Enamines in Heterocyclic Synthesis: A Novel Simple and Efficient Route to Condensed Pyridazines

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An efficient and easy preparation of enamine derivatives, *via* active methyl and methylene compounds by *in situ*-generated 1-(diethoxymethyl)piperidine, produced from the mixture of triethyl orthoformate/piperidine/DMF, are described. Some new pyridazinone derivatives have been synthesized from the reaction of enamines with hydrazine hydrate and cyanoacid hydrazide.

Key words: Enamines, Pyridazinones, Amidoacetal, Pyridazinylenamine

Introduction

Enamines are versatile reagents, and the nucleophilic character of C-2 has found extensive applications in synthetic organic chemistry [1, 2]. Recently we described several efficient approaches to heteroaromatics utilizing functionally substituted enamine precursors [3 – 7]. In conjunction with these studies and as a part of our new project directed towards developing efficient routes to pyridazinones and condensed pyridazinones with potential diuretic [8], antihypertensive [9, 10], anticonvulsant, antispasmodic and muscle relaxant [10, 11] activity. Recently the pyridazinone unit has proved to be an important pharmacophore in the search for drugs acting on the cardiovascular system [12]. In this work we report a novel synthesis of condensed pyridazinones.

Results and Discussion

One of the main important routes to enamines is condensation of dialkylamine acetals with activated methyl or methylene compounds [13 – 16]. However, the fact that dimethylformamide-dimethylacetal (DMF-DMA) is a potentially toxic reagent, and expensive, led us to look for alternative routes for the synthesis of enamine derivatives, and to see, if these routes can constitute a new general approach to enamines.

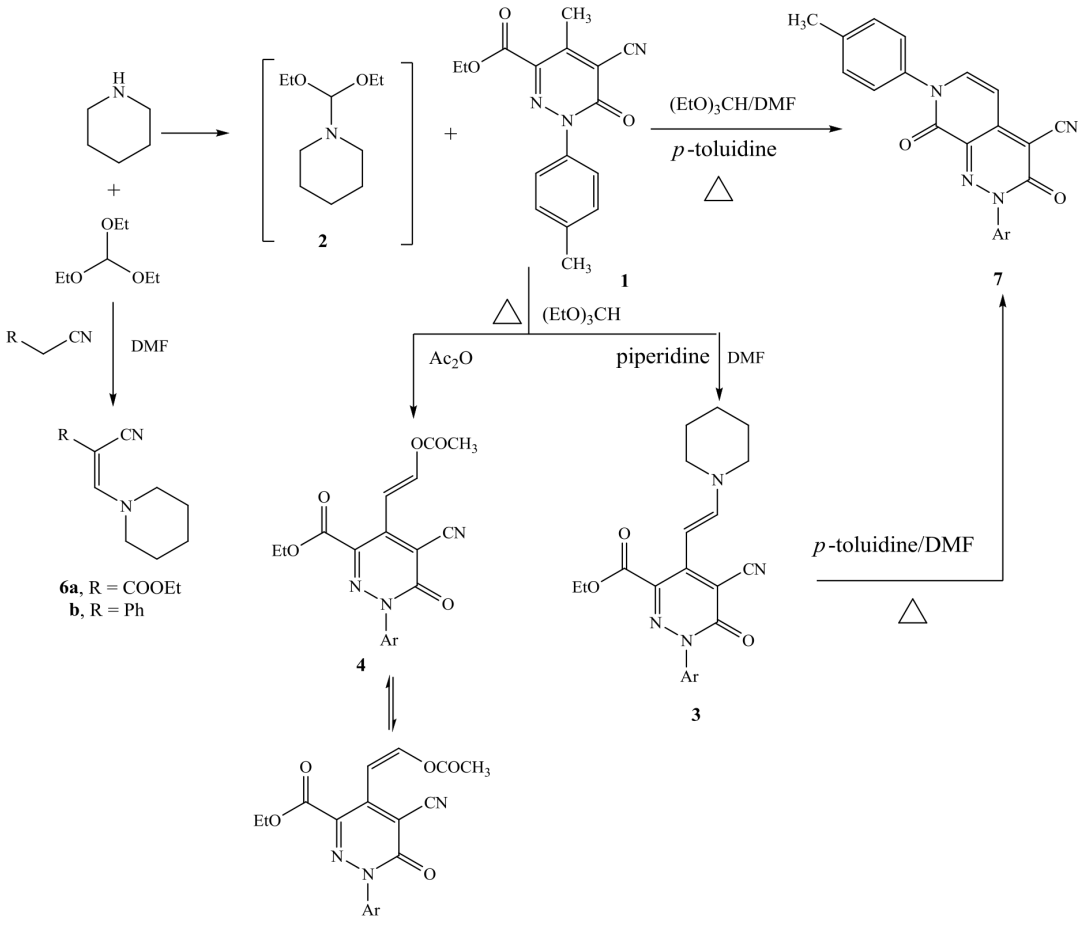
Initially we thought that reacting the pyridazine derivative **1** [17, 18] with triethyl orthoformate and piperidine in refluxing Ac_2O would afford the corresponding pyridazinylenamine **3** *via* initial formation of the *in situ*-generated amidoacetal 1-(diethoxymethyl)piperidine (**2**). However, in practice only the acetoxyvinyl pyridazine derivative **4** was obtained (Scheme 1). Although **4** can also be formulated as **5**, only **4** was formed as ^{1}H NMR revealed the *trans* olefinic protons at δ = 5.48, and δ = 8.17 ppm as two doublets with the coupling constant J = 12.8 Hz.

However, when acetic anhydride was replaced by DMF, the pyridazinylenamine **3** was formed in good yield (Scheme 1). The *trans* structure was inferred from its ^{1}H NMR spectrum which revealed two singlet signals for the piperidinyl protons at δ = 1.62 (3-CH_2) and 3.32 (2-CH_2) and the *trans* olefinic protons at δ = 5.47 and δ = 8.16 ppm as two doublets with the coupling constant J = 12.9 Hz.

The approach to generate **2** from triethyl orthoformate and piperidine in DMF seems to be a general one, as this intermediate could also be condensed with ethyl cyanoacetate and benzylcyanide [4] to afford the enamine compounds **6a** and **6b**, respectively (Scheme 1).

Replacing piperidine with *p*-toluidine in refluxing DMF resulted in the formation of the pyridopyridazine derivative **7**. Compound **7** could also be obtained *via* reaction of **3** with *p*-toluidine in refluxing DMF (Scheme 1).

The condensation of 2-(2-phenylhydrazono)-3-oxobutanenitrile (**8**) with ethyl cyanoacetate in refluxing acetic acid yielded a product that may be formulated as the 5-cyano-pyridazine-3-carboxamide derivative **9** or its isomer 6-cyanopyridazine-4-carboxamide



Scheme 1.

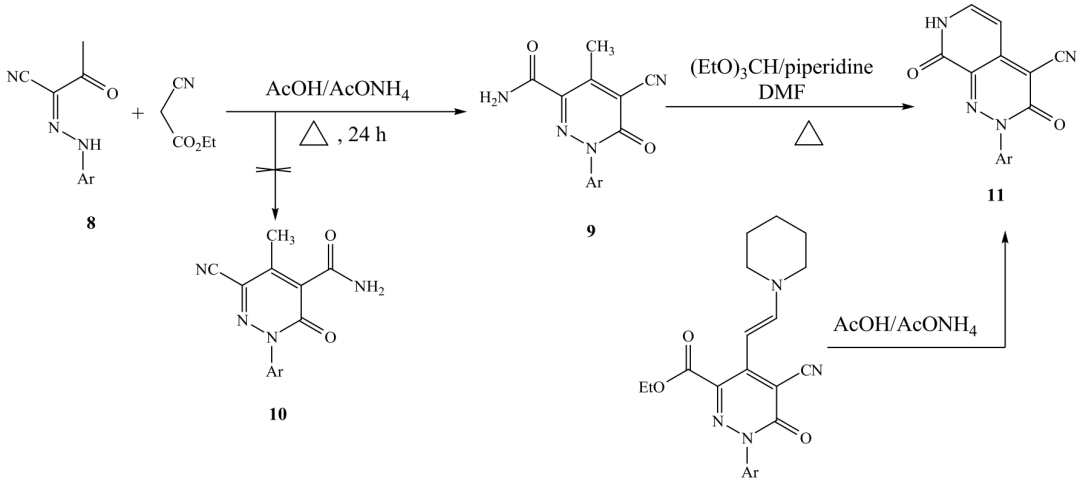
derivative **10**. Structure **9** has been established based on the fact that this product could be condensed with triethyl orthoformate and piperidine in refluxing DMF to yield the pyridopyridazine derivative **11**. Compound **11** could be also obtained from the reaction of the enamine **3** with acetic acid and ammonium acetate, and was found identical in all details (melting point and TLC analysis) to the compound obtained from the other pathway (Scheme 2).

In order to explore any further utility of the synthesized enamines, the pyridazinylenamine derivative **3** was reacted with hydrazine hydrate in refluxing ethanol or with cyanoacidhydrazide (2-cyanoacetohydrazide) in refluxing DMF, where the pyridopyridazine derivative **12** and the triazolopyridopyridazine derivative **14** were formed, respectively. Also, the pyridazinylenamine derivative **3** underwent acid hydrolysis in a refluxing mixture of $AcOH/H_2SO_4$, where the pyranopyridazine derivative **15** was formed (Scheme 3).

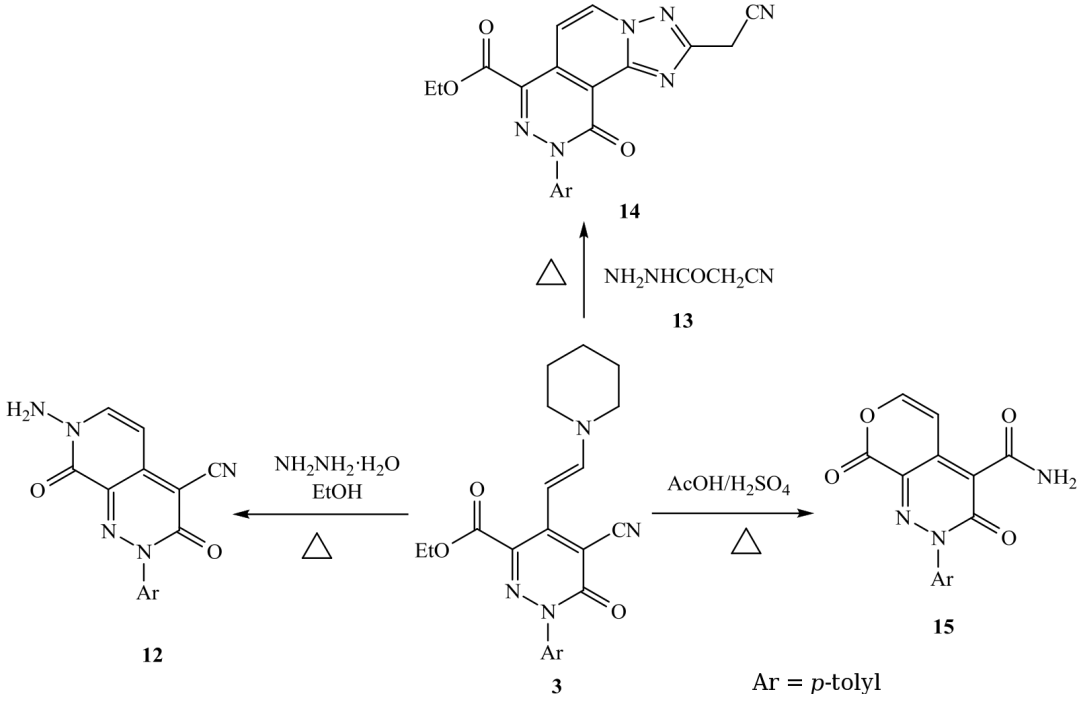
Conclusion

In conclusion we could replace the expensive, highly volatile, and toxic recommended DMF-DMA reagent for converting active methyl and methylene compounds into enamines by *in situ*-generated, less expensive, and mostly less toxic 1-(diethoxymethyl)piperidine, generated from the mixture of triethyl orthoformate/piperidine/DMF.

Although this reagent could not be condensed with the methyl function in methyl ketones, activated methyl and methylene compounds did condense readily. We could also show that enamines synthesized in this way are valuable precursors to condensed heteroaromatics.



Scheme 2.



Scheme 3.

Experimental Section

All melting points are uncorrected. IR spectra were recorded in KBr with a Bruker Vector 22 Germany spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Mercury 300 MHz spectrometer in [D_6]DMSO as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured at 70 eV using a Shimadzu GCMS-QP-1000 EX mass spectrometer. Microanalyses were performed on a LECO CHN-932 by the Microanalysis Unit of Cairo University.

*Ethyl 5-cyano-1,6-dihydro-6-oxo-4-(2-(piperidin-1-yl)vinyl)-1-p-tolylpyridazine-3-carboxylate (**3**)*

A mixture of triethyl orthoformate (0.2 mol), piperidine (0.2 mol) and ethyl 5-cyano-1,6-dihydro-4-methyl-6-oxo-1-*p*-tolylpyridazine-3-carboxylate (**1**) (0.2 mol) was heated under reflux in dimethylformamide for 24 h, allowed to cool

to r. t. and then poured into cold water. The reaction mixture was treated with 1 molar aqueous sodium acetate solution (100 mL), and the product was collected by filtration and crystallized from ethanol. The compound was obtained as red crystals. Yield 65 %; m. p. 150 – 152 °C. – IR (KBr): ν = 2198 (CN); 1720 (CO), 1664 (CO), 2942 (aliph. CH), 3030 (olef.-CH), 3118 (arom. CH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, TMS): δ = 1.27 (t, 3H, J = 7.1 Hz, CH_3), 1.62 (s, 6H, $3CH_2$, piperidine-H), 2.34 (s, 3H, CH_3), 3.32 (s, 4H, $2CH_2$, piperidine-H), 4.34 (q, 2H, J = 7.1 Hz, CH_2), 5.47 (d, 1H, J = 12.9 Hz, olef.-H), 7.24 (d, 2H, J = 9 Hz, Ar-H), 7.39 (d, 2H, J = 9 Hz, Ar-H), 8.16 (d, 1H, J = 12.9 Hz, olef.-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 14.46 (CH_3), 20.2 (CH_3), 23.53 (CH_2), 25.62 ($2CH_2$), 52.16 ($2CH_2$), 59.75 (OCH_2), 103.90 (C-5), 106.15 (*C*=CH), 121.59 (CN), 122.93 (C-2′,6′), 129.92 (C-3′,5′), 134.63 (C-4′), 138.68 (C-1′), 149.39 (C=*C*H), 152.44 (C-3), 159.94 (C-4), 166.82 (CO), 168.89 (CO). – MS (EI, 70 eV): m/z (%) = 392 (44) $[M]^+$. – $C_{22}H_{24}N_4O_3$ (392.45): calcd. C 67.33, H 6.16, N 14.28; found C 67.30, H 6.18, N 14.24.

*Ethyl 4-(2-acetoxyvinyl)-5-cyano-6-oxo-1-p-tolyl-1,6-dihydropyridazine-3-carboxylate (**4**)*

A mixture of triethyl orthoformate (0.2 mol), piperidine (0.2 mol) and ethyl 5-cyano-1,6-dihydro-4-methyl-6-oxo-1-*p*-tolylpyridazine-3-carboxylate (**1**) (0.2 mol) was heated under reflux in 30 mL of acetic anhydride for 24 h, allowed to cool to r. t. and then poured into cold water. The precipitate was collected by filtration and crystallized from ethanol. Compound **4** was obtained as a greenish yellow solid. Yield 75 %; m. p. 175 – 177 °C. – IR (KBr): ν = 2233 (CN), 1724, 1715, 1674 (CO), 1624 (C=C vinyl) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, TMS): δ = 1.27 (t, 3H, J = 7.4 Hz, CH_3), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.33 (q, 2H, J = 7.4 Hz, CH_2), 5.48 (d, 1H, J = 12.8 Hz, vinyl-H), 7.27 (d, 2H, J = 9 Hz, Ar-H), 7.37 (d, 2H, J = 9 Hz, Ar-H), 8.17 (d, 1H, J = 12.8 Hz, vinyl-H). – MS (EI, 70 eV): m/z (%) = 367 (78) $[M]^+$. – $C_{19}H_{17}N_3O_5$ (367.36): calcd. C 62.12, H 4.66, N 11.44; found C 62.11, H 4.80, N 11.10.

*General procedure for the preparation of compounds **6a**, **b***

To a mixture of ethyl cyanoacetate or 2-phenylacetonitrile (0.3 mol), triethyl orthoformate (0.32 mol) and piperidine (0.3 mol) DMF (40 mL) was added, and the solution was refluxed for 24 h. The reaction mixture was then cooled and poured onto water. The solid product formed was collected by filtration and crystallized from ethanol.

*Ethyl 2-cyano-3-(piperidin-1-yl)acrylate (**6a**)*

This compound was obtained as colorless crystals. Yield 71 %; m. p. 80 – 82 °C. – IR (KBr): ν = 2198 (CN), 1693 (CO), 2900 (aliph.-CH), 2943 (vinyl-CH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, TMS): δ = 1.17 (t, 3H, J = 7.4 Hz, CH_3), 1.61 – 170 (m, 6H, $3CH_2$), 3.54 – 3.65 (m, 4H, $2CH_2$), 4.10 (q, 2H, J = 7.4 Hz, CH_2), 7.77 (s, 1H, vinyl-H). – MS (EI, 70 eV): m/z (%) = 208 (67) $[M]^+$. – $C_{11}H_{16}N_2O_2$ (208.26): calcd. C 63.44, H 7.74, N 13.45; found C 63.39, H 7.92, N 13.74.

*2-Phenyl-3-(piperidin-1-yl)acrylonitrile (**6b**)*

Yield 80 %; m. p. 118 – 120 °C (lit.: 115 – 116 °C [4]), yellowish needles. – IR (KBr): ν = 2183 (CN), 2931 (vinyl-CH), 1616 (vinyl C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, TMS): δ = 1.58 (m, 6H, $3CH_2$), 3.64 (m, 4H, $2CH_2$), 7,07 (s, 1H, vinyl-H), 7.25 – 7.38 (m, 5H, Ar-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 24.36, 26.41, 51.96, 75.41 (*C*=CH), 121.59 (CN), 124.48, 125.51, 129.14, 137.27, 149.29 (C=*C*H). – MS (EI, 70 eV): m/z (%) = 212 (42) $[M]^+$. – $C_{14}H_{16}N_2$ (212.29): calcd. C 79.21, H 7.60, N 13.20; found C 79.29, H 7.67, N 13.17.

*2,3,7,8-Tetrahydro-3,8-dioxo-2,7-di-p-tolylpyrido[3,4-c]-pyridazine-4-carbonitrile (**7**)*

Method A. Compound **7** was obtained by the same method used for compound **3**, except that *p*-toluidine was added instead of piperidine, *via* refluxing the reactants in DMF for 24 h. The mixture was allowed to cool to r. t., then poured into cold water. Compound **7** was obtained as a solid product and crystallized from ethanol.

Method B. Compound **3** (0.2 mol) and *p*-toluidine (0.2 mol) were kept in refluxing DMF for 24 h, then the mixture was allowed to cool to r. t. and poured into cold water. The product was then collected by filtration and crystallized from ethanol to give a black solid. Yield 66 %; m. p. 320 – 323 °C. – IR (KBr): ν = 2221 (CN), 1704 (CO), 1669 (CO) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, TMS): δ = 2.38 (s, 6H, $2CH_3$), 6.18 (d, 1H, J = 6.9 Hz, Ar-H), 7.34 – 7.51 (m, 8H, Ar-H), 7.77 (d, 1H, J = 6.9 Hz, Ar-H). – MS (EI, 70 eV): m/z (%) = 368 (75) $[M]^+$. – $C_{22}H_{16}N_4O_2$ (368.39): calcd. C 71.73, H 4.38, N 15.21; found C 72.07, H 4.51, N 15.15.

*5-Cyano-1,6-dihydro-4-methyl-6-oxo-1-p-tolylpyridazine-3-carboxamide (**9**)*

A mixture of 2-(2-*p*-tolylhydrazono)-3-oxobutanenitrile (**8**, 0.3 mol), prepared as previously reported [19], ethyl cyanoacetate (0.3 mol) and ammonium acetate (0.35 mol) was heated under reflux in glacial acetic acid for 24 h, allowed to cool to r. t. and then poured into cold water. The solid product formed was collected by filtration and crystallized from glacial acetic acid. This compound was obtained as a green solid. Yield 83 %; m. p. 260 – 261 °C. – IR (KBr): ν = 3376 (NH_2), 2239 (CN), 1685, 1655 (CO), cm^{-1}. –

^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 2.18 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.32 – 7.56 (m, 4H, arom.-H), 7.72 (s, 1H, NH, D_2O-exchangeable), 7.98 (s, 1H, NH, D_2O-exchangeable). – MS (EI, 70 eV): m/z (%) = 268 (66) [M]$^+$. – $C_{14}H_{12}N_4O_2$ (268.27): calcd. C 62.68, H 4.51, N 20.88; found C 62.79, H 4.68, N 20.85.

*2,3,7,8-Tetrahydro-3,8-dioxo-2-p-tolylpyrido[3,4-c]pyridazine-4-carbonitrile (**11**)*

Method A. A mixture of triethyl orthoformate (0.2 mol), piperidine (0.2 mol) and pyridazine carboxamide **9** (0.2 mol) was heated under reflux in dimethylformamide for 24 h, allowed to cool to r. t. and poured into cold water. The solid product was filtered off and crystallized from glacial acetic acid (yield 65 %).

Method B. Compound **3** (0.2 mol) was kept in refluxing glacial acetic acid in the presence of ammonium acetate (0.21 mol) for 3 h. The mixture was allowed to cool to r. t. and then poured into cold water. The solid product was collected by filtration and crystallized from glacial acetic acid. This compound was obtained as a yellow solid. Yield 80 %; m. p. > 320 °C. – IR (KBr): ν = 3360 (br. NH), 2221 (CN), 1681 (CO), 1664 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 2.4 (s, 3H, CH_3), 6.14 (d, 1H, J = 7.6 Hz, olef.-H), 6.97 (d, 1H, J = 7.6 Hz, olef.-H), 7.46 – 7.53 (m, 4H, Ar-H), 11.74 (s, 1H, NH, D_2O-exchangeable). – ^{13}C NMR (75.4 MHz, [D$_6$]DMSO): δ = 22.29 (CH_3), 104.24 (C-4), 106.75 (C-5), 117.02 (CN), 121.93 (C-2′,6′), 122.44 (C-6), 129.62 (C-3′,5′), 136.55 (C- 4′), 139.62 (C-1′), 152.14 (C-8a), 152.54 (CO), 162.94 (C-4a), 164.84 (CO). – MS (EI, 70 eV): m/z (%) = 278 (80) [M]$^+$. – $C_{15}H_{10}N_4O_2$ (278.27): calcd. C 64.74, H 3.62, N 20.13; found C 65.11, H 3.87, N 20.29.

*2,3,7,8-Tetrahydro-7-amino-3,8-dioxo-2-p-tolylpyrido[3,4-c]pyridazine-4-carbonitrile (**12**)*

A mixture of compound **3** (0.2 mol) and hydrazine hydrate (0.2 mol) was refluxed in ethanol for 3 h. Then the reaction mixture was left to cool, and the solid product was collected by filtration and crystallized from ethanol/DMF (1 : 1). This compound was obtained as a dark-brown solid. Yield 65 %; m. p. 320 – 321 °C. – IR (KBr): ν = 3400, 3293 (NH_2), 2209 (CN), 1669 (CO), cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 2.39 (s, 3H, CH_3), 6.14 (d, 1H, J = 7.4 Hz, olef.-H), 6.45 (s, 2H, NH_2), 7.26 (d, 1H, J = 7.4 Hz, olef.-H), 7.34 – 7.49 (m, 4H, Ar-H). – MS (EI, 70 eV): m/z (%) = 293 (48) [M]$^+$. – $C_{15}H_{11}N_5O_2$ (293.28): calcd. C 61.43, H 3.78, N 23.88; found C 61.60, H 4.14, N 24.03.

*2-Cyanomethyl-6-ethyl-9-oxo-8-p-tolyl-8,9-dihydro-1,3,3a,7,8-pentaazacyclopenta [a]naphthalene-6-carboxylate (**14**)*

A mixture of compound **3** (0.1 mol) and 2-cyanoacetohydrazide (0.1 mol) was refluxed in dimethylformamide for 3 h, allowed to cool to r. t. and then poured into ice-cold water. The solid product was collected by filtration and crystallized from ethanol and a few drops of dioxane. This compound was obtained as a brown solid. Yield 71 %; m. p. 320 – 323 °C. – IR (KBr): ν = 2202 (CN), 1724 (CO), 1666 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 1.17 (t, 3H, J =7.2 Hz, CH_3), 2.14 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 4.34 (q, 2H, J = 7.2 Hz, CH_2), 7.36 – 7.51 (m, 4H, Ar-H), 8.62 (d, 1H, J = 7.8 Hz, olef.-H), 9.39 (d, 1H, J = 7.8 Hz, olef.-H). – MS (EI, 70 eV): m/z (%) = 388 (69) [M]$^+$. – $C_{20}H_{16}N_6O_3$ (388.38): calcd. C 61.85, H 4.15, N 21.64; found C 62.09, H 4.13, N 21.58.

*3,8-dihydro-3,8-dioxo-2-p-tolyl-2H-pyrano[3,4-c]pyridazine-4-carboxamide (**15**)*

Compound **3** (0.1 mol) was refluxed in a mixture of glacial acetic acid (10 mL) and sulfuric acid (5 mL) for 3 h. The reaction mixture was left to cool, then poured onto ice water and neutralized with ammonia solution. The solid product was collected by filtration and crystallized from ethanol. This compound was obtained as a green powder. Yield 75 %; m. p. 270 – 272 °C. – IR (KBr): ν = 3316 (NH_2), 1697 (CO), 1656 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 2.37 (s, 3H, CH_3), 5.66 (brs. 2H, NH_2, D_2O-exchangeable), 7.04 (d, 1H, J = 6.8 Hz, olef.-H), 7.28 – 7.42 (m, 4H, Ar-H), 7.78 (d, 1H, J = 6.8 Hz, olef.-H). – ^{13}C NMR (75.4 MHz, [D$_6$]DMSO): δ = 23.30 (CH_3), 104.95 (C-5), 121.84 (C-2′,6′), 125.92 (C-6), 130.12 (C-3′,5′), 136.15 (C-4′), 140.14 (C-1′), 142.02 (C-4), 153.14 (C-8a), 158.44 (C-4a), 159.96 (CO), 163.48 (CO), 168.92 (CO). – MS (EI, 70 eV): m/z (%) = 297 (36) [M]$^+$. – $C_{15}H_{11}N_3O_4$ (297.27): calcd. C 60.61, H 3.73, N 14.14; found C 60.54, H 3.89, N 14.20.

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