synthesis of many carbon molecules including the most complex ones.Syntheses of 2-diethylamino-4*H*-7-(Het) aryl pyrido [1,2-*a*] [1,3,5] triazin-4-ones are currently under investigation in order to obtain great potentialities in medicinal chemistry of compounds class. The methodology we propose herein is able to produce numerous 2-diethylamino-4*H*-7-(Het)arylpyrido[1,2-*a*][1,3,5]triazin-4-one and derivatives that were synthesized, purified and characterized by ^{1}HNMR, ^{13}CNMR, MS techniques. Furthermore, it allows sequential introduction of various substituents into a 2-alkylylamino-4*H*-7-(Het)arylpyrido[1,2-*a*][1,3,5]triazin-4-ones ring using a one-pot procedure. The biological evaluation as well as the physico-chemical characterisation of various products are currently under way and will be described elsewhere.

Keywords: Suzuki Cross Coupling; Palladium Catalysis; Synthesis of 2-diethylamino-4H-7-(Het)arylpyrido[1,2-a][1,3,5] triazin-4-ones; Physico-chemical characterisation (1HNMR, 13CNMR, MS)

1. Introduction

Synthesis of heterocyclic compounds is of critical importance due to their fundamental role in pharmaceutical applications. The Suzuki–Miyaura cross-coupling reaction plays a significant industrial scale role for the production of biaryl compounds which are widely used for a variety of industrial applications, such as the synthesis of natural products, herbicides, pharmaceuticals, polymers and agrochemicals [1-4]. In recent times Suzuki-Miyaura reaction which is more commonly known as "Suzuki coupling reaction" is one of the most useful cross-coupling reactions between aryl or vinyl boronic acid with aryl or vinyl halides and also with different reagents like alkenes, alkynes, amines, pseudohalides, metallorganic compounds catalyzed by palladium (0) complexes [5-8].

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Palladium-catalyzed Suzuki cross coupling reactions are amongst the most powerful and most applicable method for C—C bond formation [9-11]. The reaction is generally carried out at temperatures range of 60–80°C with generally excellent yield results. Despite the availability of other cross coupling reaction like Heck reaction:

- Milder reaction conditions.
- Commercial availability of the diverse boronic acids derivatives that is environmentally safer than the other organometallic reagents.
- The handling and removal of boron-containing byproducts is easy as compared to other organometallic reagents, especially in case of large-scale synthesis of a product.

So Accordingly, we can say that Suzuki cross coupling reaction has an edge over the other cross coupling reactions as this reaction is not only restricted to simple compounds but is frequently used in the production of complex compounds also [12]. Pd-catalyzed cross coupling reactions have revolutionized the field of organic synthesis. Among them, Suzuki cross coupling reaction is considered to be the most widely used cross coupling reactions in chemical industry as well as in academic settings [5-6]. The applications of Suzuki reactions range from medicines to materials [13-19].

Deveau and co-workers have recently reported a palladium catalyzed Suzuki-Miyaura coupling suitable for undergraduate laboratories, which also features important lessons involving medicinal chemistry and green chemistry [20-23]. In contrast with 2-alkylamino-4*H*-pyrido [1,2-*a*][1,3,5] triazin-4-one and derivatives, which have extensively been used as building blocks in medicinal chemistry, few studies have addressed their biaryl analogues. Questing for novel and versatile scaffolds used in combinatorial chemistry, we focused on the total synthesis of new 2-diethylamino-7-(Het) aryl-4*H*-pyrido[1,2-*a*][1,3,5] triazin-4-ones skeleton of type 8_{a-m}(Figure 1) starting 2-aminopyridine. Biological activity of the 2-diethylamino-4*H*-pyrido [1,2-*a*] [1,3,5] triazin-4-ones was tested against some micro-organisms, and has shown an interesting and a strong bactericidal activity. This situation prompted us to investigate a general method to prepare compounds of type 8 based on the development of Suzuki-type cross-coupling reactions [24-26].

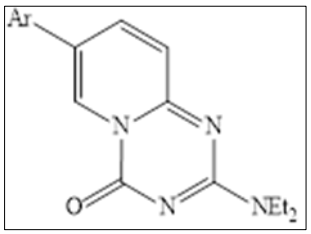

Figure 1 Target Molecule 8_{a-m}

2. Material and methods

2.1. Materials

Commercial reagents were used without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethysilane. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at an ionizing potential of 70 eV. The organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. Visualization was made with ultraviolet light. Column chromatography was carried out using silica gel 60 (0.063-0.2 mm) (Merck). Filtration was carried out using celite 545 (Prolabo).

2-amino-5-iodopyridine is prepared according to reported procedure [33] 2-amino-5-bromopyridine, 2-amino-5-chloropyridine, and 2-aminopyridine was purchased from Across Organics and were used without further purification.

2.2. Methods

2.2.1. Synthesis of 2-amino-5-iodopyridine 1_a

A mixture of 2-aminopyridine (47.2g, 0.5 mol), periodic acid dihydrate (22.9g, 0.1 mol, 0.2 equiv.) and iodine (51.1g, 0.2 mol, 0.4 equiv.) was heated in a mixed solution of 300 mL of acetic acid, 60 mL of water and 9 mL of sulfuric acid at 80°C for 4 h. The mixture was then poured into aqueous diluted solution thiosulfate to remove unreated iodine, made alkaline with aqueous diluted sodium hydroxide, and extracted with ether. Purification by column chromatography (AcOEt)

yielded 82.9g of 2-amino-5-iodopyridine (75%). White solid, mp 130 ° C (Lit.[4] 132-133 °C);IR (KBr, cm^{-1}) υ : 3029-3302 (aliphatic CH), 1546-1481-1381(deform. CH). ^{1}H NMR (DMSO- d_6) 8.02(d, J=1.6 Hz, 1H), 8.56(dd, J=8.6 Hz, 1.6 Hz, 1H), 6.33(d, J = 8.6 Hz, 1H), 6.11(s, 2H).

2.2.2. General Procedure for the preparation of 2-diethylamino-4H-7-(halogeno)pyrido[1,2-a] [1,3,5]triazin-4-one $6_{a\text{-}c}$

Ethoxycarbonyl isothiocyanate (0.01mol) and 2-amino-5-(halogeno) pyridine (0.01mol) were mixed in dimethylformamide (100 mL) at room temperature for 2 hours to form the N-ethoxycarbonyl-N'-(5-halogeno)pyridin-2-yl)thiourea intermediate. The solution was then cooled to 0°C before saturation with diethyl amine (0.025 mol) and the addition of mercuric chloride (0.01 mol). After 15 minutes, the ice bath was removed and the solution was allowed to warm to room temperature. The black color which appeared was due to the formation of mercuric sulfide. The mixture was refluxed for 2 hours.

Ethyl acetate (150 mL) was added and the reaction mixture was filtered through celite, and then dried under vacuum to give a crude product. The recrystallization from acetonitrile gave 1a, 1b, 1c.

2.2.3. General procedure for the preparation of 2-diethylamino-4H-7-(Het)aryl pyrido[1,2-a] [1,3,5]triazin-4-one 8a–m

To a mixture of compound6_a (1.032 g, 3mmol) and tetrakis-(triphenylphosphine) palladium(0) (0.2g, 0.05 mmol) in 1,4-dioxane (50mL) is added the corresponding arylboronic acid (mg,1,15 equiv., 1.2 mmol), followed by the addition of sodium bicarbonate (265mg, 2,3 equiv., 2.5m mole) in water (10mL). The reaction mixture is refluxed with vigorous stirring for 4 hours; the organic solvent is removed under reduced pressure. Recrystallization of the crude product from acetonitrile gave the products $8_{a–m}$.

3. Results

3.1. 2-Diethylamino-4*H*-7-iodopyrido[1,2-*a*][1,3,5]triazin-4-one 6_a

Recrystallization of the crude product gave **6_a** as a white powder (2,16 g, 63%), mp 146°C, IR (KBr, cm^{-1}) υ: 2970 -2932 (aliphatic CH); 1711(>C=O); 1613(>C=N); 1551; 1522; 1424; 1397 (deform. CH). ^{1}H NMR (DMSO-d_6): 1.11(ls, 6H); 3.57(m, 4H), 6.98(m, 1H), 7.99(m, 1H); 8.69(ls, 1H). ^{13}C NMR (DMSO-d_6): 12.82; 13.34; 41.03; 41.24; 76.67; 124.33; 133.68; 148.00; 148.75;153.71;160.38. MS: m/z = 343.8; 314.8; 203.8.

3.2. 2-Diethylamino-4*H*-7-bromopyrido[1,2-*a*][1,3,5]triazin-4-one 6_b

Recrystallization of the crude product gave **6 b**as a white powder (1,72 g, 58%), mp 158°C,IR (KBr, cm^{-1}) υ: 2970-2930(aliphatic CH); 1720(>C=O); 1610(>C=N); 1556; 1510;1414 (deform. CH).^{1}H NMR (DMSO-d_6): 1.11(s, 6H); 3.57(m, 4H); 6.98(m, 1H) 7.99 (m, 1H); 8.69 (s, 1H). ^{13}C NMR (DMSO-d_6): 12.84; 13.35; 41.10; 41.31; 106.42; 124.42; 129.06; 143.60; 148.84; 153.77; 160.46. MS: m/z = 297.9; 295.9; 268.9-266.9; 157.9; 155.

3.3. 2-Diethylamino-4*H*-7-chloropyrido[1,2-*a*][1,3,5]triazin-4-one 6_c

Recrystallization of the crude product gave **6_c** as a yellow powder (1,38 g, 55%), mp189°C. IR (KBr, cm^{-1}) υ: 2970 - 2932(aliphatic CH); 1715(>C=O); 1620(>C=N); 1562; 1514; 1412(deform. CH); 760 cm^{-1}. (C-Cl). ^{1}H NMR (DMSO-d_6): 1,12 (t, 3J = 7,03 Hz, 6H); 3.54 (q, ^{3}J = 7.03 Hz, 2H); 3.60 (q, ^{3}J = 7.03 Hz, 2H); 7.19 (d, J = 9.51 Hz, 1H); 7.9(d, J = 9.51 Hz, 1H); 8.57(s, 1H). ^{13}CNMR (DMSO-d_6): 12.80; 13.34; 41.09; 41.30; 119.64; 124.58; 126.93; 141.53; 148.93; 153.76; 160.51. MS: m/z = 254 - 252; 225 - 223; 182 - 180; 114 - 112.

3.4. 2-Diethylamino-7-phenyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one 8_a

White solid (0,50g, 57 %), mp 130°C. **^{1}HNMR**(DMSO-d_6): 1.14 (t, ^{3}J = 7.10 Hz, 6H); 3.56 (q, ^{3}J = 7.10 Hz, 2H); 3.63 (q, ^{3}J = 7.10 Hz, 2H); 7.27 (d,J= 9.23 Hz, 1H) ;7.42 (d, J= 7.51 Hz, 1H) ; 7.48 (d, J = 7.51 Hz, 2H) ;7.70 (d, J= 7.51 Hz, 2H); 8,24 (d, J= 9.23 Hz, 1H) ; 8,78 (s, 1H). ^{13}CNMR (DMSO-d_6): 12.91; 13.40; 41.05; 41.25; 123.22; 125.65; 125.85; 126.15; 128.34; 129.25; 134.83; 140.22; 149.76; 154.02; 160.51. MS: m/z = 294; 265; 251; 222; 196; 154; 127.

3.5. 2-Diethylamino-7-p-methylphenyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one 8_b

White solid (0,51 g, 57%), mp 142°C. ^{1}HNMR(DMSO-d_6): 1.14 (t, ^{3}J = 7.10 Hz, 6H); 2,33(s, 3H); 3.56(q, ^{3}J = 7.10 Hz, 2H); 3.63(q, ^{3}J = 7.10 Hz, 2H); 7.26(d, J= 9.23 Hz, 1H); 7.29 (d, J = 8.10 Hz, 2H); 7.58(d, J = 8.10 Hz, 2H); 8.22(d, J = 9.23 Hz, 1H); 8.76(s, 1H). ^{13}CNMR(DMSO-d_6): 12.89; 13.38; 20.65; 41.01; 41.22; 123.17; 125.13; 125.84; 125.96; 129.82; 131.91; 137.85; 140.16; 149.77; 153.92; 160.49. MS: m/z **=** 308; 279; 265; 236; 210; 168.

3.6. 2-Diethylamino-7-p-methoxyphenyl-4*H*-pyrido [1,2-*a*][1,3,5]triazin-4-one 8_c

White solid (0,58 g, 60%), mp 148°C. ^{1}HNMR(DMSO-d_6): 1.14(t, ^{3}J = 14.86 Hz, 6H); 3.56(m, 2H); 3.63(m, 2H); 3.79(s, 3H); 7.04(d, J = 8.31 Hz, 2H); 7.26(d, J = 9.15 Hz, 1H); 7.64(d, J = 8.31 Hz, 2H); 8.21(d, J= 9.15 Hz, 1H); 8.72(s, 1H). ^{13}CNMR(DMSO-d_6):12.92; 13.40; 40.12; 41.66; 55.26; 114.70; 123.13; 124.64; 126.66; 127.46; 136.66; 140.21; 150.55; 153.33; 160.02. MS: m/z = 324; 295; 281; 277; 210; 169.

3.7. 2-Diethylamino-7-(2',3',4'-trimethoxy)phenyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one8_d

White solid (0,60 g, 52%), mp 185 °C. ^{1}HNMR(DMSO-d_6): 1.15(m, 6H); 3.57(m, 2H); 3.64(m, 2H); 3.69 (s, 3H); 3.87(s, 6H); 6.94(s, 2H); 7.27(d, J= 9.80 Hz, 1H);8.29(d, J = 9.80 Hz, 1H); 8.79(s, 1H). ^{13}CNMR(DMSO-d_6): 12.86; 13.34; 40.98; 41.85; 56.06; 60.01; 103.85; 122.85; 125.56; 126.14; 130.54; 137.77; 140.66; 149.72; 153.42; 153.93; 160.48. MS: m/z = 295; 266; 262; 252; 197; 183; 155.

3.8. 2-Diéthylamino-7-(2'-furannyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one 8e

White solid (0,486g, 57%), mp 160°C. ^{1}HNMR(DMSO-d_6): 1.13(m, 6H); 3.53(m, 2H); 3.59(m, 2H); 6.59(s, 1H); 7.05(s, 1H); 7.19(d, J = 10.25Hz, 1H); 7.76(ls, 1H); 8.14(d, J = 10.25(Hz, 1H); 8.72(s, 1H). ^{13}CNMR(DMSO-d_6): 12.81; 13.33; 41.04; 41.24; 107.66; 112.14; 117.05; 122.38; 123.41; 37.03; 143.64; 148.46; 149.53; 153.73; 160.40. MS: m/z = 284; 255; 241; 233; 212; 186; 144; 116.

3.9. 2-Diéthylamino-7-(3'-furannyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one 8f

White solid (0,486, 57%), mp 163 °C. ^{1}HNMR(DMSO-d_6): 1.13(t, ^{3}J = 13.82 Hz, 6H); 3.55(q, ^{3}J = 13.82 Hz, 2H); 3.61(q, ^{3}J = 13.82 Hz, 2H); 7.05(s, 1H); 7.23(d, J = 9.30 Hz, 1H); 7.77 (s, 1H); 8.15 (d, J = 9.30 Hz, 1H); 8.33 (ls, 1H); 8.73 (s, 1H). ^{13}CNMR(DMSO-d_6):12.88; 13.37; 40.98; 41.18; 107.93; 118.56; 121.20; 123.25; 123.89; 139.49; 140.47; 144.88; 149.72; 153.92; 160.44. MS: m/z = 284; 255; 241; 212; 186; 144; 116.

3.10. 2-Diethylamino-7-(2'-thiophenyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one 8g

White solid (0,558 g, 62%), mp 146°C. ^{1}HNMR(DMSO-d_6):1.13(m, 6H); 3.56(m, 2H); 3.61(m, 2H); 7.15(m, 1H); 7.24(d, J = 9.23 Hz, 1H); 7.61(m, 2H); 8.20(d, J= 9.23 Hz, 1H); 8.71(s, 1H). ^{13}CNMR(DMSO-d_6): 12.86; 13.37; 41.04; 41.25; 120.51; 123.46; 123.68; 125.31; 126.50; 128.67; 137.58; 138.99; 149.55; 160.42. MS: m/z = 300; 271; 228; 202; 160.

3.11. 2-Diethylamino-7-(3'-thiophenyl)-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one 8_h

White solid (0,585g, 65%), mp 146°C.^{1}HNMR(DMSO-d_6): 1.14(t, ^{3}J = 13.40 Hz, 6H); 3.56(q, ^{3}J = 13.40 Hz, 2H) ;3.62(q, ^{3}J = 13.40 Hz, 2H) ; 7.25(d, J= 9.23 Hz, 1H); 7.60(d, J = 7.80 Hz, 1H) ; 7.69(d, J= 7.80 Hz, 1H) ; 8.05(s, 1H) ;8.29(d, J= 9.23, 1H); 8.84(s, 1H). ^{13}CNMR(DMSO-d_6): 12.89; 13.37; 40.99; 41.19; 121.55; 122.29; 123.18; 124.69; 125.34; 127.95; 135.92; 139.91; 149.74; 153.84; 160.46. MS: m/z = 300; 271; 262; 217; 183; 160.

3.12. 2-Diéthylamino-7-(3'-pyridinyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one 8i

White solid (0,434, 49%), mp 142°C. ^{1}HNMR(DMSO-d_6): 1.13(t, ^{3}J = 14.54 Hz, 6H); 3.55(m, 2H); 3.62(m, 2H); 7.27(d, J = 9.23 Hz, 1H); 7.36(m, 2H); 8.26(d, J= 9.23 Hz, 1H); 8.59(d, J = 4.67Hz, 1H); 8.83(s, 1H), 8.90(1s, 1H). ^{13}CNMR(DMSO-d_6): 12.89; 13.44; 41.20; 41.33; 121.90; 126.89; 128.24; 130.69; 137.02; 137.89; 141.09; 147.22; 154.34; 160.64. MS: m/z = 295(M^+); 266; 262; 252; 197; 183; 155; 107.9.

3.13. 2-Diéthylamino-7-(3'-6'-fluoropyridinyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one8j

White solid (0,404, 43%), mp 185 °C. ^{1}HNMR(DMSO-d_6): 1.14(t, ^{3}J = 14.54 Hz, 6H); 3.56(q, ^{3}J = 13.98 Hz, 2H); 3.63(q, ^{3}J = 13.98 Hz ,2H); 7.29(m, 2H); 7.36(m, 2H); 8.25(d, J = 8.87 Hz, 1H); 8.35(t, ^{3}J= 16.94 Hz, 1H); 8.59(s, 1H), 8.84(1s, 1H). ^{13}CNMR(DMSO-d_6):12.84; 13.37; 41.06; 41.27; 10.00; 121.97; 123.36; 126.46; 129.38; 140.00; 145.26; 145.40; 149.57; 154.12; 160.52. MS: m/z = 313(M^+); 298; 284; 270; 241; 215; 173.

3.14. 2-Diéthylamino-7-(3'-6'-chloropyridinyl)-4H-pyrido[1,2-a][1,3,5]triazin-4-one 8k

White solid (0.573, 58%), mp 212°C. ^{1}HNMR(DMSO-d_6): 1.14 (t, ^{3}J = 13.95 Hz, 6H); 3.57(q, ^{3}J = 13.95 Hz, 2H); 3.64(q, ^{3}J = 13.95 Hz ,2H); 7.30(d, J = 9.23 Hz, 1H); 7.61(d, J = 8.31Hz, 1H); 8.23(d, J = 8.31 Hz, 1H); 8.27(d, J= 9.23 Hz, 1H); 8.89(s, 1H). ^{13}CNMR(DMSO-d_6): 12.58; 13.09; 40.85; 41.09; 121.57; 123.17; 124.17; 126.55; 130.11; 137.17; 139.48; 147.17; 149.73; 154.04; 160.43. MS: m/z = 329(M^+); 300; 262; 223.9; 189; 153; 84.3.

3.15. 2-Diéthylamino-7-(3'-6'-bromopyridinyl)-4H-pyrido[1,2-a][1,3,5] triazin-4-one 8l

White solid (0.572, 51%), mp 230°C. ^{1}HNMR(DMSO-d_6): 1.14(t, ^{3}J = 13.95 Hz, 6H); 3.57(q, ^{3}J = 6.75 Hz, 2H); 3.64(q, ^{3}J = 6.95 Hz, 2H); 7.31(d, J = 10.70 Hz, 1H); 7.75(d, J = 8.43 Hz, 1H); 8.27(d, J = 10.70 Hz, 1H); 8.89(s, 1H). ^{13}CNMR(DMSO-d_6): 12.88; 13.42; 41.10; 41.31; 121.80; 128.20; 130.63; 137.24; 137.81; 140.99; 148.04; 154.24; 160.53. MS: m/z = 375(M^+); 346; 313.9; 277; 262; 232.9; 183; 153; 126; 108; 84.4.

3.16. 2-Diéthylamino-7-(3'-2'-chloropyridinyl)-4H-pyrido[1,2-a][1,2,3] triazin-4-one 8m

White solid (0.524, 53%), mp 157 °C. ^{1}HNMR(DMSO-d_6): 1.13(t, ^{3}J = 15.74 Hz, 6H); 3.57(q, ^{3}J = 12.83 Hz, 2H); 3.65(q, ^{3}J = 12.83 Hz, 2H); 7.28(d, J = 9.03 Hz, 1H); 7.56 (m, 1H); 8.01(m, 1H); 8.04(d, J = 9.03 Hz, 1H); 8.48(m, 1H); 8.67(s, 1H). ^{13}CNMR(DMSO-d_6): 12.89; 13.42; 41.21; 41.43; 122.50; 122.85; 123.73; 129.08; 131.24; 140.45; 142.18; 148.49; 149.60; 149.66; 154.23; 160.69. MS: m/z = 329(M^+); 314; 300; 286; 231; 189; 153; 126.

4. Discussion

Oda and al. [27]were have recently described the syntheses of new C- Deoxyribonicleosides bearing pyrido[1,2-*a*][1,3,5] triazin-4-one and derivatives, starting 2-amino-3-iodopyridine, using palladium-catalyzed Heck-type coupling. Some of these C-Deoxyribonicleosides were able to convert to phosphoramidite reagents, which can be used for DNA synthesizer. There are many reports about the constitution of the pyrido[1,2-*a*][1,3,5] triazin-4-one ring that has various substituent's [27, 29-32]. This heterocycle has a rigid planar structure [27-28] and cannot be subjected to tautomerization.

On our part, with the aim of building N, N-substituted aminopyridotriazinones [29-30] libraries of medicinal chemistry interest, we studied the total synthesis of a novel 2-diethylamino-4*H*-7-(Het)arylpyrido[1,2-*a*][1,3,5]triazin-4-one $8_{a–m}$ starting 2-aminopyridine.

4.1. Syntheses of 2-diethylamino-4*H*-7-(halogeno) pyrido[1,2-*a*] [1,3,5] triazin-4-ones.

2- Amino-5-(Bromo, Chloro) pyridine is commercially available (Across Organics), but 2-amino-5-iodopyridine is prepared from 2-aminopyridine with 75 % yield [33].

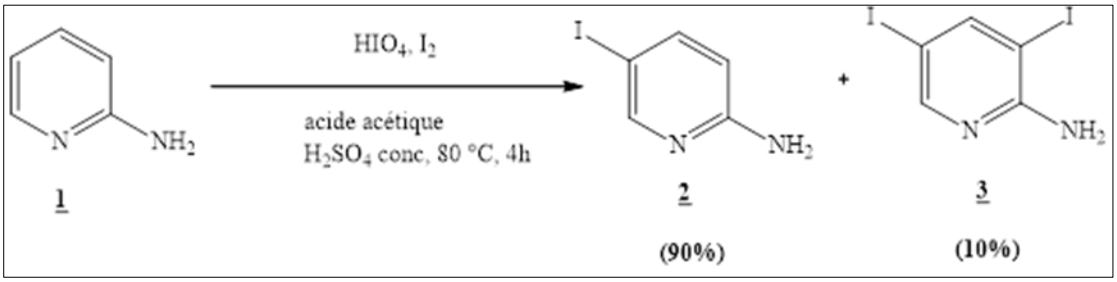

Figure 2 Syntheses of 2-amino-5-iodopyridine (Reagents: HIO_4, I_2, (AcOH, H_2O), H_2SO_4)

2-diethylamino-4*H*-7-(halogeno) pyrido[1,2-*a*] [1,3,5] triazin-4-one 1_{a-c} were synthesized as follows. 2-Amino-5-(halogeno) pyridine was converted to thiourea by treatment with ethoxycarbonylisothiocyanate. Thiourea was treated with mercury (II) salt as a scavenger in the presence of diethyl amine, and the annulation of the resulting guanidine was carried out by heating [30] (see Figure 3). The reaction of amine 2_{a-c} with ethoxycarbonyl isothiocyanate and the presence of mercury (II) salt gave guanidine derivative. 2-diethylamino-4*H*-7-(halogeno) pyrido[1,2-*a*][1,3,5]triazin-4-one 1_{a-c} was obtained by heating the DMF solution of the intermediate guanidine derivative under reflux [30] or in a microwave instrument [27].

2-Diethylamino-4*H*-7-iodopyrido[1,2-*a*][1,3,5] triazin-4-one 6_a was formed in 63% yield through a one-pot reaction starting from 2-amino-5-iodopyridine. The success of this protocol in a one-pot synthesis of compounds class type 1 further underscores the ease and efficiency of this protocol.

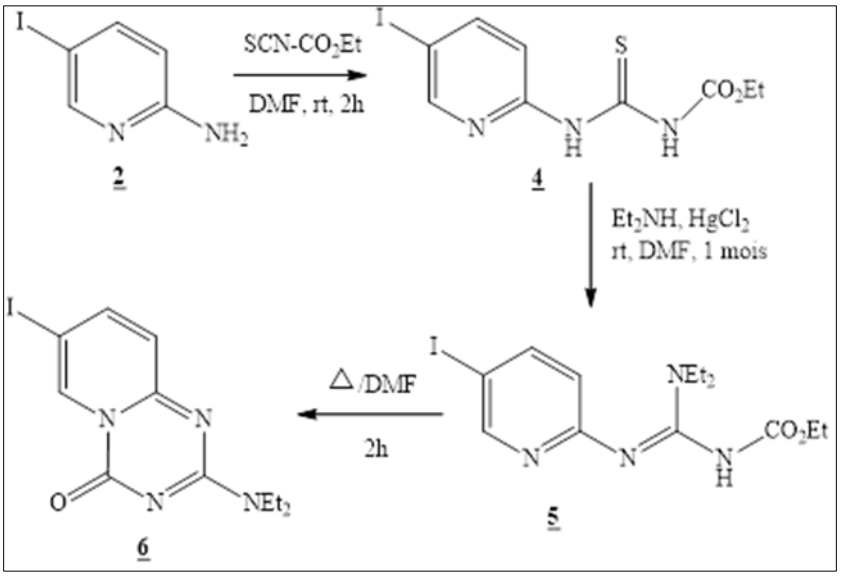

Figure 3 Syntheses of 2-diethylamino-4*H*-7-iodopyrido[1,2-*a*][1,3,5] triazin-4-one (Reagents : $SCNCO_2Et$; DMF (c) Et_2NH, $HgCl_2$ (d) Δ/DMF)

On the same procedure, we produce the corresponding $\mathbf{6_{b\text{-}c}}$ derivatives with good yields, through either stepwise or one-pot synthesis [30]**.**

4.2. Studies of reaction of 2-diethylamino-4*H*-7-iodopyrido[1,2-*a*][1,3,5]triazin-4-one 6_a with(Het)arylboronic acids $7_{a\text{-}m}$using Palladium-catalyzed Suzuki-type coupling

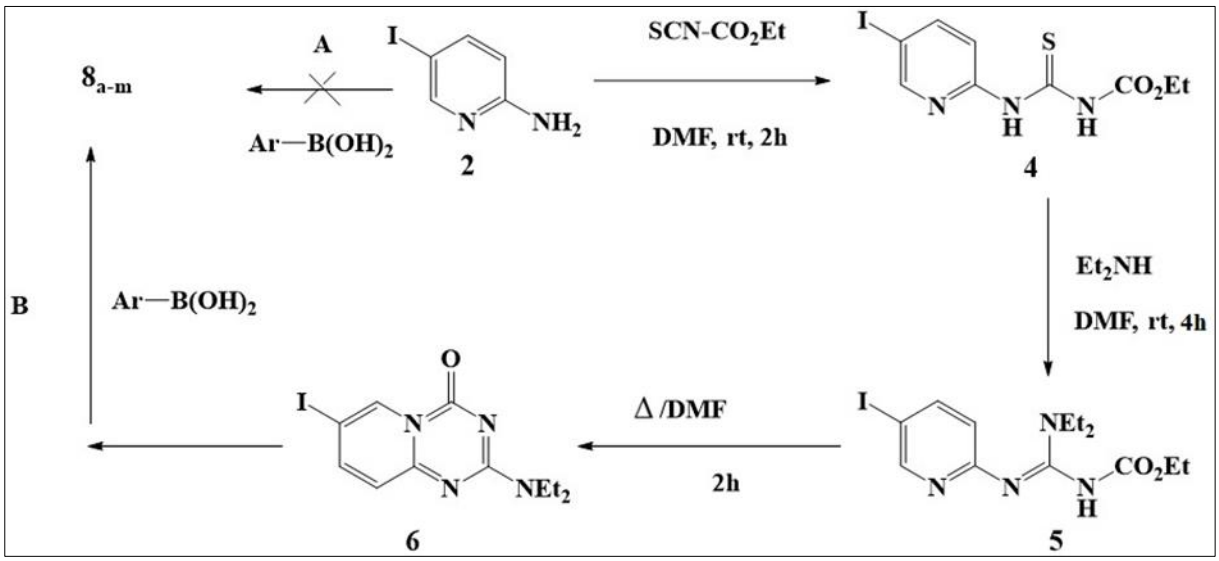

Figure 4 Routes A and B to obtain a 2-diethylamino-4*H*-7-(Het) aryl pyrido [1,2-*a*][1,3,5]triazin-4-one derivatives $8_{a–m}$ from 2-aminopyridine

Considering the growth of Suzuki type cross-coupling reaction application and in order to build new (Het)aryls bearing pyrido[1,2-*a*][1,3,5]triazin-4-ones libraries [29-30], we focused on a general method for the synthesis of new 2-diethylamino-4*H*-7-(Het) aryl pyrido [1,2-*a*][1,3,5]triazin-4-one derivatives $8_{a–m}$ from 2-aminopyridine; few studies has addressed their biaryl analogues.

With this aim, we efficiently coupled 2-diethylamino-4*H*-7-iodo pyrido[1,2-*a*][1,3,5] triazin-4-one 1a with arylboronic or heteroarylboronic acids $3_{a\text{-}h}$ under standard Suzuki-type condition [34-40], furnishing a range of unknown or other biaryls not easily accessible, most notably $8_{a–m}$.

At the initiation of this project, two routes were envisaged starting from 2-amino-5-iodopyridine 2_a, as depicted in Figure 4.

Route A, on the first step, the cross-coupling reaction of 2-amino-5-iodopyridine 1_a with boronic acids, was completely ineffective.

As for the second, route B, was the one-pot synthesis of 2-diethylamino-4*H*-7-iodopyrido[1,2-*a*][1,3,5]triazin-4-one 6_a, followed by the cross coupling reaction of 6_a with boronic acids.To improve the reactivity of the partners, we increased the solubility by adding more water, until a highly diluted and homogeneous reaction mixture was obtained.These modifications allowed a rapid coupling reaction without conditions that were found to be 6_a, 3 mmole; $ArB(OH)_2$, 1,15 equiv.; Na_2CO_3, 2,3 equiv.; Pd-$(PPh_3)_4$, 0,05 equiv.; Dioxane-1,4 / H_2O: 5/1, 65ml; 100°C; 4 hours to give 2-diethylamino-4*H*-7-(Het) aryl pyrido[1,2-*a*][1,3,5]triazin-4-ones $8_{a-m}$with 52 - 65% yield (See table 1 and Figure 5).

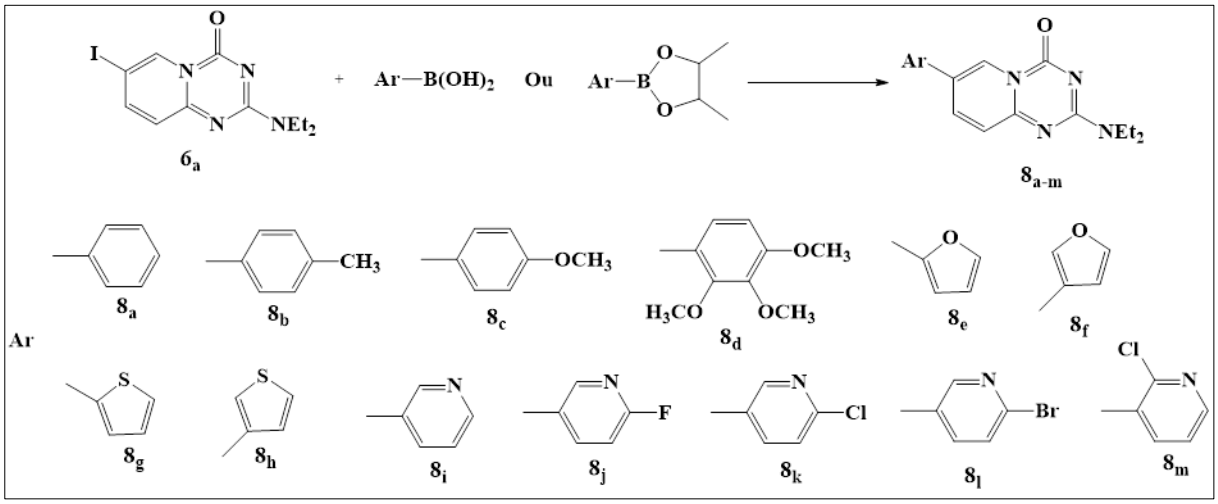

Figure 5 Suzuki cross-coupling of 2-diethylamino-4*H*-7-iodopyrido [1, 2-*a*] [1, 3, 5] triazin-4-one 6_a with (Het) arylboronic acids $\underline{7}_{a-m}$ Conditions: 3 mmole; $ArB(OH)_2$, 1,15 equiv.; Na_2CO_3 , 2,3 equiv.; Pd-$(PPh_3)_4$, 0,05 equiv.; Dioxane-1,4 /H_2O: 5/1, 65ml; 100°C; 4 hours

Table 1 Reaction conditions and yields for the cross-coupling of 6_a with arylboronic or ester boronique

Conditions	Reagents	Solvents	Basic medium	T (°C)	Time of reaction	Yield (%)
1	Boronic ester	DMF	K_3PO_4	55-65	About 4h	41
2	Boronic acid	DME	$NaHCO_3$	80-85	About 4h	22
3	Boronic acid	Toluene/Ethanol	K_2PO_3	110	About 24h	23
4	Boronic acid or ester	Dioxane-1,4	Na_2CO_4	100	About 3 à 4h	50-60

Most of the studies addressing synthesis and chemistry of fluorinated hetero-cyclic have been related to drug discovery research [41-42]. It is interesting that replacing hydrogen and other functional groups with fluorine atoms can have a dramatic effect on the modulation of electronic, lipophilic, and steric parameters, all of these can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs. Based upon these results, the present overview reports an important route of fluorine compounds substituted 1,3,5-triazine with the study of chemical reactivities and evaluation of the effects on the vital biological process [43].

The presence of fluorinated atoms often improves these properties with increasing electro negativity. It also enhances the stability of formed carbanion and it improves the hydrophobic effects which have good biological activities. In the light of all these works we synthesized an analogue of 2-Diéthylamino-7-(3'-6'-fluoropyridinyl)-4*H*-pyrido[1,2-*a*][1,2,3]triazin-4-one8_j.

5. Conclusion

The methodology we propose herein is able to produce numerous 2-diethylamino-4*H*-7-(Het) aryl pyrido [1, 2-*a*] [1, 3, 5] triazin-4-one and derivatives. It allows sequential introduction of various substituents into a 2-alkylylamino-4*H*-7-(Het) aryl pyrido [1, 2-*a*] [1, 3, 5] triazin-4-ones ring using a one-pot procedure. This sequence has become applicable in parallel chemistry.Aiming at studying mild and flexible strategies to design new (Het) aryl pyrido [1, 2-*a*][1, 3, 5] triazin-4-ones libraries; we coupled many pyridinylboronic acids and halopyrdinylboronic acids or esterswith 6_a under the same condition furnishing a range of unknown or otherwise biaryls not easily accessible of type 8. These results will be published elsewhere.

Further experiments concerning the syntheses of 2-diethylamino-4*H*-7-(Het) aryl pyrido [1, 2-*a*] [1, 3, 5] triazin-4-ones are currently under investigation in order to obtain great potentialities in medicinal chemistry of compounds class. The biological evaluation and physico-chemical characterisation of various products are currently ongoing and will be described elsewhere.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest

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