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Access to 3,4-furan dithiolate: towards 3,4-dialkylsulfanylfurans and their Diels–Alder adducts with acrylonitrile

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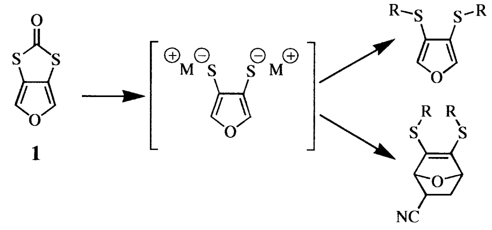
Abstract—The convenient synthesis of symmetrical and unsymmetrical 3,4-dialkylsulfanylfurans from 3,4-furandithiolate is described. The reactivity of the furan cycle as a diene in Diels–Alder reactions with acrylonitrile is discussed in relation to the presence of one or two thiolato substituents. © 2002 Elsevier Science Ltd. All rights reserved.

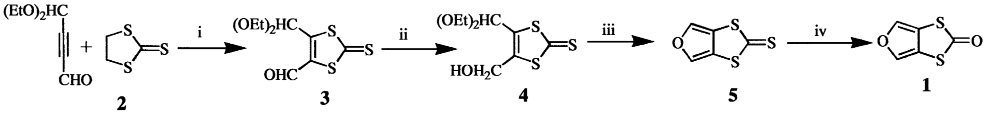
Furan derivatives exhibit a large variety of applications involving both the fields of natural compounds and organic materials.[1,2] Owing to the well-known higher reactivity of the 2- and 5-positions of electron-rich five-membered heterocycles, the synthesis of 3,4-disubstituted furan rings is often a difficult task.[3] Consequently, the definition of new synthetic routes allowing the regioselective preparation of 3,4-disubstituted furans remains a key issue for the development of these fields. A possible way of functionalization consists of the introduction of a sulfide function and the formation of alkylsulfanyl groups at the β-positions. While 3-alkylsulfanyl furans corresponding to flavor chemicals have been strongly studied,[4] the 3,4-disubstituted derivatives have been less developed. Only 3,4-dimethylsulfanylfuran obtained in very low yields has been described in the literature.[5]

On the other hand, substituted furan cycles are well-known to undergo [4+2] cycloadditions with various π-bonds and this reaction is frequently used to synthesize natural products.[6] However, the yields and the stereoselectivity often depend on the substituents grafted on the heterocycle and the nature of the dienophile. Hence, the cycloadditions need a thermal activation and/or the use of a Lewis acid catalyst, except with very reactive dienophile.

We report here the generation of the 3,4-furandithiolate, which represents an efficient precursor for a direct synthesis of 3,4-dialkylsulfanylfurans. We have also studied the Diels–Alder reactivity of the mono- or dithiolate furan with acrylonitrile compared to dialkylsulfanylfurans.



The 3,4-furandithiolate was generated by treatment of [3,4]furano-2-oxo-1,3-dithiole **1** with sodium methoxide. The synthesis of **1** has been performed following Scheme 1. Reaction of equimolar proportions of the



Scheme 1. (i) Xylene, reflux; (ii) NaBH$_4$, CH$_2$Cl$_2$–MeOH; (iii) acid amberlyst resin, CHCl$_3$; (iv) Hg(OAc)$_2$, CH$_2$Cl$_2$.

Keywords: furan; 3,4-disubstituted furans; Diels–Alder reaction.

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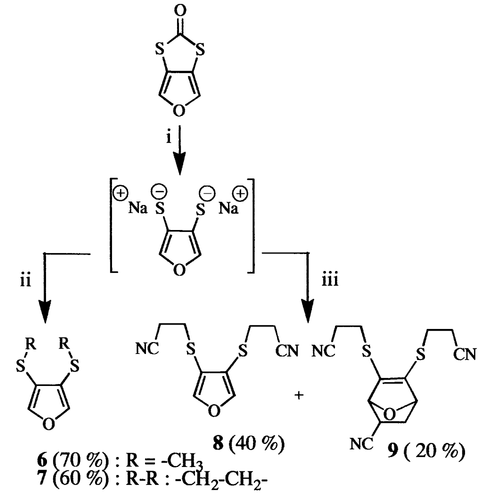
monoacetal of acetylenedicarbaldehyde[7] and ethylene trithiocarbonate **2** gave a mixture of **3** and unreacted **2** difficult to separate.[8]

Reduction of the mixture by $NaBH_4$ led to alcohol **4** (65% overall yield) and was easily separated from **2** by flash chromatography on silica gel. Treatment of **4** by acid amberlyst resin in $CHCl_3$ at room temperature afforded the dithiolethione **5**[9] (80%), which was converted into dithiolone **1** in 90% yield by treatment with mercuric acetate in CH_2Cl_2–AcOH.

The reaction of **1** with 6 equiv. of sodium methoxide in methanol at room temperature, followed by addition of iodomethane (2.1 equiv.) or 1,2-dibromoethane (1.1 equiv.) gave symmetrical 3,4-dialkylsulfanylfurans **6** and **7** in 70 and 65% yield, respectively (Scheme 2).

An excess of 3-bromopropionitrile led to the expected 3,4-bis(2-cyanoethylsulfanyl)furan **8** in 40% yield, but also to compound **9** in 20% yield, which corresponds to the cycloadduct of **8** with acrylonitrile. 3-Bromopropionitrile or the 2-cyanoethylsulfanyl group are known to generate acrylonitrile under basic conditions, which can react as dienophile with the furan cycle. The *exo* (65%) and *endo* (35%) forms of **9** were separated by crystallization of the *exo* form from a chloroform–pentane solution. Compound **8** did not directly react with acrylonitrile at room temperature, indicating that Diels–Alder reaction only occurs in the presence of the strong electron donor thiolate anions.

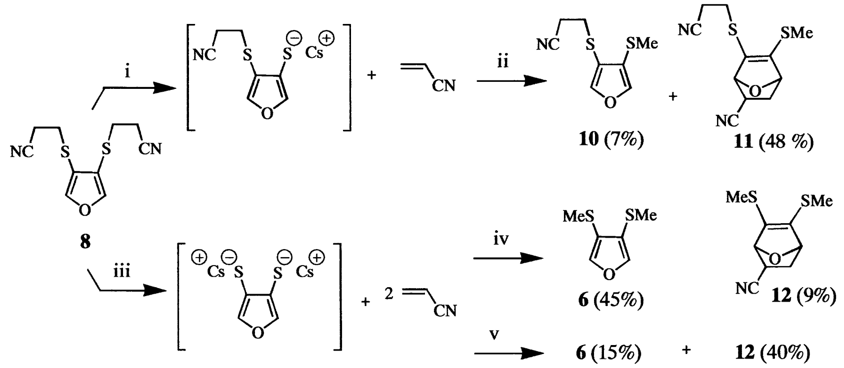


Scheme 2. (i) MeONa, MeOH; (ii) CH_3I or $BrCH_2CH_2Br$; (iii) $BrCH_2CH_2CN$.

As demonstrated in tetrathiafulvalene chemistry,[10] the cyanoethyl groups of compound **8** can be readily and selectively removed by the action of 1 or 2 equiv. of CsOH generating acrylonitrile and the mono- or the bis-thiolate anions, respectively (Scheme 3). The treatment of a solution of **8** in DMF with 1 equiv. of CsOH (in methanol solution) followed by the addition of methyl iodide after 15 min, gave unsymmetrical dialkylsulfanylfuran **10** in 7% yield and the cycloadduct **11** in 48% yield. As above, the presence of the thiolate group was necessary to drive the cycloaddition because compound **10** did not directly react with acrylonitrile at room temperature. The ^1H NMR spectrum of **11** showed that this reaction was regiospecific and only two isomers, identified as the *exo* (90%) and *endo* (10%), were formed. The *exo* form of the main adduct and the relative position of the cyano group were confirmed by X-ray analysis (Fig. 1).[11]

On the other hand, the fast addition of 2 equiv. of CsOH followed by an addition of a slight excess of MeI after 15 min led to compound **6** in 45% yield, while the cycloadduct **12** was only obtained in 9% yield. When only 1 equiv. of MeI was added at first to the dithiolate solution, followed by a second addition of 1 equiv. of MeI after 15 min, yields of **6** and **12** became 15 and 40%, respectively. Hence, in spite of the presence of the two strong electron donor groups, the 3,4-furandithiolate appeared to be less reactive with acrylonitrile than the mono-thiolate analog.

The energies of the HOMO and LUMO levels of acrylonitrile, mono- and dithiolate furans were calculated by ab initio methods.[12] Fig. 2 represents the qualitative scheme of the relative position of the energy levels for the different compounds. The LUMO of acrylonitrile and the HOMO of monothiolate furan present very similar energies, which indicates favorable interactions allowing a fast reaction. On the contrary, the interactions with the dithiolate derivative are less



Scheme 3. (i) 1 equiv. CsOH; (ii) MeI (1.2 equiv.); (iii) 2 equiv. CsOH; (iv) MeI (2.2 equiv.); (v) MeI (1 equiv.+1.2 equiv.)

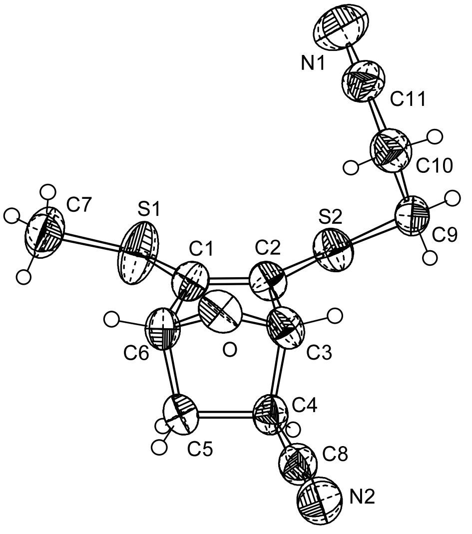


Figure 1. X-Ray structure of the *exo* form of **11**.

favorable and the cycloaddition is expected to be slower. Nevertheless, the cycloaddition can be obtained at room temperature from dithiolate anion by using a slight excess of dienophile or by addition of the electrophile agent in two steps allowing the formation of the more reactive monothiolate as intermediate.

The reaction was also carried out with the dithiolate anion generated from the dithiolone **1**. The successive addition of acrylonitrile and then methyl iodide in the dithiolate solution led to a mixture of compounds **6**, **10** and **12**, which were easily separated by chromatography on silica gel (Scheme 4). The unsymmetrical furan derivative **10** was obtained following a Michael addition of a thiolate function on acrylonitrile and further reaction of MeI on the second thiolate group. When MeI (2.2 equiv.) was added in one step 30 min after acrylonitrile, the yields of **6** and **12** were 48 and 10% respectively, while for an addition in two steps (1 equiv.+1.2 equiv. after 15 min) the yield of **12** increased 25% and that of **6** down 30%. Concerning compound **10**, the yield of 13% remained constant. Attempts to obtain furan cycle from cycloadduct by retro Diels–Alder reaction gave very low yields due to degradations. Mass spectrometry studies confirmed the difficulty in performing a retro Diels–Alder reaction. Indeed, spontaneous fragmentations of **10** and **11** under electronic impact were studied by linked scan and MIKES experiments. The comparison of the results allows us to propose that the activation energy of an unimolecular retro Diels–Alder reaction (in vacuum) is relatively high. Other fragmentations such as acrylonitrile elimination by 1–3 hybride shift from 2-cyanoethylsulfanyl group appears energetically more favorable.[13]

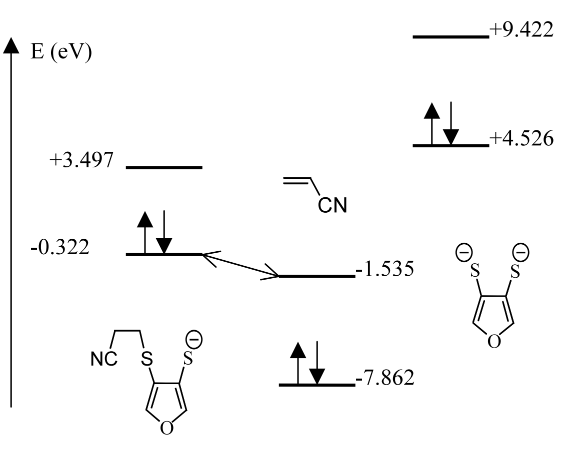
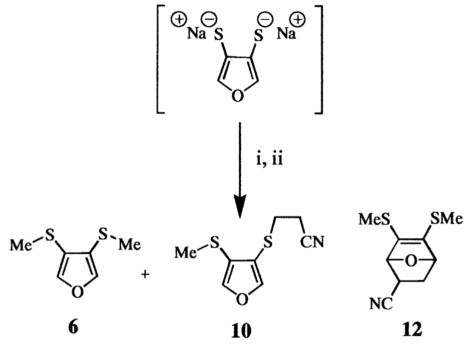


Figure 2. Schematic representation of the energy levels for the HOMO and LUMO of acrylonitrile, mono- and bis-thiolate furan.

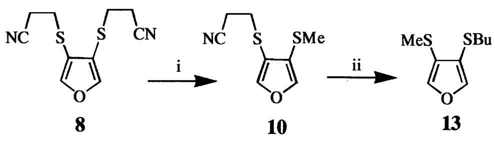


Scheme 4. (i) Acrylonitrile (1.5 equiv.); (ii) MeI (2.2 equiv.).

To achieve the synthesis of unsymmetrical 3,4-dialkylsulfanylfuran in two steps from compound **8** (Scheme 5), it was necessary to avoid the cycloaddition during the formation of the monothiolate furan anions. Thus, a rapid addition of 1 equiv. of CsOH in a DMF solution of **8** cooled at 0°C, immediately followed by MeI, gave **10** in 60% yield. Only a small amount of cycloadduct **11** was observed by TLC and the yield was inferior to 5%. For the second step, treatment of a DMF solution of **10** in the presence of bromobutyle (2 equiv.) by a slight excess of CsOH (1.5 equiv.) led to the unsymmetrical 3-methylsulfanyl-4-butylsulfanylfuran **13** in 65% yield.

In conclusion, symmetrical and unsymmetrical 3,4-dialkylsulfanylfurans have been synthesized.[14] Taking advantage of the good reactivity of the monothiolate furan as a diene, cycloadditions with acrylonitrile have been performed under mild conditions.[15]

Materials such as polymers and oligomers built from these 3,4-disubstituted furans are in progress and will be described in a future publication.



Scheme 5. (i) 1 equiv. CsOH, 0°C, MeI (1.1 equiv.); (ii) 1.2 equiv. CsOH, BuBr, rt.

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11. X-Ray structure of compound **11**. Single crystals of **11** were mounted on an Enraf–Nonius MACH3 diffractometer with graphite monochromator and Mo-Kα (λ = 0.71073 Å) radiation at T = 294 K. The data collections were performed with the $\omega/2\theta$ scan technique. The crystal structures were solved by direct method (SIR) and refined by full-matrix least-squares techniques using MolEN software.

    Crystal data of **11**: $C_{11}H_{12}N_2OS_2$, M_r = 252.36, triclinic, space group P-1, a = 7.0603(9), b = 7.5165(5), c = 12.154(2) Å, α = 82.95(1), β = 75.43(1), γ = 76.73(1)°, V = 606.1(2) Å^3, Z = 2, T = 293 K, $F(000)$ = 264, μ = 0.418 mm^{-1}, 2316 reflections measured and 1863 symmetry-independent with $I > 3\sigma(I)$, full-matrix least-squares refinement on F^2, $R_{\rm all}$ = 0.048, $wR_{\rm all}$ = 0.073. All non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were located by a Fourier difference synthesis and the missing atoms were calculated from the Hydro program. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre under reference CCDC: 173776.
12. Theoretical calculations at the ab initio density functional level were performed using the program Gaussian98 to investigate the molecular structure and the electronic properties of the molecules. Becke's three parameter gradient corrected functional (B3lyp) with a polarized 6-31G* basis for all atoms was used to optimize the geometry of every molecule and to compute one-electron properties at this minimum energy conformation. The reference for Gaussian98 is: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople J. A.; Gaussian 98 (Revision A.9); Gaussian; Inc.; Pittsburgh PA; 1998.
13. Unpublished results.
14. All compounds gave satisfactory spectroscopic data. Selected examples of furan derivatives:

    7: Yellow pale oil, EI MS $M^{+\bullet}$ $C_6H_6O_1S_2$ calcd 157.9860, found 157.9857; ^{1}H NMR ($CDCl_3$): 7.22 (s, 2H), 3.15 (s, 4H); ^{13}C NMR ($CDCl_3$): 137.37, 111.16, 26.78.

    8: White solid, mp = 93°C; EI MS $M^{+\bullet}$ $C_{10}H_{10}N_2O_1S_2$ calcd 238.0235, found 238.0245; ^{1}H NMR ($CDCl_3$): 7.62 (s, 2H), 3.03 (t, 4H, ^{3}J = 7.0 Hz), 2.61 (t, 4H, ^{3}J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): 147.71, 117.68, 30.11, 18.40.

    10: Yellow pale oil, EI MS $M^{+\bullet}$ $C_8H_9N_1O_1S_2$ calcd 199.0126, found 199.0132; ^{1}H NMR ($CDCl_3$): 7.56 (d, 1H, ^{3}J = 1.6 Hz), 7.35 (d, 1H, ^{3}J = 1.6 Hz), 2.97 (t, 2H, ^{3}J = 7.2 Hz), 2.59 (t, 2H, ^{3}J = 7.2 Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): 147.43, 142.48, 123.11, 117.85, 115.45, 29.95, 1, 18.36, 17.62.

    13: Yellow pale oil, EI MS $M^{+\bullet}$ $C_9H_{14}O_1S_2$ calcd 202.04861, found 202.0465; ^{1}H NMR ($CDCl_3$): 7.40 (d, 1H, ^{3}J = 1.7 Hz), 7.32 (d, 1H, ^{3}J = 1.7 Hz), 2.74 (t, 2H, ^{3}J = 7.4 Hz), 2.37 (s, 3H), 1.56 (m, 2H), 1.42 (m, 2H), 0.90 (t, 3H, ^{3}J = 7.4 Hz); ^{13}C NMR ($CDCl_3$): 144.87, 142.17, 122.60, 118.89, 34.45, 31.41, 21.66, 1, 17.82, 13.58.
15. Selected examples of cycloadduct derivatives:

    11: White solid, mp = 123°C; EI MS $M^{+\bullet}$ $C_{11}H_{12}N_2O_1S_2$ calcd 252.0391, found 252.0398; ^{1}H NMR ($CDCl_3$): 5.22 (d, 1H, ^{3}J = 4.5 Hz), 5.16 (s, 1H), 3.11 (m, 1H), 2.92 (m 1H), 2.68 (m, 2H), 2.58 (dd, 1H, ^{3}J = 4.0 Hz, ^{3}J = 8.7 Hz), 2.42 (s, 3H), 2.22 (dt, 1H, ^{3}J = 4.3 Hz and ^{3}J = 4.0 Hz, ^{3}J = 11.8 Hz), 1.92 (dd, 1H, ^{3}J = 11.8 Hz, ^{3}J = 8.7 Hz); ^{13}C NMR ($CDCl_3$): 147.35, 128.69, 120.71, 117.41, 84.45, 81.24, 33.48, 29.50, 27.93, 18.90, 15.06.

    12: White solid, mp = 128°C; EI MS $M^{+\bullet}$ $C_9H_{11}NO_1S_2$ calcd 213.02820, found 213.0290; ^{1}H NMR ($CDCl_3$): 5.24 (s, 1H), 5.19 (d, 1H, ^{3}J = 4.42 Hz), 2.52 (dd, 1H, ^{3}J = 3.8 Hz, ^{3}J = 8.7 Hz), 2.37 (s, 6H), 2.18 (dt, 1H, ^{3}J = 4.5 Hz and ^{3}J = 4.0 Hz, ^{3}J = 11.8 Hz), 1.90 (dd, 1H, ^{3}J = 11.8 Hz, ^{3}J = 8.7 Hz); ^{13}C NMR ($CDCl_3$): 140.35, 134.54, 121.03, 84.04, 80.98, 33.74, 29.41, 15.53, 15.23.