

# SYNTHESIS OF SOME 2- SUBSTITUTED AMINO-3-(N-m-TOLYL CARBOXAMIDO) 4, 5 TRIMETHYLENE THIOPHENES FOR ANALGESIC ACTIVITY

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## ABSTRACT

The present study was focused on the synthesis of new series of some 2-substituted amino-3-(N-m-Tolyl carboxamido) 4, 5 Trimethylene Thiophenes. The synthesized compounds were evaluated for analgesic activity.

**KEY WORDS:** Trimethylene thiophene, acetic acid.

## 1.INTRODUCTION

The chemistry of Thiophenes and its derivatives has known over 95 years. The development of Thiophenes and its derivatives have attracted maximum attraction due to their varied physiological and pharmacological properties. Some of these are found to have Thiopene derivatives are known to have a promising analgesic activity (Goodman,1992; Daries,1992; Tomiyama, 1992; Gewald,1989). In the present study, we synthesized, a new class of 2- substituted amino-3 (N-m-tolyl carboxamido) 4, 5- Trimethylene Thiophenes and evaluated for their analgesic activity.

## 2.EXPERIMENTAL

### Scheme I

A mixture of m-toludine (107g; 1.0 mole) and ethyl cyanoacetate (74 g; 0.655 mole) was heated at 160-170 °C for 8h and left at room temperature over night. The solid (1) obtained was filtered, washed with ethanol and crystallized from alcohol (m.p. 130°C, yield 45%).

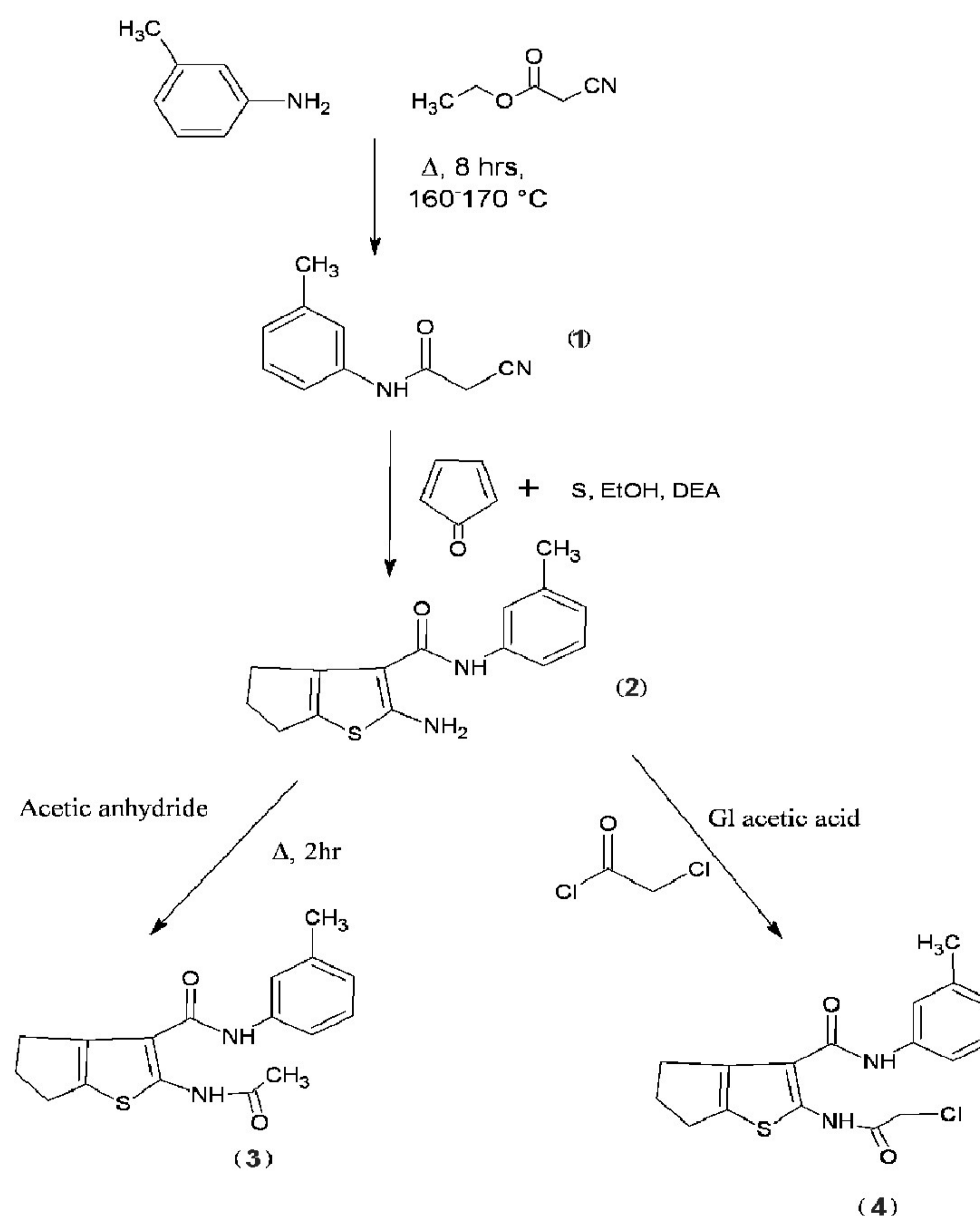
A mixture of cyclopentanone (3.36ml; 0.04 mole), N-m-tolyl cyanoacetamide(1)(6.96g; 0.04mole), ammonium acetate (1g) and glacial acetic acid(2ml) in benzene(80ml) was refluxed for 10h. The reaction mixture was cooled, diluted with benzene and washed with water. The crude  $\alpha$ -(N-m-tolyl carboxamido) alpha pentylidene acetonitrile thus obtained, was further added to sulphur (1.28; 0.04mole) in ethanol(40ml), diethyl amino (4.0ml) drop wise with stirring for 1h at 45-50°C, chilled overnight and the solid obtained was filtered, washed with ethanol and recrystallised from benzene(2) (m.p 123°C, yield 44%).

A mixture of 2(2g) and acetyl anhydride (10ml) was heated on a steam bath for 2h and mixture was cooled.

Left over night, the solid obtained was filtered, washed with cold ethanol, recrystallised from a mixture of alcohol and acetone to yield colorless crystalline compound(3) (m.p 145° C, yield 59%).

To a suspension of 3(3.12g; 0.0115 mole) in glacial acetic acid (30ml) was added chloroacetyl amide (3.9; 0.035 mole) drop wise at room temperature. The reaction mixture was refluxed for 5h, cooled and poured into water. The crude product was filtered, washed with water and recrystallised from benzene to get a grey color crystallized product (4) (m.p.180° C, yield 76.8%).

SCHEME-1



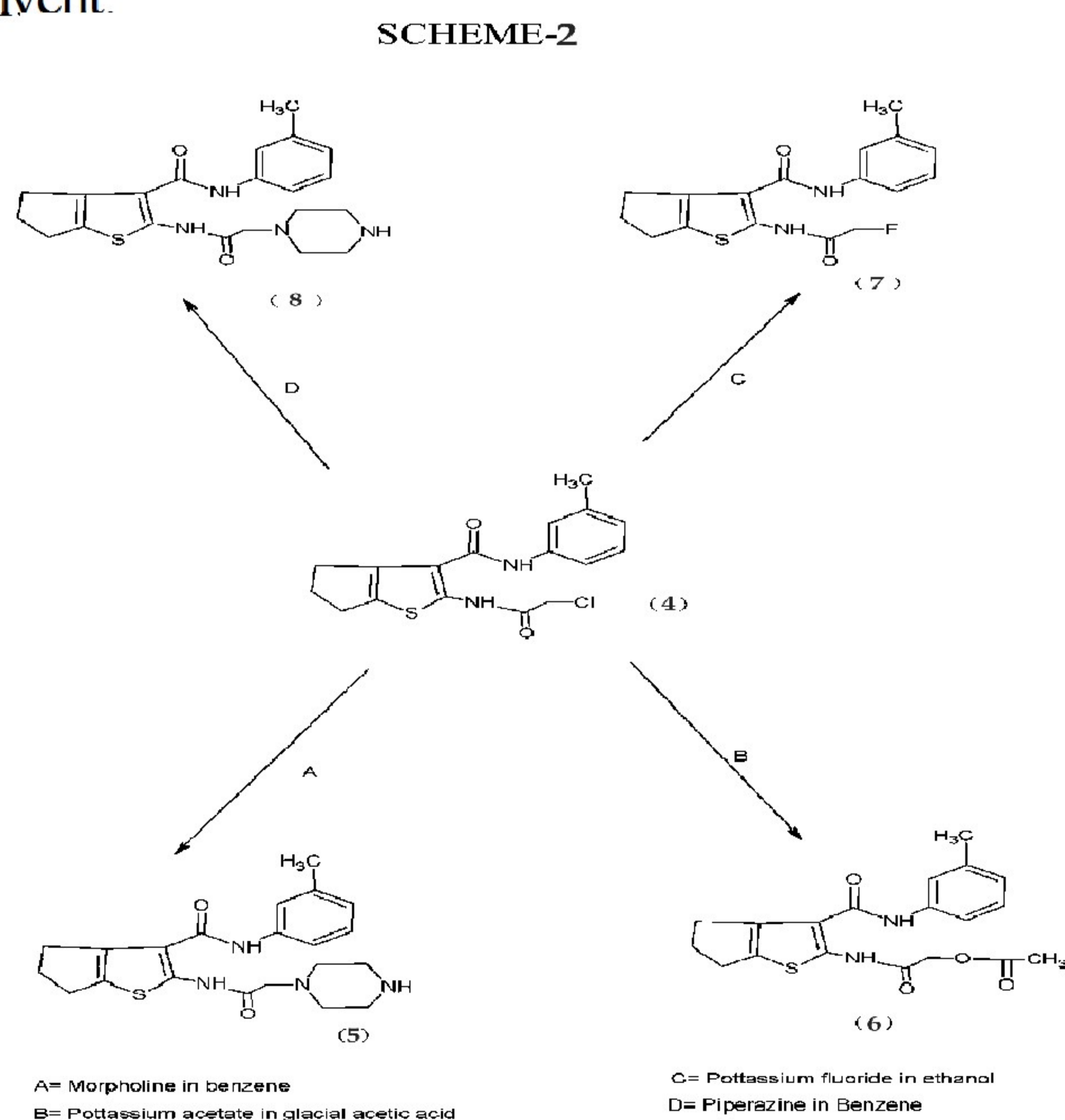
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Comp.	m.p.(°C)	Yield (%)	solvent	m.f.	Characterization data
1	130	45	n-hexane:ethylacetate 4 : 2	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O	3273cm <sup>-1</sup> (s, N-H) 2920cm <sup>-1</sup> (m, Ar C-H) 2260cm <sup>-1</sup> (m, CN) 668cm <sup>-1</sup> (s, C=O)
2	123	44	n-hexane:ethylacetate 4 : 2	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> OS	3402cm <sup>-1</sup> (s, NH <sub>2</sub> ) 3301cm <sup>-1</sup> (s, NH) 1633cm <sup>-1</sup> (s, C=O) 1400cm <sup>-1</sup> (s, Thiophene) 1242cm <sup>-1</sup> (s, Thiophene)
3	145	59	n-hexane:ethylacetate 4 : 2	C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> S	3433cm <sup>-1</sup> (s,N-H) 1678 cm <sup>-1</sup> (s, C=O) 1637cm <sup>-1</sup> (s, C=C-C=O) 1407cm <sup>-1</sup> (m,Thiophene) 1232cm <sup>-1</sup> (s, Thiophene)
4	180	76.8	n-hexane:ethylacetate 4 : 2	C <sub>17</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> SCl	3432cm <sup>-1</sup> (s, N-H) 1672cm <sup>-1</sup> (s, C=O) 1637cm <sup>-1</sup> (s, C=C-C=O) 1421cm <sup>-1</sup> (m,Thiophene) 1232cm <sup>-1</sup> (s, Thiophene) 763cm <sup>-1</sup> (s, C-Cl)

### Scheme 2

The compound 2-substituted-3-(N-m-tolyl carboxamido) 4, 5-trimethylene Thiophenes (5-8) were synthesized by refluxing 3-N-m-tolyl carboxamido-2-( $\alpha$ -chloro acetamido) 4, 5- Trimethylene thiophene (0.005mole) (4) with morpholine (0.015mole) in benzene (30ml), potassium acetate (0.07mole) in glacial acetic acid ( 75ml), potassium fluoride(0.015mole) in ethanol (40ml) and anhydrous piperazine (0.015mole) in benzene(30ml) for 8h respectively. The reaction mixture was cooled, poured into ice-water. The separated solid collected by filtration and crystallized from suitable solvent.



Comp.	m.p. °C	Yield(%)	solvent	m.f.	Characterization data
5	168	75	n-hexane:ethylacetate 4 : 2	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> S	3435cm <sup>-1</sup> (m, N-H) 1680cm <sup>-1</sup> (m, C=O) 1643cm <sup>-1</sup> (m, C=C-C=O) 1485cm <sup>-1</sup> (m, Thiophene) 1251 cm <sup>-1</sup> (m, Thiophene)
6	128	70.2	n-hexane:ethylacetate 4 : 2	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S	3429cm <sup>-1</sup> (m, N-H) 1757cm <sup>-1</sup> (m, OCO-CH <sub>3</sub> ) 1670cm <sup>-1</sup> (m, C=O) 1637cm <sup>-1</sup> (s, C=C-C=O) 1487cm <sup>-1</sup> (m, Thiophene) 1228cm <sup>-1</sup> (m, Thiophene)
7	148	62.5	n-hexane:ethylacetate 4 : 2	C <sub>17</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> F	3430cm <sup>-1</sup> (w, W-H) 1676cm <sup>-1</sup> (s, C=O) 1643cm <sup>-1</sup> (m, C=C-C=O) 1485cm <sup>-1</sup> (m, Thiophene) 1201 cm <sup>-1</sup> (m, Thiophene) 1037cm <sup>-1</sup> (w, C-H)
8	130	63	n-hexane:ethylacetate 4 : 2	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> S	3435cm <sup>-1</sup> (m,N-H) 1679cm <sup>-1</sup> (s, C=O) 1645cm <sup>-1</sup> (s,C=C-C=O) 1413cm <sup>-1</sup> (m,Thiophene) 1217cm <sup>-1</sup> (s, Thiophene)

### ANALGESIC ACTIVITY

The synthesized compounds were tested for their analgesic activity using acetic acid induced writhing method in Albino mice.

Comp.	Chemical name	Analgesic activity		Level of significance
		Mean vol (m $\pm$ S.E)	% inhibition	
3	2-acetyl amino-3-(N-M-tolyl carboxamido)4,5 Trimethylene thiophene	20.2 $\pm$ 0.86	59%	P<0.001
4	3-N-m-tolyl 2-(w-chloro acetamido)4,5 Trimethylene thiophene	16.4 $\pm$ 1.28	64%	P<0.001
5	2-w-Morpholino acetamido 3-N-m-tolyl carboxamido 4,5 Trimethylene thiophene	20 $\pm$ 0.836	60%	P<0.001
6	2-w-acetoxy acetamide-3(N-M-toyl carboxamido)4,5 Trimethylene thiophene	19.2 $\pm$ 1.35	60%	P<0.001
7	2-w-fluoro acetamido 3-(N-m-tolyl carboxamido)4,5 Trimethylene thiophene	18.2 $\pm$ 1.15	62%	P<0.001
8	2-w-piperazino acetamido 3-(N-M-tolyl carboxamido)4,5 Trimethylene thiophene	19 $\pm$ 1.30	63%	P<0.001
	Standard-(Aspirin)	16.2 $\pm$ 1.06	67%	P<0.001
	Control (Tween 80)	48.8 $\pm$ 0.86	-	-

The compounds 7 and 8 showed good activity (62% and 63%) and the remaining compounds 3, 4, 5 and 6 showed considerable analgesic activity.

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