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SYNTHESIS OF NEW 3-METHYLTHIO-4,5,6,7-TETRAHYDRO BENZO[c]THIOPHENE-4-ONES

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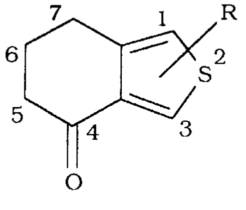
A new route to 1,3-disubstituted-4,5,6,7-tetrahydro benzo[c]thiophene-4-one is described starting from 1,3-cyclohexanedione.

We have been interested for some years in the chemistry of thieno[c]cycloalcanones as precursor of potential antifungal and antibacterial heterocyclic compounds[1]. Only some examples of mono-, di- and polyalkyl- as well as chloro-and dichloro- derivatives 1 have been described, generally obtained by cyclisation of the corresponding ω-thiophene alkanoic acids[2].



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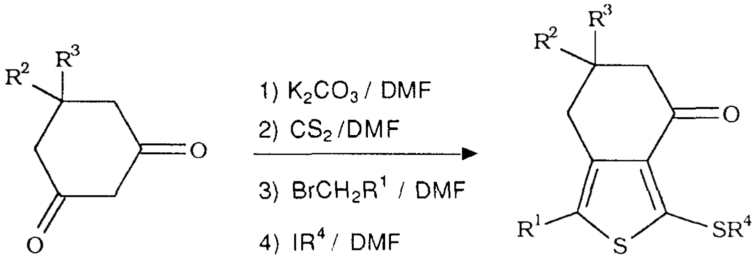
*To whom correspondence should be addressed

As part of our study of these systems, We describe here a rapid access to variously 1,3-disubstituted thiophene compounds 1 from 1,3-cyclohexanedione and carbon disulfide as the sulfur source.

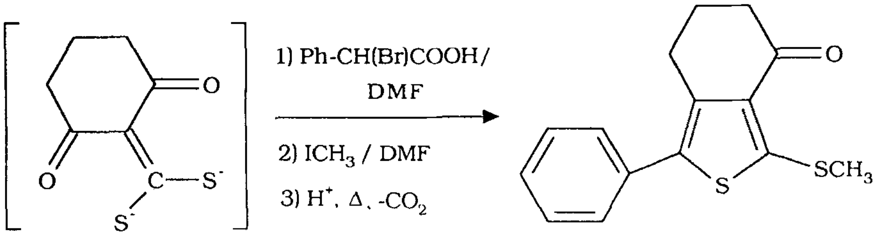
Condensation of ketones with carbon disulfide allows the formation of thiophene rings3. By reacting 1,3-cyclohexandione with carbon disulfide in presence of potassium carbonate in DMF, we are able to prepare the dithioketene anion. Successive quenching with active methylene compounds and methyl iodide leads to the formation of the 1,3-disubstituted thiophene derivatives 2 to 8 (scheme 1).



Compound	R^1	R^2	R^3	R^4	Yield (%)
2	CHO	H	H	Me	59
3	COMe	H	H	Me	64
4	$PhNO_2$	H	H	Me	61
5	CN	H	H	Me	82
6	CO_2Et	H	H	Me	80
7	Ph	H	H	Me	48
8	CO_2Et	Me	Me	Me	78

Scheme 1

Generally the cyclisation step takes place spontaneously during the reaction. However cyclisation does not occur directly with benzylbromide. In this case we used the more activated α-bromo-α.-phenylacetic acid to favor the cyclisation[4] Aromatisation is obtained with decarboxylation at the acidification step (scheme 2).



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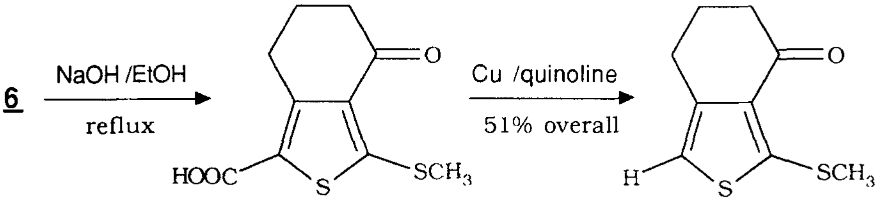
Scheme 2

Hydrolysis and decarboxylation of the ester 6 leads to the compound 9 (scheme 3).



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Scheme 3

All 3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-ones have been characterized by ^1H NMR, ^{13}C NMR and microanalysis.

EXPERIMENTAL

Melting points were determined on a Kofler bench and are uncorrected. The ^1H NMR and ^{13}C NMR were recorded on a Bruker 250 MHz spectrometer. Elemental analysis were performed on a Carlo Erba elemental analyser.

3-Methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-one: general procedure.

1,3-cyclohexane dione (5.6g, 0.05 mol) is added to potassium carbonate (21g, 0.015 mol) in DMF (45 mL). After 10 minutes carbon disulfide (4.5 mL, 0.075 mol) is added at once and the mixture stirred at room temperature for an additionnal 10 minutes. The halogeno derivative (0.05 mol) in DMF (50 mL) is then added with cooling (0-5°) and after 1 hour, methyl iodide (7.8g, 0.055 mol) in DMF (20 mL) is added dropwise. After 30 minutes, the mixture is poured into water (900 mL) and vigourously stirred for 10 hours. The crude products are filtered off and purified by recristallization or column chromatography on silica gel.

1-Formyl-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene 4-one $\underline{2}$. m. p. 98°(EtOH) ; ^1H NMR ($CDCl_3$) δ 2.2 (m, 2H, $C\underline{H}_2$), 2.5 (t, 2H, $C\underline{H}_2$), 2.6 (s, 3H, S-$C\underline{H}_3$), 3.2 (t, 2H, $C\underline{H}_2$), 9.9 (s, 1H, $C\underline{H}O$); ^{13}C NMR ($CDCl_3$) δ 15.48; 19.26; 21.58; 25.22; 124.75; 128.88; 131.26; 159.69; 190.25; 194.26; Anal. Calcd. for $C_{10}H_{10}O_2S_2$: C, 53.09; H, 4.42. Found: C, 52.95; H, 4.51.

1-Acetyl-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene 4-one $\underline{3}$. m. p. 125°(EtOH) ; ^1H NMR ($CDCl_3$) δ 2.15 (m, 2H, $C\underline{H}_2$), 2.2 (s, 3H, $C\underline{H}_3CO$), 2.6 (s, 3H, S-$C\underline{H}_3$), 2.7(t, 2H, $C\underline{H}_2$), 3.25 (t, 2H, $C\underline{H}_2$); ^{13}C NMR ($CDCl_3$) δ 18.09; 23.03; 26.22; 24.44; 26.86; 129.46; 141.0; 150.74; 192.21; 195.36; Anal. Calcd. for $C_{11}H_{12}O_2S_2$: C, 55.00; H, 5.00. Found: C, 55.09; H, 4.88.

1-(4-Nitrophenyl)-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-one 4. m. p. 158°(MeOH) ; ^{1}H NMR ($CDCl_3$) δ 2.1(m, 2H, CH_2), 2.45 (t, 2H, CH_2), 2.6 (s, 3H, S-CH_3), 3.05 (t, 2H, CH_2), 7.6 (d, 2H, Ar-H), 8.25 (d, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 18.06; 26.24; 36.95; 38.67; 123.41; 128.49; 129.74; 131.47; 151.18; 159.59; 161.60; 163.17; 193.68; Anal. Calcd. for $C_{15}H_{13}NO_3S_2$: C, 56.42; H, 4.07; N, 4.38. Found: C, 56.55; H, 4.01; N, 4.11.

1-Cyano-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene 4-one 5 . m. p. 263°(MeCN) ; ^{1}H NMR ($CDCl_3$) δ 2.15 (m, 2H, CH_2), 2.7 (t, 4H, CH_2), 3.15 (s, 3H, S-CH_3); ^{13}C NMR ($CDCl_3$) δ 17.38; 18.01; 35.24; 35.49; 112.6; 123.81; 136.28; 156.59; 161.46; 191.09; Anal. Calcd. for $C_{10}H_9NOS_2$: C, 53.81; H, 4.03; N, 6.27. Found: C, 53.99; H, 4.21; N, 6.42.

1-Ethoxycarbonyl-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-one 6 . m. p. 110°(SiO_2, Et_2O) ; ^{1}H NMR ($CDCl_3$) δ 1.6 (t, 3H, CH_3), 2.2 (m, 2H, CH_2), 2.5 (t, 2H, CH_2), 2.65 (s, 3H, S-CH_3), 3.25 (t, 2H, CH_2), 4.15 (q, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 14.36; 18.07; 22.88; 26.22; 38.52; 60.95; 121.88; 131.26; 151.32; 159.59; 161.61; 194.22; Anal. Calcd. for $C_{12}H_{14}O_3S_2$: C, 53.33 H, 5.18. Found: C, 53.19; H, 4.93.

3-Methylthio1-phenyl-5,6,7,8-tetrahydro benzo[c]thiophene 4-one 7 . m. p. 121°(Et_2O) ; ^{1}H NMR ($CDCl_3$) δ 2.2 (m, 2H, CH_2), 2.5 (t, 2H, CH_2), 2.65 (s, 3H, S-CH_3), 3.25 (t, 2H, CH_2), 7.1 (m, 2H, Ar-H), 7.3 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.14; 19.88; 36.87; 36.95; 122.53; 128.75; 129.49; 130.51; 131.62; 139.28; 149.27; 172.16; 193.58; Anal. Calcd. for $C_{15}H_{14}OS_2$: C, 65.69 H, 5.10. Found: C, 65.79; H, 4.91.

1-Ethoxycarbonyl-6,6-dimethyl-3-methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-one 8. m.p. 151° (MeCN);^{1}H NMR ($CDCl_3$) δ 1.65 (t, 3H, CH_3), 2.4 (s, 2H, CH_2), 2.65 (s, 3H, S-

C$\underline{H}_3$), 3.15 (s, 2H, C$\underline{H}_2$), 4.15 (q, 2H, C$\underline{H}_2$); ^{13}C NMR ($CDCl_3$) δ 14.35; 17.92; 28.26; 34.12; 39.71; 50.07; 60.91; 122.39; 130.37; 150.37; 158.93; 161.51; 193.72; Anal. Calcd. for $C_{14}H_{18}O_3S_2$: C, 62.40 H, 6.76. Found: C, 62.29; H, 6.98.

3-Methylthio-4,5,6,7-tetrahydro benzo[c]thiophene-4-one **9**.

Compound **6** (5.4g, 0.02 mol) is refluxed for 2 h with sodium hydroxyde (1g, 0.025 mol) in ethanol (150 mL). After removal of the solvent, the residue is taken up in water, filtered through a pad of celite and acidified. The crude acid is filtered and dried overnight. The crude acid **10** is then decarboxylated by refluxing in quinoline (5 mL quinoline for 1g acid) in presence of copper bronze (0.1g for 1g acid) for 45 min. After cooling to room temperature, the solution is poured into 50% HCl and stirred for 1 h. Methylene chloride is added and the solution is filtered. The organic layer is then separated, washed with water, dried with sodium sulfate and concentrated. Compound **9** is purified by column chromatography (petroleum ether).

3-Methylthio-4,5,6,7-tetrahydro-1-benzo[c]thiophene4-one-1-carboxylic acid **10**
m. p. 245°; ^{1}H NMR (DMSO) δ 2.35 (m, 2H, C$\underline{H}_2$), 2.7 (t, 2H, C$\underline{H}_2$), 2.85 (s, 3H, S-C$\underline{H}_3$), 2.95 (t, 2H, C$\underline{H}_2$), 5.6 (Br s, 1H, OH).

3-Methylthio-5,6,7,8-tetrahydro benzo[c]thiophene-4-one **9** ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2H, C$\underline{H}_2$), 2.5 (t, 2H, C$\underline{H}_2$), 2.55 (s, 3H, S-C$\underline{H}_3$), 2.75 (t, 2H, C$\underline{H}_2$), 6.70 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.58; 23.03; 24.44; 28.82; 129.46; 130.79; 141.0; 190.25; Anal. Calcd. for $C_9H_{10}OS_2$: C, 65.06; H, 6.02 Found: C, 64.98; H, 5.93.

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