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A facile synthesis of 10-methoxy-4,8-dinitro-6*H*-benzothieno[2,3-*c*]chromen-6-one

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Abstract: 3-Methoxy-5-nitrobenzaldehyde undergoes Knoevenagel reaction with malonic acid to give 3-methoxy-5-nitrocinnamic acid (**I**). Treatment of **I** with thionyl chloride yielded 3-chloro-5-methoxy-7-nitrobenzo[*b*]thiophene-2-carbonyl chloride (**II**) in 45 % yield. The reaction of **II** with 2-nitrophenol in benzene gave 2-nitrophenyl 3-chloro-5-methoxy-7-nitrobenzo[*b*]thiophene-2-carboxylate (**IIIa**) in 65 % yield. Finally, dehydrochlorinative photocyclization of **IIIa** in acetone in the presence of the base triethylamine afforded 10-methoxy-4,8-dinitro-6*H*-benzothieno[2,3-*c*]chromen-6-one (**IVa**). Thus, a series of derivatives **IVa-i** were synthesized in excellent yields. The structures of the obtained products were characterized by IR and ^{1}H-NMR spectroscopy, as well as elemental analysis. Their purity was ascertained by chromatographic analysis. All the compounds were tested for their antibacterial activity against *S. aureus*, *E. coli*, *B. subtilis* and *S. typhosa*.

Keywords: coumarin, cinnamic acid, antibacterial activity, photolytic cyclization.

INTRODUCTION

Coumarin is a simple oxygen-containing heterocycle present in meliot and in tonca beans. It is the odoriferous principle of wood ruff which led to its wide-spread use as a perfumery chemical in industry.[1] Coumarin derivatives have also found applications as fluorescent dyes,[2] CNS depressants,[3] antitumor agents,[4] HIV proliferators,[5] antifungals,[6] anticoagulents,[7] antibacterials[8] and insecticides.[9] In view of a greater demand for potent pharmacologically active agents, it was our goal to develop a cheap and valuable facile synthesis of therapeutically significant 10-methoxy-4,8-dinitro-6*H*-benzothieno[2,3-*c*]chromen-6-one (Scheme 1).

The synthetic route chosen involves the reaction of 3-methoxy-5-nitrobenzaldehyde with malonic acid in the presence of a base, piperidine in pyridine, also a base, as solvent to give 3-methoxy-5-nitrocinnamic acid (**I**)[10] in 75 % yield. **I** on refluxing with thionyl chloride containing a few drops of pyridine for 15 h undergoes ring cyclisation to give 3-chloro-5-methoxy-7-nitrobenzo[*b*]thiophene-2-carbonyl chloride (**II**) in 45 % yield (Scheme 2). The IR spectrum of **II** shows the absence of –COOH band which further confirms its structure.

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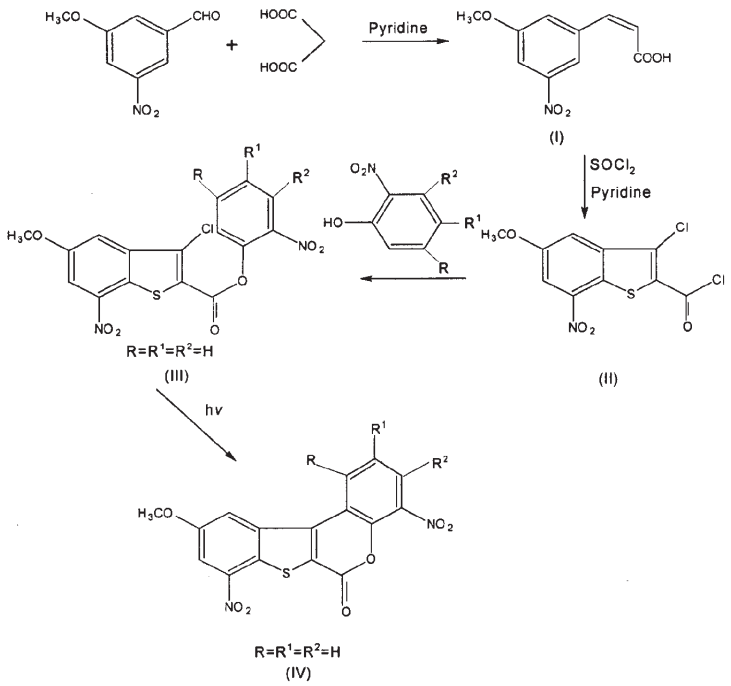


Scheme 1.

On condensation with 2-nitrophenol in the presence of a base, potassium carbonate, **II** gives 2-nitrophenyl 3-chloro-5-methoxy-7-nitrobenzo[*b*]thiophenecarboxylate (**IIIa**) in 65 % yield. Photocyclization *via* dehydrochlorination of **IIIa** in acetone in the presence of triethylamine afforded a cyclised product in 45 % yield, which was characterised as 10-methoxy-4,8-dinitro-6*H*-benzothieno[2,3-*c*]chromen-6-one (**IVa**) [Scheme 1].

Compounds **IVa-i** were synthesized by the condensation of different substituted phenols with **II** and subsequent photocyclisation.

Antibacterial activity

In view of antimicrobial activities of some coumarin derivatives, it was of interest to incorporate this moiety into various heterocyclic molecules with the hope that the resulting compounds may exhibit enchanced activity. Hence, the prepared compounds were tested *in vitro* for their antibacterial activity against *S. aureus*, *E.coli*, *B. subtilis* and *S. typhosa* using concentrations of 2 and 5 μg/ml by the ditch plate technique.[11] The tested compounds showed a much higher inhibitory effect on the growth of bacteria (Table I).

TABLE I. Antibacterial activity data of compounds **IVa-i**

Compound	*S. aureus*		*E. coli*		*B. subtilis*		*S. typhosa*	
	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml
IVa	+	+	–	–	–	+	–	+

TABLE I. Continued

Compound	*S. aureus*		*E. coli*		*B. subtilis*		*S. typhosa*	
	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml	2 μg/ml	5 μg/ml
IVb	–	+	+	++	–	+	+	++
IVc	–	+	+	+	+	+	–	–
IVd	+	+	+	+	+	++	+	+
IVe	+	+	–	–	–	+	–.	+
IVf	–	+	+	+	–	+	+	+
IVg	+	+	–	–	+	+	–	+
IVh	–	–	+	–	–	–	+	–
IVi	+	–	–	+	+	–	–	+

Inhibition zone diameter: (–) < 11 mm [inactive]; (+) 11–14 mm [weakly active]; (++) 15–18 mm [moderately active]

EXPERIMENTAL

All the melting points were taken in open capillaries on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by thin-layer chromatography. IR spectra were recorded in KBr on a Shimadzu 8201PC FTIR spectrophotometer, ^{1}H-NMR spectra on a Bruker WM 400 Spectrometer (500 MHz, $CDCl_3$, δ in ppm) using TMS as internal standard and mass spectra on a Hitachi RMU GL mass spectrometer at 70 eV.

3-Methoxy-5-nitrocinnamic acid ***(I)***

A mixture of 3-methoxy-5-nitro-benzaldehyde (5 g, 0.027 mol), malonic acid (3.1 g, 0.03 mol), pyridine (50 cm^3) and piperidine (2.5 cm^3) was refluxed for 3 h. The resulting solution was poured into ice-water. The precipitated product was separated by filtration, dried and crystallised from ethanol to give **I** (4.6 g, 75 %), m.p. 241 ºC (Found: C, 53.76; H, 3.95; N, 6.20. $C_{10}H_9NO_5$ requires: C, 53.81; H, 4.01; N, 6.28 %); IR: 3350 (–OH stretching), 3080 (aromatic C–H stretching), 2800 aliphatic C–H stretching), 1770 (C=O stretching), 1610, 1575, 1490 (C=C stretching), 1525, 1360 (–NO_2 stretching), 1380 (C–H bending).

3-Chloro-5-methoxy-7-nitrobenzo[b]*thiophene-2-carbonyl chloride* ***(II)***

A solution of **I** (2 g, 0.01 mol) in 1 cm^3 pyridine was heated to 90–95 ºC and 10 cm^3 thionyl chloride was added dropwise. The mixture was heated for a further 15 h. The excess thionyl chloride was removed by distillation and the black gummy residue was taken up in hot hexane (50 cm^3) and decanted. On cooling a yellow solid was obtained which was crystallised from methanol to give **II** (0.8 g, 45 %), m.p. 206 ºC (Found: C, 39.17; H, 1.55; N, 4.63. $C_{10}H_5Cl_2NO_4S$ requires: C, 39.22; H, 1.63; N, 4.58 %); IR: 3020 (aromatic C–H stretching), 2900 (aliphatic C–H stretching), 1770 (C=O stretching), 1610, 1575, 1490 (C=C stretching), 1525, 1360 (–NO_2 stretching), 1380 (C–H bending).

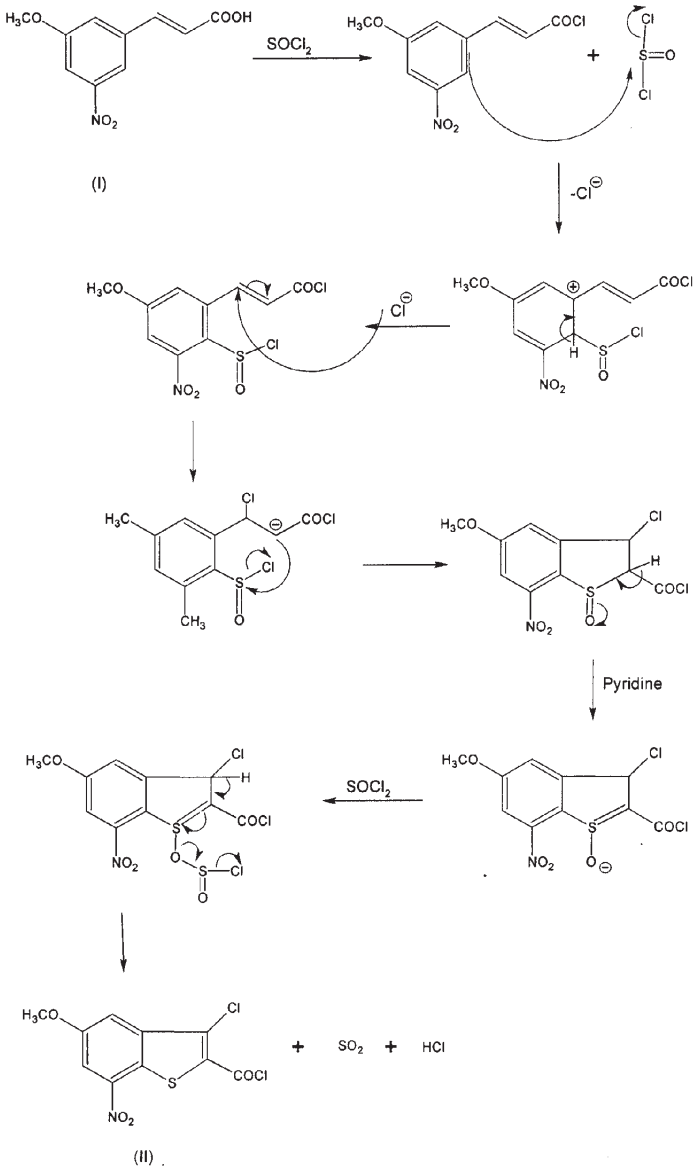
^{1}H-NMR ($CDCl_3$): 3.8 (*s*, 3H, –OCH_3), 7.2 (*dd*, 1H, Ar–H), 7.8 (*dd*, 1H, Ar–H).

Mass *m/z*: 306 (57), 291 (100), 245 (12), 209 (52), 181 (63), 153 (21), 107 (18), 93 (76), 78 (82).

2-Nitrophenyl 3-chloro-5-methoxy-7-nitrobenzo[b]*thiophene-2-carboxylate* ***(IIIa)***

A mixture of **II** (2 g, 0.005 mol), *o*-nitrophenol (0.77 g, 0.006 mol) in acetone (50 cm^3) in the presence of potassium carbonate (2 g) was refluxed on a water-bath for 5 h. The reaction mixture was cooled and fil-

Mechanism



Scheme 2.

tered. The filtrate on distillation under reduced pressure afforded a solid which was crystallised from methanol to give **IIIa** (1.7 g, 65 %), m.p. 187 ºC (Found: C, 47.03; H, 2.26; N, 6.78. $C_{16}H_9ClN_2O_7S$ requires: C, 47.00; H, 2.20; N, 6.85 %); IR: 3050 (aromatic C–H stretching), 2980 (aliphatic C–H stretching), 1770 (C=O stretching), 1610, 1575, 1490 (C=C stretching), 1525, 1360 (–NO_2 stretching), 1380 (C–H bending).

^{1}H-NMR ($CDCl_3$): 3.8 (*s*, 3H, –OCH_3), 6.8–8.2 (*m*, 6H, Ar–H).

Mass *m*/*z*: 409 (51), 394 (75), 348 (4), 306 (100), 302 (69), 291 (15), 245 (72), 211 (70), 182 (65), 150 (68), 102 (10), 93 (21), 78 (56).

*10-methoxy-4,8-dinitro-6*H-*benzothieno*[*2,3*-c]*chromen-6-one* (***IVa***)

A stirred solution of **III** (1 g, 0.003 mol) and triethylamine (0.5 cm^3) in acetone (25 cm^3) was irradiated with a 450 W Hanovia medium pressure mercury lamp for 4 h. The acetone solution was evaporated under reduced pressure and the residue was washed with water, dried and crystallized from ethanol to give **IV** (0.2 g, 45 %), m.p. 253 ºC (Found: C, 51.58; H, 2.20; N, 7.50. $C_{16}H_8N_2O_7S$ requires: C, 51.61; H, 2.15; N, 7.53 %); IR: 3020 (aromatic C–H stretching), 2950 (aliphatic C–H stretching), 1750 (C=O stretching), 1620, 1585, 1500, 1440 (C=C stretching), 1530, 1350 (–NO_2 stretching), 1390 (C–H bending), 1110 (C–O bending).

^{1}H-NMR ($CDCl_3$): 3.8 (*s*, 3H, –OCH_3), 6.8–8.1 (*m*, 5H, Ar–H).

Mass *m*/*z*: 372 (75), 357 (50), 311 (43), 306 (100), 291 (82), 265 (54), 240 (20), 211 (36), 185 (80), 150 (61), 93 (68), 78 (70).

Characterisation data of derivatives (***IVa-i***)

Comp.	Molecular formula (mol.wt)	R	R^1	R^2	Crystallised from	M.p./ºC	Yield/%
IVa	$C_{16}H_8N_2O_7S$ (372)	–H	–H	–H	Ethanol	256	62
IVb	$C_{16}H_7N_3O_9S$ (417)	–H	–NO_2	–H	Methanol	223	72
IVc	$C_{17}H_{10}N_2O_7S$ (386)	–CH_3	–H	–H	Methanol	212	68
IVd	$C_{17}H_{10}N_2O_7S$ (386)	–H	–CH_3	–H	Ethanol	252	65
IVe	$C_{17}H_{10}N_2O_7S$ (386)	–H	–H	–CH_3	DMF	198	50
IVf	$C_{17}H_{10}N_2O_8S$ (402)	–OCH_3	–H	–H	Ethanol	232	70
IVg	$C_{17}H_{10}N_2O_8S$ (402)	–H	–OCH_3	–H	Ethanol	202	65
IVh	$C_{16}H_7ClN_2O_7S$ (406.5)	–Cl	–H	–H	DMF	187	75
IVi	$C_{16}H_6Cl_2N_2O_7S$ (441)	–H	–Cl	–Cl	Acetic acid	278	60

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ИЗВОД

ЛАКА СИНТЕЗА 10-МЕТОКСИ-4,8-ДИНИТРОБЕНЗО-6*H*-ТИЕНО[2,3-*c*]ХРОМЕН-6-ОНА

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Knoevenagel-овом реакцијом 3-метокси-5-нитро-бензалдехид са малонском киселином даје 3-метокси-5-нитро-циметну киселину (**I**). Третирање **I** са тионил-хлоридом даје 3-хлоро-5-метокси-7-нитробензо[*b*]тиофен-2-карбонил-хлорид (**II**) са 45 % приносом. Реакција **II** са 2-нитрофенолом у бензену даје 2-нитрофенил-3-хлоро-5-метокси-7-нитробензо[*b*]тиофен-2-карбоксилат (**IIIa**) са приносом од 65 %. Најзад, фотоциклизација уз дехидрохлоровање **IIIa** у ацетону у присуству триетиламина као даје 10-метокси-4,8-динитро-6*H*-бензотиено[2,3-*c*]хромен-6-он (**IVa**).

На тај начин је синтетизован низ деривата **IVa-i** са одличним приносима. Структура добијених производа карактерисана је IR и ^{1}H-NMR спектроскопијама и елементалном анализом. Чистоћа ових производа утврђивана је хроматографском анализом. Сва ова једињења испитана су у односу на антибактеријску активност према *S. aureus*, *E. coli*, *B. subtilis* и *S. typhosa*.

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