Synthesis of new 3-(Trifluoromethyl)-1*H*-indoles by Reduction of Trifluoromethyloxoindoles

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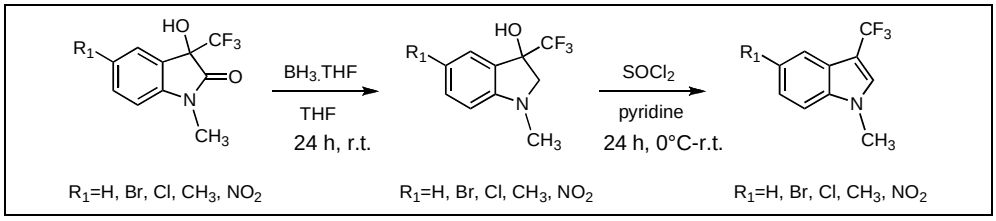

This work describes the synthesis of new 3-trifluoromethylindoles. Different isatins were trifluoromethylated using (trifluoromethyl)trimethylsilane (Me_3SiCF_3) as a nucleophilic agent giving new 3-hydroxy-3-(trifluoromethyl)indolin-2-one. Different "one-step" procedures to transform the latter compounds into the reduced indoles were attempted, but failed. For the synthesis of the new trifluoromethylindoles the corresponding 2-oxo-3-(trifluoromethyl)indoles were reduced using borane/THF complex to furnish 3-(trifluoromethyl)indolin-3-ol that additionally were dehydrated using thionyl chloride in pyridine to give excellent yields of the desired products.

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INTRODUCTION

The introduction of fluorine atoms, particularly in the form of a trifluoromethyl group, into an organic compound can bring remarkable changes in the physical, chemical and biological properties, making them suitable for different applications in the areas of materials science, agrochemicals and pharmaceuticals [1-5].

While a wide variety of methodologies have been developed for introducing trifluoromethyl groups into organic compounds [6], the use of (trifluoromethyl)-trimethylsilane (Me_3SiCF_3) as a nucleophilic trifluoromethylating agent has rapidly become the method of choice for reaction with ketones and aldehydes [7].

Isatins (1*H*-indole-2,3-diones) are synthetically versatile substrates, which can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and thus as raw material for drug synthesis. The use of isatins as organic starting materials has greatly advanced during the last twenty-five years due to their importance as pharmacologically active compounds [8].

Many specific methods have been used for the reduction of isatins [9-18] but none of these can be generally applied. Garden and our group have described the ready conversion of isatins to 3-fluoroindoles in a two-step process, which involves an initial reaction with diethylaminosulfur trifluoride (DAST) to yield the 3,3-difluoro-2-oxindole derivative, and subsequent reduction using borane/THF. The reaction course was shown to proceed by formation of the 3,3-difluoroindolines which subsequently, eliminated HF. The presence of electron withdrawing groups on the aromatic nucleus retarded elimination of HF, resulting in 3,3-difluoroindolines as the major products [19].

Indoles are present in numerous natural and bioactive compounds, but are often prone to instability due to a great sensitivity to oxidizing conditions [20], in particular at the position C-3. The presence of the electron-withdrawing trifluoromethyl substituent at this site could disfavor electrophilic processes.

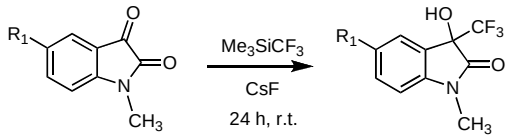
To obtain indoles, many synthetic methodologies have been devised and continue to be developed, reflecting the importance of their skeletal structure [20]. We have been interested in obtaining trifluoromethylindoles as part of our program for the discovery of new drugs for neglected diseases [21].

RESULTS AND DISCUSSION

In this present study, we have investigated the reduction of 3-hydroxy-1-methyl-3-(trifluoromethyl)-indolin-2-one derivatives (**6-10**) under various conditions. Compounds **6-10** were obtained by trifluoromethylation reactions using (trifluoromethyl)trimethylsilane as a nucleophilic agent with different isatins in the presence of catalytic CsF. A 2:1 ratio of reagent: starting material and room temperature were found to be the best conditions. After 24 hours of reaction time the corresponding trifluoromethylated products were obtained (Scheme 1).

All these compounds were obtained in high purity and characterized by NMR spectra.

Scheme 1



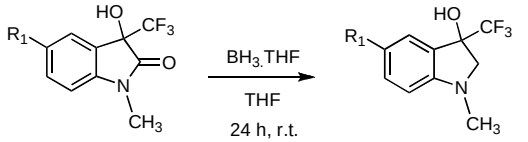
(1) R_1=H
(2) R_1=Br
(3) R_1=Cl
(4) R_1=CH_3
(5) R_1=NO_2

(6) R_1=H (90%)
(7) R_1=Br (52%)
(8) R_1=Cl (96%)
(9) R_1=CH_3 (71%)
(10) R_1=NO_2 (72%)

$LiAlH_4$ and THF were initially used to reduce 3-hydroxy-trifluoromethylindolin-2-one derivatives (**6-10**), at room temperature, but the starting materials were completely recovered, even in the presence of an excess of $LiAlH_4$.

Reduction of derivatives **6-10** with 3 equiv. of BH_3.THF for 24 hours at room temperature, afforded products of reduction of the carbonyl group at position C-2, namely 3-(trifluoromethyl)indolin-3-ol compounds (**11-15**), but not the expected dehydrated indoles (**16-20**) (Scheme 2). Compounds **11-15** have not been previously described in the literature. They were obtained in high purity and characterized by NMR analysis.

Scheme 2



(6) R_1=H
(7) R_1=Br
(8) R_1=Cl
(9) R_1=CH_3
(10) R_1=NO_2

(11) R_1=H (81%)
(12) R_1=Br (87%)
(13) R_1=Cl (89%)
(14) R_1=CH_3 (88%)
(15) R_1=NO_2 (79%)

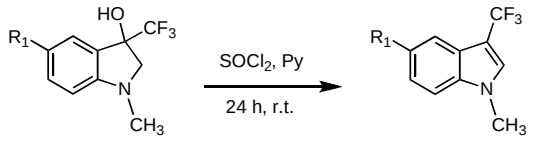
The formation of a more reactive BH_3-carbonyl complex than the one with $LiAlH_4$, could explain these results. THF is a weaker base than H^- and the AlH_3 concentration at equilibrium in the reactional medium is very low. Nerverthless, the BH_3 concentration is high and a significant concentration of the BH_3-carbonyl complex exists [22].

It has been observed that the reduced compounds **11-15** are thermally unstable [23] when warmed on a water bath, during removal of solvent. This decomposition is consistent with previous observations on the reduction of 3,3-difluoro-2-oxoindoles [20]. In order to circumvent the thermal instability problem, the solvent was removed without warming and the products were obtained in good yields.

Although tertiary trifluoromethyl alcohols are stable even in acidic conditions, benzylic ones are more often susceptible to elimination or substitution [24]. However compounds **11-15** do not undergo elimination of H_2O. According to the literature, reduction of various 3-hydroxy-2-oxoindoles resulted in the consumption of the starting material and the formation of the corresponding indole over the period of a couple of hours [25]. It is well established that introduction of fluorine atoms, with their small size, very high electronegativity and strong bond energies, induce important modifications in the chemical properties of vicinal groups [2]. In our case, the presence of the trifluoromethyl group in the oxoindole nucleus could disfavor the subsequent dehydration into corresponding indoles.

Thus we searched for good conditions for indolinol dehydration. There are only few reported trifluoroalkyl-indoles in the literature, and most of the described approaches are not regioselective and gave rise to a mixture of products [26]. Bonnet-Delpon and co-workers have shown that 3-(trifluoromethyl)indolin-3-ol derivatives can be dehydrated using thionyl chloride ($SOCl_2$) in pyridine [26]. During ongoing investigations from our laboratory, the dehydration of compounds **11-15** using this methodology has proven to be a versatile method for the synthesis of new indole derivatives **16-20** (Scheme 3).

Scheme 3



(11) R_1=H
(12) R_1=Br
(13) R_1=Cl
(14) R_1=CH_3
(15) R_1=NO_2

(16) R_1=H (98%)
(17) R_1=Br (98%)
(18) R_1=Cl (90%)
(19) R_1=CH_3 (93%)
(20) R_1=NO_2 (82%)

HPLC analysis were performed with a Shim-pack CLC-C8 column (250mm x 4.6mm i.d.), injection volume 20 μL, using acetonitrile: water at 30 °C and a gradient of these solvents varying between 30-90% in 40 minutes, flow rate between 0.7-1.0 mL/min, and run time of 60 minutes. The spectral data were acquired between 190-800 nm and the effluent was monitored at 215 nm.

The above-described method was modified to allow for scaling up to a semi preparative separation of products **18**, **19** and **20** from starting materials. The semi preparative HPLC was performed with a Shim-pack PREP-C8 column (250mm x 20mm i.d.). The mobile phase was acetonitrile:water at 30 °C with an average gradient of 10 to 90% during 50 minutes, flow rate between 5 and 7 mL/min, with an average run time of 60 minutes. The injection volume was 400 μL of concentrated product. Compounds **18**, **19** and **20** were obtained in 75, 78, 70%

yields, respectively with 98% purity. All other compounds were obtained in high purity and characterized, so no further purification was necessary.

In conclusion, we have found that the use of BH_3.THF solutions for the reduction of 3-trifluoromethyloxoindoles derivatives is a useful method for the synthesis of 3-(trifluoromethyl)indolin-3-ol compounds. The reduced compounds can be converted into corresponding 3-trifluoromethylindoles using thionyl chloride ($SOCl_2$) in pyridine. This new approach is a particularly efficient and concise method for the conversion into desired indoles. The synthesis provided analytically pure compounds (**11-20**) in overall yields of 70-98%, in three steps, from isatin derivatives. Ten new compounds were obtained in this study.

EXPERIMENTAL

All solvents and reagents were used as obtained from commercial sources, unless otherwise indicated. Dry tetrahydrofuran was purchased from Vetec and used after redistillation. All reactions were monitored by thin-layer chromatography over precoated Merck Silica gel 60 F254 plates and visualized by UV irradiation. Melting points were measured on a Büchi B-545 instrument. The GC-MS spectra were obtained on a Hewlett Packard 5960 MS connected to a Hewlett Packard 5890 gas chromatograph. NMR spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts were reported as δ values (ppm) downfield from internal Me_4Si in the solvent shown. Coupling constants (*J*) are expressed in Hertz (Hz). The following NMR abbreviations are used: s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quartet), m (multiplet). Infrared (IR) spectra were recorded on KBr pellets with a Nicolet 670 FT-IR spectrometer. HPLC were carried out using a Merck-Hitachi LaChrom model equipped with a 7100 pump and a 7455 photodiode array detector. All analytical assays and semipreparative chromatography were performed under the conditions given previously. The abbreviation THF refers to tetrahydrofuran.

Isatins derivatives **1-5** were prepared from their corresponding isatins by reaction of each starting material with CaH_2 in DMF [27] in the presence of iodomethane. The reaction mixture was heated to 100 °C for 4 hours. After treatment with 0.5 *M* hydrochloric acid, the isatins were obtained in 90%, 85%, 92%, 88% and 54% yields [27-28]. *N*-Methylisatins were characterized by GC-MS, NMR and melting point measurements.

General procedure for the synthesis of compounds (6-10). Isatin derivatives (1 mmol) were dissolved in THF (10 mL). (Trifluoromethyl)trimethylsilane (2 mmol) and catalytic amounts of cesium fluoride (CsF) were added. The reaction mixture was stirred at room temperature. After 24 hours, the solution was extracted with cold water (20 mL), and the aqueous phase was subsequently re-extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure.

3-Hydroxy-1-methyl-2-oxo-3-trifluoromethylindole (6). m.p. 173-175 °C; Yield 90%; ^{1}H NMR (acetone-d_6) δ 3.22 (s, 1H), 6.55 (s, 1H), 7.10 (d, 1H, *J*= 8.0 Hz), 7.16-7.19 (m, 1H), 7,48-7.52 (m, 2H); ^{13}C NMR (acetone-d_6) δ 26.63, 75.72 (q, *J*= 30 Hz), 110.06, 121.21, 123.48, 123.93, 124.69, 125.74, 126.38, 128.00, 132.46, 145.69, 171.09; ^{19}F NMR (acetone-d_6) δ - 79.86; MS (GC) *m/z* 231 (M^+). Anal. Calcd. for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.25; H, 3.74; N, 5.95.

5-Bromo-3-hydroxy-1-methyl-2-oxo-3-trifluoromethylindole (7). m.p. 196-198 °C; Yield 52%; ^{1}H NMR (acetone-d_6) δ 3.24 (s, 3H), 6.78 (s, 1H), 7.11 (d, 1H, *J*= 8.5 Hz), 7.64 (s, 1H), 7.68 (d, 1H, *J*= 8.0 Hz); ^{13}C NMR (acetone-d_6) δ 26.84, 75.61 (q, *J*= 30 Hz), 112.16, 115.78, 120.93, 123.18, 125.45, 126.72, 127.70, 129.27, 135.33, 145.02, 170.54; ^{19}F NMR (acetone-d_6) δ - 79.81; MS (GC) *m/z* 309 (M^+). Anal. Calcd. for $C_{10}H_7BrF_3NO_2$: C, 38.74; H, 2.28; N, 4.52. Found: C, 38.52; H, 2.19; N, 4.26.

5-Chloro-3-hydroxy-1-methyl-2-oxo-3-trifluoromethylindole (8). m.p. 192-194 °C; Yield 96%; ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 3H), 6.83 (d, 1H, *J*= 8.0 Hz), 7.42 (dd, 1H, *J*= 2.0 Hz, 8.0 Hz), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.51, 110.70, 114.50, 120.54, 124.67, 126.22, 127.34, 130.03, 132.41, 143.74, 171.49; ^{19}F NMR ($CDCl_3$) δ - 80. 15; MS (GC) *m/z* 265 (M^+). MS (EIS) Calcd. *m/z* 265.616 (MH^+). Found: *m/z* 265.616 (MH^+).

1,5-Dimethyl-3-hydroxy-2-oxo-3-trifluoromethylindole (9). m.p. 166-168 °C; Yield 71%; ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3H), 3.19 (s, 3H), 6.49 (s, 1H), 6.98 (d, 1H, *J*= 8.0 Hz), 7.30 (dd, 1H, *J*= 1.0 Hz, *J*= 8.0 Hz), 7.35 (s, 1H); ^{13}C NMR (acetone-d_6) δ 20.92, 26.64, 75.83 (q, *J*= 30 Hz), 109.80, 121.26, 123.51, 124.70, 125.78, 127.05, 128.03, 132.60, 133.53, 143.29, 171.05; ^{19}F NMR (acetone-d_6) δ - 79.79; MS (GC) *m/z* 245 (M^+). Anal. Calcd. for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.62; H, 4.49; N, 5.91.

5-Nitro-3-hydroxy-1-methyl-2-oxo-3-trifluoromethylindole (10). m.p. 149-151 °C; Yield 72%; ^{1}H NMR (DMSO-d_6) δ 3.26 (s, 3H), 7.40 (d, 1H, *J*= 9.0 Hz), 8.14 (s, 1H), 8.21 (d, 1H, *J*= 2.0 Hz), 8.45 (dd, 1H, *J*= 2.5 Hz); ^{13}C NMR (DMSO-d_6) δ 26.94, 74.01 (q, *J*= 30 Hz), 110.27, 118.72, 120.60, 121.56, 124.39, 124.48, 128.51, 143.08, 149.93, 170.50; ^{19}F NMR (DMSO-d_6) δ - 78.12; MS (GC) *m/z* 276 (M^+).

General procedure for the synthesis of compounds (11-15). The trifluoromethyl derivatives **6-10** (1 mol equiv.) were dissolved in dry THF (10 mL) under a nitrogen atmosphere. To the solution was added a solution of BH_3.THF (1 *M*, 3 mol equiv.). The reaction mixture was stirred at room temperature for 24 hours. Aqueous HCl (3 *M*) was added dropwise and the mixture was subsequently neutralized with aqueous NaOH (2.5 *M*). Saturated aqueous NaCl (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 15 mL). The organic phase was further washed with water (2 x 15 mL), dried over Na_2SO_4, filtered and evaporated at reduced pressure at room temperature.

1-Methyl-3-(trifluoromethyl)indolin-3-ol (11). Oil. Yield 81%; ^{1}H NMR (acetone-d_6): 2.77 (3H, s), 3.32-3.34 (1H, m), 3.61 (1H, d, *J*= 11 Hz), 6.64-6.72 (2H, m), 6.80 (1H, s), 7.13-7.25 (2H, m); ^{13}C NMR (DMSO-d_6): 34.8, 62.7, 78.1, 107.9, 117.3, 124.2, 124.6, 125.4, 127.0, 130.7, 153.2; ^{19}F NMR (acetone-d_6): -80.9; MS (GC) *m/z* (%): 217 ($M^{+\cdot}$).

5-Bromo-1-methyl-3-(trifluoromethyl)indolin-3-ol (12). Oil. Yield 87%; ^{1}H NMR (acetone-d_6): 2.84 (3H, s), 3.47-3.51 (1H, m), 3.75 (1H, d, *J*= 11 Hz), 5.90 (1H, s), 6.60 (1H, d, *J*= 8 Hz), 7.35-7.38 (1H, m), 7.38 (1H, s); ^{13}C NMR (acetone-d_6): 34.9, 63.9, 79.4, 108.9, 110.5, 125.1, 127.9, 128.4, 128.6, 134.6, 153.6; ^{19}F NMR (acetone-d_6): -80.9; MS (GC) *m/z* (%): 295 ($M^{+\cdot}$).

5-Chloro-1-methyl-3-(trifluoromethyl)indolin-3-ol (13). Oil. Yield 89%; ^{1}H NMR (acetone-d_6): 2.86 (3H, s), 3.49-3.53

(1H, m), 3.77 (1H, d, *J*= 8 Hz), 6.65 (1H, d, *J*= 8 Hz), 7.24 (1H, d), 7.26-7.27 (1H, m); ^{13}C NMR (acetone-d_6): 34.1, 63.0, 78.4, 109.0, 121.2, 124.1, 124.6, 126.9, 127.2, 130.7, 152.3; ^{19}F NMR (acetone-d_6): -80.9; MS (GC) *m/z* (%): 251 ($M^{+\cdot}$).

1,5-Dimethyl-3-(trifluoromethyl)indolin-3-ol (**14**). Oil. Yield 88%; ^{1}H NMR (acetone-d_6): 2.23 (3H, s), 2.78 (3H, s), 3.38-3.40 (1H, m), 3.64 (1H, d, *J*= 12 Hz), 5.64 (1H, s), 6.55 (1H, d, *J*= 8 Hz), 7.05-7.07 (1H, m), 7.13 (1H, s); ^{13}C NMR (acetone-d_6): 20.7, 35.8, 64.4, 79.9, 109.0, 123.4, 125.6, 126.0, 126.7, 127.6, 127.9, 130.1, 132.4, 152.7; ^{19}F NMR (acetone-d_6): -80.6. MS (GC) *m/z* (%): 231 ($M^{+\cdot}$).

5-Nitro-1-methyl-3-(trifluoromethyl)indolin-3-ol (**15**). Oil. Yield 79%; ^{1}H NMR (acetone-d_6): 3.09 (3H, s), 3.77-3.81 (1H, m), 4.06 (1H, d, *J*= 12 Hz), 6.70 (1H, d, *J*= 9 Hz), 8.16 (1H, s), 8.19 (1H, dd, *J*= 2.5 Hz); ^{13}C NMR (acetone-d_6): 33.4, 63.4, 78.6, 106.4, 122.5, 124.8, 126.2, 127.6, 129.7, 138.6, 157.9; ^{19}F NMR (acetone-d_6): -80.7. MS (GC) *m/z* (%): 262 ($M^{+\cdot}$).

General procedure for the synthesis of compounds (**16-20**). To a solution of an indolinol derivative (11-15) (1 mol equiv.) in freshly distilled pyridine (5 mL) was added thionyl chloride (1.5 mol equiv.), at 0 °C, under a nitrogen atmosphere. After 24 hours at room temperature, an aqueous solution 3 *M* of HCl (19 mL) was added to the mixture. After extraction with dichloromethane (3 x 30 mL), the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated.

1-Methyl-3-(trifluoromethyl)-1*H*-indole (**16**). m.p. 55-57 °C; Yield 98%; ^{1}H NMR (DMSO-d_6): 3.85 (s, 3H), 7.22 (t, *J*= 7.2 Hz), 7.31 (t, *J*= 7.2 Hz), 7.57–7.61 (m, 2H); ^{13}C NMR (DMSO-d_6): 32.8, 102.9 (q, *J*= 36 Hz), 110.9, 118.3, 120.6, 123.3, 125.9, 128.6 (q, *J*= 265 Hz), 121.1, 122.7, 123.2, 130.2, 136.5; ^{19} F NMR (DMSO-d_6): -54.8. MS (GC) *m/z* (%): 199 ($M^{+\cdot}$).

5-Bromo-1-methyl-3-(trifluoromethyl)-1*H*-indole (**17**). m.p. 58-60 °C; Yield 98%; ^{1}H NMR (DMSO-d_6): 3.85 (s, 3H), 7.44 (dd, 1H, *J*= 2,0 Hz e *J*= 6,8 Hz), 7.58 (d, 1H, *J*= 8,8 Hz), 7.71 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (DMSO-d_6): 33.1, 102.6 (q, *J*= 36,8 Hz), 113.2, 113.8, 120.2, 122.8, 125.5, 128.1 (q, *J*= 265 Hz), 120.3, 124.8, 125.3, 131.7, 135.3; ^{19}F NMR (DMSO-d_6): -55.0. MS (GC) *m/z* (%): 277 ($M^{+\cdot}$).

5-Chloro-1-methyl-3-(trifluoromethyl)-1*H*-indole (**18**). m.p. 59-61 °C; Yield 75%; ^{1}H NMR (DMSO-d_6): 3.85 (s, 3H), 7.33 (dd, 1H, *J*= 2,0 Hz *e J*= 6,8 Hz), 7.57 (s, 1H), 7.63 (d, 1H, *J*= 8,8 Hz), 8.08 (s, 1H); ^{13}C NMR (DMSO-d_6): 33.1, 102.7 (q, *J*= 36,6 Hz), 112.8, 117.3, 120.2, 122.8, 125.5, 128.1 (q, *J*= 264 Hz), 122.8, 124.1, 125.9, 131.9, 135.1; ^{19}F NMR (DMSO-d_6: -55,0. MS (GC) *m/z* (%): 233 ($M^{+\cdot}$).

1,5-Dimethyl-3-(trifluoromethyl)-1*H*-indole (**19**). Yield 78%. MS (GC) *m/z* (%): 213 ($M^{+\cdot}$).

5-Nitro-1-methyl-3-(trifluoromethyl)-1*H*-indole (**20**). m.p. 155-156 °C; Yield 70%; ^{1}H NMR (DMSO-d_6): 3.93 (s, 3H), 7.81 (d, 1H, *J*= 9,5 Hz), 8.17 (dd, 1H, *J*= 2,0 Hz e 7,0 Hz), 8.30 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (DMSO-d_6): 33.4, 105.4, (q, *J*= 36,7 Hz), 112.0, 114.6, 117.8, 122.2, 122.7, 124.8, 126.9 (q, *J*= 265 Hz), 134.3, 139.3, 142.1; ^{19}F NMR (DMSO-d_6): -55.2. MS (GC) *m/z* (%): 244 ($M^{+\cdot}$).

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