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A substituent directed regioselective synthesis of aryl/pyronyl pendant unusual adipate and tetrahydronaphthalene

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Abstract

An efficient regioselective synthesis of pyronyl pendant ethyl methylthiocarbonylalkanoates **5** has been delineated from the base catalyzed reaction of suitably functionalized 2-pyranone **1** and 2-carbethoxycycloalkanones **2**, **6** through successive substitution and regioselective ring opening by in situ generated mercaptide ion. To assess the effect of C-4 substituent on regioselectivity, reactions of 6-aryl-3-cyano-4-(piperidin-1-yl)-2-oxopyran **8** with 2-carbethoxycyclohexanone **6a** and 2-carbethoxy-2-methylcyclohexanone **6b** were carried out separately under analogous reaction conditions but the compounds isolated were identical and characterized as 4-aryl-8-methyl-2-piperidin-1-yl-5,6,7,8-tetrahydronaphthalene-1-carbonitriles **9**. Ethyl 2-(5-amino-4′-bromo-4,6-dicyanobiphenyl-3-yl)-5-methylsulfanylcarbonylpentanoate **10** has also been prepared through base catalyzed ring transformation of ethyl 2-[6-(4-bromophenyl)-3-cyano-2-oxo-2*H*-pyran-4-yl]-5-methylsulfanylcarbonylpentanoate **5d** by malononitrile in DMF.

Keywords: 2-Carbethoxycyclopentanone; 2-Oxopyran; Ring transformation; Mercaptide ion

Suitably functionalized 2-pyrones constitute an important class of compounds, and are present as substructure unit in numerous natural products[1] of diverse therapeutic importance as antimalarial,[2] antifungal,[3] pheromonal,[4] androgen like,[5] cardiotonic,[6] and antiHIV[7] agents. Besides these, they are also very useful building blocks[8,9] for the construction of various congested arenes and heteroarenes. As a consequence, attention has been focused to explore the versatility of 2-pyrones through substituent dependent base catalyzed substitution with successive ring opening and ring transformation by 2-substituted cycloalkanones for the construction of pyronyl and aryl pendant ethyl methylthiocarbonylalkanoates and highly congested tetrahydronaphthalenes.

A comprehensive literature survey revealed that not a single example is known so far for the construction of pyronyl and aryl pendant ethyl methylthiocarbonylalkanoates. A synthesis of simple ethyl methylsulfanylcarbonylalkanoates has been reported from the reaction of ethyl mercaptan with dicarboxylic acid chloride ester in pyridine.[10] It has also been obtained through the irradiation of *S*-phenylchlorothioformate and alkyl iodide in the presence of bis(tributyltin) in benzene.[11] Lubell et al.[12] have also prepared this class of compounds by the acetylation of thiophenols with α-*tert*-butyl *N*-(PhF)-α-aminoadipate and DCC-DMAP in acetonitrile as intermediate. The lack of appropriate procedures to introduce ethyl methylsulfanylcarbonylalkanoate as a substituent to aryl or heteroaryl ring system, necessitated to develop an easy access to the synthesis of this class of compounds to explore their chemistry and biodynamic properties.

The precursors employed in this study were 6-aryl-3-cyano-4-methylsulfanyl-2-oxopyrans **1** and 6-aryl-3-cyano-4-(piperidin-1-yl)-2-oxopyrans **8**, in which the former was

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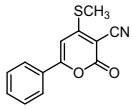
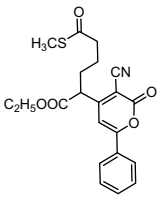
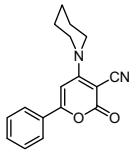
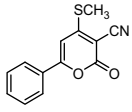
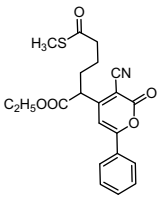
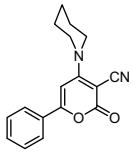
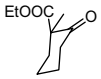
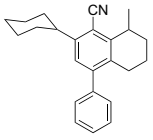
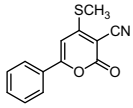
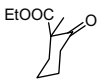
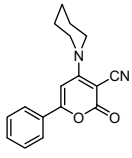
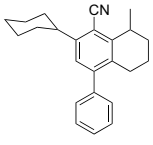
prepared[13] from the reaction of aryl methyl ketone and methyl 2-cyano-3,3-dimethylthioacrylate, while the latter was obtained[14] by the amination of **1** with piperidine in boiling ethanol.

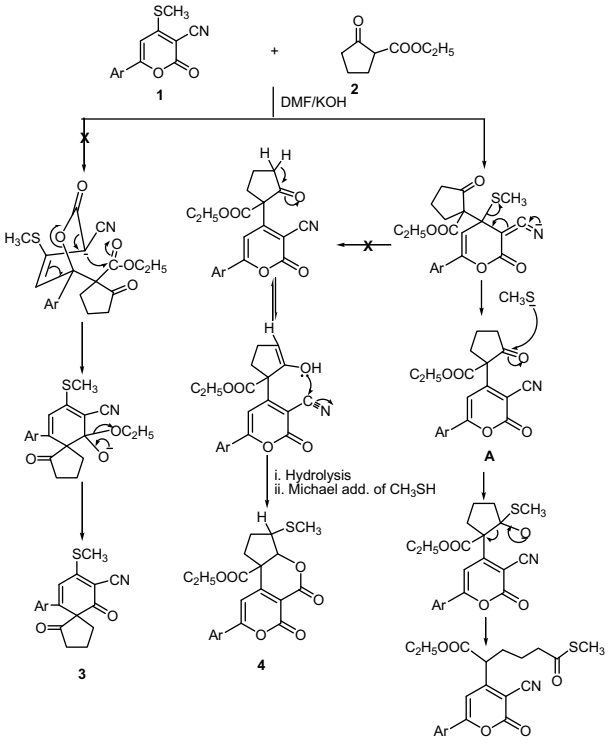
Herein, we report a short and efficient synthesis of ethyl 2-(6-aryl-3-cyano-2-oxopyran-4-yl)-5-methylsulfanylcarbonylpentanoates **5** and ethyl 2-(6-aryl-3-cyano-2-oxopyran-4-yl)-6-methylsulfanylcarbonylhexanoate **7** should base catalyzed successive substitution and regioselective ring opening by mercaptide ion, generated in situ from the reaction of 6-aryl-3-cyano-4-methylsulfanyl-2-oxopyran **1** and 2-carbethoxycycloalkanones in DMF. In these reactions 2-carbethoxycyclopentanone **2** and 2-carbethoxycyclohexanone **6** were used as a source of carbanion. The optimization of reaction conditions is presented in Table 1. The presence of carbonyl function adjacent to the carbon linked to the carbethoxy substituent made position 2 highly reactive. Thus, a reaction of **1** and **2** or **6** separately is possibly initiated by an attack of a carbanion generated from 2-carbethoxycycloalkanone at C-4 of the pyran ring to give a substitution product as an intermediate **A** with the liberation of methyl mercaptan which intern acts as a nucleophile and attacks regioselectively at carbonyl function of cycloalkanone ring of the intermediate with ring opening to afford ethyl 2-(6-aryl-3-cyano-2-oxopyran-4-yl)methylsulfanylcarbonylalkanoates **5** and **7** (Schemes 1 and 2).

There are two other possibilities for the formation of products **3** and **4** depending upon the attack of carbanion at C-6 or C-4 of 2-pyrone **1**. The formation of product **3** may possibly arise through the attack of carbanion at C-6 with ring closure involving C-3 of pyran and carbethoxy of **2**, while the formation of the other expected product **4** is based on the attack of carbanion at C-4 with the liberation of methyl mercaptan followed by enolization and Michael addition as depicted in Scheme 1. The proton NMR and HRMS data of the isolated compounds did not match with the proposed structures **3** and **4**. In addition, the presence

Table 1
Optimization of reaction conditions

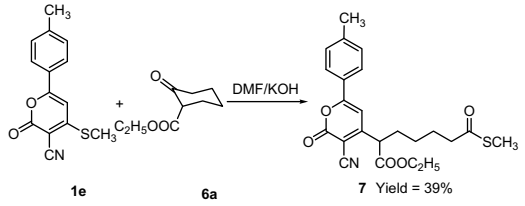
S.No.	Pyran-2-one	Ketone	Product	Conversion (%)
1				100
2			—	0[a,b]
3				80[a,c]
4				100
5			—	0[b]
6				100

[a] Starting material recovered through column chromatography.
[b] No product formation.
[c] Reaction performed using NaH/THF.



1, 5	Ar	Yields (%)
a	C_6H_5	89
b	4-F-C_6H_4	94
c	4-Cl-C_6H_4	87
d	4-Br-C_6H_4	96
e	4-CH_3-C_6H_4	89
f	4-CH_3O-C_6H_4	84
g	2,4-$(CH_3)_2$-C_6H_3	95
h	2-thienyl	90
i	2-naphthyl	91

Scheme 1. Plausible mechanism for the synthesis of ethyl 2-(6-aryl-3-cyano-2-oxopyran-4-yl)-5-methylsulfanylcarbonylpentanoates **5.**



Scheme 2. Synthesis of ethyl 2-(6-*p*-tolyl-3-cyano-2-oxopyran-4-yl)-6-methylsulfanylcarbonylhexanoate **7**.

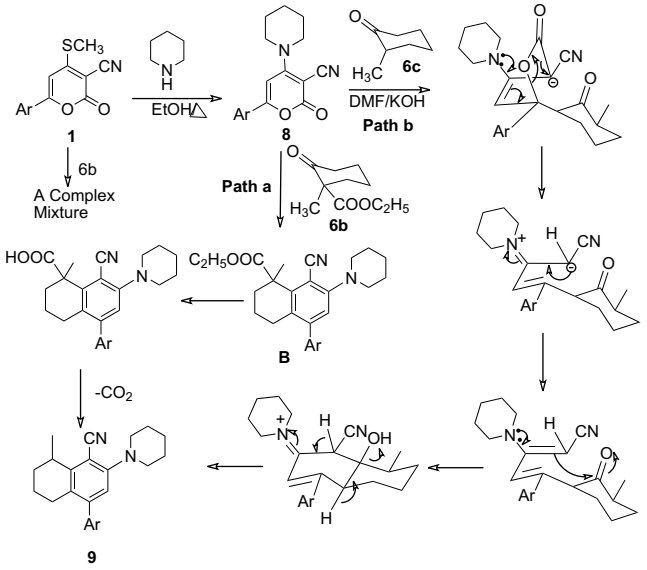
of CN frequency (2210–2260 cm^{-1}) in the IR spectrum completely ruled out the possibility of product **4**.

It was interesting to note that the ring opening of 2-carbethoxycyclohexanon-2-yl pendant intermediate by mercaptide ion, generated in situ from the reaction of **1e** and **6a**, gave ethyl 2-[6-(4-methylphenyl)p-tolyl-3-cyano-2-oxopyran-4-yl]-6-methylsulfanylcarbonylhexanoate **7** in 39% yields. Under analogous conditions, a reaction of 3-cyano-6-(4-methylphenyl)-4-(piperidin-1-yl)-2*H*-pyran-2-one **8** with 2-carbethoxycyclohexanone **6a** ended with the recovery of starting materials while with 2-methylcyclohexanone **6c** under identical conditions afforded 4-aryl-2-(piperidin-1-yl)-8-methyl-5,6,7,8-tetrahydronaphthalene-1-carbonitriles **9**. Attempts to force the ring transformation of 2-pyrone **1** by 2-carbethoxy-2-methylcyclohexanone **6b** to obtain 4-aryl-2-methylsulfanyl-8-methyl-5,6,7,8-tetrahydronaphtha-lene-1-carbonitrile failed and ended with an inseparable complex mixture, while under analogous conditions a reaction of **8** with **6b** produced a ring transformed product **9**. This reaction is possibly initiated by the attack of a carbanion at C-6 of the pyran ring with ring closure followed by the loss of carbon dioxide and water to form an intermediate, 4-aryl-2-(piperidin-1-yl)-8-carbethoxy-8-methyl-5,6,7,8-tetrahydronaphthalene-1-carbonitriles **B** which under experimental conditions hydrolyzed and decarboxylated to afford **9**. These reactions confirmed the impact of substituents at C-4 of 2-pyranone and C-2 position of cycloalkanones on the regioselectivity of the reaction. Attempts were made to trap the intermediate but could not succeed. The reaction of **8** with 2-methylcyclohexanone **6c** followed the same mechanism to produce **9**. The probable mechanism and yields of the compounds are shown in Scheme 3.

Our attempts for the ring transformation of 2-[6-(4-bromophenyl)-3-cyano-2-oxo-2*H*-pyran-4-yl)]-5-methylsulfanylcarbonylpentanoate **5d** by malononitrile succeeded, and the isolated compound was characterized as ethyl 2-(5-amino-4′-bromo-4,6-dicyanodiphenyl-3-yl)-5-methylsulfanylcarbonylpentanoate **10** in moderate yield.

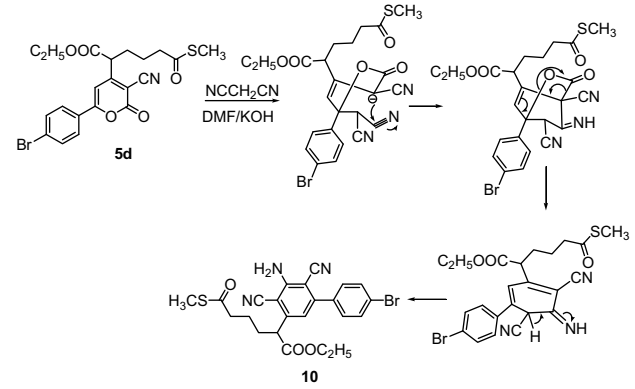
In this reaction, the carbanion generated at the reactive methylene carbon attacks at C-6 with ring closure involving C-3 of the pyran ring and nitrile functionality of the malononitrile. The probable mechanism of the reaction is shown in Scheme 4.

All the synthesized compounds were characterized by HRMS and other spectroscopic techniques.[15]



9	Ar	[a]Yields (%)	[b]Yields (%)
a	C_6H_5	33	79
b	4.Cl-C_6H_4	29	71
c	4.Br-C_6H_4	43	77
d	2-naphthyl	39	69

Scheme 3. A plausible mechanism involved in the formation of 4-aryl-2-(piperidin-1-yl)-8-methyl-5,6,7,8-tetrahydronaphthalene-1-carbonitriles **9**.



Scheme 4. Mechanism for the synthesis of ethyl 2-(5-amino-4′-bromo-4,6-dicyanobiphenyl-3-yl)-5-methylsulfanylcarbonylpentanoate **10**.

In conclusion, we have developed a substituent directed regioselective concise synthesis of pyronyl pendant ethyl methylsulfanylcarbonylalkanoates from the reaction of 6-aryl-3-cyano-4-methylsulfanyl-2-oxopyran with 2-carbethoxycycloalkanones separately through substitution followed by ring opening of the latter by methyl mercaptide ion, generated in situ. The highly congested aryl tethered ethyl methylsulfanylcarbonylpentanoate has also been prepared through the ring transformation of ethyl 2-[6-(4-bromophenyl)-3-cyano-2-oxo-2*H*-pyran-4-yl]-5-methylsulfanylcarbonylpentanoate. The yields of the product were directly related to the stability of 2-carbethoxycycloalkanone rings. An increase in the size of the cycloalkanone

rings from 5 to 6 reduced the yield due to higher stability of the cyclohexanone ring. The presence of 4-(piperidin-1-yl) substituent in 2-pyranone ring changes the course of the reaction from substitution to ring transformation. This methodology opens a new avenue for the synthesis of various aryl and pyronyl pendant alkyl methylsulfanyl-carbonylalkanoates not obtainable by any available literature procedures.

Acknowledgements

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15. *Representative procedure for the synthesis of ethyl 2-(3-cyano-2-oxo-6-phenyl-2H-pyran-4-yl)-5-methylsulfanylcarbonylpentanoate* **(5a):** A mixture of 3-cyano-4-methylsulfanyl-6-phenyl-2-oxopyran **1a** (243 mg, 1 mmol) and 2-carbethoxycyclopentanone **2** (0.234 mL, 1.5 mmol) in DMF (5 mL) in the presence of powdered KOH (112 mg, 2 mmol) was stirred for 6 h. Excess of DMF was removed under reduced pressure and the residue poured onto crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl (5 mL) and the gummy material obtained was washed with water and purified on silica gel column, using 40% hexane in chloroform as eluent. It was isolated as a yellow solid; yield: 356 mg (89%); mp: 56–58 °C; IR: (KBr) 2367, 2210, 1697, 1600, 1449, 1352, 1282, 1227, 1173, 1064, 906, 765, 733, 687 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 1.29 (t, $J = 7.11$ Hz, 3H, CH_3), 1.65–1.88 (m, 2H, CH_2), 1.90–1.97 (m, 1H, CH), 2.15–2.27 (m, 1H, CH), 2.28 (s, 3H, SCH_3), 2.65 (t, $J = 6.97$ Hz, 2H, CH_2), 3.98 (t, $J = 7.30$ Hz, 1H, CH), 4.17–4.30 (m, 2H, CH_2), 6.97 (s, 1H, ArH), 7.49–7.60 (m, 3H, ArH), 7.90 (d, $J = 7.92$ Hz, 2H, ArH); ^{13}C NMR: (75 MHz, $CDCl_3$): 10.3, 12.8, 21.7, 28.3, 29.6, 41.5, 48.6, 61.0, 97.5, 99.2, 125.4, 128.0, 128.4, 131.6, 156.7, 162.8, 162.7, 168.3, 197.4; MS m/z 400 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{21}H_{21}NO_5S$ 399.1140 (M^+) found for m/z 399.1138. Compound (**5e**): It was obtained from the reaction of **1e** (257 mg, 1 mmol) and **2** (0.234 mL, 1.5 mmol) in the presence of powdered KOH (112 mg, 2 mmol) in dry DMF. Usual work-up and purification on silica gel column using 40% hexane in chloroform as eluent afforded yellow solid; yield: 359 mg (89%); mp: 98–100 °C; IR: (KBr) 2965, 2367, 2219, 1728, 1686, 1613, 1525, 1456, 1348, 1276, 1236, 1207, 1159, 1062, 1017, 858, 824, 768, 712 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 1.28 (t, $J = 7.13$ Hz, 3H, CH_3), 1.66–1.81 (m, 2H, CH_2), 1.82–1.91 (m, 1H, CH), 2.12–2.22 (m, 1H, CH), 2.29 (s, 3H, SCH_3), 2.43 (s, 3H, CH_3), 2.63 (t, $J = 6.89$ Hz, 2H, CH_2), 3.97 (t, $J = 7.13$ Hz, 1H, CH), 4.18–4.25 (m, 2H, CH_2), 6.87 (s, 1H, ArH), 7.31 (d, $J = 8.16$ Hz, 2H, ArH), 7.78 (d, $J = 8.28$ Hz, 2H, ArH); ^{13}C NMR: (75 MHz, $CDCl_3$): 10.3, 12.8, 20.4, 21.7, 29.8, 41.5, 48.6, 61.6, 96.8, 98.4, 112.0, 125.5, 125.7, 128.7, 128,8, 142.8, 150.8, 162.9, 163.3, 168.5, 197.4: MS m/z 414 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{22}H_{23}NO_5S$ 413.1296(M^+) found for m/z 413.1293.
General procedure for the synthesis of 4-aryl-2-(piperidin-1-yl)-8-methyl-5,6,7,8-tetrahydronaphthalene-1-carbonitriles (**9**): A mixture of 6-aryl-3-cyano-4-(piperidin-1-yl)-2-oxopyran **8** (1.0 mmol) and 2-carbethoxy-2-methylcyclohexanone **6b** (230 mg, 1.5 mmol) or 2-methylcyclohexanone (160 mg, 1.5 mmol) in DMF (5.0 mL) in the presence of powdered KOH (112 mg, 2 mmol) was stirred for 1–1.5 h. Excess of DMF was removed under reduced pressure and the residue poured onto crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl (5.0 mL) and the precipitate obtained was filtered, washed with water and purified on silica gel column, using hexane/chloroform mixture (70:30) as eluent. Compound (**9b**): White powder, yield: 260 mg (71%); mp: 126–128 °C; IR: (KBr) 3021, 2934, 2367, 2216, 1522, 1365, 1216, 1024, 910, 763, 670 cm^{-1}; ^1H NMR: (200 MHz, $CDCl_3$): 1.38 (d, $J = 7.0$ Hz, 3H, CH_3), 1.57–1.62 (m, 2H, CH_2), 1.72–1.77 (m, 8H, CH_2), 2.38–2.45 (m, 2H, CH_2), 3.05–3.12 (m, 4H, NCH_2), 3.38–3.42 (m, 1H, CH), 6.65 (S, 1H, ArH), 7.18 (d, $J = 8.72$ Hz, 2H, ArH), 7.38 (d, $J = 8.38$ Hz, 2H, ArH); MS m/z 365 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{23}H_{25}ClN_2$ 364.1706 (M^+) found for m/z 364.1707.
Synthesis of ethyl 2-(5-amino-4′-bromo-4,6-dicyanobiphenyl-3-yl)-5-methylsulfanylcarbonylpentanoate (**10**): A mixture of **5d** (96 mg, 0.2 mmol), malononitrile (18 mg, 0.25 mmol) and KOH (17 mg, 0.3 mmol) in DMF (2.0 mL) was stirred for 1–2 h. Completion of the reaction was monitored by TLC. After completion, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10 % HCl. The precipitate obtained was filtered, washed with water, dried and purified with silica gel column chromatography using hexane/chloroform (1:1) mixture as eluent affording light yellow crystalline solid. Yield: 78 mg (78%); mp: 108–110 °C; IR: (KBr) 3452, 3357, 3242, 2920, 2850, 2218, 1731, 1687, 1635, 1581, 1492, 1467, 1441, 1393, 1369, 1280, 1190, 1073, 1011, 827, 759 cm^{-1}; ^1H NMR: (200 MHz, $CDCl_3$): 1.23–1.30 (m, 3H, CH_3), 1.66–1.84 (m, 3H, CH_2 and CH), 2.10–2.15 (m, 1H, CH), 2.28 (s, 3H, SCH_3), 2.59 (t, $J = 6.78$ Hz, 2H, CH_2), 3.91 (t, $J = 6.85$ Hz, 1H, CH), 4.09–4.22 (m, 2H, CH_2), 5.33 (br s, 2H, NH_2), 6.81 (s, 1H, ArH), 7.41 (d, $J = 8.38$ Hz, 2H, ArH), 7.63 (d, $J = 8.25$ Hz, 2H, ArH); MS m/z 500 (M^+) and 502 (M^++2); HRMS: (EI, 70 eV) calcd for $C_{23}H_{22}BrN_3O_3S$ 499.056(M^+) found for m/z 499.0563.