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Synthesis of Functionally Congested α-Pyranones Using Ketene Dithioacetal as Parent Precursor

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ABSTRACT

A general approach for the synthesis of functionally congested α-pyranones 8a-e and 10a-g is described and illustrated by reaction of polarized ketene dithioacetal 6 with diverse functionalized propiophenones 7 as source of nucleophile in high yields. This is an important approach that offers the flexibility of introducing the electron-donor or -acceptor functionalities in the molecular architecture of pyranone scaffolds.

Keywords: Ketene dithioacetal, Propiophenone, α-Pyranones, Nucleophiles

INTRODUCTION

α-Pyranones represents an important class of lactones that are substructures of many natural products [1-4] showing a wide range of biological activity, such as potent HIV protease inhibitor [5], antimicrobial [6,7], androgen-like [8], antifungal [9], anti-diabetic [10], anti-HCV activity [11,12], anti-malarial [13,14], anti-HSV activity [15] and phenomenal [16,17] effects. The phenomenal presence of this ring system in plants, animals, marine organisms, bacteria, insects and their involvement in different biological processes such as defense against other organisms, biosynthetic intermediates and as metabolites have made this scaffold as an important chemical entity. Although 2*H*-pyran-2-ones have been known for more than 100 y, due to their inaccessibility studies before the 1960s were limited to a small group of 6-unsubstituted-2-pyranones. Over recent decades, the chemistry of substituted and unsubstituted 2-pyranones has been investigated intensively and has led to the development of 2*H*-pyran-2-one (Figure 1) [18].

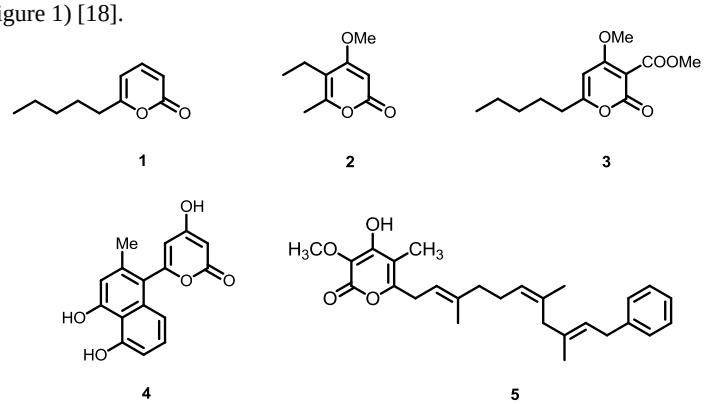


Figure 1: The structures of naturally occurring 2-pyranones 1-5

The naturally occurring 6-alkyl-2*H*-pyran-2-ones have been isolated from various strains of microorganism of genus *Trichoderma*. 6-*n*-Pentyl-2*H*-pyran-2-one 1 was the first metabolite identified as a fungal product of *Trichoderma viride* [19]. The 2*H*-pyran-2-one 1 possess a coconut aroma [20] and has been reported to be a component of peach [21] and nectarine essence [22-24]. The flavouring property of the 6-alkyl-2*H*-pyran-2-one has attracted great interest in the food industry. The macomellin 2 has been isolated from *Macrophoma commelinae* which is a causal agent of fruit rot disease of apple and other plants [25]. A new methyl 4-methoxy-6-pentylpyran-2-one-3-carboxylate, daldiniapyrone 3, together with several polycyclic compounds have been isolated from an EtOAc extract of fruit bodies of *Daldinia concentrica* [27]. A novel 6-naphthyl-2*H*-pyran-2-ones, dehydromutactin [26] 4 has been isolated from recombinant strains of *Streptomyces roseofulvus.* Few, marine sponges are rich source of prenylated pyranones having a broad range of biological activities [28,29]. Recently, new cytotoxic polyketide marine natural product such as Lehualide A5 has been isolated from a Hawaiian sponge of the genus *Plakortis* [30].

MATERIALS AND METHODS

Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) spectra were recorded on an AV-400 Bruker using the solvents indicated with 400 and 100 MHz, respectively. Deuterated Chloroform ($CDCl_3$) was used as the solvent. Chemical shifts are reported in parts per million (ppm) shift (δ-value) from Me_4Si (δ=0 ppm for ^{1}H) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constants (J) are given in hertz. Infrared (IR) spectra were recorded on a Perkin–Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm^{-1}). Melting points were obtained in open capillary tubes. All the reactions were carried out in dry Dimethyl Sulfoxide (DMSO) and were monitored by Thin Layer Chromatography (TLC); visualization was done with UV-light (254 nm).

General procedure for the synthesis of ethyl 2-cyano-3,3-dimethylsulfanylacrylate 6

Sodium ethoxide was prepared by dissolving sodium metal (1.72 g, 75 mmol) in ethanol (20 ml) at 0°C. After that ethyl cyanoacetate (5.65 ml, 50.0 mmol) was added drop wise for a period of 15 min at same temperature and resulted reaction mixture was vigorously stirred for another 15 min. Furthermore, carbon disulphide (3.2 ml, 50 mmol) was added drop wise at 20°C. Dimethyl sulfate (11.8 ml, 124 mmol) was added drop wise to the stirred solution over a period of 30 min and reaction mixture was stirred for another 15 min. After that excess ethanol was removed under vacuum and reaction mixture was poured into ice-cold water with constant stirring. The yellow crystalline solid compound was filtered, washed with cold water, dried and recrystallized in EtOAc-hexane (1:4).

General procedure for the synthesis of 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8a-e

A mixture of ethyl 2-cyano-3,3-dimethylsulfanylacrylate 6 (2.17 g, 10.0 mmol, 1.0 equiv.), propiophenones **7** (12 mmol, 1.2 equiv.) and KOH (0.84 g, 15 mmol, 1.5 equiv.) in dry DMSO (20 ml) was stirred at room temperature for 16-18 h. After completion, the reaction mixture was poured into ice water with constant stirring. The precipitate thus obtained was filtered and crude product was purified on a silica gel column chromatography using chloroform as eluent and isolated products were characterized as compound 8 by their spectroscopic analysis.

5-Methyl-4-methylsulfanyl-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile 8a

Yellow solid; m.p. 172-174°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=2.18 (s, 3H, Me), 3.03 (s, 3H, SMe), 7.43-7.55 (m, 5H, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ=14.8, 18.3, 112.6, 115.1, 129.0, 129.7, 131.5, 131.7, 158.3, 158.9, 171.0; IR (KBr) 1708 cm^{-1} (CO), 2214 cm^{-1} (CN); GC-MS: 258 (M^++1).

6-(4-Chlorophenyl)-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8b

Yellow solid; m.p. 188-190°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=2.15 (s, 3H, Me), 3.02 (s, 3H, SMe), 7.48 (s, 4H, ArH); IR (KBr) 1712 cm^{-1} (CO), 2217 cm^{-1} (CN); GC-MS: 292 (M^++1).\

5-Methyl-4-methylsulfanyl-2-oxo-6-*p*-tolyl-2*H*-pyran-3-carbonitrile 8c

Yellow solid; mp 128-130°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=2.16 (s, 3H, Me), 2.41 (s, 3H, Me), 3.01 (s, 3H, SMe), 7.23 (d, *J*=8.0 Hz, 2H, ArH), 7.41 (d, *J*=8.0 Hz, 2H, ArH); IR (KBr) 1722 cm^{-1} (CO), 2217 (CN) cm^{-1}; GC-MS: 272 (M^++1).

6-(4-Methoxyphenyl)-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8d

Yellow solid; mp 176-178°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=2.20 (s, 3H, Me), 3.00 (s, 3H, SMe), 3.88 (s, 3H, OMe), 6.94 (d, *J* 8.8 Hz, 2H, ArH), 7.50 (d, *J*=8.8 Hz, 2H, ArH); IR (KBr) 1713 cm^{-1} (CO), 2211 cm^{-1} (CN); GC-MS: 288 (M^++1).

6-(4-Isopropoxyphenyl)-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8e

Yellow solid; m.p. 192-194°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.38 (d, *J*=6.0 Hz, 6H, 2Me), 2.23 (s, 3H, Me), 3.01 (s, 3H, SMe), 4.56-4.70 (m, 1H, CH), 6.93 (d, *J*=8.8 Hz, 2H, ArH), 7.47 (d, *J*=8.8 Hz, 2H, ArH); IR (KBr) 1717 cm^{-1} (CO), 2216 cm^{-1} (CN); GC-MS: 316 (M^++1).

General procedure for the synthesis of 5-methyl-2-oxo 6-aryl-4-amino-2*H*-pyran-3-carbonitriles 10a-g

A mixture of 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8a-e (1.0 mmol, 1.0 equiv.) and secondary amines 9 (1.2 mmol, 1.2 equiv.) was refluxed in methanol (10 ml) for 6-8 h. The course of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool at room temperature for approximately 4-5 h. Finally, the reaction products were filtered and washed with methanol (2 × 5 ml) to yield desired 5-methyl-2-oxo 6-aryl-4-amino-2*H*-pyran-3-carbonitriles 10a-g.

5-Methyl-2-oxo-6-phenyl-4-piperidin-1-yl-2*H*-pyran-3-carbonitrile 10a

Yellow solid; m.p. 170-172°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.74-1.81 (m, 6H, $3CH_2$), 2.07 (s, 3H, Me), 3.52-3.57 (m, 4H, $2CH_2$), 7.38-7.46 (m, 3H, ArH), 7.49-7.60 (m, 2H, ArH); IR (KBr) 1724 cm^{-1} (CO), 2220 cm^{-1} (CN); GC-MS: 295 (M^++1).

5-Methyl-4-(4-methyl-piperidin-1-yl)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile 10b

White solid; m.p. 160-162°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.02 (d, *J*=6.3 Hz, 3H, Me), 1.26-1.39 (m, 2H, CH_2), 1.59-1.87 (m, 3H, CH & CH_2), 2.08 (s, 3H, Me), 3.30-3.42 (m, 2H, CH_2), 3.74-3.88 (m, 2H, CH_2), 7.41-7.52 (m, 3H, ArH), 7.52-7.61 (m, 2H, ArH); IR (KBr) 1712 cm^{-1} (CO), 2214 cm^{-1} (CN); GC-MS: 309 (M^++1).

6-(4-Chlorophenyl)-5-methyl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitrile 10c

White solid; m.p. 196-198°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.72-1.79 (m, 6H, $3CH_2$), 2.06 (s, 3H, Me), 3.52-3.58 (m, 4H, $2CH_2$), 7.38 (d, *J*=8.6 Hz, 2H, ArH), 7.49 (d, *J*=8.6 Hz, 2H, ArH); IR (KBr) 1701 cm^{-1} (CO), 2209 cm^{-1} (CN); GC-MS: 329 (M^++1).

5-Methyl-2-oxo-4-piperidin-1-yl-6-*p*-tolyl-2*H*-pyran-3-carbonitrile 10d

White solid; m.p. 214-216°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.71-1.81 (m, 6H, $3CH_2$), 2.08 (s, 3H, Me), 2.42 (s, 3H, Me), 3.51-3.62 (m, 4H, $2CH_2$), 7.25 (d, *J*=8.8 Hz, 2H, ArH), 7.48 (d, *J*=8.8 Hz, 2H, ArH); IR (KBr) 1715 cm^{-1} (CO), 2218 cm^{-1} (CN); GC-MS: 309 (M^++1).

6-(4-Methoxyphenyl)-5-methyl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitrile 10e

White solid; mp 158-160°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.72-1.77 (m, 6H, $3CH_2$), 2.10 (s, 3H, Me), 3.50-3.61 (m, 4H, $2CH_2$), 3.88 (s, 3H, OMe), 6.94 (d, *J*=8.8 Hz, 2H, ArH), 7.54 (d, *J*=8.8 Hz, 2H, ArH); IR (KBr) 1688 cm^{-1} (CO), 2206 cm^{-1} (CN); GC-MS: 325 (M^++1).

6-(4-Methoxyphenyl)-5-methyl-2-oxo-4-(4-phenyl-piperazin-1-yl)-2*H*-pyran-3-carbonitrile 10f

White solid; mp 228-230°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=2.15 (s, 3H, Me), 3.30-3.43 (m, 4H, $2CH_2$), 3.74-3.85 (m, 4H, $2CH_2$), 3.87 (s, 3H, OMe), 6.86-7.02 (m, 5H, ArH), 7.27-7.39 (m, 2H, ArH), 7.56 (d, *J*=8.6 Hz, 2H, ArH); IR (KBr) 1714 cm^{-1} (CO), 2215 cm^{-1} (CN); GC-MS: 402 (M^++1).

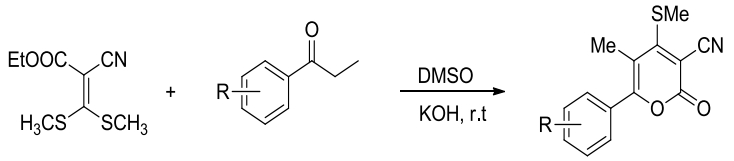
6-(4-Isopropoxyphenyl)-5-methyl-2-oxo-4-(4-phenyl-piperazin-1-yl)-2*H*-pyran-3-carbonitrile 10g

Yellow solid; m.p. 206-208°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.37 (d, *J*=6.0 Hz, 6H, 2Me), 2.16 (s, 3H, Me), 3.30-3.41 (m, 4H, $2CH_2$), 3.74-3.86 (m, 4H, $2CH_2$), 4.56-4.69 (m, 1H, CH), 6.87-7.01 (m, 5H, ArH), 7.28-7.36 (m, 2H, ArH), 7.54 (d, *J*=8.8 Hz, 2H, ArH); IR (KBr) 1708 cm^{-1} (CO), 2213 cm^{-1} (CN); GC-MS: 430 (M^++1).

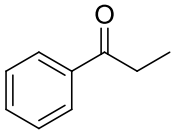
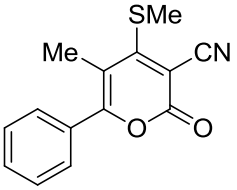
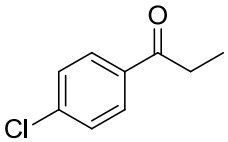
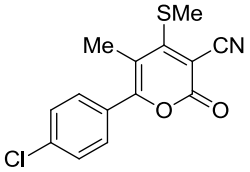
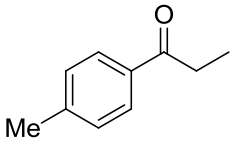
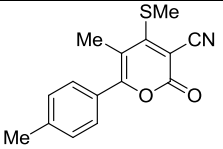
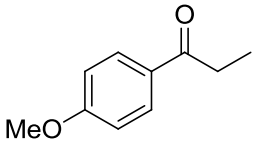
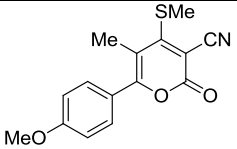
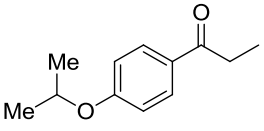
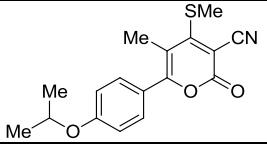
RESULTS AND DISCUSSION

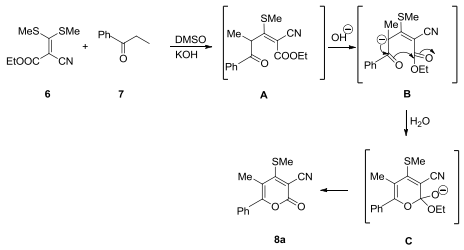
Numerous synthetic methodologies have been recently developed for the synthesis of α-pyranones. The most common strategy for the synthesis of α-pyranone ring system is through acid catalysed condensation cyclization of β-ketoesters [31]. Rossi and co-workers [32,33] developed a convenient protocol for the synthesis of natural and unnatural 6-substituted and 5,6-disubstituted α-pyran-2-ones, which involved iodolactonization of 5-substituted-(z)-2-ene-4-ynoic acids. 4,6-Disubstituted and 4,5,6-trisubstituted α-pyranones have been synthesized by heating phosphorane with different 1,3-diketones [34]. Yao and Larock [35] have synthesized 5-halo-6-alkyl-2*H*-pyran-2-ones by the intramolecular cyclization of (Z)-2-alken-4-ynoates using inter-halogen compound ICl, other approaches include reaction of β-substituted functionalized alkenes with diethyl malonate using K_2CO_3 as a catalyst [36], reaction of acetylenic aldehyde and 5-substituted Meldrum's acid [37], thermal or photochemical cyclization of 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones [38]. Recently Kim and co-workers [39-42] have synthesized 3,5,6-trisubstituted α-pyranones by the reaction of Baylis-Hillman acetate with deoxybenzoin in the presence of *t*-BuOK followed by alkaline hydrolysis.

Table 1: Synthesis of α-pyranones 8 by the reaction of ethyl 2-cyano-3,3-dimethylsulfanylacrylate 6 with propiophenones 7



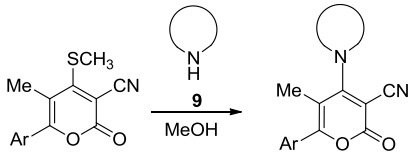
6 **7** **8**

Entry	Structure 7	Structure 8	Yield (%)
a			72
b			68
c			76
d			74
e			77



Scheme 1: Synthesis of α-pyranones

Table 2: Synthesis of 5-methyl-2-oxo 6-aryl-4-amino-2*H*-pyran-3-carbonitriles 10a-g from α-pyranones 8



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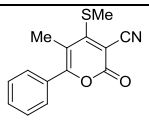
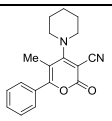
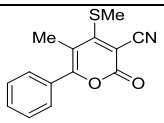
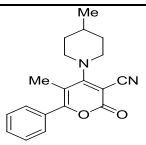
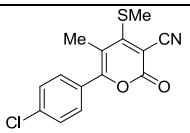
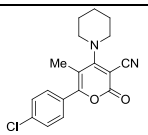
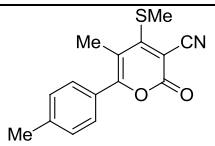
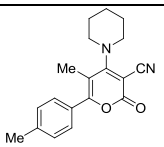
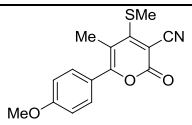
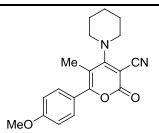
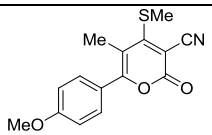
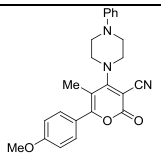
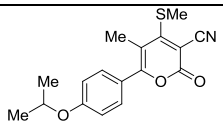
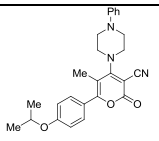
a			75
b			76
c			78
d			72
e			74
f			77
g			70

The importance of 2-pyranones as synthon in the field of synthetic and medicinal chemistry has been recognized due to its unique structural features and diverse pharmacological properties [43]. Tominaga et al. [44] reported the synthesis of 2*H*-pyran-2-ones from the reaction of polarized ketene dithioacetals with aryl ketones. Ketene dithioacetals used as a parent precursor were conveniently prepared by alkyl cyanoacetate, carbon disulfide and methyl iodide in the presence of a base in good yield [45]. These thioacetals are versatile intermediates to develop a wide range of heterocycles when reacted with different nucleophilic substrates.

Herein, we report an efficient and convenient procedure for the synthesis of 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles 8a-e through the reaction of ethyl 2-cyano-3,3-dimethylsulfanylacrylate 6 with propiophenones 7 in high yields at room temperature.

In order to prepare 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles 8a-e, we performed a reaction of ketene dithioacetal 6 with different propiophenones 7 in DMSO in the presence of potassium hydroxide at room temperature afforded 6-aryl-5-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile 8a-e in moderate to good yields (Table 1). All the synthesized compounds were characterized by the spectroscopic analysis.

The possible mechanism for the synthesis of α-pyranones 8a-e is depicted in Scheme 1. The reaction is possibly initiated by Michael addition of an enolate of 7 to ketene dithioacetal 6 to form an intermediate A. This intermediate in the presence of a base intramolecular cyclizes to intermediate C, which on elimination of ethanol afforded alkylated α-pyranones 8a-e.

α-Pyranones 8 have three electrophilic centers C-2, C-4 and C-6, in which C-6 is likely more prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing group at position 3. Further we performed a reaction of α-pyranones 8a-e with different cyclic secondary amines 9 in methanol at reflux temperature afforded 5-methyl-2-oxo 6-aryl-4-amino-2*H*-pyran-3-carbonitriles 10a-g in 70-78% yields (Table 2).

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