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Article

On the One Pot Syntheses of Chromeno[4,3-*b*]pyridine-3-carboxylate and Chromeno[3,4-*c*]pyridine-3-carboxylate and Dihydropyridines

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Os cromenos, dihidropiridinas e piridinas substituídos têm-se revelado importantes na síntese de compostos com propriedades farmacológicas interessantes. Consequentemente, achamos importante a síntese de cromenopiridinas e cromenodihidropiridinas (ou seja, anéis fundidos do cromeno e da dihidropiridina ou da piridina) de forma a pesquisar a sua atividade biológica. Neste estudo, propomos a síntese "one-pot" para 2,4-dimetil-5-oxo-5H-cromeno[4,3-*b*]piridina-3-carboxilatos de etilo, 2,4-dimetil-5-oxo-5H-cromeno[3,4-*c*]piridina-3-carboxilatos de etilo substituídos e as suas respectivas 1,4 dihidropiridinas, baseada numa síntese modificada da piridina de Hantzsch usando 2-hidroxiaril aldeído, com os grupos que retiram e doam elétrons no anel fenil, como reagentes iniciais. Dezesseis compostos foram sintetizados pelo método descrito e completamente caracterizados. Um rendimento médio de 37% foi obtido para os diferentes derivados.

Substituted chromenos, dihydropyridines and pyridines have been important in the syntheses of compounds having interesting pharmacological properties. Therefore, we found of interest to synthesize chromenopyridines and chromenodihydropyridines (*i.e.*, fused chromeno and dihydropyridine or pyridine rings) to further study their biological activity. Here, we propose one-pot syntheses for substituted ethyl-2,4-dimethyl-5-oxo-5H-chromeno[4,3-*b*]pyridine-3-carboxylates, ethyl-2,4-dimethyl-5-oxo-5H-chromeno[3,4-*c*]pyridine-3-carboxylates and their respective 1,4-dihydropyridines based on a modified Hantzsch pyridine synthesis using 2-hydroxyaryl aldehydes, with electron withdrawing and electron donating groups on the phenyl ring, as starting reactants. Sixteen compounds were synthesized by the described method and fully characterized. An average yield of 37% was obtained for the different derivatives.

Keywords: chromeno[4,3-*c*]pyridine, chromeno[3,4-*c*]dihydropyridine, chromenopyridine synthesis, chromenopyridine cyclization

Introduction

The chromene moiety appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[1-4] Only few synthetic approaches to chromenopyridines employing different reaction conditions and using salicylaldehyde have been previously described in literature by Sakurai *et al.*[5] and O'Callaghan *et al.*[6,7] Sakurai *et al*.[5] obtained two benzopyrano[3,4-*c*]pyridines in 7-10% yields working with salicylaldehydes, ethyl acetoacetic ester and ammonium acetate in ethanol. The main product of the reaction was a tetrahydropyridine derivative. They did not obtain dihydropyridines in any case.

O'Callaghan states in the last communication[7] that the previously reported compounds obtained by Sakurai[5] and himself[6] were incorrectly formulated. This author also described reactions between substituted salicylaldehydes (R^2=MeO, R^3= MeO, Cl) and aminocrotonate in acetic acid at room temperature for four days with yields of 22-36%. The reaction of aromatic aldehydes and α,β-unsaturated carbonyl compounds with ethyl-3-aminocrotonate generally gives dihydropyridines and pyridines.[8-10] The condensation of salicylaldehyde derivatives with active methylene

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compounds in the presence of ammonium acetate, pyridine, or piperidine usually leads to coumarins,[11] or coumarin imines, which can be hydrolyzed to coumarins.[12] Here we propose a facile synthesis of 7,8,9-substituted-1-ethoxycarbonyl-2,4-dimethyl-5-oxo-5H-chromeno[4,3-*b*] pyridines; 7,8,9-substituted-1-ethoxycarbonyl-2,4-dimethyl-5-oxo-5H-chromeno[3,4-*c*]dihydropyridines and their respective pyridines in one easy step. Both, electro-attracting and donating groups were tested as substituents on the phenyl ring of the molecules. The reaction may be applied to any aromatic aldehyde having a hydroxyl group at 2-position in the aromatic ring. The synthesized compounds are described in Table 1.

Table 1. Substitutions of synthesized chromenodihydropyridines and chromenopyridines

Compound	R^1	R^2	R^3
1a	H	H	H
1b	H	H	Br
2a	H	H	H
2b	H	H	Br
3a	H	H	H
3b	H	H	Br
3c	H	OH	H
3d	H	H	OH
3e	Me	H	H
3f	NO_2	H	H
3g	H	MeO	H
3h	H	H	Me
3i	H	H	MeO
3j	H	H	NO_2
3k	H	H	Cl
3l	OH	H	H

Results and Discussion

The key for the achievement of the products depends on the availability of an *ortho*-hydroxy group on the aromatic aldehyde. Reaction yields are comparable with total yields of previously described syntheses of chromenopyridines, starting either from an aldehyde or by using other synthetic strategies.[12-15]

The end product of the reaction is strongly dependent on the conditions of temperature, reactants and solvents used. In Table 2 are summarized the optimal reaction conditions for obtaining either [3,4-*c*]dihydropyridines or [4,3-*b*]pyridines moieties. We obtained the best results working always in anhydrous medium for obtaining both types of regioisomers.

Concerning the reactants and solvent used, if the reaction is carried out in acetic acid/absolute ethanol (1/1), aldehyde, ethyl acetoacetate and ammonium salts, the main product corresponds to the chromeno[3,4-*c*]dihydropyridine as it is shown in the synthesis of the non-substituted derivative chromeno[3,4-*c*]dihydropyridine (**1a**) and 9-bromo-chromeno[3,4-*c*]dihydropyridine (**1b**). These compounds can be easily oxidized to the corresponding chromeno[3,4-*c*] pyridines (**2a-b**). If the reaction is carried out in acetic acid, aldehyde and ethylaminocrotonate, the main products are the chromeno[4,3-*b*]pyridines (**3a-l**) (see Figure1 and Table 1).

It seems that working in pure glacial acetic acid favours the 1,4-amino addition to the coumarin moiety shown in step 3 (Figure 3) on the proposed mechanism of formation of the [4,3-*b*] compounds. Working with AcOH/EtOH (1:1) decreases the acidity of the medium favouring the 1,4 addition of the C_α on the aminocrotonate to the coumarin system (Figure 2, step 3).

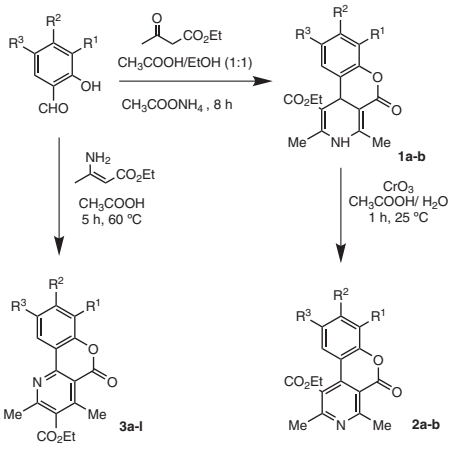

Figure 1. Synthetic pathways leading from hydroxyphenyl aldehydes to chromeno[4,3-*b*]pyridines (**3a-l**) and chromeno[3,4-*c*]pyridines (**2a-b**).

Table 2. Summary of reaction conditions for optimal yields

Compound	Solvent	Temp (ºC)	Time (h)	Yield (%)	Comments
1a – 1b	ethanol/acetic acid	reflux	8	14 - 34	A dark, viscous oily mixture of products is obtained when using aqueous ammonia solution instead of ammonium acetate. Increasing the time reaction does not improve the yields of the syntheses.
2a – 2b	Anhydrous acetic acid	25	1	50 - 66	Mild oxidation of dihydropyridines (**1**) to pyridines
3a – 3l	Anhydrous acetic acid	60	5	28 - 54	Decomposition when heating over 60 ºC. Increasing the time reaction does not improve the yields of the syntheses.

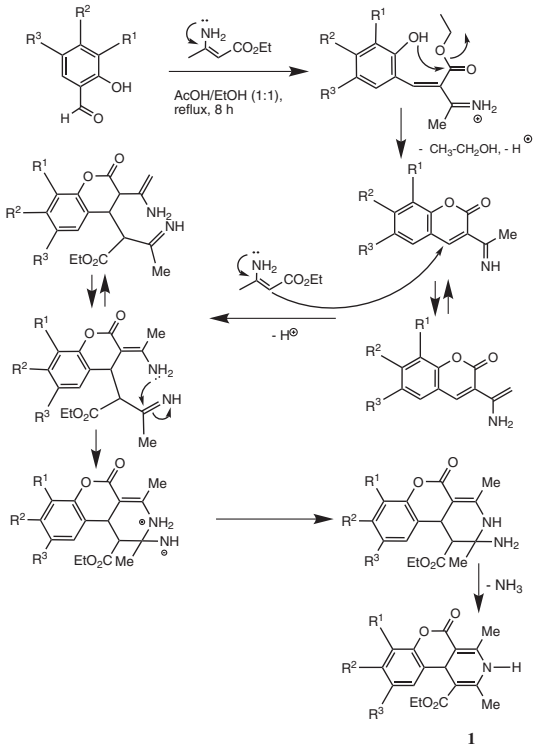

Figure 2. Mechanism proposal of chromeno[3,4-*c*]dihydropyridines formation.

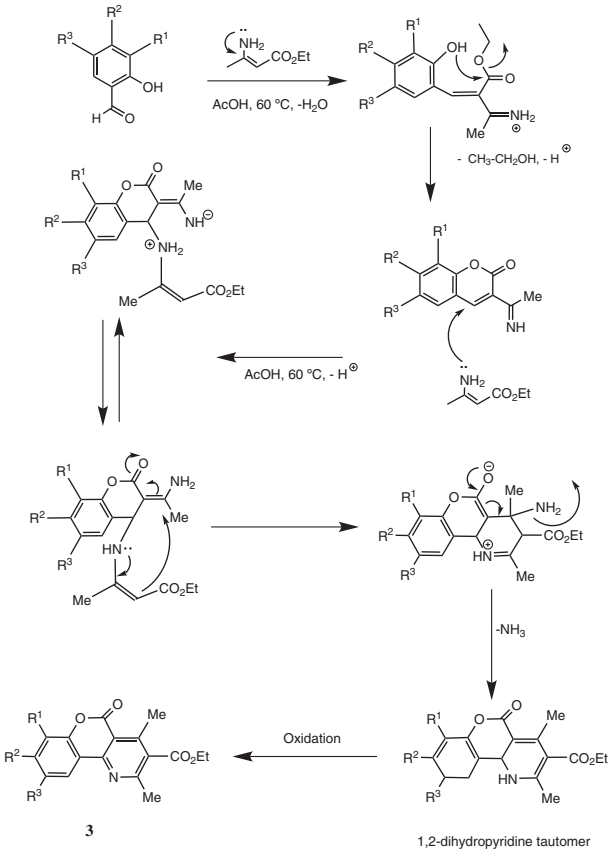

Figure 3. Mechanism proposal of chromeno[4,3-*b*]pyridines formation.

Scheme 1. Proposal for key intermediates leading from the aldehydes to chromeno[3,4-*c*]dihydropyridines (Figure 2) and chromeno[4,3-*b*] pyridines (Figure 3).

A proposal for key intermediates leading from the aromatic aldehydes to chromenopyridines could be as follows (Scheme 1).

In a previous paper of O'Callaghan,[7] it was stated that heating the reactants in acetic acid solution destroys any 1,2-dihydropyridines which may be formed leaving 1,4-dihydropyridines as the only stable, isolable product. Our investigation shows, however, that heating a mixture of 2-hydroxy aromatic aldehydes with 3-aminocrotonates in anhydrous acetic acid yield the chromeno[4,3-*b*]pyridines instead. We tested the reaction with twelve 2-hydroxyaryl aldehydes with both electron donating and electron withdrawing groups as substituents in the aldehydes. The resulting chromenopyridines are shown in Table 1. It includes three previously synthesized chromeno pyridines by O`Callaghan himself and we compare their IR and ^{1}H NMR spectra for the compounds having R= 9-Cl (**3k**), R= 9-MeO (**3i**), R= 8-MeO (**3g**). Since, ^{1}H NMR and FT-IR spectra of synthesized compounds did not permit the discrimination between chromeno[4,3-*b*]pyridines and chromeno[3,4-*c*]pyridines derivatives, HMQC, HMBC and ^{13}C NMR were applied to differentiate them. The HMQC spectrum permits us to correlate the protons with their respective carbon atoms. In the HMBC spectrum, the protons at carbons A and F (Figure 4), are coupled long range with the common quaternary carbons, C and D. This coupling can only be observed in the chromeno[4,3-*b*] pyridine compounds (**II**) and therefore it is possible to differentiate between regioisomers **I** and **II**.

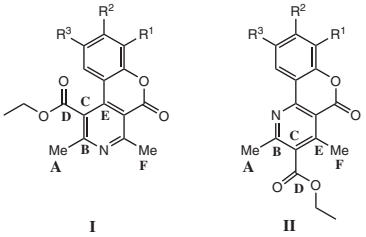

Figure 4. Regioisomers I and II.

Experimental

Synthesis of ethyl substituted-2,4-dimethyl-5-oxo-5H-chromeno[3,4-c] dihydropyridine -3-carboxylates: general procedure

To a mixture of 5 mmol of aldehyde and 15 mmol of ethyl acetoacetate in ethanol/acetic acid (1/1, 120 mL)

is added an excess of ammonium acetate. The reaction mixture is refluxed under nitrogen during 8 h. The crude product is extracted with dichloromethane and purified using column chromatography (stationary phase: alumina, mobile phase:dichloromethane/ethyl acetate: 4/1).

*Ethyl 2,4-dimethyl-5-oxo-5H-chromeno[3,4-c]dihydropyridine-1-carboxylate (**1a**)*

Physical Characterization: yield 34%, mp 275-277 ºC, IR (KBr) ν_{max}/cm^{-1}: 3301.8, 1695.5, 1621.0, 1500.8, 1383.3, 1307.2, 1224.5, 1194.6, 1128.6, 1078.9, 1022.1, 762.9, 473.8. ^{1}H NMR (300 MHz, DMSO-d$_6$): 1.1 (t, 3H, CH_2-CH_3, *J* 7.2), 2.0 (s, 3H, -CH_3), 2.2 (s, 3H, -CH_3), 4.1 (m, 2H, -CH_2-, *J* 7.2), 4.7 (s, 1H, 10b-H), 6.9 (m, 4H, Ar-H), 8.8 (s, 1H, -NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 14.54, 17.10, 18.76, 33.68, 59.63, 96.32, 97.48, 116.88, 124.14, 124.36, 127.62, 132.52, 146.08, 147.96, 150.28, 165.01, 167.57. Anal. Calc. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.10; H, 5.74; N, 4.69%.

*Ethyl 9-Bromo-2,4-dimethyl-5-oxo-5H-chromeno[3,4-c]dihydropyridine-1-carboxylate (**1b**)*

Physical Characterization: yield 14%, mp 116-119 ºC, IR (KBr) ν_{max}/cm^{-1}: 3321.2, 1698.7, 1497.0, 1304.2, 1226.1, 1192.8, 1074.6. ^{1}H NMR (300 MHz, DMSO-d$_6$): 1.1 (t, 3H, -CH_3, *J* 7.24), 2.0 (s, 3H, -CH_3), 2.2 (s, 3H, -CH_3), 4.0 (c, 2H, -CH_2-, *J* 7.24), 4.7 (s, 1H, 10b-H), 7.0 (m, 3H, Ar-H), 9.0 (s, 1H, -NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 13.98, 16.31, 18.37, 33.34, 79.28, 78.99, 94.89, 96.34, 115.56, 118.63, 126.75, 129.79, 134.38, 146.14, 148.28, 149.04, 166.83. Anal. Calc. for $C_{17}H_{16}NO_4Br$: C, 53.99; H, 4.26; N, 3.70. Found: C, 54.11; H, 4.25; N, 3.69%.

Synthesis of ethyl substituted-2,4-dimethyl-5-oxo-5H-chromeno[3,4-c]pyridine-3-carboxylates: general procedure

Chromium oxide (0.2 mg) in water (0.1 mL) is added to a solution of the dihydropyridine **1** (0.13 mmol) in acetic acid (1 mL). The mixture is stirred at room temperature for about 1 h. An excess of concentrated ammonium solution is added. The precipitate is collected and recrystallized from methanol.

*Ethyl 2,4-dimethyl-5-oxo-5H-chromeno[3,4-c]pyridine-1-carboxylate (**2a**)*

Physical Characterization: yield 66.3%, m.p 137-140 ºC, IR (KBr) ν_{max}/cm^{-1}: 3425.4, 1742.8, 1608.4, 1550.5, 1443.1, 1287.1, 1234.8, 1192.3, 1087,9, 1018.2, 768.4. ^{1}H NMR (300 MHz, $CDCl_3$) 1.4 (t, 3H, -CH_3, *J* 7.2), 2.6 (s, 3H, -CH_3), 3.1 (s, 3H, -CH_3), 4.4 (c, 2H, -CH_2-, *J* 7.24), 7.6 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84, 22.94, 27.38, 62.43, 112.91, 115.49, 118.04, 121.80, 124.36, 125.76, 132.76, 139.77, 152.63, 159.16, 159.40, 164.55, 169.44. Anal. Calc. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.50; H, 5.08; N, 4.69%.

*Ethyl 9-Bromo-2,4-dimethyl-5-oxo-5H-chromeno[3,4-c]pyridine-1-carboxylate (**2b**)*

Physical Characterization: yield 50.1%, m.p 125-128 ºC, IR (KBr) ν_{max}/cm^{-1}: 3390.0, 1730.5, 1607.2, 1570.5, 1453.3, 1290.0, 1180.3, 1056,5, 1015.0. ^{1}H NMR (300 MHz, $CDCl_3$) 1.5 (t, 3H, -CH_3, *J* 7.2), 2.7 (s, 3H, -CH_3), 3.1 (s, 3H, -CH_3), 4.5 (c, 2H,-CH_2-, *J* 7.24), 7.8 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.89, 23.01, 27.58, 62.68, 112.96, 115.69, 118.54, 122.03, 124.41, 124.65, 134.76, 140.27, 153.01, 159.98, 160.01, 164.97, 170.11. Anal. Calc. for $C_{17}H_{14}NO_4Br$: C, 54.28; H, 3.75; N, 3.72. Found: C, 54.31; H, 3.74; N, 3.73%.

Synthesis of ethyl 7,8,9-substituted-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b]pyridine-3-carboxylates: general procedure

14.5 mmol of the respective aldehyde were weighed and dissolved in 8 mL of glacial acetic acid. This solution is added drop to drop over a mixture previously prepared of 3.74 g (29 mmol) of ethyl-3-aminocrotonate in 4 mL of glacial acetic acid. The mixture is warmed, not exceeding a temperature of 60 ºC, for 5 h with constant stirring. The formation of a precipitate was observed. The solution is left at room temperature during 12 h to assure that all the product precipitates. The precipitate is filtered off and recrystallized in ethanol. The pale yellow coloured precipitate is filtered, washed with EtOH/H_2O: 1/1 and oven dried at 50 ºC.

*Ethyl 2,4-dimethyl-5-oxo-5H-chromeno[4,3-b]pyridine-3-carboxylate (**3a**)*

Physical Characterization: yield 54%, mp 114-117 ºC, IR (KBr) ν_{max}/cm^{-1}: 3444.2, 3030, 1731.7, 1448.3, 762.90. ^{1}H NMR (300 MHz, acetone-d$_6$) 1.3 (t, 3H, -CH_3, *J* 7.24), 2.5 (s, 3H, -CH_3), 2.6 (s, 3H, -CH_3), 4.37 (c, 2H, -CH_2-, *J* 7.24), 7.81 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, acetone-d$_6$) δ 13.80, 18.83, 23.23, 62.08, 114.35, 116.69, 119.25, 124.72, 125.52, 132.79, 149.65, 152.26, 153.04, 159.56, 159.80, 160.33, 167.70. Anal. Calc. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.48; H, 5.10; N, 4.70%.

*Ethyl 9-bromo-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b]pyridine-3-carboxylate (**3b**)*

Physical Characterization: yield 40%, mp 178-180 ºC, IR (KBr) ν_{max}/cm^{-1}: 3435.8, 3071.4, 2987.2, 1735.6, 1726, 1594.8, 1565.3, 1551.1, 1443.8, 1382.1, 1281.2, 1225.2, 1191.2, 1018.9, 831.1. ^{1}H NMR (300 MHz, $CDCl_3$-d$_1$) 1.37 (t, 3H, -CH_3, *J* 7.13), 2.62 (s, 3H, -CH_3), 2.73 (s, 3H, -CH_3),

4.42 (q, 2H, -CH_2-, *J* 7.15), 7.15 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$-d_1) δ 13.2, 18.3, 22.7, 61.1, 112.8, 116.5, 117.3, 119.5, 127, 131.2, 134, 148.9, 149.9, 150.4, 158.2, 159.8, 168.5. Anal. Calc. for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 53.20; H, 3.76; N, 3.31%.

*Ethyl 8-hydroxy-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3c**)*

Physical Characterization: yield 40%, mp 195 ºC, IR (KBr) ν_{max}/cm^{-1}: 3330.4, 2998.7, 2984.3, 2936.1, 2917.7, 1724.0, 1699.0, 1629.5, 1565.9, 1441.5, 1241.9. ^{1}H NMR (300 MHz, DMSO-d_6) 1.35 (t, 3H, -CH_3, *J* 7,29), 2.5 (s, 3H, -CH_3), 2.6 (s, 3H, -CH_3), 4.4 (q, 2H, -CH_2-, *J* 7.29), 7.5 (m, 3H, Ar-H), 10.54 (s, 1H, -OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.9, 17.9, 22.4, 60.8, 100.1, 109.3, 110.8, 112.3, 125.4, 128.8, 147.9, 151.0, 152.7, 158.6, 160.7, 166.4, 166.9. Anal. Calc. for $C_{17}H_{15}NO_5$: C, 65.16; H, 4.83; N, 4.47. Found: C, 64.67; H, 4.96; N, 4.84%.

*Ethyl 9-hydroxy-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3d**)*

Physical Characterization: yield 35%, mp 247-249 ºC, IR (KBr) ν_{max}/cm^{-1}: 3253.3, 3073.0, 2984.3, 2936.1, 1726.0, 1686.4, 1612.2, 1554.3, 1463.7, 1400.1, 1364.4, 1344.1, 1231.3, 1187.9, 1102.1, 1027.9, 819.6, 619.0. ^{1}H NMR (300 MHz, DMSO-d_6) 1.35 (t, 3H, -CH_3, *J* 7.29), 2.55 (s, 3H, -CH_3), 2.62 (s, 3H, -CH_3), 4.43 (q, 2H, -CH_2-, *J* 7.29), 7.4 (m, 3H, Ar-H), 9.7 (s, 1H, -OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.34, 19.36, 23.77, 62.34, 109.49, 114.06, 117.8, 119.38, 121.00, 131.45, 145.84, 149.34, 151.88, 154.48, 159.82, 167.70, 168.46. Anal. Calc. for $C_{17}H_{15}NO_5$: C, 65.16; H, 4.83; N, 4.47. Found: C, 63.86; H, 4.89; N, 4.56%.

*Ethyl 7-methyl-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3e**)*

Physical Characterization: yield 29%, mp 114-116 ºC, IR (KBr) ν_{max}/cm^{-1}: 3030, 2962, 1722.9, 1550, 1226.6, 779.9. ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (t, 3H, -CH3), 2.469 (s, 3H, -CH_3), 2.670 (s, 3H, -CH_3), 2.79 (s, 3H, -CH_3), 4.499 (c, 2H, -CH_2-), 7.67 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.70, 15.11, 18.91, 20.48, 23.29, 61.51, 113.02, 118.30, 124.64, 124.88, 131.06, 133.08, 149.37, 150.23, 151.86, 159.74, 159.86, 167.58. Anal. Calc. for $C_{18}H_{17}O_4$: C, 69.44; H, 5.50; N, 4.50; O, 20.56. Found: C, 68.47; H, 6.11; N, 4.16%.

*Ethyl 7-nitro-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3f**)*

Physical Characterization: yield 28%, mp 184-185 ºC, IR (KBr) ν_{max}/cm^{-1}: 3030, 2962, 1743.6, 1564.4, 1466.2, 1285.6, 798.4. ^{1}H NMR (300 MHz, $CDCl_3$) 1.38 (t, 3H, -CH_3), 2.63 (s, 3H, -CH_3), 2.73 (s, 3H, -CH_3), 4.45 (c, 2H, -CH_2-), 7.39 (t, 1H, Ar-H), 8.06 (d, 1H, Ar-H), 8.86 (d, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.12, 17.37, 18.24, 22.75, 57.38, 61.28, 112.79, 120.19, 122.72, 126.77, 129.66, 131.77, 144.22, 149.24, 149.66, 160.33, 166.49. Anal. Calc. for $C_{17}H_{14}N2O6$: C, 59.65; H, 4.12; N, 8.18; O, 28.04. Found: C, 59.23; H, 4.25; N, 8.03%.

*Ethyl 8-methoxy-2,4-dimethyl-5-oxo-5H-chromeno [4,3-b]pyridine-3-carboxylate (**3g**)*

Physical Characterization: yield 40%, mp 137-138 ºC, IR (KBr) ν_{max}/cm^{-1}: 3030, 2962, 1722, 1442.9, 1342.0, 799.2. ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (t, 3H, -CH_3), 2.64 (s, 3H, -CH_3), 2.76 (s, 3H, -CH_3), 3.89 (s, 3H, -CH_3), 4.49 (c, 2H, -CH_2-), 7.37 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.18, 18.37, 22.78, 54.72, 60.96, 99.25, 111.14, 111.20, 111.61, 125.60, 129.65, 148.85, 151.51, 153.01, 159.54, 159.88, 162.12, 167.21. Anal. Calc. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 64.59; H, 5.39; N, 4.21%.

*Ethyl 9-methyl-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3h**)*

Physical Characterization: yield 37%, mp 114-116 ºC, IR (KBr) ν_{max}/cm^{-1}: 3030, 2962, 1724.8, 1569.8, 809.4. ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (t, 3H; -CH_3), 2.44 (s, 3H, -CH_3), 2.66 (s, 3H, -CH_3), 2.77 (s, 3H, -CH_3), 4.49 (c, 2H, -CH_2-), 7.59 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.70, 18.91, 20.48, 23.23, 61.51, 113.25, 115.83, 118.07, 124.64, 131.06, 132.80, 133.72, 149.37, 150.23, 151.86, 159.74, 159.86, 167.58. Anal. Calc. for $C_{18}H_{17}O_4$: C, 69.44; H, 5.50; N, 4.50; O, 20.56. Found: C, 68.47; H, 6.11; N, 4.16%.

*Ethyl 9-methoxy-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3i**)*

Physical Characterization: yield 36%, mp 170-171 °C, IR (KBr) ν_{max}/cm^{-1}: 3423, 3085.6, 2994.3, 1722.1, 1609, 1568.5, 1552.4, 1495.9, 1281.2, 1255.4, 1222, 1189.9, 1137.2, 1096.7, 1020.8, 819.6. ^{1}H NMR (300 MHz, $CDCl_3$-d_1) 1.46 (t, 3H, -CH_3, *J* 7.01), 2.70 (s, 3H, -CH_3), 2.81 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 4.5 (q, 2H, -CH_2-, *J* 7.14), 7.49 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$-d_1) δ 13.70, 18.95, 23.26, 55.43, 61.56, 106.47, 113.34, 117.28, 118.98, 120.21, 131.28, 146.59, 149.49, 151.70, 155.92, 159.80, 159.90, 167.61. Anal. Calc. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 64.42; H, 5.58; N, 3.81%.

*Ethyl 9-nitro-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3j**)*

Physical Characterization: yield 32%, mp 209-210 ºC, IR (KBr) ν_{max}/cm^{-1}: 3083.2, 2998,6, 1749.2, 1731.5, 1602.5,

1560.5, 1531.1, 1343.2, 1227.1, 1189.7. ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (t, 3H, -CH_3), 2.67 (s, 3H, -CH_3), 2.78 (s, 3H, -CH_3), 4.49 (c, 2H, -CH_2-), 7.68 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.79, 23.29, 61.84, 113.56, 117.46, 119.30, 121.59, 126.53, 132.45, 144.12, 149.76, 150.15, 155.54, 158.23, 161.10, 167.02. Anal. Calc. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 60.98; H, 4.04; N, 7.99%.

*Ethyl 9-chloro-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3k**)*

Physical Characterization: yield 42%, mp 181-184 ºC, IR (KBr) ν_{max}/cm^{-1}: 3030, 2962, 1598.4, 1446.1, 1743.5, 833.29. ^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (t, 3H, -CH_3), 2.67 (s, 3H, -CH_3), 2.78 (s, 3H, -CH_3), 4.48 (q, 2H, -CH_2-), 7.95 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.70, 18.85, 23.23, 61.66, 113.44, 117.63, 119.80, 124.61, 124.98, 129.72, 131.80, 149.56, 150.51, 150.69, 159.07, 160.35, 167.31. Anal. Calc. for $C_{17}H_{14}NO_4Cl$: C, 61.55; H, 4.25; N, 4.22; Cl, 10.69; O, 19.29. Found: C, 64.67; H, 4.96; N, 4.84%.

*Ethyl 7-hydroxy-2,4-dimethyl-5-oxo-5H-chromeno[4,3-b] pyridine-3-carboxylate (**3l**)*

Physical Characterization: yield 30%, mp 205-207 ºC, IR (KBr) ν_{max}/cm^{-1}: 3253.3, 3068.1, 2980.47, 2934.4, 1725.0, 1698.0, 1620.8, 1564.0, 1551.4, 1428.0, 1366.32, 1294.9, 1228.4, 1187.9, 1042.3, 789.7. ^{1}H NMR (300 MHz, DMSO-d_6) 1,40 (t, 3H, -CH_3, *J* 7.29), 2,60 (s, 3H, -CH_3), 2.70 (s, 3H, -CH_3), 4,44 (q, 2H, -CH_2-, *J* 7.29), 7.5 (m, 3H, Ar-H), 10.2 (s, 1H, -OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 19.5, 23.8, 62.4, 114.2, 115.1, 119.0, 119.9, 124.7, 131.4, 141.5, 145.3, 149.3, 152.4, 159.5, 159.9, 167.7. Anal. Calc. for $C_{17}H_{15}NO_5$: C, 65.16; H, 4.83; N, 4.47. Found: C, 64.67; H, 4.92; N, 4.71%.

Conclusions

We did not obtain "normal" Hantszch products using 2-hydroxiphenyl aldehydes in any case and moreover a small modification of the reaction medium leads to chromeno[3,4-*c*]dihydropyridine or chromeno[4,3-*b*] pyridine derivatives with yields ranging between 15%-60% depending on the substituents on the phenyl ring of the 2-hydroxyphenylaldehydes.

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