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Electrogenerated base-promoted synthesis and antimicrobial activity of 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile

Kaouthar Hamrouni[a], Taieb Saied[ab], Nariman El Abed[c], Sami Ben Hadj Ahmed[c], Khaled Boujlel[a] & Mohamed Lamine Ben Khoud[a]

[a] Laboratoire de Chimie Analytique et Electrochimie, Faculté des Sciences de Tunis, Université Tunis El-Manar, Campus Universitaire, Tunis, Tunisie

[b] Département de Chimie et de Biologie Appliquées, Institut National des Sciences Appliquées et de Technologie, Tunis, Tunisie

[c] Laboratoire de protéines et molécules bioactives Ingénierie, Institut National des Sciences Appliquées et de la Technologie Centre Urbain Nord, Université de Carthage, Tunis, Tunisie

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Electrogenerated base-promoted synthesis and antimicrobial activity of 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile

Kaouthar Hamrouni[a], Taieb Saied[a,b*], Nariman El Abed[c], Sami Ben Hadj Ahmed[c], Khaled Boujlel[a] and Mohamed Lamine Ben Khoud[a]

[a]*Laboratoire de Chimie Analytique et Electrochimie, Faculté des Sciences de Tunis, Université Tunis El-Manar, Campus Universitaire, Tunis, Tunisie;* [b]*Département de Chimie et de Biologie Appliquées, Institut National des Sciences Appliquées et de Technologie, Tunis, Tunisie;* [c]*Laboratoire de protéines et molécules bioactives Ingénierie, Institut National des Sciences Appliquées et de la Technologie Centre Urbain Nord, Université de Carthage, Tunis, Tunisie*

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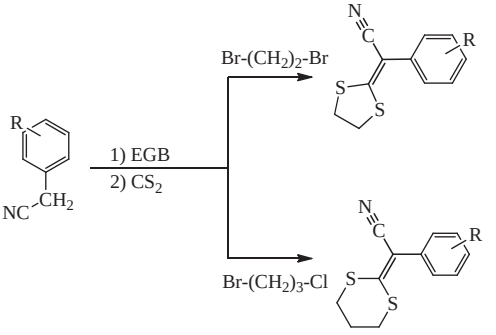
The new preparation of 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiol-2-ylidene)-2-arylacetonitrile is described. The electrogenerated cyanomethyl base/anion obtained from the electroreduction of acetonitrile promotes reactions between arylacetonitrile, carbon disulfide and 1-bromo-3-chloropropane or 1,2-dibromoethane. Obtained products have been identified according to their spectroscopic data (IR and ^{1}H NMR and ^{13}C NMR) and elemental analysis. The possible antibacterial activities of some of these compounds were investigated. Promising results were found against few types of bacteria.

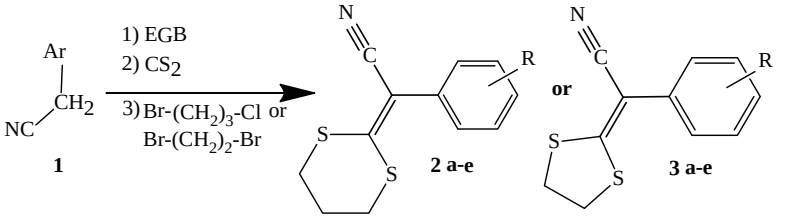


Keywords: 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile; 2-(1,3-dithiol-2-ylidene)-2-arylacetonitrile; anion EGBs; carbone disulfur; antimicrobial activity

1. Introduction

Ketene dithioacetals are well known as versatile intermediates in organic synthesis. Therefore, functionalized ketene dithioacetals have revealed to be a push pull system in synthetic organic

*Corresponding author. Email: saied.taieb@gmail.com



Scheme 1. Synthesis of 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiol-2-ylidene)-2-arylacetonitrile.

sulfur chemistry.[1] Thereby, many methods of synthesis of substituted ketene dithioacetals have been developed.[2] Extensive research, since the last decade, has shown the importance of the use of these molecules in several syntheses such as the synthesis of 4-functionalized quinoline derivatives, 4-((1,3-dithian-2-ylidene)methyl)quinolines.[3] On the other hand, arylacetonitriles are of great importance due to their use in the synthesis of several biologically active molecules such as flavonoïd pigments,[4] antibiotics [5] and vitamin A.[6] Herein and as an extension to our works,[7,8] we have combined two interesting functions ketene dithioacetal and arylacetonitrile to obtain new sulfur heterocycles having five **2** and six atoms **3**.

As a result of mild reaction conditions and elimination of the use of toxic and harmful chemicals, we synthesized these products by an electrochemical approach which is based on the use of electrogenerated base (EGB). This entity is obtained by simple galvanostatic reduction of acetonitrile in the presence of quaternary ammonium salts as supporting electrolyte.[9] One of the most important advantages of the use of EGB is the excellent control of the base strength depending on the choice of the solvent acidity, the current imposed density and the duration of the electrolysis.[10,11]

In the last few years, numerous papers reported the use of EGB, particularly the electrogenerated acetonitrile anion.[9,12–16] The reactivity of this anion makes it an important reagent in organic chemistry.[17] It is well established that the electrochemical reduction of acetonitrile in the presence of quaternary ammonium salt as a supporting electrolyte produces the corresponding cyanomethyl anion which is strong enough (pKa value of 31.3) to remove weak acidic protons and is also able to act as a nucleophile.[18–20]

In previous works, we have successfully exploited electrochemical approach for the synthesis of acyclic dithiocarbamates, N-benzylic rhodanines and thiazolidine-2-thiones.[21–23] More recently, we reported on an EGB-promoted synthesis of a series of 3,3-bis(ethylthiol)-2-arylacrylonitriles, of 3,3-bis(ethoxyacetatethiol)-2-arylacrylonitriles and 2-aryl-3,3-bis ((perfluoroalkyl)thio) acrylonitriles starting from arylacetonitrile.[7,8] In these works, we failed to obtain expected sulfur heterocyclic compounds; this is probably due to the weak reactivity of esters regarding thiocarbamate anion. Herein, as an extension to the previous results, 1-bromo-3-chloropropane and 1,2-dibromoethane are used through the same methodology in aim to synthesize 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile. As presumed, some of the heterocyclic prepared in this study have shown significant antibacterial activity (Scheme 1).

2. Electrochemical synthesis

2.1. *Experimental*

The current–potential curves of all arylacetonitriles used in this work were recorded in a solution of acetonitrile and tetrabutylammonium tetrafluoroborate (0.1 mol·L^{-1}) with a platinum

electrode and a reference electrode Ag/Ag^+ and showed that arylacetonitriles are not reducible under these conditions. Thus, arylacetonitriles can be introduced at the beginning of electrolysis according to the method of Feroci *et al.*[24]

Electrolysis of arylacetonitriles (3 mmol) in the presence of tetrabutylammonium tetrafluoroborate (0.1 $mol \cdot L^{-1}$) as the supporting electrolyte and acetonitrile as solvent (100 mL) was carried out under galvanostatic conditions ($i = 80$ mA). The solution was placed in an undivided electrochemical cell cooled at $-20\,°C$, with a magnesium rod as a sacrificial anode and a stainless steel grid cathode, maintained under inert atmosphere of nitrogen.

The acetonitrile is reduced at the cathode leads to the formation *in situ* of the cyanomethyl carbanions $^-CH_2CN$. This EGB was stabilized as $(NC\text{-}CH_2)_2Mg$ by the magnesium cation generated from the anode oxidation. Then, it deprotoned the arylacetonitrile into the corresponding anion.

The electrolysis is stopped when the desired quantity of EGB is produced, then, carbon disulfide in small excess (5 mmol) is added immediately to the solution followed by 1-bromo-3-chloropropane or 1,2-dibromoethane (5 mmol) 15 min later. The mixture is continually stirred over night at ambient temperature.

After the removal of excess acetonitrile, the obtained residue was extracted with ether. The solvent was removed and the residue was purified by column chromatography on silica gel 60. A mixture of ethyl acetate/petroleum ether (2:8) was used as eluant. All the resulting products (**2a**–**2e**) and (**3a**–**3e**) are reported in Table 1 and were identified on the basis of their spectroscopic data.

For this reaction, we used 2 F per mole of arylacetonitrile. According to a formal study realized within our research group, the best yield was obtained using 2–2.5 F per mole of substrate.[23]

As indicated in Scheme 2, the reduction of acetonitrile gave the corresponding EGB, which attacked the arylacetonitrile to produce the appropriate anion. In the second step, arylacetonitrile anion reacted with carbon disulfide to form a stabilized carbamodisulfide intermediate which is probably stabilized by ion-pairing with the electrogenerated magnesium cations from the sacrificial magnesium anode. Addition of 1.2- or 1.3-dihalogenated alkyl gave the corresponding five or six rings heterocyclic compounds with good yields. We did not detect the presence of acyclic intermediates resulting from a single attack of carbamodisulfide on the dihalogenated alkyl.

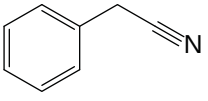
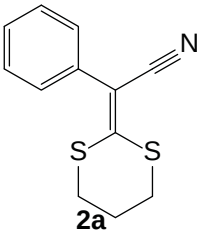
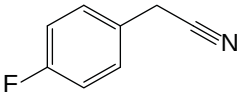
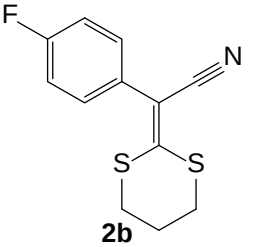
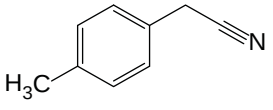
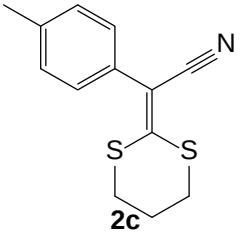
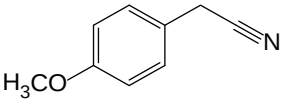
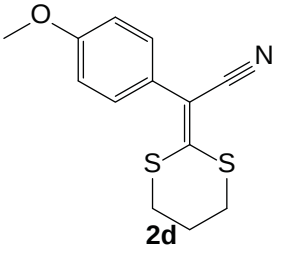
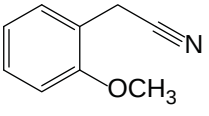
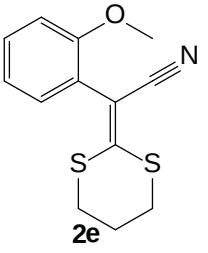
Obtained products have been identified according to their spectroscopic data (IR and ^1H NMR and ^{13}C NMR) and elemental analysis.

3. Biological activity

3.1. *Bacterial strains and growth conditions*

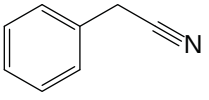
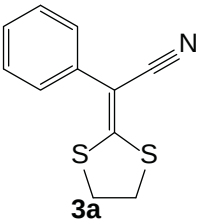
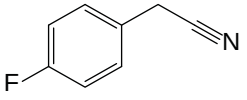
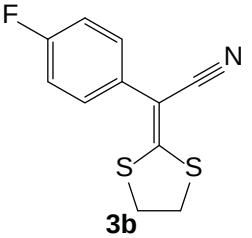
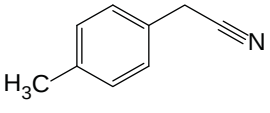
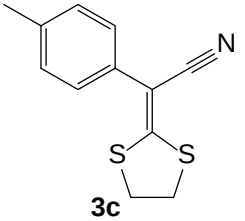
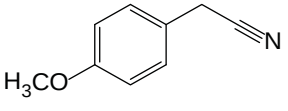
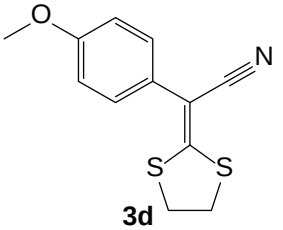
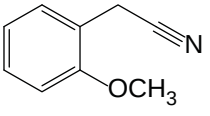
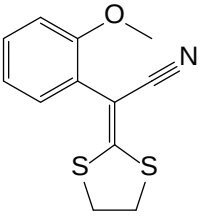
Bacteria tested in this study were obtained from international culture collections ATCC and the local culture collection of *Pasteur Institute of Tunis.* Test organisms included six Gram-negative bacterial strains: *Escherichia coli* (ATCC 25922), *Proteus mirabilis* (ATCC 29906), *Salmonella typhimurium* (ATCC 14028), *Shigella flexneri* (ATCC 29903), *Enterobacter cloacae* (ATCC 18147) and *Pseudomonas aeruginosa* (ATCC 27853); and three Gram-positive bacterial strains; *Staphylococcus aureus* (ATCC 25923), *Listeria monocytogenes* (ATCC 19118) and *Bacillus cereus* (ATCC 11778). All bacterial strains were cultivated in Luria Bertani (LB) Medium (Oxoid Ltd, UK) at 37 °C except for *Bacillus* species, which were incubated at 30 °C. Working cultures were prepared by inoculating a loopful of each test bacteria in 5 ml of LB Medium (Oxoid Ltd, UK), and were incubated at 37 °C for 18 h.

Table 1. Synthesized 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile **2** and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile **3**.

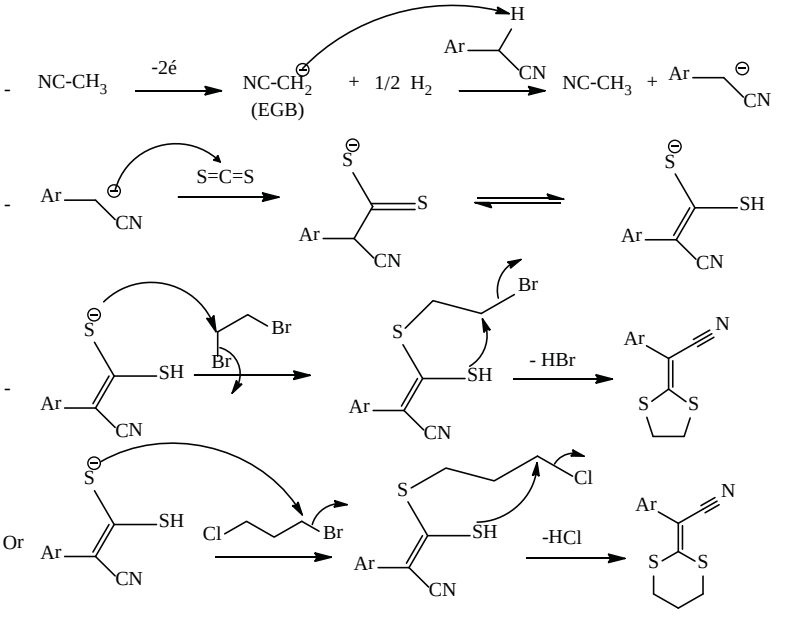
Entry	Starting arylacetonitrile	Electrophile	Product	Yield[a] (%)
1		A	 **2a**	69
2		A	 **2b**	73
3		A	 **2c**	77
4		A	 **2d**	75
5		A	 **2e**	78

(*Continued*)

Table 1. Continued

Entry	Starting arylacetonitrile	Electrophile	Product	Yield[a] (%)
6		B	 **3a**	67
7		B	 **3b**	70
8		B	 **3c**	75
9		B	 **3d**	80
10		B	 **3e**	70

Notes: A, 1-bromo-3-chloropropane; B, 1,2-dibromoethane.
[a]The yield was calculated in regard to the starting arylacetonitrile. $Q = 2$ Fmol^{-1}.



Scheme 2. Proposed mechanism of the preparation of products (**2** and **3**) by EGB-promoted reaction.

3.2. In vitro *antibacterial bioassay: agar well-diffusion method*

The *in vitro* antibacterial activity of the synthesized compounds has been evaluated against various Gram-negative and Gram-positive bacteria by the agar well-diffusion method, as described by Murthy *et al.*[25] Briefly, a suspension (0.1 mL of 10^6 CFU/mL) of each microorganism was spread using a sterile cotton swab on the surface of solid LB media plates. Cylindrical plugs were removed from the agar plates by a sterile cork borer (Pyrex, UK) to produce wells with a diameter of approximately 6 mm. On the other hand, solutions of the test compounds were prepared in ethanol and adjusted at a concentration of 20 mmol·L^{-1}, and then a 50 µL of each sample solution was added to the respective wells and allowed to diffuse at room temperature for 2 h. Then, the plates were incubated for 18 h at 37 °C. Results were recorded by measuring the diameter inhibitory zones in millimeter, including the well diameter. The diameters of the zone of inhibition produced by the agent were compared with those produced by the commercial control antibiotics, Streptomycin B (15 µg/mL).

3.3. *Result and discussions*

The results of the antibacterial activity of the newly synthesized heterocyclic compounds have been presented in Table 2. It can be noted from these data that, in general, all the test compounds possessed moderate-to-good antibacterial activity against Gram-positive and Gram-negative bacteria, except for *L. monocytogenes* where the size of their inhibition zones ranges from 8 to 15 mm. On the basis of the zone of inhibition against the test bacterium, compounds **2d**, **2a** and **3e** were found to be the most effective against *E. coli* (ATCC 25922), whereas compound **2b** exhibited a high antibacterial activity against *B. cereus* (ATCC 11778) and *P. mirabilis* (ATCC 29906). Compound **3b** showed a moderate activity towards *E. coli* (ATCC 25922) and *E. cloacae* (ATCC 18147). However, Compound **3d** showed moderate activity against *S. flexneri*

Table 2. Antibacterial activity of selected compounds, using the agar well-diffusion method.

Strains	Agar well-diffusion method (DD)						
	Compounds						Antibiotic: streptomycin
	2d	**2b**	**2a**	**3b**	**3d**	**3e**	
E. coli (ATCC 25922)	15	10	14	13	12	13	12
S. aureus (ATCC 25923)	9	13	8	11	12	11	22
B. cereus (ATCC 11778)	11	15	Inactive	Inactive	11	12	16
P. aeruginosa (ATCC 27853)	14	12	Inactive	11	10	11	12
E. cloacae (ATCC 18147)	11	9	Inactive	13	12	12	14
P. mirabilis (ATCC 29906)	Inactive	14	Inactive	Inactive	Inactive	Inactive	NT
S. flexneri (ATCC 29903)	10	9	Inactive	12	13	10	15
L. monocytogenes (ATCC 19118)	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	23
S. typhimurium (ATCC 14028)	9	8	8	9	8	8	15

Note: NT, not tested.

(ATCC 29903). Also, the results revealed that new compound **2a** was weakly active against the tested microorganisms compared to other test compounds.

On the other hand, our investigations presented in this study showed that the test 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile compounds express promising antibacterial properties *in vitro* comparable or even better than those of the antibiotic streptomycin (positive control).

To the best of our knowledge, the mechanism of the antibacterial activity of the test compounds has not been elucidated. In fact, it seems that the mechanism is not related to the synthesis of the cell envelope, as Gram-positive and Gram-negative bacteria exhibit sensitivity. Thus, the selectivity of the compounds was dependent on their molecular structure.[26]

From the structure–activity relationship viewpoint, we propose that the membrane disrupting and antibacterial potential of the test synthesized compounds correlated with their chain lengths, [27,28] an increase in the positive charge and hydrophobicity, which is apparently the more important for membrane interaction.[29,30] In addition, these findings of our study indicated that the test compounds have the potential to generate novel antibacterial proprieties by displaying moderate to high affinities for most of the receptors.[31] This allows us to create a bank of bioactive compounds for discovery and development of new, innovative therapeutic agents.[32]

4. Conclusion

The use of an EGB as a new electrochemical methodology that allows the preparation of 2-(1,3-dithian-2-ylidene)-2-arylacetonitrile (**2**) and 2-(1,3-dithiolan-2-ylidene)-2-arylacetonitrile (**3**) from arylaceyonitrile, carbon disulfide and 1-bromo-3-chloropropane or 1,2-dibromoethane in high yields, under mild conditions and avoiding the use of polluting or hazardous chemicals or the addition of a base is reported. The mechanism of the reaction is investigated and the obtained products have been identified according to their spectroscopic data (IR and ^{1}H NMR and ^{13}C NMR) and elemental analysis.

Antibacterial activities of some of these compounds were tested for their antibiotic properties. Some of the tested compounds showed an interesting antibiotic activity against bacteria *E. coli*, *S. aureus*, *B. cereus*, *P. aeruginosa*, *E. cloacae*, *P. mirabilis*, *S. flexneri*, *L. monocytogenes* and *S. typhimurium*.

4.1. *2a-2-(1,3-dithian-2-ylidene)-2-phenylacetonitrile*

Yield: 69%: IR (cm^{-1}, $CHCl_3$); ν: 2196 (CN); 1603 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.10 (m, 2H, CH_2); 2.83 (t, 2H, CH_2); 3.01 (t, 2H, CH_2); 7.20–7.40 (m, 5H, CHarom.). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 22.69; 29.28; 29.73; 106.12; 117.97; 128.48; 128.57; 128.89; 129.17; 129.32; 133.30; 158.29. Elemental analysis: %C = 61.06; %H = 4.92; %N = 5.95 (experimental). %C = 61.76; %H = 4.75; %N = 6.00 (calculated).

4.2. *2b-2-(1,3-dithian-2-ylidene)-2-(4-fluorophenyl)acetonitrile*

Yield: 73%: IR (cm^{-1}, $CHCl_3$); ν: 2199 (CN); 1608 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.16 (m, 2H, CH_2); 2.91 (t, 2H, CH_2); 3.06 (t, 2H, CH_2); 6.98–7.36 (m, 4H, CHarom.). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 23.05; 29.24; 29.23; 106.19; 115.47; 115.78; 129.31; 129.36; 129.62; 129.73; 130.80; 130.91; 158.33. ^{19}F NMR (282.37 MHz, CDCl3) δ: -111.99 (s, 1F, CFarom.). Elemental analysis: %C = 58.95; %H = 4.86; %N = 5.33 (experimental). %C = 57.34; %H = 4.01; %N = 5.57 (calculated).

4.3. *2c-2-(1,3-dithian-2-ylidene)-2-(p-tolyl)acetonitrile*

Yield: 77%: IR (cm^{-1}, $CHCl_3$); ν: 2198 (CN); 1604 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.15 (m, 2H, CH_2); 2.29 (s, 3H, CH_3); 2.89 (t, 2H, CH_2); 3.05 (t, 2H, CH_2); 7.11–7.26 (m, 4H, CHarom.). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 21.32; 23.23; 29.21; 29.70; 106.69; 117.90; 127.81; 128.76; 129.21; 129.78; 130.45; 138.55; 156.80. Elemental analysis: %C = 62.13; %H = 5.44; %N = 5.98 (experimental). %C = 63.12; %H = 5.30; %N = 5.66 (calculated).

4.4. *2d-2-(1,3-dithian-2-ylidene)-2-(4-methoxyphenyl)acetonitrile*

Yield: 75%: IR (cm^{-1}, $CHCl_3$); ν: 2196 (CN); 1603 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.22 (m, 2H, CH_2); 2.98 (t, 2H, CH_2); 3.12 (t, 2H, CH_2); 3.83 (s, 3H, CH_3); 6.91–7.38 (m, 4H, CHarom.). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 23.15; 29.21; 29.24; 55.36; 106.32; 113.92; 117.99; 125.70; 128.53; 128.89; 130.25; 155.99; 159.54. Elemental analysis: %C = 60.14; %H = 6.08; %N = 5.33 (experimental). %C = 59.28; %H = 4.98; %N = 5.32 (calculated).

4.5. *2e-2-(1,3-dithian-2-ylidene)-2-(2-methoxyphenyl)acetonitrile*

Yield: 78%: IR (cm^{-1}, $CHCl_3$); ν: 2217 (CN); 1601 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.11 (m, 2H, CH_2); 2.81 (t, 2H, CH_2); 3.02 (t, 2H, CH_2); 3.78 (s, 3H, CH_3); 6.84–7.27 (m, 4H, CHarom.). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 21.98; 27.93; 28.01; 54.63; 101.72; 110.40 116.32; 119.36; 120.84; 129.59; 130.16; 155.87; 157.61. Elemental analysis: %C = 59.92; %H = 6.11; %N = 5.17 (experimental). %C = 59.28; %H = 4.98; %N = 5.32 (calculated).

4.6. *3a-2-(1,3-dithiolan-2-ylidene)-2-phenylacetonitrile*

Yield: 67%: IR (cm^{-1}, $CHCl_3$); ν: 2199 (CN); 1602 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 3.42 (s, 4H, 2 CH_2 cyclic); 7.15–7.30 (m, 5H, CHarom.). ^{13}C NMR (75.47 M Hz, $CDCl_3$); δ:

38.03; 40.28; 97.85; 118.97; 127.49; 128.06; 128.78; 129.51; 134.81; 162.72; 167.55. Elemental analysis: %C = 59.15; %H = 4.07; %N = 6.67 (experimental). %C = 60.24; %H = 4.14; %N = 6.39 (calculated).

4.7. *3b-2-(1,3-dithiolan-2-ylidene)-2-(4-fluorophenyl)acetonitrile*

Yield: 70%: IR (cm^{-1}, $CHCl_3$); ν: 2200 (CN); 1603 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 3.51 (s, 4H, 2 CH_2 cyclic); 7.00–7.41 (m, 4H, CHarom.). ^{13}C NMR (75.47 M Hz, $CDCl_3$); δ: 38.08; 40.13; 96.99; 115.61; 115.90; 127.49; 129.46; 129.57; 129.84; 160.40; 162.47. ^{19}F NMR (282.37 MHz, $CDCl_3$); δ: -112.51(s, 1F, CFarom). Elemental analysis: %C = 58.66; %H = 3.35; %N = 6.10 (experimental). %C = 55.67; %H = 3.40; %N = 5.90 (calculated).

4.8. *3c-2-(1,3-dithiolan-2-ylidene)-2-(p-tolyl)acetonitrile*

Yield: 75%: IR (cm^{-1}, $CHCl_3$); ν: 2120 (CN); 1600 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 2.26 (s, 3H, CH_3); 3.45 (s, 4H, 2 CH_2 cyclic); 7.09–7.33 (m, 4H, CHarom.). ^{13}C NMR (75.47 M Hz, $CDCl_3$); δ: 21.26; 37.93; 40.12; 98.06; 118.92; 127.39; 127.39; 129.39; 129.39; 132.02; 138.04; 161.34. Elemental analysis: %C = 58.93; %H = 5.02; %N = 6.40 (experimental). %C = 61.76; %H = 4.75; %N = 6.00 (calculated).

4.9. *3d-2-(1,3-dithiolan-2-ylidene)-2-(4-methoxyphenyl)acetonitrile*

Yield: 80%: IR (cm^{-1}, $CHCl_3$); ν: 2206 (CN); 1603 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 3.47 (s, 4H, 2 CH_2 cyclic); 3.73 (s, 3H, CH_3); 6.78–7.37 (m, 4H, CHarom.). ^{13}C NMR (75.47 M Hz, $CDCl_3$); δ: 37.99; 40.00; 55.39; 97.76; 114.07; 114.96; 118.97; 127.36; 128.93; 129.06; 159.18; 160.44. Elemental analysis: %C = 56.20; %H = 5.07; %N = 5.80 (experimental). %C = 57.80; %H = 4.45; %N = 5.62 (calculated).

4.10. *3e-2-(1,3-dithiolan-2-ylidene)-2-(2-methoxyphenyl)acetonitrile*

Yield: 70%: IR (cm^{-1}, $CHCl_3$); ν: 2200 (CN); 1601 (C=C). ^1H NMR (300 MHz, $CDCl_3$); δ: 3.30 (t, 2H, CH_2); 3.40(t, 2H, CH_2); 3.70 (s, 3H, CH_3); 6.80–7.30 (m, 4H, CHarom.). ^{13}C NMR (75.47 M Hz, $CDCl_3$); δ: 38.76; 39.53; 55.69; 94.18; 111.43; 118.42; 120.62; 123.72; 130.39; 130.53; 156.50; 164.36. Elemental analysis: %C = 56.18; %H = 4.62; %N = 6.02 (experimental). %C = 57.80; %H = 4.45; %N = 5.62 (calculated).

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