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A facile and efficient synthesis of 4-substituted derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile

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ABSTRACT

The reaction of acetyl molecules with a ketene thioacetal, have been developed a facile and efficient synthesis of 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2H-pyran-3-carbonitrile from efficient method by using aromatic ketone refluxing with ethyl 2-isocyano-3,3-bis(methylthio) acrylate in presence of anhydrous K_2CO_3 in DMF.

Keywords: Aromatic ketone, anhydrous K_2CO_3, DMF, ethyl 2-isocyano-3,3-bis(methylthio) acrylate.

INTRODUCTION

The ketene dithioacetal derivatives are used for formation of various heterocyclic compounds. The 2*H*- pyran-2-ones moieties are extensive literature survey in heterocyclic compound 6-aryl-3-cyano-4-substitued phenoxy-2*H*-pyran-2-ones are prepared from 6-aryl -3-cyano-4-methylthio-2H-pyran-2-one. The ketene dithioacetal of 2*H*-pyra-2-ones revealed that they possess pharmacological activities such as Antifungal[1-2] , Antipyretic[3] , Antitumor[4-5] , analgesic[6] , Anti-inflammatory[6] , 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile these synthetic derivatives has found to exhibit pharmacological activities.

Organic chemists reported various methods for synthesis of ketene dithioacetal of 2*H*-pyra-2-ones derivatives. F.V. Singh *et al*[7] , have synthesized of 6-aryl -3-cyano-4-methylthio-2*H*-pyran-2-ones from by using KOH in DMF as catalyst. Yoshinori Tominaga *et al* [8] , have synthesis of have synthesis of 4-(methylthio)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile by using methyl-2-cyano -3,3-bis (methyl thio) acrylate[9] and aromatic ketone in presence of potassium hydroxide ,DMS as solvent. Vishnu Ji Ram *et al*[10] , synthesis of 6-phenyl-4-methylthio-2*H*-pyran-2-one-3-carbonitrile[11-14] . From the reaction of methyl 2-cyano-3,3-dimethylthioacrylate with aryl methyl ketone in the presence of KOH in DMSO at room temperature .Overall, all these reported methods are effective but which require long time, less yield. So, in order to overcome problem, keeping less time approach in mind, in the present investigation a we have reported synthesis of 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2H-pyran-3-carbonitrile derivatives by using anhydrous K_2CO_3 as a catalyst and DMF. By simple and efficient methods. With good nucleophiles such as phenol it gave the product from replacement of the thiomethyl group by the nucleophile as substituted phenol having good yield. Potassium carbonate is useful as an efficient in heterocyclic molecules.

MATERIALS AND METHODS

All Melting points were determined on electro-thermal (i.e. capillary tube) melting point apparatus and are uncorrected. Infrared, IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer. Mass spectral

data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H-NMR and ^{13}C- NMR spectra were recorded on various spectrometers at 400MHz and 100MHz respectively with Tetramethylsilane (TMS) as an internal standard.

General procedure for the synthesis of 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile (5a-5g):

A mixture of Acetophenone (3mmol), ethyl 2-cyano-3,3-bis (methyl thio) acrylate (3mmol) was gently refluxed for five to seven hours at 50 ^{0}C in the presence of powered anhydrous potassium carbonate and N,N-Dimethylformamide (DMF) (15ml) to form 3-cyano -3-methylthio -6-phenyl -2H-pyran-2-one. The formed compound was refluxed with different substituted phenols in presence of potassium carbonate and DMF for four to five hours at 50 ^{0}C, to give 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile. After cooling the reaction mixture was poured into ice-cold water and neutralized by dil. Hydrochloric acid the precipitate obtained was collected by filtration, washed with cold water and recrystalised from methanol.

Spectral Analysis:

2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile (5a):

M.P. 156-159^{0}C, Yield 56% IR (KBr/ cm^{-1}): 2200 (-CN), 1715(C=O),1130(R-O-R');^{1}H-NMR:(400MHz,DMSO-d_{6}/ ppm) δ 7.08-7.42 (m,5H-Ar), δ 6.82-7.08 (m,4H-Ar), δ 6.78 (s,1H), ES-MS (m/z: RA %): 290 (M+1) , Elemental analysis calculated for $C_{18}H_{11}NO_3$ C, 74.73; H, 3.83; N, 4.84; found C, 74.71; H, 3.81; N, 4.82.

4-(4-methoxyphenoxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile(5b):

M.P. 176-179^{0}C, Yield 82%. IR (KBr/ cm^{-1}) 2250 (CN), 1710(CO),1140 (R-O-R$^{'}$);^{1}H-NMR:(400MHz,DMSO-d_{6}/ppm) δ7.08-7.42(m,5H-Ar), δ 6.82-7.08(m,4H-Ar), δ 6.78(s,1H), δ 3.70 (s,3H), ES-MS (m/z: RA %): 320 (M+1), Elemental analysis calculated for $C_{19}H_{13}NO_4$ C, 71.47; H, 4.10; N, 4.39;.found C, 71.45; H, 4.08; N, 4.37.

4-(p-tolyloxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile (5c):

M.P. 135-138^{0}C, Yield 79%. IR (KBr/ cm^{-1}) 2245(CN), 1690 (CO),1132 (R-O-R$^{'}$); ^{1}H-NMR:(400MHz,DMSO-d_{6}/ppm) δ7.10-7.50 (m,5H-Ar), δ 6.76-7.15 (m,4H-Ar), δ 6.85 (s,1H), δ 2.35 (s,3H), ES-MS (m/z: RA %): 304 (M+1), Elemental analysis calculated for $C_{19}H_{13}NO_3$ C, 75.24; H, 4.32; N, 4.62. found C, 75.22; H, 4.30; N, 4.60.

4-(4-bromophenoxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile(5d):

M.P. 190-193^{0}C , Yield 80%.IR (KBr/ cm^{-1}): 2262(CN), 1706 (CO),1170 (R-O-R').^{1}H-NMR:(400MHz,DMSO-d_{6}/ppm)δ7.05-7.63(m,5H-Ar), δ 6.62-7.30(m,4H-Ar), δ 6.79(s,1H), ES-MS(m/z: RA %): 369 (M+1), Elemental analysis calculated for $C_{18}H_{10}BrNO_3$ C, 58.72; H, 2.74; Br, 21.70; N, 3.80. found C, 58.70; H, 2.72; Br, 21.68; N, 3.78.

4-(4-chlorophenoxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile(5e):

M.P. 185-188^{0}C, Yield 77 % IR (KBr/ cm^{-1}): 2235(CN), 1712 (CO),1140 (R-O-R'), ^{1}H-NMR:(400MHz,DMSO-d_{6}/ppm)δ7.10-7.72(m,5H-Ar), δ 6.68-7.42(m,4H-Ar), δ 6.89(s,1H), ES-MS (m/z: RA %): 324 (M+1), Elemental analysis calculated for $C_{18}H_{10}ClNO_3$ C, 66.78; H, 3.11; Cl, 10.95; N, 4.33. found C, 66.76; H, 3.09; Cl, 10.93; N, 4.31.

4-(4-nitrophenoxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile(5f):

M.P. 200-203^{0}C, Yield 60%. IR (KBr/ cm^{-1}): 2246(CN), 1720 (CO),1135 (R-O-R').^{1}H-NMR:(400MHz,DMSO-d_{6}/ppm) δ7.14-7.78 (m,5H-Ar), δ 6.98-8.02 (m,4H-Ar), δ 6.80(s,1H), ES-MS (m/z: RA %): 335 (M+1), Elemental analysis calculated for $C_{18}H_{10}N_2O_5$ C, 64.67; H, 3.02; N, 8.38. ,found C, 64.65; H, 3.00; N, 8.36.

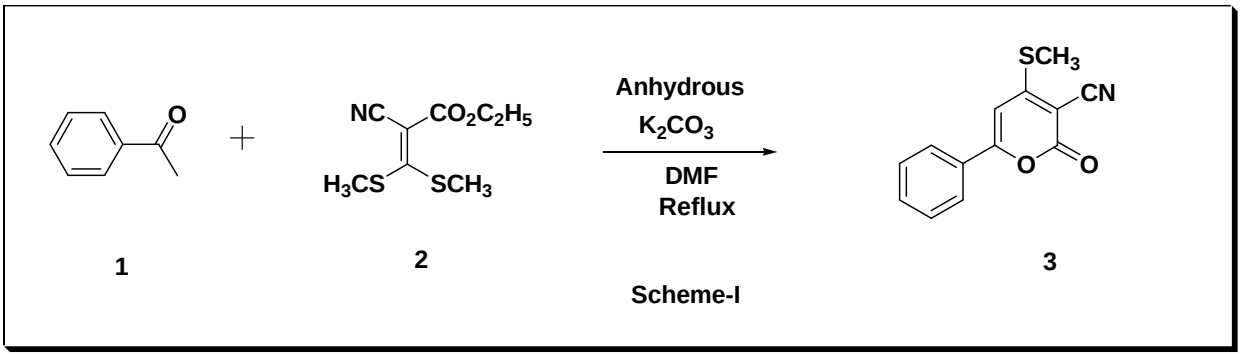
4-(4-fluorophenoxy)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile(5g):

M.P. 161-163^{0}C, Yield 58%. IR (KBr/ cm^{-1}) 2235(CN), 1718 (CO), 1154 (R-O-R'). ^{1}H-NMR:(400MHz,DMSO-d_{6}/ ppm) δ7.16-7.64 (m,5H-Ar), δ 6.71-7.32(m,4H-Ar), δ 6.69(s,1H). ES-MS (m/z: RA %): 308 (M+1), Elemental analysis calculated for $C_{18}H_{10}FNO_5$ C, 70.36; H, 3.28; F, 6.18; N, 4.56.,found C, 70.34; H, 3.26; F, 6.16; N, 4.54.

RESULTS AND DISCUSSION

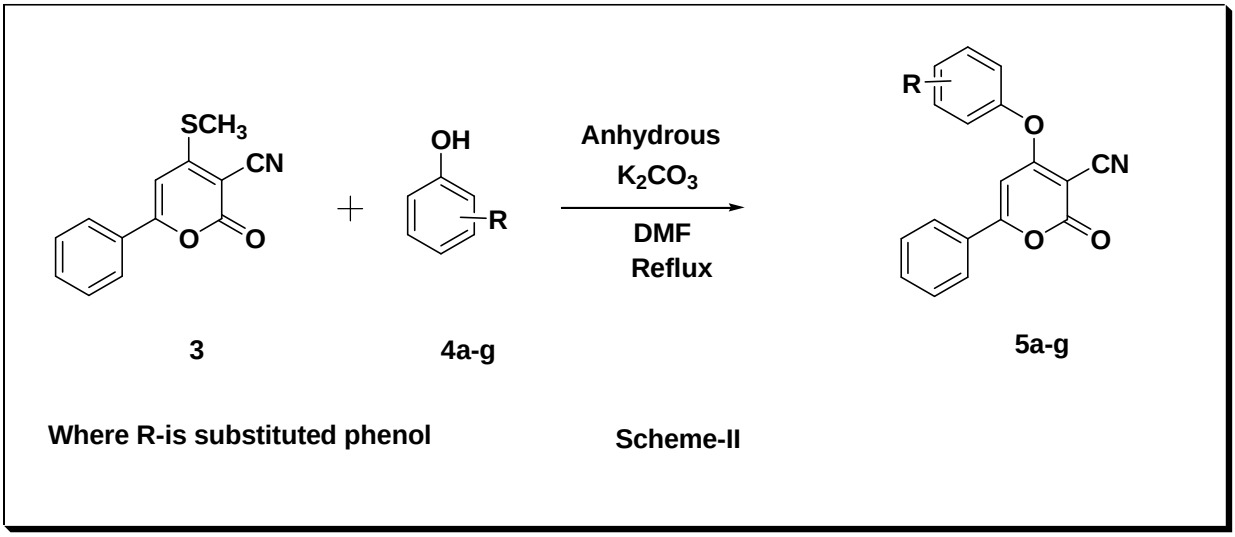
Reaction procedure: A mixture of Acetophenone (3mmol) **(1),** ethyl 2-cyano-3,3-bis (methyl thio) acrylate (3mmol) **(2)** was refluxed for five to seven hours at 50 ^{0}C in presence of powered anhydrous potassium carbonate in N,N- Dimethylformamide (DMF) (15 ml) to form 3-cyano -3-methylthio-6-phenyl-2*H*-pyran-2-one **(3).** 3-cyano -3-methylthio -6-phenyl -2*H*-pyran-2-one **(3)** was refluxed with different substituted phenols **(4)** afford in presence of potassium carbonate and DMF for five to six hours at 50 ^{0}C, to afford 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile **(5)**. The reaction mixture was poured into ice-cold water and neutralized

by dil. Hydrochloric acid. The formed solid was collected by filtration, washed with water and recrystalised from methanol to give 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile. The progress of reaction is monitored by TLC .(Scheme-I & II)



1 **2** **3**

Scheme-I



3 **4a-g** **5a-g**

Where R-is substituted phenol

Scheme-II

The structures of these compounds were assigned on the basis of elemental analysis and spectral data. All synthesized compound exhibits IR (KBr) absorption bands at 2160 cm^{-1} is due to –CN stretching, carbonyl group of ketone at 1690 cm^{-1} and the stretching at ,1100-1230 cm^{-1} due to - C-O-C- ether stretching.

Table No. 1

Entry	Phenol (Ar-OH)	Time (Hrs)	Yield%	Found M.P.^{0}C
5a	-C_6H_5	7	56%	156-159
5b	4-OCH_3 C_6H_4	5	82%	176-179
5c	4-CH_3 C_6H_4	4	79%	135-138
5d	4-Br C_6H_4	4.5	80%	190-193
5e	4-Cl C_6H_4	6	77%	185-188
5f	4-NO_2 C_6H_5	6.5	60%	200-203
5g	4-F C_6H_4	5	58%	161-163

CONCLUSION

In conclusion, we have demonstrated an environmentally benign potassium carbonate catalyzed reaction in DMF for the synthesis of 4-substitued derivatives of 2-oxo-4-phenoxy-6-phenyl-2*H*-pyran-3-carbonitrile. The method was quite efficient, economical, easy to workup, eliminates the use of hazardous organic solvents and toxic catalysts and thus provides a better and practical alternative to exisisting procedures.

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