The Reaction of Methyl 3-Amino-4-cyano-5-methylthiothiophene-2-carboxylate with DMAD. A New Synthesis of Polyfunctionalized Quinolines

Yoshinori Tominaga, Jiann-Kuan Luo and Raymond N. Castle*

Department of Chemistry, University of South Florida, Tampa, FL 33620-5250 USA

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The reaction of methyl 3-amino-4-cyano-5-methylthiothiophene-2-carboxylate (**2**), which was prepared by the reaction of bis(methylthio)methylenepropanedinitrile (**1**) with methyl thioglycolate followed by dimethyl acetylenedicarboxylate (DMAD) in the presence of potassium carbonate in dimethyl sulfoxide gave the polyfunctionalized quinoline, pentamethyl 4-amino-5-mercaptoquinoline-2,3,6,7,8-pentacarboxylate (**3**). The oxidation of **3** with iodine in DMSO provided the novel ring system in the form of the derivative, pentamethyl 2*H*-isothiazolo[3,4,5-*de*]quinoline-3,4,6,7,8-pentacarboxylate (**4**).

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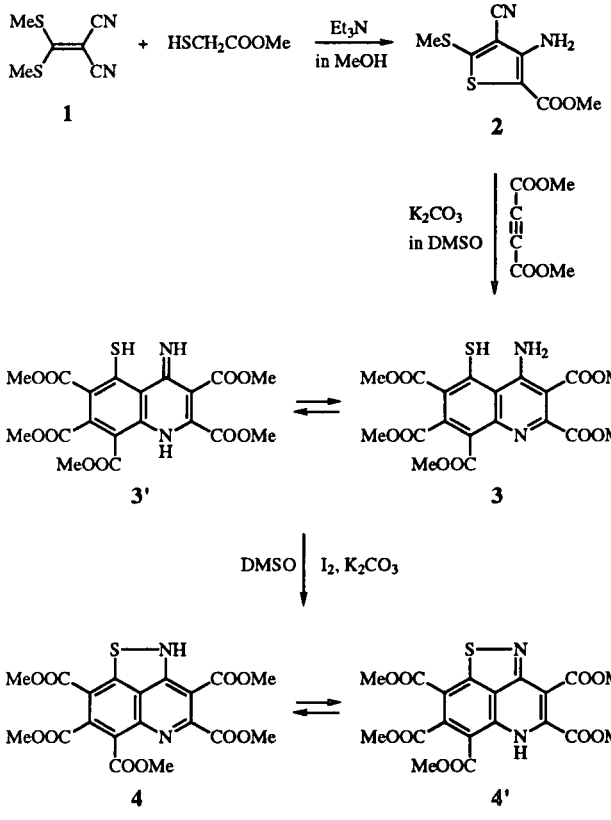
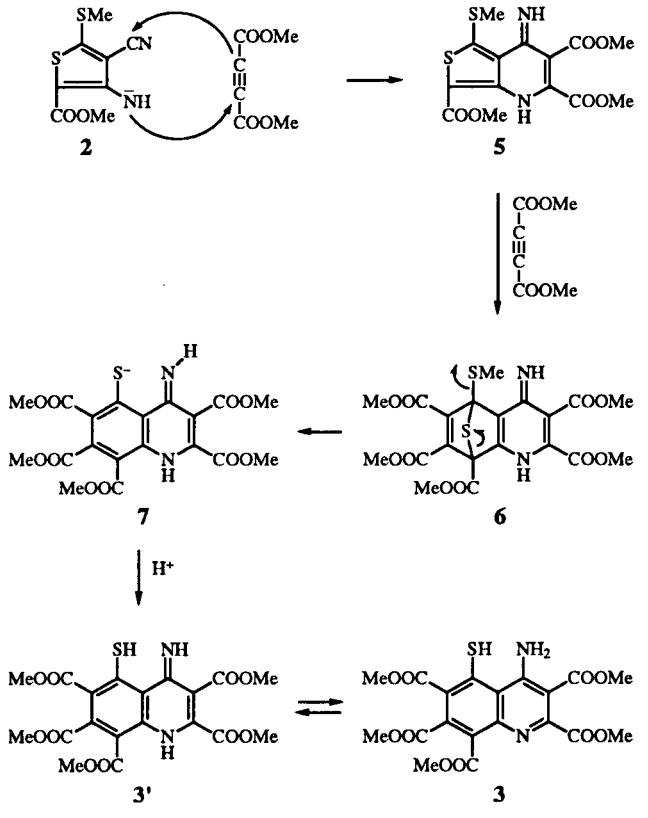
We report the novel synthesis of a polyfunctionalized quinoline using an aminocyanothiophene as the starting substrate. The reaction of malononitrile with carbon disulfide in the presence of sodium hydroxide in DMSO followed by methylation with dimethyl sulfate in one pot to give bis(methylthio)methylenepropanedinitrile (**1**) has been reported [1-4], however our method reported herein provides a better yield (81%) and proceeds with greater facility. The reaction of **1** with methyl thioglycolate in the presence of methanol and triethylamine afforded methyl 3-amino-4-cyano-5-methylthiothiophene-2-carboxylate (**2**) [5] in 84% yield. The cycloaddition [6-12] of **2** with dimethyl acetylenedicarboxylate (DMAD) in the presence of potassium carbonate in DMSO solution provided the unexpected pentamethyl 4-amino-5-mercaptoquinoline-2,3,6,7,8-pentacarboxylate (**3**) (26% yield) [13-14] which may exist as the 4-imino-1,4-dihydro tautomer **3'**. The reaction of **3** or **3'** with iodine in DMSO [15] afforded pentamethyl 2*H*-isothiazolo[3,4,5-*de*]quinoline-3,4,6,7,8-pentacarboxylate (**4**) or its **4'** tautomer in 75% yield, a

Scheme 1



Reaction Pathway



novel heterocyclic ring system.

It is obvious that the reaction pathway involves extrusion of the thiophene ring sulfur atom. Compound **2** reacts with the first equivalent of DMAD to produce **5**, trimethyl 7-imino-1-methylthio-4,7-dihydrothieno[3,4-*b*]-pyridine-3,5,6-tricarboxylate which was too labile for isolation and reacts *in situ* with a second equivalent of DMAD to give the epithio intermediate **6**, which upon loss of the 5-methylthio group and ring opening of the epithio thiophene moiety affords the anion **7**. Protonation of **7** by the solvent provides **3'** in equilibrium with the product **3**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT1100 spectrometer as potassium bromide discs and frequencies are expressed in cm^{-1}. The ^1H-nmr spectra were obtained on a JEOL FX-90Q spectrometer in the solvent indicated with TMS as the internal standard and chemical shifts are reported in ppm (δ) and J values are in Hz. Elemental analyses were preformed by M-H-W Laboratories, Phoenix, AZ.The electron impact mass spectra were acquired by the Midwest Center for Mass Spectroscopy at the University of Nebraska-Lincoln, using a Kratos MS-50 mass spectrometer which has Nier-Johnson geometry.

Bis(methylthio)methylenepropanedinitrile (**1**).

A 1 liter three-neck round-bottom flask was fitted with a mechanical stirrer and two dropping funnels. The flask was charged with a solution of 66.06 g (1 mole) of malononitrile in 500 ml of dimethyl sulfoxide and this solution was maintained at 10-15°. One half of a 20% sodium hydroxide solution (sodium hydroxide, 80 g, 2 moles) was added to the above solution with stirring and cooling at 10-15°. The mixture was stirred for 10 minutes. Then 38.1 g (0.5 mole) of carbon disulfide was added slowly to the mixture with stirring at 10-15° over a period of 30 minutes. Stirring was continued for an additional 20 minutes at the same temperature. The remaining one half of the solution of sodium hydroxide was added to the reaction mixture and stirring was continued for 10 minutes. Then 38.1 g (0.5 mole) of carbon disulfide was again slowly added to the above reaction mixture and stirring was continued for 1 hour at the same temperature. To the reaction product in solution of dimethyl sulfoxide, 252.2 g (2 moles) of dimethyl sulfate was slowly added dropwise while the reaction mixture was stirred vigorously at 10-20°. Stirring was continued for 30 minutes. After stirring for 2 hours at room temperature, the reaction mixture was poured into 2 liters of ice-water and then was allowed to stand for 1 hour. The resulting precipitate was collected by filtration and washed several times with water. After air drying, the product was recrystallized from methanol to give 138.0 g (81%) of colorless needles, mp 81-82°, lit mp [3] 81°; ir (potassium bromide): 2211 (CN) cm^{-1}.

Methyl 3-Amino-4-cyano-5-methylthiothiophene-2-carboxylate (**2**).

A mixture of 8.50 g (50 mmoles) of bis(methylthio)-methylenemalononitrile, 5.3 g (50 mmoles) of methyl thioglycolate, 5 ml of triethylamine, and 200 ml of methanol was refluxed for 1 hour. After cooling, the resulting precipitate was collected by filtration to give 9.62 g (42.2 mmoles, 84%) of tan needles. An analytical sample was recrystallized from methanol to give colorless needles, mp 202-206°; ir (potassium bromide): 3425, 3335 (NH_2), 2219 (CN), 1676 (CO) cm^{-1}.

Anal. Calcd. for $C_8H_8N_2O_2S_2$: C, 42.09; H, 3.53; N, 12.27; S, 28.09. Found C, 42.18; H, 3.61; N, 12.39; S, 28.13.

Pentamethyl 4-Amino-5-methylthioquinoline-2,3,6,7,8-pentacarboxylate (**3**).

A mixture of 6.84 g (30 mmoles) of **2**, 10 g of potassium carbonate, 7.0 g (150 mmoles) of dimethyl acetylenedicarboxylate (DMAD), and 200 ml of dimethyl sulfoxide was stirred 48 hours at room temperature. The reaction mixture was poured into 500 ml of water. The precipitate that appeared was removed by filtration. This compound was the starting material **2**. The filtrate was acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration. After air drying, the product was recrystallized from benzene-methanol (1:3) to give 3.59 g (7.7 mmoles, 26%) of red needles, mp 208-210°; ir (potassium bromide): 3363, 3335 (NH or SH), 1754, 1748, 1743, 1735, 1730, 1725, 1707, 1681 (COOMe),1622 (C=C), 1434, 1290, 1257, 1137, 1093 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.98 (s, 3H, OMe), 3.99 (s, 3H, OMe), 4.02 (s, 3H, OMe), 9.03 (bs, 1H, NH); ms: FAB m/z 466 (M^+, 78), 465 (M^+-1, 100), 464 (M^+-2, 85), 433 (M^+-33, 73), 401 (82), 373 (45), 343 (52), 307 (68), 289 (65).

Anal. Calcd. for $C_{19}H_{18}N_2O_{10}S$, 466.42: C, 48.92; H, 3.89; N, 6.01; S, 6.87. Found: C, 49.15; H, 3.87; N, 5.97; S, 7.00.

Pentamethyl 2*H*-Isothiazolo[3,4,5-*de*]quinoline-3,4,6,7,8-pentacarboxylate (**4**).

A mixture of 0.093 g (0.2 mmole) of **3**, 0.10 g of iodine, and 20 ml of dimethyl sulfoxide was stirred for 12 hours. After the reaction, the reaction mixture was poured into 100 ml of water and then basified with sodium bicarbonate. The precipitate that appeared was collected by filtration to give 70 mg (0.15 mmole, 75%) of tan crystals. An analytical sample was recrystallized from benzene-methanol (1:2) to give tan prisms, mp 280-284°; ir (potassium bromide): 3458 (NH), 1753 (CO), 1748, 1743, 1736, 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.30 (s, 2/3H, OMe), 3.62 (s, 2/3H, OMe), 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.98 (s, 3H, OMe), 4.03 (s, 2/3H, OMe), 4.09 (s, 2/3H, OMe).

Anal. Calcd. for $C_{19}H_{16}N_2O_{10}S$: C, 49.14; H, 3.47; N, 6.03; S, 6.90. Found: C, 49.30; H, 3.50; N, 6.05; S, 6.87.

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