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The first synthesis of dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepinols and a new alternative approach for diazepinone analogues

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Abstract—The first synthesis of a series of 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols, where aryl = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4,4′-biphenyl, 1-naphthyl and heteroaryl = 2-thienyl, 2-furyl obtained from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones with 2,3-diaminopyridine in 54–71% yield, is reported. Another alternative and efficient route for the synthesis of a series of 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones from the reaction 4-methoxy-1,1,1-trichloroalk-3-en-2-ones with 2,3-diaminopyridine, in 54–70% yield, is also reported.

Benzodiazepine compounds have been considered the most extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity. However, many undesirable side effects have been associate with the use of benzodiazepines. Modifications in the structure of these heterocycles have been made, and the anxiolytic effect of benzodiazepines (clobazam) has been described. However, considerably less is known about the effects of substituents on 1,5-benzodiazepines, and few studies on the synthesis and pharmacological effects of new 1,4-diazepines fused to six-membered heterocycles have been carried out.[1] On the other hand, the trihaloacetylation of enol ethers or acetals has produced 4-aryl(heteroaryl)-4-methoxy-1,1,1-trifluoro(chloro)-alk-3-en-2-ones (**1**, **2**) in one step and in good yields. Compounds **1** and **2** proved to be useful building blocks for the synthesis of five-, six- and seven-member-trihalomethylated heterocyclic compounds. Moreover, these trihalomethyl vinyl ketones have been considered the best method for attaching a trihalomethyl group to heterocyclic rings due to their chemical versatility and easy obtainment.[2]

The classical haloform reaction in which the trichloromethyl substituent is a leaving group has long been known[3] but just a few references from the literature report the use of the trichloromethyl substituent as a good leaving group in heterocyclic syntheses involving cyclocondensation reactions with 4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**2**).[4]

Recently, we reported the synthesis of 2-trifluoro- and 2-trichloromethyl-3*H*-1,5-benzodiazepines from the reaction of ketones (**1**, **2**) with *o*-phenylenediamine in good yields.[5] Next, we demonstrated that 4-phenyl-2-trichloromethyl-3*H*-1,5-benzodiazepine hydrogen sulfate possessed anxiolytic activity and produced motor uncoordination similar to that observed in mice with diazepam.[6] In the same year, we also reported that the same trichloro-substituted benzodiazepines presented an inhibitory effect on acetylcholinesterase and ATPDase activities from the cerebral cortex of adult rats.[7]

In recent years, Savelli et al.[8] described pyrido[2,3-*b*]-[1,4]diazepinone structures, some of which revealed interesting neuroleptic properties. However, because of the failure of the reactions of simple β-diketones, that is, pentan-2,3-dione or benzoylacetone with 2,3-diaminopyridine to yield 3*H*-pyrido[2,3-*b*][1,4]diazepine structures since 1964 acyclic and cyclic β-ketoesters have only been used as precursor for a series of pyrido[2,3-*b*]-[1,4]diazepin-2-ones and/or the respective pyridodiazepin-4-one isomers.[8a,9–11] Moreover, no publication has

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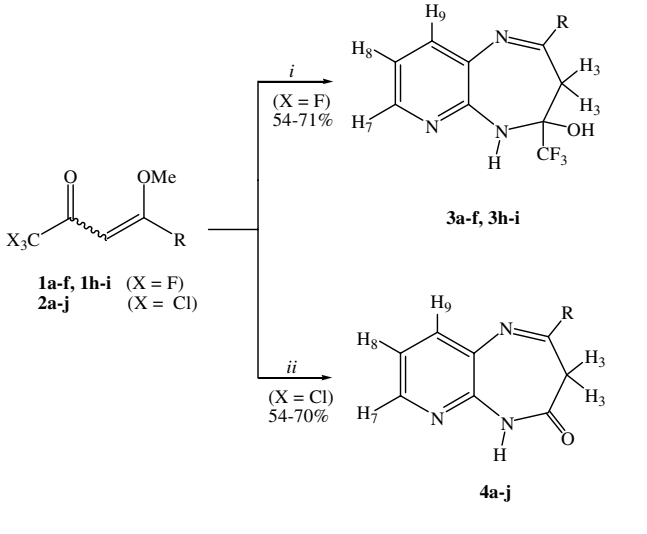
been found with the objective of carrying out a regiospecific and simultaneous introduction of a trifluoromethyl or a trichloromethyl and substituted aryl groups at the pyrido[2,3-*b*][1,4]diazepine derivatives starting from trihalomethyl substituted 1,3-diketones or 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones. Thus, the inexistence of data about the reactions involving simple 1,3-diketones and 2,3-diaminopyridine led us to try **1** and **2**, as possible cyclizing agents, especially in view of the successful synthesis of 2-trifluoro- and 2-trichloromethyl-3*H*-1,5-benzodiazepines and in the search of new heterocyclic structures with promising biological activity. However, an extension of the reaction of **1** and **2** with 2,3-diaminopyridine, a non-symmetrical heteroaromatic diamine, necessarily introduces the additional problem of two possible isomeric diazepine products. The formation of the pyridodiazepine system presumably will depend on whether the initial reaction at the more nucleophilic 3-amino function to occur at the β-olefinic carbon of vinyl ketones **1** and **2** or at the carbonyl carbon.

Striving for future biological evaluations, it seemed desirable to develop a general method for the synthesis of pyridodiazepine derivatives (3*H*-1,5-benzodiazepine analogues), in which a trihalomethyl or carbonyl, aryl and heteroaryl groups could be introduced as substituents on this promising triaza fused heterocyclic family. Thus, as an extension of our research programme we wish to report the first regiospecific preparation of a series of 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols (**3a–f**, **3h–i**), as well as a new alternative and efficient route to obtain 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-one (**4a–j**) analogues from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**1a–f**, **1h–j**) and 4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**2a–j**) with 2,3-diaminopyridine, respectively (Scheme 1).



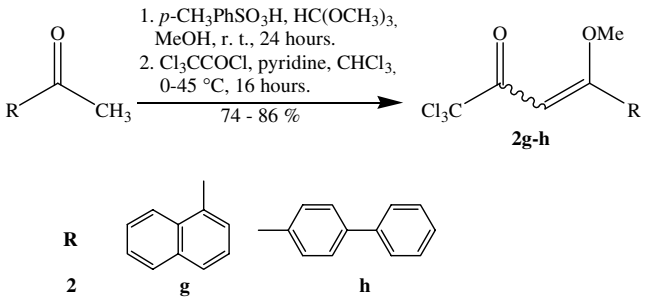
Scheme 1. Reagents and conditions: (i) 2,3-$(NH_2)_2C_5H_3N$, MeOH, 60–65 °C, 24 h; (ii) 2,3-$(NH_2)_2C_5H_3N$, MeONa, MeOH, 60–65 °C, 24 h.

Ketones **1** and **2** are readily available *CCC* synthetic blocks and were prepared from trifluoroacetylation or trichloroacetylation reactions of enol ethers generated in situ from the respective aryl- or heteroaryl methyl ketone acetals with trifluoroacetic anhydride or with trichloroacetyl chloride, respectively.[12]

In this study we found that trifluoromethylated ketones **1** when treated with 2,3-diaminopyridine at a molar ratio of 1:1, respectively, in methanol as solvent for 24 h, at 60–65 °C, regiospecifically produced 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]-diazepin-4-ols (**3a–f**, **3h–i**) in a one-step reaction and in 54–71% yield.[13,14] Somewhat surprisingly, when these reactions were carried out, employing ketones **2**, also at a molar ratio of 1:1, respectively, in anhydrous methanol as solvent under reflux for 24 h, 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones (**4a–j**) were easily isolated in 54–70% yields, as pure isomers.[15,16] The above described conditions allowed us to regiospecifically obtain diazepinones (**4**) instead of the analogues 2-aryl(heteroaryl)-4-trichloromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ol or the respective 2-keto-pyridodiazepine isomer.

Although previously similar reaction conditions were employed to synthesize 5*H*-thiazolo[2,3-*a*]pyrimidin-5-ones and 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, we found in this case an unexpected reactivity of the 2-amino group of the π-deficient pyridine ring towards the carbonyl group of the 4-aryl(heteroaryl)-4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**2**) promoting a efficient haloform reaction. Only compound **4a** was synthesized previously by Israel et al.[10,11] and by Barchet and Merz[9a] in 65% yield from the reaction of 2,3-diaminopyridine with ethyl benzoylacetate, but under difficult reaction conditions (boiling xylene for 4 h with azeotropic distillation of the formed water). Our procedure gives the same compound under milder conditions (refluxing methanol for 24 h) and in a similar yield (54%), as well as increasing the scope of the reaction with the possibility of introducing other aryl and heteroaryl substituents on this pyridodiazepinone system.

In order to obtain other new pyridodiazepin-2-ones bearing interesting aryl substituents and owning 10- and 12-π-electron systems at the 2-position of these heterocycles, novel 4-aryl-1,1,1-trichloro-4-methoxybut-3-en-2-ones (**2g–h**) were prepared from the reaction of 1-acetonaphthone and 4,4′-acetylbiphenyl, respectively, with trimethyl orthoformate in the presence of *p*-toluenosulfonic acid (Scheme 2).[17] The subsequent acylation reaction of the respective acetals using trichloroacetyl chloride in pyridine and chloroform as solvent was carried out at a molar ratio of 1:2:2 (acylating agent/pyridine/acetal) to obtain **2g–h**. The most satisfactory reaction condition was found to be 16 h at a temperature ranging from 0 to 45 °C for both trichloroacetylation reactions.



Scheme 2.

The unambiguous ^{1}H and ^{13}C NMR chemical shift assignments of 4-trifluoromethylated pyridodiazepin-4-ols (**3a**–**f**, **3h**–**i**) and pyridodiazepin-4(5*H*)-ones (**4a**–**j**) were obtained with the help of 1D- and DEPT 135-NMR experiments, by comparison with NMR data of other diazepinones formerly synthesized in our laboratory and by structural analyses by X-ray diffraction performed on the N^3-[1-(*p*-tolyl)-3-oxo-4,4,4-trifluoro-(chloro)but-1-en-1-yl]-2,3-diaminopyridine intermediates, which demonstrated clearly that the first reaction step occurs when the N-3 of 2,3-diaminopyridine adds to the β-olefinic carbon of the vinyl ketones **1b** and **2b**.

Diazepinols **3a**–**f**, **3h**–**i**, show ^{1}H NMR chemical shifts, in DMSO-d_6, of the diastereotopic methylene protons (H-3a and H-3b) as a characteristic AB system and as a doublet in the range of 3.38–3.45 ppm and another doublet in the range of 2.85–2.90 ppm, respectively, with a *geminal* coupling constant in the range of $^{2}J = 14.3$–19.4 Hz. Still show a signal characteristic of NH as a singlet in the range of 6.07–6.45 ppm, and the hydrogenius of hydroxyls shows a signal in the range 7.04–7.9 ppm. The signals for the pyridine hydrogens H-7, H-8, H-9, for compounds **3a**–**f**, **3h**–**i** and **4a**–**j**, are in the range of 8.14–8.06 ppm, 7.13–7.09 ppm and 7.66–7.59 ppm, respectively. Diazepinones **4a**–**j** show the ^{1}H NMR chemical shifts of the methylene protons (H-3) as a singlet in the range of 3.5–3.7 ppm. The trifluoromethylated heterocycles **3a**–**f**, **3h**–**i** present the ^{13}C chemical shifts of diazepine ring C-3 at the average of 34.1 ppm. The C-3 for compounds **4a**–**j** present a signal at the average of 40 ppm. Pyridodiazepines **3a**–**f**, **3h**–**i** and **4a**–**j** present the typical ^{13}C chemical shifts of pyridine ring carbons at the average of 146 ppm (C-7), 129 ppm (C-8) and 117 ppm (C-9). The carbonyl carbon for compounds **4a**–**j** shows signals in the range of 166–168 ppm. The NMR signals of the furan (**3i**, **4i**) and thiophene (**3j**, **4j**) derivatives were assignmented by comparison with NMR data of other compounds previously synthesized in our laboratory.[18]

In summary, we developed the first efficient and regiospecific preparation of 3*H*-pyrido[2,3-*b*][1,4]diazepinol system **3**, as well as, a useful and alternative approach to obtaining regiospecific 3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-one **4**, under mild conditions by a conventional procedure in a moderate to good yields. A specific synthesis and the properties of trifluoromethyl substituted 4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols are not yet known.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 for **3a**–**f**, **3h**–**i** and **4a**–**j** using TMS as internal reference. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University—USP/Brazil).

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11. Synthesis of 2-phenyl-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones (**4a**).[10] Procedure: A mixture of 0.01 mol (1.09 g) of 2,3-diaminopyridine and 0.015 mol (2.88 g) of ethyl benzoylacetate in 80 mL of xylene was brought to a boil. The water, which was formed during the reaction, was separated by azeotropic distillation. Tan crystals began to form after 1 hour and the mixture was heated for an additional 3 h to complete the reaction. After being cooled, product **4a** was separated by filtration and was recrystallized twice from xylene to give pale yellow needles, 1.5 g (65%), mp 258 °C.
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13. Synthesis of 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols (**3a**–**f**, **3h**–**j**). General procedure: A stirred solution of 2,3-diaminepyridine (2 mmol, 0.218 g) with 4-aryl(heteroaryl)-4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1a**–**f**, **1h**–**j**) (2 mmol) in 6 mL of dry methanol was stirred at 60–65 °C for 24 h. After the reaction time the solvent was removed under reduced pressure and the crude solids products were washed with chloroform, obtaining a pure dark solid (**3a**–**g**) (yields 54–71%).
14. Compound **3a** was obtained as a dark solid, yield 56%, mp 141–143 °C. Compounds **3a**–**f**, **3h**–**i** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **3a**: ^{1}H NMR (DMSO) $\delta = 8.14$–8.13 (dd, 1H, $J = 1.5$, $J = 1.5$, H7), 8.06–8.03 (m, 2H, $J = 8.8$, $J = 8.8$, aromatic-H), 7.67–7.63 (dd, 1H, $J = 1.5$, $J = 1.5$, H9), 7.52–7.49 (m, 3H, aromatic-H, 1H, OH), 7.12-7.09 (dd, 1H, $J = 4.7$, $J = 4.7$, H8), 6.45 (s, 1H, NH), 3.45–2.91 (dd, 2H, $J = 14.0$, $J = 14.0$, CH_2). ^{13}C NMR (DMSO) $\delta = 154.88$ (C2), 153.02 (C5a), 145.70 (C7), 144.03 (aromatic-C), 129.22 (C9), 128.83 (aromatic-C), 128.27 (aromatic-C), 126.93 (aromatic-C), 124.15 (CF_3, $J = 288.2$), 119.70 (C8), 118.36 (C9a), 91.54 (C4, $J = 31.0$), 26.78 (C3). Melting points and yields of new compounds **3**: Compd. [Mp (°C), yield (%)]: **3a**[(141–143), 54]; **3b** [(140–142), 57]; **3c** [(137–139), 67]; **3d** [(160–162), 69]; **3e** [(148–150), 70]; **3f** [(145–147), 66]; **3h** [(134–136), 71]; **3i** [(151–153), 64]; **3j** [(129–131), 67].
15. Synthesis of 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones (**4a**–**j**). General procedure: To a stirred solution of 2,3-diaminopyridine (2 mmol, 0.218 g), in 6 mL of dry methanol, was added 2 mmol of CH_3ONa. After 10 min was added 4-aryl(heteroaryl)-4-methoxy-1,1,1-trichlorobut-3-en-2-ones (**2a**–**j**) (2 mmol) in one portion and the solution was stirred at 60–65 °C for 24 h. Thereafter the reaction time the solvent was removed under reduced pressure and the crude solids products were washed with water and then with chloroform, obtaining a dark solid (**4a**–**j**), as pure compounds (yields 54–70%).
16. Compound **4a** was obtained as a dark solid, yield 54%, mp 250–252 °C. See lit.[10] yield 65%, mp 258 °C. Compounds **4a**–**j** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **4a**: ^{1}H NMR (DMSO) $\delta = 10.98$ (s, 1H, NH), 8.37–8.34 (dd, 1H, $J = 1.5$, $J = 1.5$, H7), 8.11–8.06 (m, 2H, aromatic-H), 7.88–7.85 (dd, 1H, $J = 1.5$, $J = 1.5$, H9), 7.58–7.54 (m, 3H, aromatic-C), 7.35–7.31 (dd, 1H, $J = 4.3$, $J = 4.3$, H8), 3.61 (s, 2H, CH_2). ^{13}C NMR (DMSO) $\delta = 166.0$ (C=O), 159.3 (C2), 146.0 (C7), 142.4 (C5a), 136.7 (aromatic-C), 136.3 (C9), 134.4 (aromatic-C), 131.2 (aromatic-C), 128.6 (aromatic-C), 127.6 (C8), 120.0 (C9a), 40.1 (C3). Melting points and yields of new compounds **4**: Compd. [Mp (°C), yield (%)]: **4a** [(250–252), 54]; **4b** [(257–259), 55]; **4c** [(245–247), 57]; **4d** [(252–254), 60]; **4e** [(262–264), 64]; **4f** [(266–268), 53]; **4g** [(251–253), 59]; **4h** [(248–250), 59]; **4i** [(218–220), 62]; **4j** [(264–266), 70].
17. Synthesis of 4-methoxy-4-(1-naphthyl)-1,1,1-trichlorobut-3-en-2-one (**2g**) and the 4-(4,4′-biphenyl) analogue (**2h**). General procedure: To an ice-cold stirred mixture of 1-acetonaphthone and 4,4′-acetylbiphenyl dimethyl acetals (30 mmol), pyridine (60 mmol), and anhydrous chloroform (30 mL) is added dropwise pure trichloroacetyl chloride (60 mmol) and after the end of the slow addition, the mixture is stirred for more 16 h at 45 °C. Then, the mixture is washed with 0.1 M aqueous solution of hydrochloric acid (3×15 mL) and water (2×15 mL), and is dried with magnesium sulfate. The solvent is evaporated to give the practically pure products **2g** (86% yield) or **2h** (74% yield). The pure compounds **2g**–**h** are obtained by recrystallization from methanol. Compounds **2g**–**h** were fully characterized by spectroscopic methods and gave satisfactory analytical and spectral data. Compound **2g**: $C_8H_{11}Cl_3O_2$, mw 245.53; red oil; ^{1}H NMR ($CDCl_3$): δ 5.97 (s, H3), 3.81 (s, OCH_3), 2.77 (t, CH_2), 1.58 (sext, CH_2), 0.98 (t, CH_3); ^{13}C NMR ($CDCl_3$): δ 183.8 (C4), 179.8 (C2), 97.9 (CCl_3), 89.7 (C3), 56.2 (OCH_3), 35.2 (CH_2), 20.5 (CH_2), 13.8 (CH_3). Compound **2h**: $C_9H_{13}Cl_3O_2$, mw 259.56; mp 88–90 °C; ^{1}H NMR ($CDCl_3$): δ 6.00 (s, H3), 3.80 (s, OCH_3), 2.70 (d, CH_2), 2.03 (m, CH), 0.96 (d, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 183.2 (C4), 179.9 (C2), 98.0 (CCl_3), 90.3 (C3), 56.1 (OCH_3), 41.7 (CH_2), 27.4 (CH), 22.3 ($2CH_3$).
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