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Synthesis of thiophenes and pyranone fused thiophenes by base induced inter and intramolecular C–S and C–C bond formation: a non-catalytic approach

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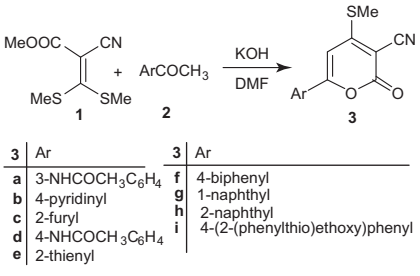
ABSTRACT

An efficient and concise one pot synthesis of highly functionalized thiophenes and pyranone fused thiophenes has been delineated through base induced ring transformation of suitably functionalized 2*H*-pyran-2-ones by ethyl thioglycolate by inter and intramolecular C–S and C–C bond formation.

Thiophenes are important class of heterocyclic system, abundantly present as sub-structure in various natural products[1] and pharmaceuticals.[2] These are useful intermediates in the preparation of novel conducting polymers,[3] nonlinear optical materials[4] and for isosteric replacement for phenyl group in medicinal chemistry.[5] Diazathiophenes, derived from the coupling of 2-aminothiophenes with various heterocycles are highly colored brilliant shade dyes[6] as well as aroylthiophenes are agonist allosteric enhancer at A_1 adenosine receptor.[7,8]

One of the principal routes for the construction of highly functionalized 3-aminothiophenes is the interaction of β-halonitriles with mercaptans having reactive methylene, activated by the presence of electron acceptor.[9] This reaction is very useful even for the construction of fused thiophene ring system with amino substituent at position 3. Another alternative route for the synthesis of 3-aminothiophene is based on the reaction of sodium or potassium 1-cyanoethylene-2,2-dithiolates with α-halocarbonyl compounds or activated alkyl halide in basic medium.[10] 3,5-Diaminothiophenes are also prepared by the base induced reaction of ketene N,S acetals, obtainable from the reaction of activated nitriles with isothiocyanates with activated alkyl or aralkyl halide.[11–15] Besides these, they are also prepared by ring opening and ring-closure of 1,3-oxathiolium salt with malononitrile in the presence of base.[16–20] Recently, a practical and high yield two steps procedure is developed for the synthesis of ethyl 3-aminothiophene-2-carboxylate by the reaction of mercaptoacetic acid and 2-chloroacrylonitrile followed by esterification.[21] A reaction of alkylnitrile (RCH_2CN) with ethyl formate followed by ring-closure on reaction with ethyl thioglycolate led to the formation of functionalized 3-aminothiophenes.[22]

The wide ranging applications of thiophene derivatives aroused considerable interest to develop new methodology which could be efficient, economical and compatible to the functional groups, without use of expensive catalyst/reagent, easy work up and mild reaction conditions. Our methodology relies on mild conditions, with easy workup using economically viable reagents. The advantage of the procedure lies in the synthesis of cyanomethyl tethered



3	Ar
a	3-NHCOCH$_3$C$_6$H$_4$
b	4-pyridinyl
c	2-furyl
d	4-NHCOCH$_3$C$_6$H$_4$
e	2-thienyl

3	Ar
f	4-biphenyl
g	1-naphthyl
h	2-naphthyl
i	4-(2-(phenylthio)ethoxy)phenyl

Scheme 1. Synthesis of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitrile **3**.

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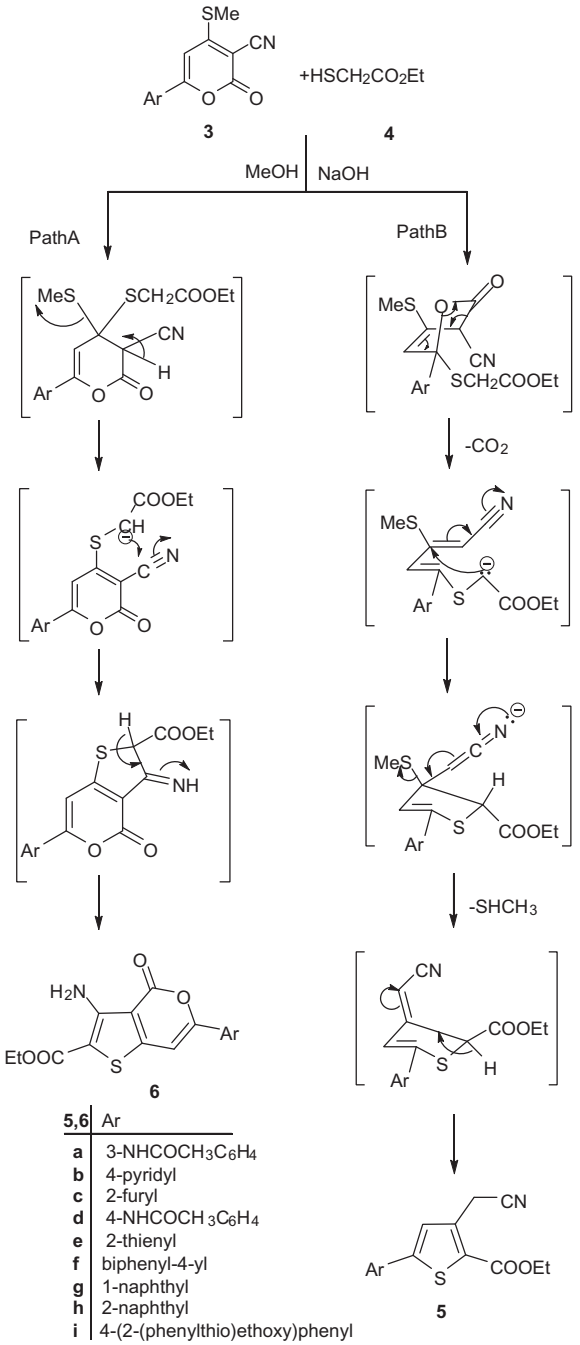


Scheme 2. Plausible mechanism for the synthesis of ethyl 3-cyanomethyl-5-arylthiophene-2-carboxylates (**5**) and 3-amino-6-aryl-2-carbethoxy-4*H*-thieno[*3,2-c*]pyran-4-ones (**6**).

thiophenes at position 3 and carbethoxy group at position 2, which can be further exploited for the construction of new heterocycles.

Herein, we report a novel approach to the synthesis of highly functionalized thiophenes from base induced ring transformation of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles[23] obtainable from the reaction of aryl methyl ketones (**2**) and methyl 3,3-dimethylthio-2-cyanoacrylate (**1**) by ethyl thioglycolate, Scheme 1. The molecular makeup of the lactone (**3**) reveals that positions 2,4 and 6 are electron deficient and prone to nucleophilic attack. The electrophilicity of these three position is in order of C-6 > C-4 > C-2.[26] Thus, C-6 position is highly vulnerable to nucleophiles because of extended conjugation and the presence of electron withdrawing CN substituent at position 3. Regioselectivity of reac-

Table 1
Yields and Mps of compounds synthesized in Scheme 2

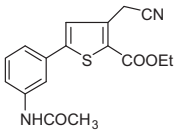
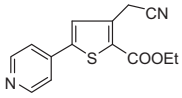
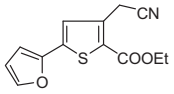
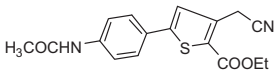
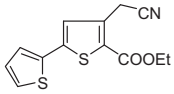
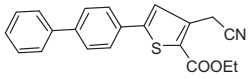
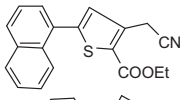
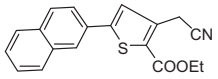
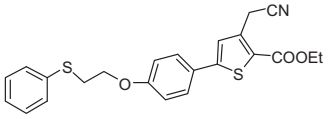
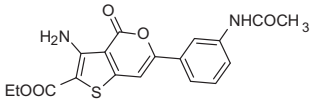
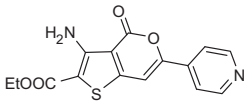
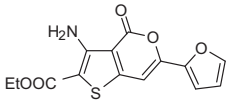
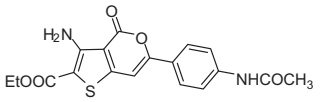
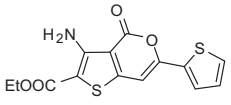
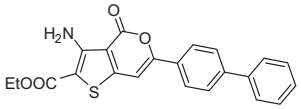
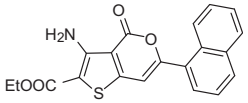
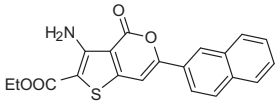
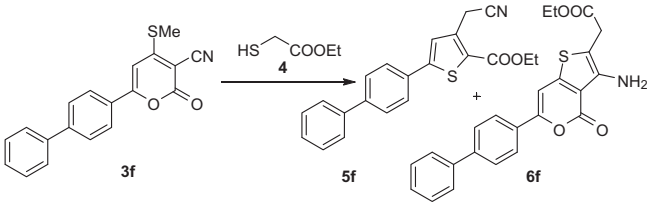
5, 6	Compound	Mp (°C)	Yield (%)
5a		112	38
5b		Waxy	40
5c		Waxy	41
5d		121	42
5e		152	42
5f		108	46
5g		50	49
5h		142	50
5i		118	60
6a		130	30
6b		124	30
6c		117	37
6d		167	25
6e		124	38
6f		218	21
6g		110	43
6h		118	39

Table 2
Reaction conditions for the synthesis of **5f** and **6f**



S.No	Base	Solvent	Temp	*T* (h)	Yield (%) **5f**	Yield (%) **6f**
1	Et_3N	MeOH	Reflux	7	—	71
2	DBU	MeOH	Reflux	7	—	62
3	NaOH	DMF	rt	8	20	10
4	NaH	THF	rt	24	40	46
5	KOH	MeOH	Reflux	7	42	45
6	NaOH	EtOH	Reflux	7	44	39
7	NaOH	MeOH	Reflux	7	46	21

tion depends upon the nature of nucleophile and size of aromatic substituent used for the ring transformation.

Thus, the reaction of 2-pyranones (**3**) with ethyl thioglycolate in the presence of triethyl amine as a base in methanol at reflux temperature exclusively gave 3-amino-6-aryl-2-carbethoxy-4*H*-thieno[3,2-*c*]pyrane-4-ones (**6**).[24] The plausible mechanism of the reaction is depicted in Scheme 2, Path A.

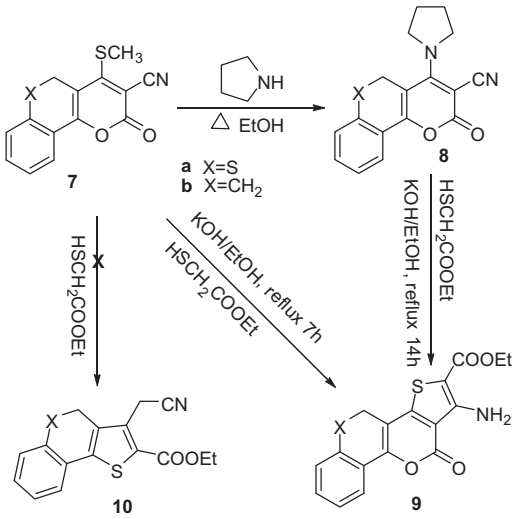
However, when powdered NaOH was used as a base in methanol at reflux temperature besides product **6**, ethyl 3-cyanomethyl-5-(aryl)thiophene-2-carboxylates (**5**) was also isolated due to competitive reaction at C-6 position of the lactone (**3**) with bulky aromatic substituent. Basically the reaction is initiated by attack of mercaptide ion generated in situ from ethyl thioglycolate with formation of Michael adduct which undergoes ring-closure with liberation of carbon dioxide followed by elimination of methyl mercaptan to give thiophene as shown in Scheme 2, Path B. Observation of various reactions and their yields as shown in Table 1, demonstrated that as the bulky Ar group has been introduced at position 6 in lactone (**3**), the yield of thiophene (**5**) has been increased.

In order to optimize the reaction conditions and to improve the yields of **5**, a pilot reaction was performed using different solvents, bases, time and, temperature as summarized in Table 2. It is pertinent to note that use of NaOH as a base and DMF as a solvent (Table 2) due to the formation of complex mixture only compound **5f** and **6f** was isolated in 20% and 10% yields, respectively, the other compounds could not be isolated from the complex mixture by column chromatography.(See Scheme 3)

The various cyanomethyl substituted thiophenes (**5**) and thienopyrans (**6**), prepared are listed in Table 1. Thus, use of strong base as NaOH in methanol leads to the formation of both the products **5** and **6** in which **5** has been isolated in better yields. This methodology provides a new avenue for the construction of thiophenes (**5**) as well as thienopyrans (**6**) as a useful precursor for the synthesis of variety of heterocyclic ring systems.

Under analogous conditions, reactions of tricyclic lactones (**7**)[25] with ethyl thioglycolate was carried out in anticipation to obtain analogous products, tetracyclic thienopyran-2-carboxylates (**9**) and tricyclic thiphene-2-carboxylates (**10**) based on the nucleophilic attack at C-4 and C-6 position respectively but practically only product **9** was isolated and characterized.

In another set of experiment, the substrate **8**[25] was used in lieu of **7** due to poor electrophilicity of C-4 position in the presence of amino substituent which could favor preferential nucleophilic attack at C-10b rather than C-4 to give **10**. However, this exercise was also futile as the isolated product was characterized as **9** possibly due to steric factor.



9	X	Mp (°C)	Yields(%)from 7	8
a	S	>310	90	78
b	CH_2	170	85	63

Scheme 3. Synthesis of tetracyclic thienopyrans.

All the synthesized compounds were characterized by spectroscopic analyses.[27]

In conclusion, we have developed an expeditious one pot synthesis of (2-carbethoxythiophen-3-yl)acetonitriles from 2*H*-pyran-2-ones not reported so far. These thiophene derivatives can be used as useful precursors for the preparation of ketenedithioacetals[28] as synthons for making various class of heterocycles depending upon the reagents used and will open a new avenue for the synthesis of thiophene based heterocycles. The pyranone fused thiophenes derived from 2-pyranone, benzo[*c*]chromenone and benzo[*c*]thiochromenone will be further used for making polycyclic heterocycles.

Acknowledgments

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27. **Data for Compounds**: *General procedure for the synthesis of ethyl 3-(cyanomethyl)-5-(aryl)thiophene-2-carboxylate* (**5**) *and 3-amino-2-carbethoxy-6-aryl-4H-thieno[3,2-c]pyran-4-one* (**6**). A mixture of 3-cyano-6-aryl-4-methylthio-2*H*-pyran-2-one (**3a**) (1 mmol) and ethyl thioglycolate (**4**) (1 mmol) in methanol was refluxed in the presence of powdered NaOH (1.2 mmol) for 6–8 h and thereafter reaction mixture was poured onto crushed ice with vigorous stirring. The precipitate obtained was filtered and the crude product was purified on silica gel column, using hexane:chloroform (5–10%) as eluent.
Ethyl 3-(cyanomethyl)-5-(2-thienyl)thiophene-2-carboxylate (**5e**): white solid; mp. 152 °C, yield 42%; R_f: 0.92 (hexane/chloroform, 9:1); IR (KBr): 2936 (CH_2), 2200 (–CN) 1747 (>C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.34 (t, 3H, CH_3), 4.35 (br s, 4H, CH_2), 6.63 (s, 1H, Ar-H), 7.19 (m, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 7.41 (d, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.27, 15.66, 59.96, 117.25, 124.17 (2C), 127.16, 129.35, 137.09, 145.17 (2C), 148.73, 161.55; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}NO_2S_2$: 277.0231 (M^+); found: 277.0234 (M^+).
Amino-2-carbethoxy-6-(2-thienyl)-4H-thieno[3,2-c]pyran-4-one (**6e**): light yellow solid; mp. 124 °C, yield 38%; R_f: 0.33 (hexane/chloroform, 9:1); IR (KBr): 3490, 3380 (-NH_2), 2936 (–CH_2), 1740(>C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.34 (t, 3H, CH_3), 4.47 (m, 2H, -CH_2), 4.80 (s, 2H, NH_2), 6.21 (s, 1H, Ar-H), 7.14 (t, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 7.41 (d, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.27, 59.90, 103.25, 124.83, 128.15 (2C), 130.57, 135.17 (2C), 137.89, 145.87, 148.74, 153.01, 160.45; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}NO_4S_2$: 321.0129 (M^+); found: 321.0128 (M^+).
Ethyl 1-amino-11-oxo-5,11-dihydro-4H-benzo[h]thieno[3,2-c]chromene-2-carboxylate (**9b**): yellow tiny crystal from chloroform; mp 170 °C, yield 63%; IR (KBr): 3487, 3383 (–NH_2), 2932 (–CH_2), 1734 (>C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.28 (t, *J* = 7.2 Hz, 3H, CH_3), 2.76 (t, *J* = 5.6, 2H, CH_2), 3.00 (t, *J* = 5.6, 2H, CH_2), 4.25 (q, *J* = 7.2 Hz, 2H, OCH_2), 6.91 (br sH, NH_2), 7.39 (m, 3H, Ar-H), 7.69 (m, 1H, Ar-H); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO_4S_2$: 342.0800 (MH^+); found: 342.0812 (MH^+).
28. Sturrock, K. R.; Bremner, D. H.; Wishart, G. *Heterocycles* **2011**, *82*, 1657.