A facile synthesis of 3-amino-2,5-dihydropyridazines and 4-deazatuxoflavin analogues via [3+3] atom combination

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ARTICLE INFORMATION

DOI: 10.5155/eurjchem.7.1.73-80.1371
Received: 23 November 2015
Accepted: 19 December 2015
Published online: 31 March 2016
Printed: 31 March 2016

ABSTRACT

Michael addition reactions of arylhydrazone derivatives with different functionalized α-cyanoacrylamides were conducted and yielded new pyridazine-4-carboxamide compounds. A further reaction with acetic anhydride was investigated resulting in the formation of a 4-deazatuxoflavin analogue. A one step synthesis of 4-deazatuxoflavin was also carried out by reacting azaenamine with N-carbamoyl-2-cyano-3-phenylacrylamide to give deazatuxoflavin. Unambiguous structural elucidation was done using 2D-HMBC spectroscopy.

KEYWORDS

Azaenamine
Michael addition
Cyanoacrylamides
4-Deazatuxoflavin
α-Cyanoacrylamide
HMBC spectroscopy

1. Introduction

The biological importance of pyridazines and their fused compounds as antimicrobial and anticancer agents rendered them a target of enormous scientific efforts [1-5]. The synthetic approaches of pyridazines involve two main strategies: the first one (Figure 1, method A) is the cycloaddition of diazomethane derivatives to cyclopropene compounds [6-10], and the other method (Figure 1, method B) is the retro Diels-Alder cycloaddition of substituted 1,2,4,5-tetrazines to functionalized dienophiles [11-16]. Both methods, in spite of their prevalence in literature, have various disadvantages of expensive starting materials, tedious experimental work, hazard reagents, etc. A third relatively new method to synthesize dihydropyridazines (Figure 1, method C) implies a [3+3] atom combination of arylhydrazones to activated acrylonitrile derivatives yielding 3-amino-2,5-dihydropyridazines [17-21]. In this case, the nitrogen lone pair resonance makes the azomethine carbon relatively electron rich and enamine-like reactivity takes place [22,23].

The present work aims at studying the potency of [3+3] atom combination reaction of azaenamines, as Michael donors, with various α-cyanoacrylamides as an interesting strategy for the synthesis of partially unsaturated aminopyridazines. Also, extending these reactions to prepare some novel pyrimido [4,5-c]pyridazines (4-deazatuxoflavin analogues) is also investigated.

2. Experimental

2.1. Instrumentation

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide pellets using a FT-IR Bruker-vector 22 spectrophotometer. All the 1H and 13C NMR spectra were recorded with a Varian Gemini NMR spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard. The samples were dissolved in DMSO-d6, or CDCl3 and the chemical shifts are reported as δ in ppm. Electron ionization mass spectra (EI-MS) were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Microanalytical Center, Cairo University.
2.2. Synthesis

Azaenamines 1a, b were prepared in a similar procedure to that reported by Reynolds et al. [24]. All α-cyanocarboxamide derivatives (2a–e and 16) in this paper were prepared via a typical Knoevenagel condensation procedure [25]. The synthetic strategies, physical data and spectral characterization of the newly synthesized products are stated below.

2.2.1. Synthesis of 6-acetyl-3-amino-N,2,5-triphenyl-2,5-dihydropyridazine-4-carboxamide (8a)

A mixture of azaenamine 1a (162 mg, 1 mmol) and activated cyanocarboxamide derivative 2a (248 mg, 1 mmol) was heated at reflux in dioxane (10 mL) in the presence of piperidine (0.2 mL, 2 mmol) for 5 h. The solvent was evaporated under reduced pressure and the collected solid was crystallized from ethanol/dioxane mixture (5:1, v/v, 10 mL) to give compound 8a (Scheme 1). Yield: 375 mg, 915 mmol, 91%. Color: Bright yellow crystals. M.p.: 190-192 °C. FT-IR (KBr, v, cm⁻¹): 3360, 3181 (NH) (br, CONH and NH₂), 1673 (CO) (CONH), 1634 (CO) (CONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.39 (s, 3H, CH₃), 5.72 (s, 1H, pyridazine-H), 6.96-7.59 (m, 17H, Ar-H and NH), 9.05 (br s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 25.6 (CH₃), 33.4 (CH), 66.6 (C), 78.4 (C), 121.4 (CH), 123.1 (CH), 126.2 (CH), 127.2 (CH), 128.1 (CH), 128.6 (CH), 129.1 (CH), 130.0 (CH), 140.1 (C), 143.3 (C), 146.5 (C), 151.2 (C), 167.9 (C), 176.9 (C). MS (EI, m/z (%)): 410 [M⁺] (5), 318 [M⁺] (2), 366 (1), 333 (8), 318 (10), 291 (100), 248 (22), 93 (7), 77 (23). HRMS (EI) calc. for C₃₂H₂₁N₄O₂: 410.1743; found: 410.1766. Anal. calc. for C₃₂H₂₁N₄O₂: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.09; H, 5.36; N, 13.42%.

2.2.2. Synthesis of 6-acetyl-3-amino-N-(p-tolyl)-2,5-dihydropyridazine-4-carboxamide (8b)

Following the procedure given for compound 8a, azaenamine 1a (162 mg, 1 mmol) and cyanocarboxamide derivative 2b (262 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol/dioxane mixture (5:1, v/v, 10 mL) afforded the compound 8b (Scheme 1). Yield: 382 mg, 901 mmol, 90%. Color: Golden yellow crystals. M.p.: 198-200 °C. FT-IR (KBr, v, cm⁻¹): 3392 (NH) (br, CONH and NH₂), 1631 (CO) (br, COOH and CONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.23 (s, 3H, CH₃), 2.36 (s, 3H, CH₂CO), 5.65 (s, 1H, pyridazine-H), 7.00-7.56 (m, 16H, Ar-H and NH), 8.95 (br s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 20.9 (CH₃), 25.3 (CH₃), 33.4 (CH), 78.4 (C), 121.4 (CH), 126.1 (CH), 127.2 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 129.0 (CH), 132.0 (C), 137.4 (C), 140.7 (C), 143.3 (C), 1465. (C), 150.7 (C), 167.9 (CONH), 196.5 (COOH). MS (EI, m/z (%)): 424 [M⁺] (5), 318 (10), 290 (100), 248 (15), 214 (4), 106 (5), 77 (21). HRMS (EI) calc. for C₃₅H₃₅N₄O₂: 424.1899; found: 424.1876. Anal. calc. for C₃₅H₃₅N₄O₂: C, 73.56; H, 5.70; N, 13.18%.

2.2.3. Synthesis of 6-acetyl-3-amino-N-(4-nitrophenyl)-2,5-dihydropyridazine-4-carboxamide (8c)

Following the procedure given for compound 8a, azaenamine 1a (162 mg, 1 mmol) and cyanocarboxamide derivative 2c (293 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol/dioxane mixture (5:1, v/v, 10 mL) afforded the compound 8c (Scheme 1). Yield: 398 mg, 877 mmol, 88%. Color: Orange solid. M.p.: 192-194 °C. IR (KBr, v, cm⁻¹): 3460 (NH) (br, CONH and NH₂), 3640 (NH) (br, CONH and NH₂), 1684 (CO) (COOH), 1644 (CO) (CONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.37 (s, 3H, CH₃CO), 5.76 (s, 1H, pyridazine-H), 7.17-8.16 (m, 16H, Ar-H and NH), 9.56 (br s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 25.3 (CH₃), 33.2 (CH), 77.9 (C), 120.0 (CH), 124.9 (CH), 126.3 (CH), 127.3 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 140.5 (C), 141.7 (C), 143.2 (C), 147.0 (C), 151.9 (C), 168.1 (C), 196.7 (C). MS (EI, m/z (%)): 455 [M⁺] (3), 409 (9), 318 (12), 290 (100), 248 (13), 92 (27), 77 (30). HRMS (EI) calc. for C₃₅H₃₅N₄O₂: 455.1594; found: 455.1578. Anal. calc. for C₃₅H₃₅N₄O₂: C, 65.93; H, 4.65; N, 15.38. Found: C, 65.88; H, 4.63; N, 15.36%.

2.2.4. Synthesis of 6-acetyl-3-amino-2-(4-chlorophenyl)-N,5-dihydropyridazine-4-carboxamide (8d)

Following the procedure given for compound 8a, azaenamine 1b (196 mg, 1 mmol) and cyanocarboxamide derivative 2a (248 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol/dioxane mixture (5:1, v/v, 10 mL) afforded the compound 8d (Scheme 1). Yield: 414 mg, 932 mmol, 93%. Color: Pale yellow solid. M.p.: 194-196 °C.
2.2.5. Synthesis of 6-acetyl-3-amino-2-(4-chlorophenyl)-5-phenyl-N-(p-tolyl)-2,5-dihydropyridazine-4-carboxamide (8e)

Following the procedure given for compound 8a, azaenamine 1b (196 mg, 1 mmol) and cyanoacrylamide derivative 2b (262 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, v:v, 10 mL) afforded the compound 8e (Scheme 1). Yield: 403 mg, 880 mmol, 88%. Color: Beige solid. M.p.: 186-188 °C. IR (KBr, \( \nu, \text{cm}^{-1} \)): 3410 (NH) (br, CONH and NH2), 1678 (CO) (COCH3), 1662 (CO) (CONH). \( ^1 \text{H NMR} \) (400 MHz, DMSO-d6, \( \delta, \text{ppm} \)): 2.22 (s, 3H, C\(_\text{H}_3\)), 2.36 (s, 3H, C\(_\text{H}_3\)CO), 5.64 (s, 1H, pyridazine-H), 7.02-7.58 (m, 15H, Ar-H and NH2), 8.96 (br s, 1H, NH). MS (ESI, \( m/z \) (%)): 461 (2) \([M+2]^+\), 460 (1), 459 (M\(^+\)) (5), 444 (17), 424 (23), 416 (12), 401 (26), 380 (19), 318 (36), 290 (100), 166 (13), 92 (54), 77 (62). HRMS (ESI) calcd. for C\(_{26}\)H\(_{23}\)ClN\(_4\)O\(_2\): 460.1522 \([M+2]^+\), found: 460.1522 \([M+2]^+\), 458.1502 \([M]^+\), found: 458.1502 \([M]^+\). Anal. calcd. for C\(_{26}\)H\(_{23}\)ClN\(_4\)O\(_2\): C, 68.04; H, 5.05; N, 12.17. Found: C, 68.06; H, 5.02; N, 12.17.

2.2.6. Synthesis of methyl 2-(6-acetyl-3-amino-2,5-diphenyl-2,5-dihydropyridazine-4-carboxamido)benzoate (8f)

Following the procedure given for compound 8a, azaenamine 1a (162 mg, 1 mmol) and cyanoacrylamide derivative 2d (306 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, v:v, 10 mL) afforded the compound 8f (Scheme 1).
Yield: 399 mg, 853 mmol, 85%. Color: Bright yellow crystals. M.p.: 206-208 °C IR (KBr, v, cm⁻¹): 3411, 3173 (NH) (br, CONH and NH₂), 1685 (CO) (COOCH₃), 1644 (CO) (br, COCH₃ and CONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.09 (s, 3H, CH₃CO), 2.91 (s, 3H, COOCH₃), 5.47 (s, 1H, pyridazine-H), 7.06-8.59 (m, 16H, Ar-H and NH₂), 10.91 (br s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 25.3 (CH₃), 34.2 (CH), 53.3 (CH₃), 77.9 (C), 115.4 (C), 120.7 (CH), 122.2 (CH), 126.2 (CH), 127.5 (CH), 128.0 (CH), 128.3 (CH), 129.2 (CH), 130.2 (CH), 131.2 (CH), 134.7 (CH), 140.5 (C), 142.1 (C), 142.2 (C), 146.5 (C), 151.8 (C), 167.8 (C), 1685 (C), 196.7 (C). MS (EL m/z (%)): 468 [M⁺] (3), 453 (5), 425 (11), 440 (19), 409 (37), 394 (43), 360 (22), 318 (36), 290 (100), 248 (22), 146 (19), 77 (28). HRMS (EI) calcd. for C₂₃H₂₆N₄O₂: 390.2056; found: 390.2034. Anal. calcd. for C₂₃H₂₆N₄O₂: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.77; H, 6.68; N, 14.34.

2.2.8. Synthesis of 3-acetyl-7-methyl-1,4,6-trithenyl-4,6-dihydroproridazine-5(1H)-one (11)

Compound 8a (0.41 g, 1 mmol) was heated at reflux in acetic anhydride (10 mL, 106 mmol) for 5 h. The solvent was evaporated under reduced pressure and the residue was washed with 25% aq ammonia solution (10 mL, 260 mmol) then filtered and washed with distilled water (20 mL). The crude dry product was crystallized from ethanol-dioxane (5:1, v/v, 10 mL) to give compound 11 (Scheme 2).

Yield: 332 mg, 765 mmol, 76%. Color: Deep yellow solid. M.p.: 268-270 °C IR (KBr, v, cm⁻¹): 1664 (CO) (COOCH₃), 1638 (CO) (CONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.65 (s, 3H, CH₃), 2.42 (s, 3H, CH₃CO), 5.36 (s, 1H, pyridazine-H), 7.22-7.64 (m, 15H, Ar-H). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 24.5 (CH₃), 25.0 (CH₃), 34.0 (CH), 98.0 (C), 125.8 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 130.0 (CH), 137.7 (C), 141.7 (C), 141.9 (C), 144.2 (C), 150.2 (C), 158.7 (C), 161.4 (C), 1962 (C). MS (EL m/z (%)): 434 [M⁺] (6), 420 (11), 391 (35), 357 (19), 318 (27), 290 (100), 168 (13), 91 (63), 77 (72). HRMS (EI) calcd. for C₂₇H₂₂N₄O₂: 434.1743; found: 434.1719. Anal. calcd. for C₂₇H₂₂N₄O₂: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.61; H, 5.07; N, 12.90%.

2.2.9. Synthesis of 6-acetyl-2,5-diphenyl-4,5-dihydro pyridazin-3(2H)-one (15)

Compound 8a (0.41 g, 1 mmol) was heated at reflux in formic acid (10 mL, 265 mmol) for 3 h. The excess solvent was removed at reduced pressure and the crude substance was treated with 25% aq ammonia solution (10 mL, 260 mmol) then filtered and washed with water (20 mL). The dry solid was crystallized from ethanol (10 mL) to give compound 15 (Scheme 3).

Yield: 212 mg, 726 mmol, 63%. Color: Colorless crystals. M.p.: 122-124 °C IR (KBr, v, cm⁻¹): 1705 (CO) (COOCH₃), 1687 (CO) (CONH). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.50 (s, 3H, CH₃CO), 3.05 (m, 2H, CH₂CH₃), 4.71 (m, 1H, CH₂CH₃), 7.22-7.57 (m, 10H, Ar-H). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 24.8 (CH₃CO), 35.0 (CH₃CO), 35.4 (CH₃), 124.8 (CH), 126.9 (CH), 127.4 (CH), 127.9 (CH), 128.8 (CH), 129.3 (CH), 137.5 (C), 140.4 (C), 150.4 (C), 164.8 (CONH), 196.0 (COOCH₃). MS (EL m/z (%)): 292 [M⁺] (15), 277 (10), 249 (35), 215 (22), 172 (14), 77 (100). HRMS (EI) calcd. for C₂₇H₂₀N₄O₂: 292.1212; found: 292.1123. Anal. calcd. for C₂₇H₂₀N₄O₂: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.88; H, 5.48; N, 9.63%.

2.2.10. Synthesis of 3-Acetyl-1,4-diphenyl-6,8-dihydro pyrimido[4,5-c]pyridazine-5(1H,4H)-dione (19)

Following the procedure given for compound 8a, azazenamine 1a (162 mg, 1 mmol) and N-carbomaryl-2-cyano-3-phenylcylamide 16 (0.22 g, 1.0 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol)
Mechanistic pathway for the reaction of azaenamine 1a with (E)-N-carbamoyl-2-cyano-3-phenylacrylamide 2.

Crystallization of the isolated product from ethanoldioxane mixture (5:1, v/v, 10 mL) afforded the compound 19 (Scheme 4). Yield: 319 mg, 886 mmol, 89%. Color: Canary-yellow crystals. M.p.: 290-292 °C. IR (KBr, ν, cm⁻¹): 1681 (CO), 1619 (CO) (br, CONH and NHCONH). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.36 (s, 3H, CH₃CO), 5.18 (s, 1H, pyridazine-H), 7.11-7.53 (m, 12H, Ar-H and 2NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 25.1 (C), 33.3 (CH), 85.5 (C), 125.8 (CH), 126.0 (CH), 126.6 (CH), 127.7 (CH), 128.5 (CH), 128.7 (CH), 143.3 (C), 144.3 (C), 144.5 (C), 155.4 (C), 157.8 (C), 165.4 (C), 196.6 (C). MS (EI, m/z (%)): 360 [M⁺] (13), 345 (24), 317 (47), 290 (100), 184 (16), 77 (72). HRMS (EI) calcd. for C₂₁H₁₈N₄O₃: 360.1222; found: 360.1188. Anal. calcd. for C₂₁H₁₈N₄O₃: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.67; H, 4.50; N, 15.53%.

3. Results and discussion

As a part of sequential work aimed at manifesting the proper pattern of the azaenamine reactivity as nucleophilic carbon species towards activated cinnamionitriles [17-21], we report here the aza-Michael addition of azaenamines 1a,b with α-cyano-N-arylacrylamide derivatives 2a-e. The reaction may proceed through one of three reasonable pathways A, B or C (Scheme 1). Pathway A, involving the Michael addition of the nucleophilic acyl methyl carbon to activated acrylonitrile followed by ring closure caused by the attack of azomethine carbon to give 4 (I) and their tautomeric forms 4 (II) was readily excluded as the H NMR spectrum revealed a characteristic peak at δ 2.39 ppm corresponding to the acetyl protons (Scheme 1). Thus, the reaction can take place according to either pathway B, that comprises the first addition of hydrazone lone pair to the activated double bond followed by azomethine carbon attack forming 5-amino-2,3-dihydropyridazines 6, or pathway C, that employs a lone pair resonance causing the azomethine carbon to be nucleophilic and consequently, attack the activated acylnitriles to yield 3-amino-2,5-dihydropyridazines 8.
Using the simple spectroscopic tool we cannot make an unambiguous decision concerning the exact chemical structure of the products, yet the inspection of the HMBC spectrum of compound 8a supported the pathway C as it indicated a 3J-cross coupling between pyridazine-H5 at δ 5.72 ppm and each of the acetyl carbonyl carbon atoms at δ 196.9 ppm and the carboxamide carbon atom at δ 167.9 ppm (Figure 2). Under the usual reaction conditions compounds 1 were obtained in high yield (Table 1). Further support of the constitution of the prepared compounds was established on the basis of the other spectroscopic tools. The mass spectrum of 8a showed a molecular ion peak at m/z = 410 [M+]. The IR spectrum of compound 8a displayed broad NH2 bands at ν = 3360 and 3181 cm⁻¹. The two bands at ν = 1673 and 1643 cm⁻¹ were assigned to the amide and amide carbonyl carbon atoms, respectively. The 1H NMR spectrum exhibited a singlet signal at δ 2.39 ppm for the acetyl methyl group, a singlet at δ 5.72 ppm for pyridazine-H5. The multiplet at δ 6.96-7.59 ppm integrated for 17 protons and was assigned to aromatic and amino group protons. Attribution of all the singlets in the spectrum showed a broad signal at δ 9.05 ppm for the amide proton. The 13C NMR spectrum showed a methyl signal at δ 25.8 ppm, a pyridazine-CS signal at δ 33.4 ppm, a signal for the carbonitrile carbon atom at δ 121.4 ppm and two characteristic signals at δ 167.9 and 196.9 ppm for the carboxamide and ketonic carbonyl carbon atoms, respectively.

Table 1. The yield percentages of compounds 8a-g.

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<th>R²</th>
<th>Yield (%)</th>
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<td>92</td>
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<tr>
<td>8b</td>
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</tr>
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The chemistry of pyrimido[4,5-c]pyridazines was not extensively investigated in literature [26-28]. Pyrimido[4,5-c]pyridazines could be regarded as analogues of 4-deazatoxoflavins [29-34]. These compounds are extensively utilized in the field of the auto-recycling oxidation of amines and alcohols [35-37]. Moreover, toxoflavin has antibiotic properties and impedes the xanthene oxygenase [38]. In an extension of the program to prepare 4-deazatoxoflavin analogues through compound 8a in acetic anhydride, the pyrimido[4,5-c]pyridazine derivative 11 was obtained in good yield (Scheme 2). Compound 11 was characterized spectroscopically revealing the disappearance of NH and NH2 signals and bands. Thus the 1H NMR spectrum showed a singlet at δ 1.65 ppm for methyl, a singlet at δ 2.42 ppm for the acetyl methyl and a singlet at δ 5.36 ppm for pyridazine-H5. The 13C NMR spectrum showed two methyl signals at δ 24.4 and 25.0 ppm. It also featured signal at δ 34.0 ppm for pyridazine-C5. The signals at δ 161.3 and 196.1 ppm were assigned to carboxamide and acety carbonyl.

Attempts to extend this methodology to synthesize the other target analogue 12 using formic acid have unexpectedly failed. Instead, tetrahydropyridazine 15 was obtained in 73 % yield. The formation of 15 presumably takes place via hydrolysis of the enamine group giving the intermediate 13, which undergoes a hydrolytic aniline cleavage to form β-oxoacid derivative 14, which then loses CO₂ to form the pyridazinone derivative 15 (Scheme 3). The identity of 15 has been confirmed by spectral data which indicated the presence of two sp² carbon atoms in addition to the acetyl methyl group. Thus 1H NMR spectrum exhibited a singlet at δ 2.55 ppm for the acetyl methyl protons, a multiplet at δ 3.05 ppm for pyridazine-CH₂ and a multiplet at δ 4.71 ppm for pyridazine-H5. The 13C NMR spectrum showed the acetyl methyl signal at δ = 24.8 ppm, pyridazine-CH₂ signal at δ 35.0 ppm, pyridazine-CH signal at δ 35.4 ppm, amide and acetyl carbonyls appeared at δ 164.8 and 196.0 ppm, respectively.

In an attempt to affect a one pot synthesis of pyrimido[4,5-c]pyridazine derivatives, we treated pyruvaldehyde-1-phenylhydrazone 1a with N-carbamoyl-2-cyano-3-phenylacrylamide 16 in dioxane at reflux in the presence of piperidine (Scheme 4). Similar to the aforementioned discussion, this reaction adopts Pathway C (Scheme 1) and the consti-tution of the product 19 can be assessed by HMBC showing J-cross coupling between pyrimido[4,5-c]pyridazine-H4 at δ 5.18 ppm with acetyl carbonyl at δ 196.6 ppm and amide carbonyl at δ 165.4 ppm (Figure 3). Compound 19 was presumably formed as a result of Michael addition of 1a to 16 giving 17, which then cyclized to 18 followed by ammonia elimination.
Compounds 19 was also fully characterized through the different spectral tools: the mass spectrum showed a molecular ion peak at m/z = 360 [M⁺]. The IR spectrum indicated the presence of broad band at ν = 3424 cm⁻¹ for N-H stretch of the two NH functional groups, acetyl absorption band at ν = 1681 cm⁻¹ and a broad band at ν = 1619 cm⁻¹ for the amide groups. The 1H NMR spectrum demonstrated a signal at δ 2.56 ppm for the acetyl protons, a singlet at δ 5.10 ppm for pyridazine-H4 and a multiplet at δ 7.11-7.53 ppm for the aromatic and two NH protons. The 13C NMR fits with the deduced structure involved acyl methyl signal at δ 25.08 ppm, a pyridazine-CH signal at δ 33.34 ppm, two amide signals at δ 157.91 and 165.36 ppm and the acetyl carboxyl signal at δ 196.57 ppm.

4. Conclusion

Azaenamides were proven to be suitable C-nucleophilic candidates in Michael addition to various α-cyano-N-arylacrylamide derivatives 2a-c in a regioselective manner yielding different N-Substituted 2,5-dihydropyridazine-4-carboxamide derivatives. The newly synthesized pyridazine compounds could be transformed by a simple acetylation procedure into pyrimido[4,5- c]pyridazine (deazotosolfin analogue) 15. The formation of pyrimido[4,5-c]pyridazine compound in a single step was successfully achieved by the reaction of azaenamine with N-carbamoyl-2-cyano-3-phenylacrylamide under the same conditions.

Acknowledgements

Ismail Abdelshafy Abdelhamid and Amr Mohamed Abdelmoniem gratefully acknowledge postdoctoral fellowships by the Alexander von Humboldt foundation (AvH).

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