Synthesis and Characterization 3-Amino-N'-substituted benzylidene-4-cyano-5-(methylsulfonyl) thiophene-2-carbohydrazide derivatives

Satish M. Chavan*
Department of Chemistry, Gokhale Education Society's R.N. Chandak Arts, J.D. Bytco Commerce & N.S. Chandak Science College, Nashik-Pune Road, Nashik-Road-422101, Maharashtra, India,
Affiliated to Savitribai Phule Pune University, Pune-411007.

Abstract:
The reaction of ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **1** gave ethyl 3-amino-4-cyano-5-(methylsufonyl)thiophene-2-carboxylate **2**. The later compound undergoes a series of reactions to give novel 3-amino-N'-substituted benzylidene-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide derivatives.

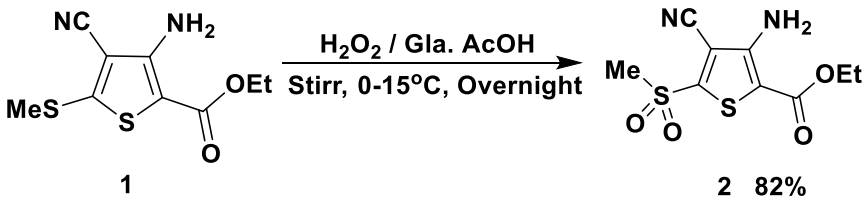
Keywords: Methyl group, thiomethyl group, methylsulfonyl group, thiophene-2-carbohydrazide .

I. INTRODUCTION

Thiophene-based analogs have shown a potential class of biologically active compounds. They play a vital role in medical field for the improvement of advanced compounds with a variety of biological effects. The methyl group is one of the most common group found in organic compounds. Due to the magic methyl effect of the methyl group, it has broad applications in pharmaceutical and many biological processes [1, 2]. Approximately more than 67% of the top-selling drugs contain at least one methyl group [3]. Our interest in sulfonyl compounds, we specifically focus on the methylsulfonyl unit, which is found broadly in drugs [4]. Therefore, presence of the methylsulfonyl group will be highly desirable in the compound. Due to the broad applications of methylsulfonyl-containing compounds in many bioactive molecules and drugs, continuous efforts have been made for the preparation of methylsulfonyl containing compounds [5, 6, 7]. Molecules with the thiophene ring system exhibit many pharmacological properties such as anticancer [8], anti-inflammatory [9], antimicrobial [10], antihypertensive [11], and anti-atherosclerotic properties [12]. For example, nonsteroidal anti-inflammatory drug Suprofen, the antidepressant drug Duloxetine, the antihypertensive Eprosartan and the antipsychotic Olanzapine [13]. The hydrazine-hydrazide derivatives of heterocyclic compounds have marked their importance due to diverse biological properties including antibacterial, antifungal, anticonvulsant, anti-inflammatory, antimalarial and antituberculosis activities [14-26]. On the basis of these literatures, we decided perform oxidation of the in situ generated methylsulfanyl group of ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **1** into the ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate **2** reactions which could be a useful and economic methyl source in the compound.

II. MATERIALS AND METHODS

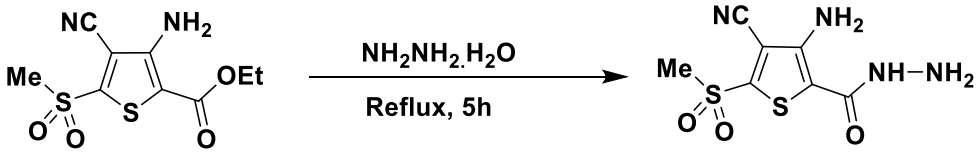
In this research paper we have reported the synthesis of 3-amino-N'-substituted benzylidene -4-cyano-5-(methylsufonyl)thiophene-2-carbohydrazide derivatives **4a-f** from ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate **2**. The compound 2 was obtained from ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **1** which was synthesized as described in our previous paper [27].



1 2 82%

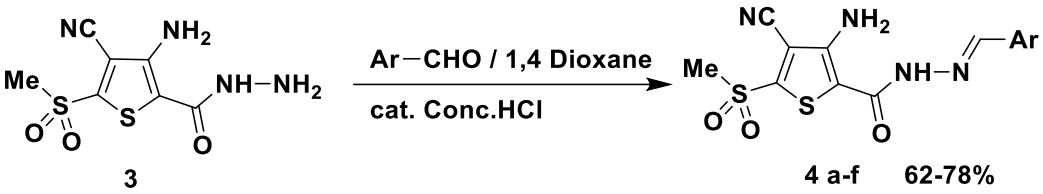
Scheme 1: Synthesis of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate, 2

Synthesis of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate **2** was achieved by overnight stirring ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **1** in 3:1 mixture of glacial acetic acid and hydrogen peroxide at 0-5° C with 82 % yield. ***(Scheme 1)***



2 3 70%

Scheme 2: Synthesis of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide, 3



Scheme 3: Syntheses of 3-Amino-N'- substituted benzylidene- 4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide derivatives, 4(a-f)

Table 1: Compounds 4(a-f) Practical Yield

Comp. No.	Ar	Yield (%)	M.P. (ºC
4a	-C_6H_5	72	152
4b	3Cl-C_6H_4	69	164
4c	3NO_2-C_6H_4	77	158
4d	4-Me-C_6H_4	77	162
4e	4-Cl-C_6H_4	72	154
4f	4-NO_2-C_6H_5	74	148

The compound 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide **3** was synthesized from compound **2** after it was reacted with hydrazine hydrate at room temperature for 2 hrs ***(Scheme 2)***. The progress of reaction was monitored by TLC (TLC Check, Hexane: Ethylacetate, 8:2). Then reaction mass was refluxed for 3-5 hr to yield the product in good yield (70 %). The structures of both products were elucidated by spectral and analytical methods. For example, IR spectrum of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate **1** showed stretching frequencies at 3437, 3336, 3269, 2981, 2218, 1666, 1411, 1260, 1073 cm^{-1} which were assigned for NH, CN, COOEt and SO_2 groups.The ^1H NMR spectrum of compound **2** showed triplet at δ 1.33-1.36, singlet at δ 3.04, quartet at δ 4.27-4.32, singlets at δ 5.76 - 5.86 ppm were assigned to CH_3, SO_2CH_3, OCH_2, NH_2 groups.IR spectrum of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide 2 showed stretching frequencies at 3441, 3336, 3197, 2981, 2218, 1670, 1411, 1195, 1076 cm^{-1} which were assigned for NH_2, NH, CN, COOEt and SO_2 Me groups. The ^1H NMR spectrum of compound **3** showed singlet at δ 2.68, singlet at δ 6.77, singlets at δ 8.16 and singlet at δ 9.46 ppm were assigned to SO_2CH_3, NH_2 groups, NH and NH_2 of hydrazide group. The ^1H NMR spectrum of compound **4a** showed singlet at δ 3.07 for SO_2CH_3, singlet at δ 6.69 for -NH_2, multiplets at δ 7.59-7.64 and δ 7.99-8.01 for aromatic protons (ArH) and singlet at δ 8.39 for =CH and singlet at δ 11.69 ppm NH of hydrazide group.

III. EXPERIMENT AND RESULT

Synthesis of ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate, 2

Ethyl 3-amino-4-cyano-5- (methylthio) thiophene-2-carboxylate, **1** (2.42 g, 0.01 mol) dissolved in 10 ml ethanol and stirred at the 0ºC temperature for 20-30 minutes. The mixture of H_2O_2: Glacial CH_3COOH (3:7) was added dropwise to the reaction mixture and stirred at the temperature of 0-15ºC for 1-2 hr and further stirring was continued overnight. (TLC check, n-hexane: ethyl acetate, 7:3). The excess ethanol evaporated by vacuum and the solid separated was filtered and washed with little ethanol, dried and recrystallized from ethanol: DMF (9.8: 0.2) as purple powder [28, 29].

Yield 82%, 1.972 g, M.P. 152 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3437-3336 (NH_2), 2978 (CH), 2218 (CN), 1666 (C=O), 1608, 1535 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^1H NMR (500 MHz $CDCl_3$) 1.32 – 1.38 (t, J=7 Hz, 3H, CH_3), 3.04 (s, 3H, SO_2CH_3), 4.26 - 4.37 (q, J=7 Hz & J=14 Hz, 2H, OCH_2,) 5.86 (s, 2H, NH_2); MS m/z (%): 276.01 (M+1,100), 278.00 (13.6), 277.01 (12.4); *Anal. Calcd.for* $C_9H_{10}N_2O_4S_2$: C, 39.41; H, 3.67; N, 10.21; Found: C, 39.11; H, 3.58; N, 10.14.

Synthesis of 3-Amino-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide, 3

Ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate, **2** (0.65g, 2.5 mmol) was dissolved in 10 ml ethanol and stirred at the room temperature. Hydrazine hydrate (0.25 g, 0.3 ml, 5 mmol) was added dropwise and the reaction mixture refluxed for 7-8 hr. Reaction was monitored by TLC (TLC check, n-hexane: ethyl acetate, 7:3). The excess ethanol evaporated by vacuum and the solid separated was washed with little ethanol. The solid product obtained was isolated by filtration under vacuum, dried and recrystallized from ethanol: DMF (9.8: 0.2) as faint purple powder [30].

Faint purple powder; Yield 70%, 1.23 g; M.P. 160°C; IR (Platinum ATR, ν_{max} cm^{-1}): 3441-3336(2NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^1H NMR (500 MHz $CDCl_3$) 3.07 (s, 3H, $SOCH_3$), 4.61 (s, 2H, NH_2), 6.65 (s, 2H, NH_2), 9.46 (s, 1H, NH); *Anal. Calcd.for* $C_7H_8N_4O_3S_2$ (Mol. Wt.260.29): C, 32.30; H, 3.10; N, 21.52; Found: C, 32.38; H, 3.21; N, 21.62.

3-Amino-N'-benzylidene-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide, 4a

Benzaldehyde (1.21 g, 0.01 mol) was added to a solution of 3-Amino-4-cyano-5-(methylsulfonyl) thiophene-2-carbohydrazide, **3** (0.99 g, 0.01 mol) in 1,4-dioxane (20 mL). 1-2 drops of Conc. HCl were added as catalyst. The reaction mixture was heated under reflux for 2 h. After completion of reaction (TLC check, n-hexane: ethyl acetate, 7:3), it was poured onto an ice/water mixture. The formed solid product was collected by filtration, washed with ethanol and dried to give faint purple powder [31].

Faint purple powder; Yield 72%, 1.23 g; M.P. 152°C; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^1H NMR (500 MHz

$CDCl_3$) 3.07 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.59-7.64 (m, J=8 & 1.5 Hz, 3H, ArH),7.99-8.01(m, J=8 Hz & 1.5 Hz, 2H, ArH), 8.39 (s, 1H, =CH), 11.69 (s, 1H, NH); *Anal. Calcd.for* $C14H_{12}N_4O_3S_2$ (Mol. Wt.348.40): C, 48.27; H, 3.47; N, 16.08; Found: C, 48.39; H, 3.44; N, 16.11

3-Amino-N'-(3-chlorobenzylidene)-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide, 4b

Yield 69%, 1.262 g, m.p.164 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^{1}H NMR (500 MHz $CDCl_3$) 3.07 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.51 (m, J=8 & 8 Hz, 1H, ArH), 7.56 (m, J=8, 1.5 & 1.5 Hz, 1H, ArH),7.64 (m, J=8,1.5 & 1.5 Hz, 3H, ArH),7.99 (m, J=1.5 Hz & 1.5 Hz, 1H, ArH), 8.42 (s, 1H, =CH), 11.69 (s, 1H, NH); *Anal. Calcd.for* $C_{14}H_{12}ClN_4O_3S_2$ (Mol. Wt.382.84): C, 43.92; H, 2.90; N, 14.63; Found: C, 43.91; H, 2.93; N, 14.64

3-Amino-4-cyano-5-(methylsulfonyl)-N'-(3-nitrobenzylidene)thiophene-2-carbohydrazide,4c

Yield 77%, 1.36 g, m.p.158 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^{1}H NMR (500 MHz $CDCl_3$) 3.07 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.73 (m, J=8 & 8 Hz, 1H, ArH), 8.11 (m, J=8, 1.5 & 1.5 Hz, 2H, ArH), 8.49 (s, 1H, =CH), 8.54 (dd, 1.5 & 1.5 Hz, 1H, ArH), 11.69 (s, 1H, NH); *Anal. Calcd.for* $C_{14}H_{11}N_5O_5S_2$ (Mol. Wt.393.39): C, 42.74; H, 2.82; N, 17.80; Found: C, 42.71; H, 2.87; N, 17.78

3-Amino-4-cyano-N'-(4-methylbenzylidene)-5-(methylsulfonyl)thiophene-2-carbohydrazide, 4d

Yield 77%, 1.391 g, m.p.156 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^{1}H NMR (500 MHz $CDCl_3$) 2.43 (s, 3H, CH_3), 3.07 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.48 (d, J=8 Hz, 2H, ArH), 7.81 (d, J=8 Hz, 2H, ArH), 8.38 (s, 1H, =CH), 11.69 (s, 1H, NH); *Anal. Calcd.for* $C_{15}H_{14}N_4O_3S_2$ (Mol. Wt.362.42): C, 49.71; H, 3.89; N, 15.48; Found: C, 49.71; H, 3.87; N, 15.50

3-Amino-N'-(4-chlorobenzylidene)-4-cyano-5-(methylsulfonyl)thiophene-2-carbohydrazide, 4e

Yield 72%, 1.428 g, m.p.162 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^{1}H NMR (500 MHz $CDCl_3$) 3.07 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.48 (m, J=8 & 1.5 Hz, 2H, ArH), 7.84 (m, J=8, 1.5 Hz, 2H, ArH), 8.36 (s, 1H, =CH), 11.65 (s, 1H, NH); *Anal. Calcd.for* $C_{14}H_{12}ClN_4O_3S_2$ (Mol. Wt.382.84): C, 43.92; H, 2.90; N, 14.63; Found: C, 43.91; H, 2.93; N, 14.64

3-Amino-4-cyano-5-(methylsulfonyl)-N'-(4-nitrobenzylidene)thiophene-2-carbohydrazide,4f

Yield 74%, 1.421 g, m.p.148 ºC; IR (Platinum ATR, ν_{max} cm^{-1}): 3440 (NH_2), 3197 (NH), 2978 (CH), 1670 (C=O), 1608, 1539 (aromatic C=C), 1300 (C-O stretching), 802 (=C-H twisting), 759 (aromatic C-H bending); ^{1}H NMR (500 MHz $CDCl_3$) 3.08 (s, 3H, $SOCH_3$), 6.69 (s, 2H, NH_2), 7.97 (d, J=8 & 1.5 Hz, 2H, ArH), 8.30 (d, J=8, 1.5 Hz, 2H, ArH), 8.43 (s, 1H, =CH), 11.69 (s, 1H, NH); *Anal. Calcd.for* $C_{14}H_{11}N_5O_5S_2$ (Mol. Wt.393.39): C, 42.74; H, 2.82; N, 17.80; Found: C, 42.71; H, 2.87; N, 17.78

IV. CONCLUSION

In this research paper we have reported the synthesis of novel 3-amino-N'-substituted benzylidene -4-cyano-5-(methylsufonyl)thiophene-2-carbohydrazide derivatives from ethyl 3-amino-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate.

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