Reactions of Methyl 3-Hydroxythiophene-2-carboxylate. Part 4. Synthesis of Methyl 5-Azolyl-3-hydroxythiophene-2-carboxylates

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The indirect introduction of an azolyl group in position 5 of compound **1** by an easy two-step procedure taking place at room temperature is described. A similar procedure yields the 4-chloro derivatives of these 5-azolyl compounds. The same method is applied for the introduction of a 5-azido group and from the 5-azido compounds, 5-*v*-triazolyl derivatives are obtained by a known method.

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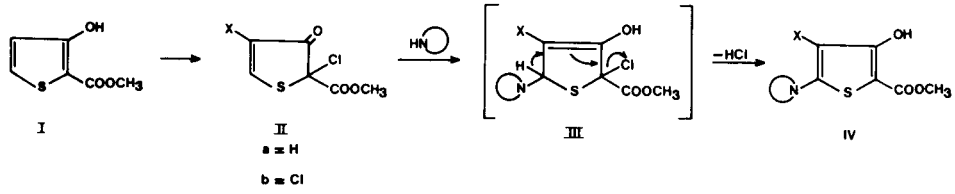
Azoles (pyrazole, imidazole and triazole) and hydrazoic acid are known to add to activated double bonds [1]. The α,β-enone system of compounds **II**, easily obtained of **I** by chlorination, has already been shown to add different compounds (alcohols, mercaptanes, hydrogen chloride, sulphinic acids) to yield the corresponding 5-substituted methyl 3-hydroxythiophene-2-carboxylates [2,3,4] as final products. In this work, the reaction of compounds **II** with different azoles was attempted under a variety of experimental conditions. It was found that by reacting **II** with 2 molar equivalents of pyrazole, 1,2,4-triazole, indazole and benzotriazole in acetic acid solution at room temperature for two days, pure or near pure compounds nicely crystallized in acceptable overall yields from **1** were obtained. The compounds obtained were shown to have structure **IV**, resulting (Scheme 1) from 1,4-addition of the azole to **II** followed by spontaneous loss of hydrogen chloride by a γ-elimination, which is taken off by the azole in excess, thus restoring the thiophene system. Imidazole and benzimidazole reacted very slowly with **II** under these conditions, but substitution of chloroform for acetic acid led to the corresponding compounds **IV**, although in lower yields. Tetrazole did not react with compounds **II**.

Since 1,2,3-triazole is not a commercial product, its reaction with **II** was not tested. However, an indirect approach in order to obtain 5-*v*-triazolyl derivatives of type **IV** was tried (Scheme II).

Hydrazoic acid, generated from sodium azide in acetic acid, reacted in this solvent with compounds **II** to give, by the above described mechanism, the corresponding 5-azido derivaties **V** in good yield. Arylazides are known to react with an array of doublely activated methylene compounds to yield, by 1,3-dipolar cycloaddition, 1-aryl-*v*-triazole derivatives in a regiospecific manner. As an example of the utility of this approach, compounds **V** were

Scheme 1

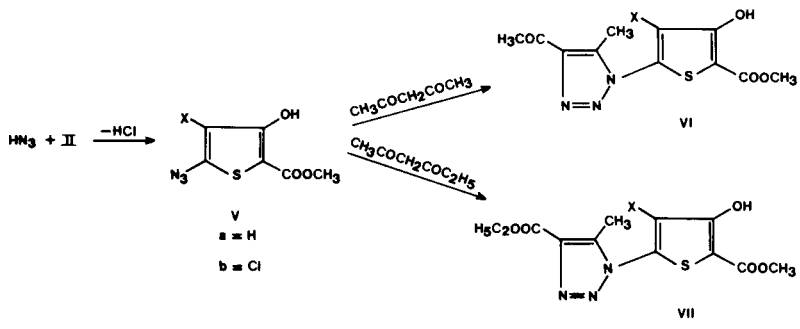


I II III IV

a = H

b = Cl

Scheme II



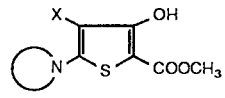
V VI VII

a = H

b = Cl

Table

Methyl 5-Azolyl-3-hydroxythiophene-2-carboxylates



N–	X	Mp (°C)	Yield % (method)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (nujol) ν (cm⁻¹) OH	C=O	¹H-NMR (δ ppm) (deuteriochloroform)
pyrazolyl	H	162-164	75 [a] (A)	$C_9H_8N_2O_3S$	48.21 48.37	3.57 3.71	12.50 12.63	3300,	1680	3.90 (s, 3H, OCH_3), 6.44-6.50 (q, 1H, pyr), 6.67 (s, 1H, thioph), 7.63-7.70 (d, 1H, pyr), 7.73-7.80 (d, 1h, pyr), 9.73 (s, 1H, OH)
pyrazolyl	Cl	135-137	41 [a] (A)	$C_9H_7ClN_2O_3S$	41.77 41.83	2.71 3.00	10.83 11.07	3290,	1680	3.90 (s, 3H, OCH_3), 6.41-6.52 (q, 1H, pyr), 7.63-7.70 (d, 1H, pyr), 8.40-8.45 (d, 1H, pyr), 9.85 (s, 1H, OH)
s-triazol-1-yl	H	166-167	56 [a] (A)	$C_8H_7N_3O_3S$	42.66 42.51	3.11 3.07	18.66 18.48	3310,	1680	3.90 (s, 3H, OCH_3), 6.83 (s, 1H, thioph), 8.00 (s, 1H, triaz), 8.43 (s, 1H, triaz)
s-triazol-1-yl	Cl	171-173	42 [a] (A)	$C_8H_6ClN_3O_3S$	36.99 37.13	2.31 2.56	16.18 16.33		1700	3.90 (s, 3H, OCH_3), 8.10 (s, 1H, triaz), 9.03 (s, 1H, triaz), 9.85 (s, 1H, OH)
imidazolyl	H	112-113	53 [a] (B)	$C_9H_8N_2O_3S$	48.21 48.49	3.57 3.71	12.50 12.39	3290,	1670	3.87 (s, 3H, OCH_3), 6.67 (s, 1H, thioph), 7.03-7.30 (m, 2H, imid), 7.70-7.90 (s, 1H, imid)
imidazolyl	Cl	175-177	10 [b] (B)	$C_9H_7ClN_2O_3S$	41.78 41.93	2.71 2.87	10.83 11.02		1700	3.82 (s, 3H, OCH_3), 7.20 (s, 1H, imid), 7.61 (s, 1H, imid), 8.17 (s, 1H, imid), (dimethylsulfoxide-d_6)
indazol-1-yl	H	183-185	46 [c] (A)	$C_{13}H_{10}N_2O_3S$	56.93 57.09	3.65 3.56	10.22 10.43	3290,	1650	3.87 (s, 3H, OCH_3), 6.87 (s, 1H, thioph), 7.28-7.62 (m, 2H, benz), 7.68-7.86 (m, 2H, benz), 8.15 (s, 1H, pyr), 9.77 (s, 1H, OH)
indazol-1-yl	Cl	124-125	42 [d] (A)	$C_{13}H_9ClN_2O_3S$	50.57 50.65	2.92 2.86	9.08 9.41		1670	3.90 (s, 3H, OCH_3), 7.20-7.50 (m, 3H, benz), 7.68-7.81 (m, 1H, benz), 8.25 (s, 1H, pyr), 9.85 (s, 1H, OH)
benzotriazol-1-yl	H	185-187	72 [a] (A)	$C_{12}H_9N_3O_3S$	52.36 52.08	3.27 3.21	15.27 15.43		1660	3.90 (s, 3H, OCH_3), 7.06 (s, 1H, thioph), 7.30-7.86 (m, 3H, benz), 8.00-8.16 (m, 1H, benz)
benzotriazol-1-yl	Cl	152-155	45 [d] (A)	$C_{12}H_8ClN_3O_3S$	46.53 46.71	2.58 2.73	13.57 13.46		1670	3.90 (s, 3H, OCH_3), 7.40-7.65 (m, 3H, benz), 8.10-8.30 (m, 1H, benz)
benzimidazolyl	H	128-129	22 [d] (B)	$C_{13}H_{10}N_2O_3S$	56.93 57.12	3.65 3.49	10.22 10.31		1680	3.87 (s, 3H, OCH_3), 6.77 (s, 1H, thioph), 7.21-7.40 (m, 2H, benz), 7.53-7.83 (m, 2H, benz), 8.07 (s, 1H, imid)
benzimidazolyl	Cl	168-169	31 [b] (B)	$C_{13}H_9ClN_2O_3S$	50.57 50.71	2.92 3.05	9.08 9.17		1720	3.90 (s, 3H, OCH_3), 7.30-7.55 (m, 3H, benz), 7.75-8.00 (m, 1H, benz), 8.25 (s, 1H, imid)

[a] Recrystallized from acetic acid. [b] Recrystallized from methanol. [c] Recrystallized from chloroform. [d] Recrystallized from 2-propanol.

made to react with acetylacetone and ethyl acetoacetate in the presence of triethylamine at room temperature affording the corresponding compounds **VI** and **VII**.

Finally, it must be pointed out that azolylthiophenes are practically not known, due to obvious synthetic difficulties, the only exception being some described pyrazolylthiophene derivatives [5,6].

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (90 MHz) spectrometer with TMS as internal reference. Chemical shifts are given in δ (ppm) units.

Methyl 5-Azolyl-3-hydroxythiophene-2-carboxylates **IV** (Table).

Method A.

A solution of crude compound **II** [1] (0.02 mole) and the corresponding azole (0.04 mole) in acetic acid (25 ml) was left at room temperature for two days. The crystalline compound obtained was filtered and recrystallized from the appropriate solvent.

Method B.

A solution of crude compound **II** (0.02 mole) and the corresponding azole (0.04 mole) in chloroform (40 ml) was left at room temperature for two days, washed with water and the solvent evaporated *in vacuo*. The residual product was crystallized from the appropriate solvent.

Methyl 5-Azido-3-hydroxythiophene-2-carboxylates **V**.

To a stirred ice-cooled solution of crude compounds **II** (0.05 mole) in 40 ml of acetic acid, sodium azide (3.9 g, 0.06 mole) was added in portions. The solution was left at room temperature for 2 days in a stopped flask. Solvent was evaporated *in vacuo* (40°) and the residue was treated with water and diethyl ether. The dried ethereal solution was evaporated and the residue recrystallized. The following compounds were obtained in this way.

Methyl 5-Azido-3-hydroxythiophene-2-carboxylate **Va**.

This compound had mp 71-72° (chilled methanol), yield 53%; ir (nujol): ν cm^{-1} 3300 (broad) (OH), 2140 (N_3), 1655 (C=O); pmr (deuteriochloroform): 4.05 (s, 3H, OCH_3), 6.50 (s, 1H, thiophene).

Anal. Calcd. for $C_6H_5N_3O_3S$: C, 36.18; H, 2.51; N, 21.10; S, 16.08. Found: C, 36.07; H, 2.63; N, 21.37; S, 16.04.

Methyl 5-Azido-4-chloro-3-hydroxythiophene-2-carboxylate **Vb**.

This compound had mp 88-89° (methanol), yield 67%; ir (nujol): ν cm^{-1} 3250 (OH), 2135 (N_3), 1675 (C=O).

Anal. Calcd. for $C_6H_4ClN_3O3S$: C, 30.85; H, 1.73; N, 17.98; S, 13.72. Found: C, 31.02; H, 1.68; N, 17.85.

Methyl 5-Triazolyl-3-hydroxythiophene-2-carboxylates **VI** and **VII**.

Triethylamine (0.02 mole) was added to a solution of **V** (0.01 mole) and the corresponding cetonic compound (0.015 mole) in 50 ml of methanol. After two days at room temperature, the solvent was evaporated and the residue treated with dilute hydrochloric acid and diethyl ether. The ethereal solution was evaporated and the residue recrystallized. The following compounds were thus obtained.

Methyl 5-(4-Acetyl-5-methyl-*v*-triazol-1-yl)-3-hydroxythiophene-2-carboxylate.

This compound had mp 167-168° (methanol), yield 67%; ir (nujol): ν cm^{-1} 3260 (OH), 1690 (C=O), 1655 (C=O); pmr (deueriochloroform): 2.75 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 7.05 (s, 1H, thiophene), 9.87 (s, 1H, OH).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: C, 46.97; H, 3.91; N, 14.94. Found: C, 47.03; H, 3.83; N, 14.71.

Methyl 5-(4-Ethoxycarbonyl-5-methyl-*v*-triazol-1-yl)-3-hydroxythiophene-2-carboxylate.

This compound had mp 130-131° (methanol), yield 62%; ir (nujol): ν cm^{-1} 1730 (C=O), 1670 (C=O); pmr (deuteriochloroform): 1.33-1.53 (t, 3H, CH_3-CH_2), 2.73 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.30-4.63 (q, 2H, CH_2), 6.90 (s, 1H, thiophene), 9.66 (s, 1H, OH).

Anal. Calcd. for $C_{12}H_{13}N_3O_5S$: C, 46.30; H, 4.18; N, 13.50. Found: C, 46.23; H, 4.01; N, 13.50.

Methyl 5-(4-Acetyl-5-methyl-*v*-triazol-1-yl)-4-chloro-3-hydroxythiophene-2-carboxylate.

This compound had mp 213° dec (toluene, yield 76%; ir (nujol): ν cm^{-1} 3260 (OH), 1690 (C=O), pmr (deuteriochloroform): 2.50 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 9.75 (s, 1H, OH).

Anal. Calcd. for $C_{11}H_{10}ClN_3O_4S$: C, 41.85; H, 3.19; N, 13.31. Found: C, 41.65; H, 3.12; N, 13.52.

Methyl 4-Chloro-5-(4-ethoxycarbonyl-5-methyl-*v*-triazol-1-yl)-3-hydroxythiophene-2-carboxylate.

This compound had mp 102-104° (chilled 2-propanol), yield 73%; ir (nujol): ν cm^{-1} 1740 (C=O), 1655 (C=O); pmr (deuteriochloroform): 1.30-1.40 (t, 3H, CH_3-CH_2), 2.50 (s, 3H, CH_3), 4.30-4.56 (q, 2H, CH_2), 9.75 (s, 1H, OH).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_5S$: C, 41.68; H, 3.50: N, 12.15. Found: C, 41.53; H, 3.42; N, 12.23.

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