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PAPER

Transition metal-free procedure for the synthesis of *S*-aryl dithiocarbamates using aryl diazonium fluoroborate in water at room temperature†

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A convenient, efficient and green procedure for the synthesis of *S*-aryl dithiocarbamates has been developed by a simple one-pot condensation of aryl diazonium fluoroborate, carbon disulfide and amine in the absence of any transition metal catalyst in water at room temperature. The reactions of a variety of substituted aryl diazonium fluoroborates, and cyclic and open chain amines, have been addressed. The products are purified by crystallization from ethanol and the process does not involve any hazardous solvent.

1. Introduction

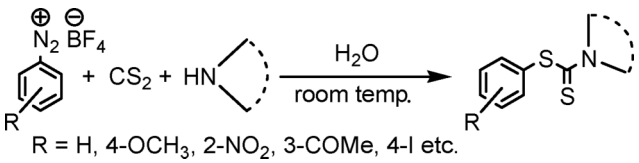
In recent years, there has been an intense drive towards developing green chemical processes using more environmentally acceptable chemicals, reagents, solvents and catalysts.[1] A part of this drive is to avoid or minimise the use of metals in chemical reactions, as these are sometimes toxic and difficult to dispose off properly in large quantities. Moreover, the difficulty of their separation leaves a chance of their contamination of the product. The presence of a metal, even at the lowest level, in pharmaceutical products is closely regulated. Thus, a metal free process is desired as a part of the requirements for industry and a clean environment.

The use of large volumes of volatile, hazardous organic solvents in chemical processes also poses a serious threat to the environment, because these solvents contribute significantly to chemical waste.[2] Thus, reactions in water have attracted considerable interest in recent times because of their environmental acceptability and unique reactivity that cannot be attained in conventional organic solvents.[3] The development of an efficient procedure using water as the reaction medium, and environmentally benign solvents for isolation and purification of products has received high priority in the design of green processes.[4]

Organic dithiocarbamates are receiving attention because of their potential as useful synthetic intermediates,[5] protecting groups in peptide synthesis[6] and linkers in solid phase organic synthesis.[7] Moreover, their occurrence in a variety of biologically active compounds,[8] their pivotal roles in agriculture[9] and their biological properties[10] have led to the development of synthetic procedures for these compounds.

Conventional methods involve reactions of amines with thiophosgenes, which are not environmentally acceptable.[11] Several one-pot procedures by the reactions of amines with carbon disulfide and alkyl halides/acrylates have been reported.[12] Although these methods are quite satisfactory for the synthesis of alkyl dithiocarbamates, they are not greatly effective for aryl dithiocarbamates. Usually, the synthesis of aryl dithiocarbamates involves metal-mediated reactions.[13] A couple of metal-free procedures involving the reaction of the sodium salt of dithiocarbamic acid with diazonium chloride[14a] and diaryl diazonium salts in the presence of hypervalent iodine[14b] have been developed. However, the sodium salt of dithiocarbamic acid is difficult to prepare,[14a] expensive and toxic.[15] Nevertheless, the multi-component reaction is a useful and attractive tool in organic synthesis as it provides a cost- and energy-effective process.[16]

We report here a one-pot multi-component condensation of aryl diazonium tetrafluoroborates, carbon disulfide and an amine in water at room temperature without using metal or other catalysts (Scheme 1).



Scheme 1

2. Results and discussion

In a typical experimental procedure, an amine was added to a suspension of carbon disulfide in water at 0–5 °C, followed by

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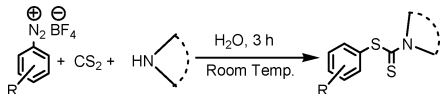
† Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C-NMR spectra of all products in Table 1. See DOI: 10.1039/c1gc00001b

Table 1 Transition metal-free coupling of aryl diazonium tetrafluoroborate with dithiocarmate anions



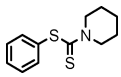
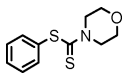
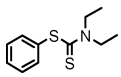
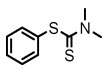
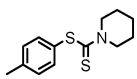
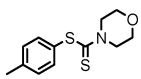
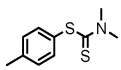
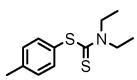
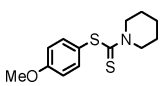
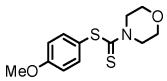
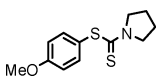
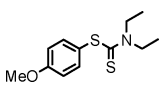
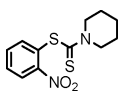
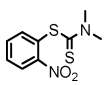
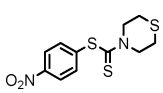
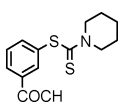
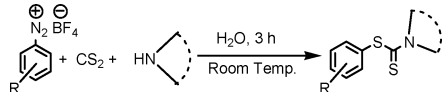
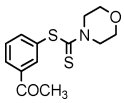
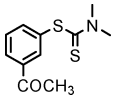
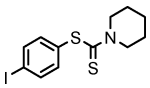
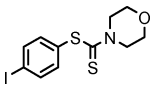
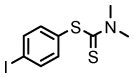
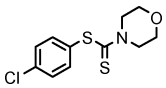
Entry	R	Amine	Product	Yield (%)[a]	Time/h	Ref.
1	H			85	3	13*a*
2	H			90	3	13*a*
3	H			78	3.5	13*a*
4	H			82	3	13*a*
5	4-CH_3			88	3	14*b*
6	4-CH_3			91	2.8	
7	4-CH_3			85	3.5	14*b*
8	4-CH_3			80	3	14*b*
9	4-OCH_3			90	2.8	14*b*
10	4-OCH_3			94	2.5	
11	4-OCH_3			81	3.5	13*a*
12	4-OCH_3			82	3	14*c*
13	2-NO_2			79	2.5	
14	2-NO_2			74	3	
15	4-NO_2			80	2.8	
16	3-$COCH_3$			80	3	

Table 1 *(Contd.)*



Entry	R	Amine	Product	Yield (%)[a]	Time/h	Ref.
17	3-$COCH_3$			84	3	
18	3-$COCH_3$			3.5	76	
19	4-I			3	84	
20	4-I			2.8	91	
21	4-I			3	83	
22	4-CI			3	92	

[a] Isolated yields of pure products (by ^{1}H- and ^{13}C-NMR).

aryl diazonium tetrafluoroborate. The mixture was then stirred at room temperature for the required period of time (TLC). The solid product was isolated by filtration and purified by recrystallization from ethanol.

A wide range of substituted phenyl diazonium tetrafluoroborates underwent reactions with carbon disulfide, and cyclic and open chain amines, by this procedure to produce the corresponding dithiocarbamates. The results are summarized in Table 1. A variety of electron-donating and electron-withdrawing substituents, such as OMe, CH_3, I, NO_2 and COMe, are compatible in this reaction, although electron withdrawing group-substituted phenyl diazonium fluoroborates provide marginally lower yields compared to those having electron donating groups (Table 1, entries 5–12 *vs.* entries 13–19). The *o*, *m* and *p*-substituents also provide equally good results. Cyclic and open chain amines provide uniformly good yields of products. The reactions of several cyclic amines, such as piperidine, morpholine and thiomorpholine, were addressed.

The reactions are, in general, very clean and high yielding, and no side product was isolated. The products are obtained in high purity (by NMR) following a single crystallization. Reactions scaled up to multigram quantities provided uniform results. The starting diazonium fluoroborates were prepared easily from the corresponding anilines by diazotization, followed by quenching with sodium tetrafluoroborate. These are stable solid compounds. In comparison to the earlier procedure[14a] using toxic diazonium chloride and the sodium salt of dithiocarbamic acid,[15] our procedure is more user-friendly, using stable diazonium tetrafluoroborates,[17] and commercially available and cheap carbon disulfide in place of the difficult to access and expensive sodium salt of dithiocarbamic acid. Moreover, the present procedure provides a much simpler operation, higher yields of products and a wide scope for the synthesis of a library of dithiocarbamates by the manipulation of diversely-substituted aryl amines as precursors of diazonium fluoroborates, and cyclic and acyclic amines, whereas the earlier method[14a] was restricted to only a few substrates.

To understand the reaction pathway, we carried out two separate experiments. It was found that CS_2 underwent a very fast (5 min) reaction with piperidine in water at 0–5 °C to produce piperidine-1-dithiocarbamic acid (**1**), which was isolated and characterized fully by its spectroscopic (^{1}H-NMR, ^{13}C-NMR and HRMS) data. This solid product upon reaction (3 h) with phenyl diazonium fluoroborate provided the corresponding dithiocarbamate in 86% yield. Thus, we propose that the reaction proceeds *via* an S_N2Ar pathway, which is favoured over the unimolecular S_N1 reaction in water; the ideal S_N1 pathway is more likely in non-nucleophilic solvents.[18] The argument for S_N2Ar attack by the dithiocarbamate moiety at C-1 of ArN_2^+ gains support from the Hammett correlation plot[19] of log *I* (where *I* represents the ratio of the peak intensity of the disappearance of the starting material after 15 min with that of the starting material at 0 min by UV analysis) *vs.* σ (substituent constant) for the reaction of piperidine

with differently-substituted aryl diazonium salts under identical reaction conditions (with the same reaction concentration) (Fig. 1). This shows a linear correlation with a small positive slope (ρ = 0.035), which strongly suggests the S_N2 reaction path, considering S–C bond formation as the rate-determining step. It is speculated that the *in situ*-generated dithiocarbamate unit attacks C-1 of the aryl diazonium salt to form transient intermediate **2**, which through N_2 elimination forms the *S*-aryl dithiocarbamate (Scheme 2). Water being a much weaker nucleophile than the dithiocarbamate moiety, the possibility of phenol formation was minimized during the process.

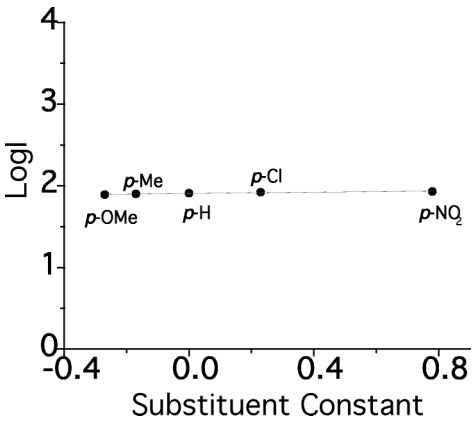
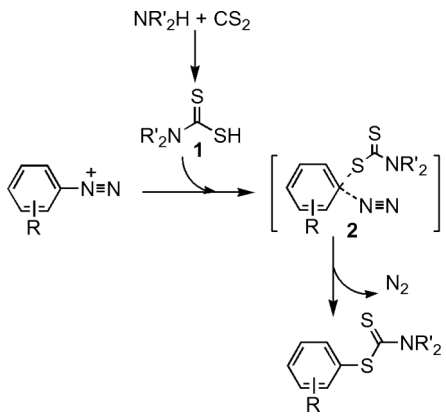


Fig. 1 Hammett plot.



Scheme 2

3. Experimental

General comments

IR spectra were recorded on a Shimadzu 8300 FTIR spectrometer. ^{1}H- and ^{13}C-NMR spectra were run on Bruker DPX-300 and DPX-500 instruments. HRMS were acquired on a Microtek Qtof Micro YA263 spectrometer. All commercial reagents were distilled before use. Aryl diazonium tetrafluoroborates were prepared from the corresponding aniline by diazotization by following a previously reported protocol.[20]

Representative experimental procedure for the condensation of piperidine, CS_2 and phenyl diazonium tetrafluoroborate (Table 1, entry 1). To a well stirred suspension of carbon disulfide (190 mg, 2.5 mmol) in water (2 mL) was added piperidine (102 mg, 1.2 mmol) drop-wise at 0–5 °C. After stirring for 5 min, phenyl diazonium tetrafluoroborate (192 mg, 1 mmol) was added and the reaction mixture stirred at room temperature (25 °C) for 3 h (TLC). The water layer was decanted and the organic product purified by simple crystallization from ethanol to provide the corresponding dithiocarbamate, piperidine-1-carbodithioic acid phenyl ester, as a white solid (201.77 mg, 85%), mp 113–116 °C, IR (KBr) 2945, 2852, 1577, 1471, 1427, 1278, 1242, 1130, 1008, 976, 896, 854, 750, 684 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.73 (s, 6H), 3.99 (br, 2H), 4.28 (br, 2H), 7.41–7.48 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.2, 25.4, 26.2, 52.0, 53.2, 129.2 (2C), 129.9, 131.7, 137.1 (2C), 195.9.

This procedure was followed for all the reactions in Table 1.

A few of these products are known compounds (see the references in Table 1) and were easily identified by comparison of their spectroscopic data with those previously reported. The unknown compounds were fully characterized by their IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra, and C, H, N-analyses. These data are given below in order of their entry in Table 1.

Morpholine-4-carbodithioic acid *p*-tolyl ester (Table 1, entry 6). Yellow solid (mp 131–133 °C); IR (KBr) 2972, 2920, 2856, 1591, 1487, 1462, 1425, 1265, 1230, 1111, 1030, 983, 804, 538, 503 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.77–3.82 (m, 4H), 4.19 (br, 4H), 7.26 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.6, 51.4 (2C), 66.3 (2C), 127.5, 130.1 (2C), 136.9 (2C), 140.6, 198.6; anal calc. for $C_{12}H_{15}NOS_2$: C 56.88, H 5.97, N 5.53; found: C 56.71, H 5.82, N 5.78%.

Morpholine-4-carbodithioic acid 4-methoxy-phenyl ester (Table 1, entry 10). Yellowish solid (mp 133–135 °C); IR (KBr) 2970, 2926, 2948, 1589, 1570, 1491, 1456, 1415, 1249, 1166, 1111, 1028, 991, 825, 540, 524, 503 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.77–3.81 (m, 4H), 3.84 (s, 3H), 4.06 (br, 2H), 4.30 (br, 2H), 6.96 (d, J = 9 Hz, 2H), 7.37 (d, J = 9 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 51.1 (2C), 55.4, 66.3 (2C), 114.8 (2C), 121.6, 138.6 (2C), 161.3, 199.2; HRMS calc. for $C_{12}H_{15}NO_2S_2$ $[M + H]^+$: 270.0625; found: 270.0617.

Piperidine-1-carbodithioic acid 2-nitro-phenyl ester (Table 1, entry 13). Dark grey solid (mp 92–93 °C); IR (KBr) 2941, 2856, 1589, 1568, 1531, 1479, 1429,1350, 1303, 1280, 1242, 1226, 1134, 1111, 1006, 972, 852, 736 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 6H), 4.01 (br, 2H), 4.22 (br, 2H), 7.58–7.67 (m, 3H), 7.97–8.00 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 24.2, 25.5, 26.4, 53.3, 125.1, 127.1, 130.8, 132.7, 139.6, 152.5, 192.3; HRMS calc. for $C_{12}H_{14}N_2O_2S_2Na$ $[M + Na]^+$: 305.0394; found: 305.0392.

Dimethyl-dithiocarbamic acid 2-nitro-phenyl ester (Table 1, entry 14). Red-ish solid (mp 113–114 °C); IR (KBr) 2926, 1699, 1589, 1568, 1519,1348, 1246, 1141, 981, 854, 783, 734; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 6H), 7.61–7.66 (m, 3H), 7.97 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 42.6, 45.7, 125.0, 126.7, 131.1, 132.7, 139.7, 152.7, 194.0; HRMS calc. for $C_9H_{10}N_2O_2S_2Na$ $[M + Na]^+$: 265.0081; found: 265.0081.

Thiomorpholine-4-carbodithioic acid 4-nitro-phenyl ester (Table 1, entry 15). Yellow solid (mp 112–114 °C); IR (KBr) 3093, 2914, 1597, 1575, 1516, 1469, 1413, 1342, 1282, 1139,

1107, 949, 852, 740 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.82 (s, 4H), 4.22–4.37 (m, 2H), 4.50–4.56 (m, 2H), 7.61 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 27.5 (2C), 54.7 (2C), 124.5 (2C), 137.9 (2C), 138.9, 148.8, 194.3; HRMS calc. for $C_{11}H_{12}N_2O_2S_3$ $[M + H]^+$: 301.0134; found: 301.0135.

Piperidine-1-carbodithioic acid 3-acetyl-phenyl ester (Table 1, entry 16). Yellow solid (mp 80–81 °C); IR (KBr) 2939, 2854, 1681, 1477, 1429, 1356, 1242, 1224, 1132, 1116, 1008, 970, 684 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.75 (s, 6H), 4.00 (br, 2H), 4.24 (br, 2H), 7.53 (t, J = 8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 8.03–8.04 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.1, 25.3, 26.2, 26.6, 52.1, 53.4, 129.1, 129.5, 132.6, 137.0, 137.7, 141.6, 194.8, 197.0; HRMS calc. for $C_{14}H_{17}NOS_2Na$ $[M + Na]^+$: 302.0649; found: 302.0648.

Morpholine-4-carbodithioic acid 3-acetyl-phenyl ester (Table 1, entry 17). Light red solid (mp 133–135 °C); IR (KBr) 2856, 1683, 1421, 1406, 1357, 1232, 1111, 1030, 985, 862, 810, 538 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.82–3.85 (m, 4H), 4.11 (br, 2H), 4.30 (br, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 10 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.7, 51.6 (2C), 66.3 (2C), 129.4, 129.9, 131.9, 137.1, 138.0, 141.6, 196.9, 197.0; anal calc. for $C_{13}H_{15}NO_2S_2$: C 55.49, H 5.37, N 4.98; found: C 55.31, H 5.65, N 4.76%.

Dimethyl-dithiocarbamic acid 3-acetyl-phenyl ester (Table 1, entry 18). Yellow solid (mp 79 °C); IR (KBr) 3010, 2928, 1683, 1568, 1504, 1377, 1253, 1149, 983, 755, 684 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.49 (s, 3H), 3.54 (s, 3H), 7.52 (t, J = 8 Hz, 1H), 7.63–7.65 (m, 1H), 8.03 (d, J = 8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.7, 42.1, 45.8, 129.3, 129.7, 132.7, 137.0, 137.9, 141.5, 196.6, 197.1; HRMS calc. for $C_{11}H_{13}NOS_2$ $[M + H]^+$: 240.0547; found: 240.0511.

Piperidine-1-carbodithioic acid 4-iodo-phenyl ester (Table 1, entry 19). White solid (mp 121–122 °C); IR (KBr) 2937, 2854, 1562, 1469, 1427, 1379, 1242, 1226, 1132, 1112, 1006, 972, 808, 723 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.74 (s, 6H), 3.97 (br, 2H), 4.26 (br, 2H), 7.18 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.3, 25.5, 26.3, 52.2, 53.4, 97.0, 131.6, 138.4 (2C), 138.7 (2C), 195.0; HRMS calc. for $C_{12}H_{14}INS_2$ $[M + H]^+$: 363.9688; found: 363.9685.

Morpholine-4-carbodithioic acid 4-iodo-phenyl ester (Table 1, entry 20). Dirty white solid (mp 148–150 °C); IR (KBr) 2924, 2860, 1460, 1423, 1381, 1263, 1228, 1112, 1028, 985, 804 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.80 (t, J = 5 Hz, 4H), 4.11 (br, 2H), 4.30 (br, 2H), 7.18 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 51.4 (2C), 66.3 (2C), 97.3, 130.7, 138.4 (2C), 138.6 (2C), 196.8; anal calc. for $C_{11}H_{12}INOS_2$: C 36.17, H 3.31, N 3.83; found: C 36.30, H 3.42, N 3.61%.

Dimethyl-dithiocarbamic acid 4-iodo-phenyl ester (Table 1, entry 21). Light red solid (mp 86–87 °C); IR (KBr) 2922, 1498, 1465, 1373, 1244, 1147, 1004, 970, 808 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.59 (s, 3H), 7.22 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 42.1, 45.7, 97.2, 131.6, 138.3 (2C), 138.5 (2C), 196.5; HRMS calc. for $C_9H_{10}INS_2$ $[M + H]^+$: 323.9375; found: 323.9372.

Morpholine-4-carbodithioic acid 4-chloro-phenyl ester (Table 1, entry 22). Pale yellow solid (mp 95–96 °C); IR (KBr) 2968, 2920, 2856, 1572, 1471, 1421, 1386, 1265, 1230, 1112, 1091, 1030, 987, 815, 750 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.80–3.86 (m, 4H), 4.27 (br, 2H), 4.31(br, 2H), 7.40–7.44 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 51.5 (2C), 66.4 (2C), 129.6 (2C), 131.4 (2C), 134.5, 136.9, 195.9; anal calc. for $C_{11}H_{12}ClNOS_2$: C 48.25, H 4.42, N 5.12; found: C 48.42, H 4.24, N 5.34%.

4. Conclusions

In conclusion, the present procedure provides a convenient and efficient transition metal-free synthesis of aryl dithiocarbamates by a facile reaction of aryl diazonium tetrafluoroborate, carbon disulfide and an amine in water at room temperature. The significant advantages offered by this protocol are simple operation, easy accessibility of reactants, the use of stable and user-friendly diazonium tetrafluoroborate in place of diazonium chloride, reaction in water, use of environmentally-friendly ethanol for purification, the involvement of no materials as catalysts other than water, reaction at room temperature (energy efficient), access to a wide range of functionalized dithiocarbamates and high yields of products. We believe this procedure, endowed with several green parameters, will be an attractive alternative for the synthesis of aryl dithiocarbamates.

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