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UNCATALYZED SYNTHESIS OF NEW FUNCTIONALIZED FURO-PYRAN DERIVATIVES VIA PSEUDO FOUR-COMPONENT REACTION (3+1) OF ISOCYANIDES WITH BENZYLIDENE-SUBSTITUTED MELDRUM'S ACID

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ABSTRACT

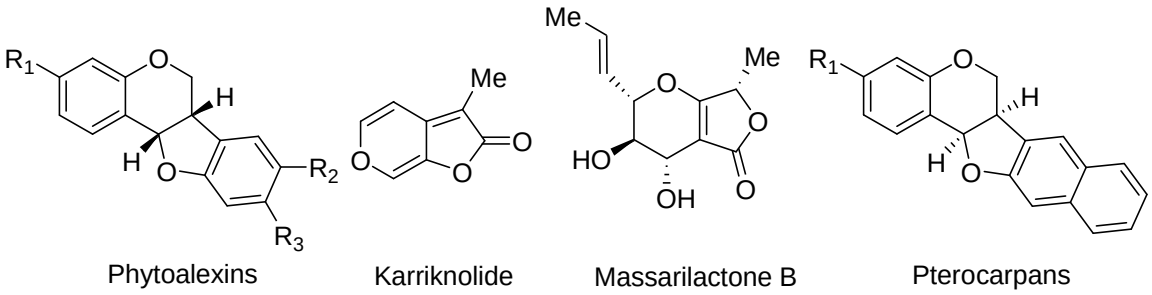
Knoevenagel condensation reaction of aromatic aldehyde containing ethylene and acetylene groups with Meldrum,s acid in aqueous media produces benzyliden-substituted Meldrum's acid in high yields. A pseudo four-component (3 + 1) reaction of an alkyl isocyanide with functionalized benzylidene-substituted Meldrum's acid at room temperature produced new furo [3, 4-b] pyran-5(7*H*)-one derivatives in good yields. It is interesting that tree molecule of alkyl isocyanide were added to unsaturated arylidene meldrum's acid. The structures of the synthesized compounds (furo-pyran skeleton) were confirmed by IR, 1H NMR, 13C NMR spectroscopy and elemental analysis. The products are structurally similar to 2H-furo [2, 3-c] pyran-2-one natural products.

KEY WORDS: Furo-pyran,Meldrum's acid, Alkyl isocyanide, Furo-pyran, Isocyanide based multicomponent reactions (IMCR)

Introduction

Rich structural diversity and complexity of natural products have prompted chemists over the ages to produce these compounds in the laboratory while having therapeutic applications on the mind in most of the cases. Overall, many drugs which are used today are natural products or natural product derivatives. Most of these pharmaceuticals have improved life quality and expectancy of those people living in the developed world. Furo-pyran skeleton could be frequently found in various natural and biological products such as Phytoalexins, Massarilactone B, pterocarpans and Karrikinolide(Fig. 1.) (Wagner and Gompper 1974, Nicolaou et al. 2001, Genisson et al. 1994, Genisson and Young 1994, Chapman et al. 1971). Phytoalexins and pterocarpans are generally provided using o-quinonemethides generated in situ from *O*-hydroxybenzaldehydes and alkenols. This method is a useful access for fused pyranobenzopyrans (Miyazaki et al. 1999, Yadav et al. 2002, Saito et al. 2003). Karrikinolide, 3-methyl-2*H*-furo[2,3-c]pyran-2-one and analogous compounds have been isolated from plant-derived smoke and act to promote seed germination of a wide range of plant species at extremely low concentrations (Scaffidi et al. 2011, Matsuo and Shindo 2011, Flematti et al. 2005). Antibacterial Massarilactone B was isolated by Gloer from the freshwater aquatic fungus, Massarinatunicate (Oh et al. 2001). These compounds are usually synthesized usinga multi-step approach which is often done in very forcing reaction conditions

(Gao and Snider 2004, Gao et al. 2003).



Phytoalexins Karriknolide Massarilactone B Pterocarpans

Fig. 1. Natural compounds containing furo-pyran skeleton

Isocyanide-based multi-component reactions (IMCRs) which have been of particular interest due to using easily available starting materials tolerate a variety of functional groups. Numerous variations and subsequent transformations make a fairly large number of unique structures available, which would otherwise need lengthy preparations. During the past two decades, field of IMCR research has had tremendous developmentas a result of discovering and developing new variations of classical Passerini and Ugi IMCRs and obtained significant interest in the scientific community as an efficient, convenient, time-saving and atom-economical approach toward a large group of drug-like small heterocyclic molecules (Dömling and Ugi 2000, Zhu 2003, Akritopoulou-Zanze 2008, Sadjadi and Heravi 2011, Banfi et al. 2008, Domling 2006).

As a part of the present authors' continuing interest in development of new synthetic methods in heterocyclic chemistry and also in isocyanide-based multi-component reactions (Sheikhhosseini et al. 2011 and 2014, Balalaie et al. 2012), reaction of alkylidene or arylidene Meldrum's acid and isocyanide that led to furo[3,4-b]pyran derivatives was reported here (Habibi et al. 2011 and 2013). In order topromote this method (3+1 IMCR) for synthesizing novel functionalized furo[3,4-b]pyran derivatives, the result of this approach was intended to be reported for synthesizing some novel furopyran derivatives.

Experimental

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and are uncorrected. IR spectra were obtained on an *ABB* FT-IR *FTLA 2000* spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were run on *Bruker*spectrometers at 300, 400 MHz for ^{1}H-NMR, and 75, 100 MHz for ^{13}C-NMR. $CDCl_3$ was used as solvent. Elemental analyses were performed using a Heraeus CHN-S-O-Rapid analyzer.

*General procedure for the synthesis of O-propargylatedsalicylaldehyde **2b, c, d**:*

In a round-bottomed flask, salicylaldehyde derivatives (8 mmol), propargyl bromide (10 mmol) and K_2CO_3(10 mmol) in DMF (15 ml) were stirred at room temperature for 48 h. after completion

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reaction, was diluted with water (15 mL) and the solid product was filtered on Buchner funnel. *The general procedure for the synthesis of benzylidene-substituted Meldrum's acid* ***3:*** A mixture of Meldrum's acid (4.5 mmol) and cinnamaldehyde **2a** or *O*-propargylatedsalicylaldehyde **2b, c, d** (4 mmol) in water/ethanol (10 mL, 1: 1) was stirred at reflux for 3 h. After cooling to room temperature the solid product was filtered on Buchner, recrystallized from ethanoland dried under vacuum.

General procedure for the synthesis of 5a–e: A mixture of 3 mmol of isocyanide **4** in 3 mL of CH_2Cl_2 was added dropwise to a solution of functionalized alrylidene-substituted Meldrum's acid **3** (1 mmol) in absolute CH_2Cl_2 (15 mL) at room temperature. The reaction mixture was stirred until the disappearance of the starting material (6-10 h), (monitored by TLC), solution was evaporated and was diluted with ethanol (15 mL), precipitate solid product was recrystallized from ethanol.

(2Z,7Z)-3-(cyclohexylamino)-2,7-bis(cyclohexylimino)-4-styryl-2H-furo[3,4-b]pyran-5(7H)-one ***(5a)****.* Mp: 176-178°C. IR (KBr) (υ_{max}/cm^{-1}): 3279, 1793, 1693, 1662. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23-1.80 (m,30H, 15CH_2), 3.56 (m, 1H, CH-N), 3.84 (m, 1H, CH-N), 4.02 (m, 1H, CH-N), 5.90 (d, *J* = 7.6 Hz, 1H, NH), 7.05 (d, *J* = 16.5 Hz, 1H, HC=), 7.22 (d, *J* = 16.5 Hz, 1H, HC=), 7.26 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.36 (t, *J* = 7.4 Hz, 2H, H-Ar), 7.49 (d, *J* = 7.5 Hz, 2H, H-Ar) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.1, 24.2, 24.6, 25.5, 25.6, 25.9, 33.1, 33.5, 33.6, 52.7, 53.6, 58.0, 107.0, 111.9, 119.2, 126.5, 127.9, 128.7, 134.6, 134.7, 137.2, 141.7, 145.7, 162.7. Anal. Calc. for $C_{33}H_{41}N_3O_3$ (527.31): C, 75.11; H, 7.83; N, 7.96. Found: C, 75.36; H, 7.72; N, 7.84.

(2Z,7Z)-3-(tert-butylamino)-2,7-bis(tert-butylimino)-4-styryl-2H-furo[3,4-b]pyran-5(7H)-one ***(5b)****.* Mp: 66-69°C. IR (KBr) (υ_{max}/cm^{-1}): 3292, 1798, 1699, 1655. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9H, *t*-But), 1.39 (s, 9H, *t*-But), 1.42 (s, 9H, *t*-But), 4.85 (br. s, 1H, NH), 7.20 (d, *J* = 16.8 Hz, 1H, HC=), 7.27 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.37 (t, *J* = 7.4 Hz, 2H, H-Ar), 7.54 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.86 (d, *J* = 16.8 Hz, 1H, HC=) ppm.^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 29.7, 30.2, 31.0, 54.7, 56.5, 57.4, 108.3, 120.6, 122.3, 126.8, 127.9, 128.6, 134.0, 136.7, 137.4, 138.9, 146.1, 135.6, 162.8. Anal. Calc. for $C_{27}H_{35}N_3O_3$ (449.27): C, 72.13; H, 7.85; N, 9.35. Found: C, 72.36; H, 7.82; N, 9.17.

(2Z, 7E)-3-(cyclohexylamino)-2, 7-bis (cyclohexylimino)-4-(2-(prop-2-ynyloxy) phenyl)-2H-furo [3, 4-b] pyran-5(7H)-one ***(5c)****.* Mp: 159-160 °C. IR (KBr) (υ_{max}/cm^{-1}): 3332, 3292, 2211, 1811, 1662, 1652. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02-1.87 (m, 30H, 15CH_2), 2.48 (t, *J* = 2.4 Hz, CH), 3.80-3.87 (m, 2H, CH-N), 4.08 (m, 1H, CH-N), 4.70 (d, *J* = 2.4, CH_2-O), 5.94 (d, *J* = 9.2 Hz, 1H, NH), 7.03 (t, *J* = 7.6 Hz, H-Ar), 7.13 (d, *J* = 8.4 Hz, H-Ar), 7.24 (dd, *J* = 7.4, 2.0 Hz, H-Ar), 7.40 (td, *J* = 8.4, 1.6 Hz, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.3, 24.6, 25.5, 25.6, 25.9, 33.1, 33.4, 51.9, 53.4, 55.9, 57.8, 75.4, 78.8, 111.8, 113.5, 120.8, 122.3, 129.7, 129.8, 131.6, 134.1, 145.3, 150.2, 155.9, 161.9. Anal. Calc. for $C_{34}H_{41}N_3O_4$ (555.31): C, 73.49; H, 7.44; N, 7.56. Found: C, 73.70; H, 7.38; N, 7.64.

(2Z,7Z)-3-(tert-butylamino)-2,7-bis(tert-butylimino)-4-(2-(prop-2-ynyloxy)phenyl)-2H-furo[3,4-b]pyran-5(7H)-one ***(5d)****.* Mp: 211-214 °C. IR (KBr) (ϑ_{max}/cm^{-1}): 3344, 3298, 2208, 1795, 1704, 1565. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9H, *t*-But), 1.41 (s, 9H, *t*-But), 1.80 (s, 9H, *t*-But), 2.50 (t, *J* = 2.4 Hz, CH), 4.71 (d, *J* = 2.4, CH_2-O), 4.83 (br. s, 1H, NH), 7.06-7.12 (m, 2H, H-Ar), 7.25 (dd, *J* = 7.2, 1.6 Hz, H-Ar), 7.39 (td, *J* = 8.4, 1.6 Hz, H-Ar)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2, 31.5, 31.7, 54.3, 55.7, 56.4, 56.8, 76.2, 78.3, 110.9, 112.9, 120.7, 121.4, 129.5,

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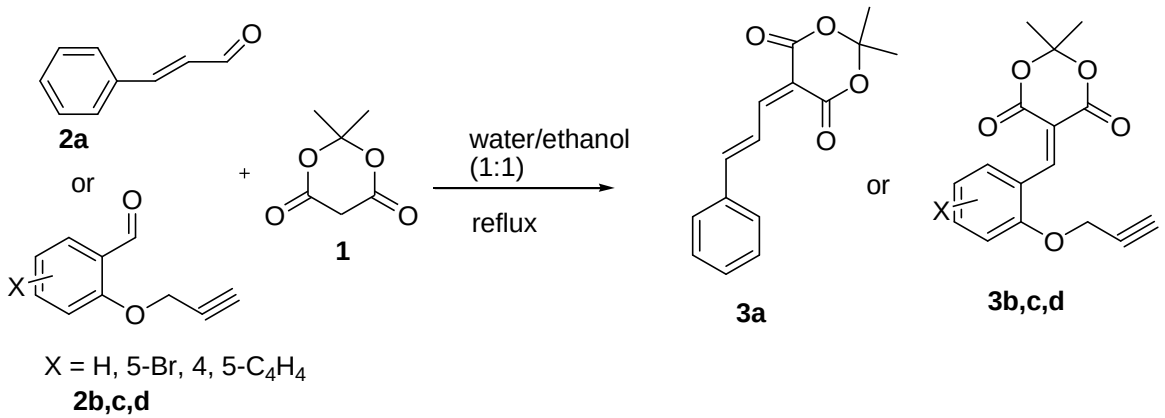
129.8, 130.7, 134.0, 145.2, 149.9, 156.2, 161.8. Anal. Calc. for $C_{28}H_{35}N_3O_4$ (477.26): C, 70.42; H, 7.39; N, 8.80. Found: C, 70.61; H, 7.35; N, 8.59.

*(2Z,7Z)-3-(tert-butylamino)-2,7-bis(tert-butylimino)-4-(5-bromo-2-(prop-2-ynyloxy)phenyl)-2H-furo[3,4-b]pyran-5(7H)-one (**5e**).* Mp: 150-152 ^{o}C. IR (KBr) (υ_{max}/cm^{-1}): 3338, 3304, 2211, 1808, 1703, 1690. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9H, *t*-But), 1.40 (s, 9H, *t*-But), 1.44 (s, 9H, *t*-But), 2.52 (t, *J* = 2.4 Hz, CH), 4.70 (d, *J* = 2.4, CH_2-O), 5.20 (s, 1H, NH), 7.01 (d, J = 9.2, H-Ar), 7.45-7.48 (m, 2H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 30.2, 30.4, 54.7, 55.9, 56.4, 56.5, 75.8, 78.2, 11.1, 113.4, 113.7, 125.8, 132.5, 134.3, 137.2, 138.7, 146.2, 150.4, 155.7, 161.9. Anal. Calc. for $C_{28}H_{34}BrN_3O_4$ (555.17): C, 60.43; H, 6.16; N, 7.55. Found: C, 60.55; H, 7.24; N, 8.38.

Result and Discussion

Due to the importance of furo-pyran skeleton, Initially,The*O*-propargylatedsalicylaldehydes**2b,c,d** were prepared from the corresponding substituted salicylaldehydes with good to excellent yields by applying Williamsons ether synthesis.Then benzylidene-substituted Meldrum's acid **3a-d** was obtained from the reaction of functionalized aldehyde and Meldrum's acid in water with high yield (Scheme 1).



Scheme **1**: Synthesis of benzylidene-substituted Meldrum's acid

In continuance, one-pot four-component reaction (3+1) between arylidene-substituted Meldrum's acid **3a-d** and isocyanide **4a**,**b** led to the substituted furopyrans **5** in moderate yields and high bond forming efficiency at ambient temperature without using any catalyst (Scheme 2). It was satisfying to observe that the reaction was complete in 6 hours and was typically characterized by the separation of a solid product from the concentrated reaction mixture by adding methanol.

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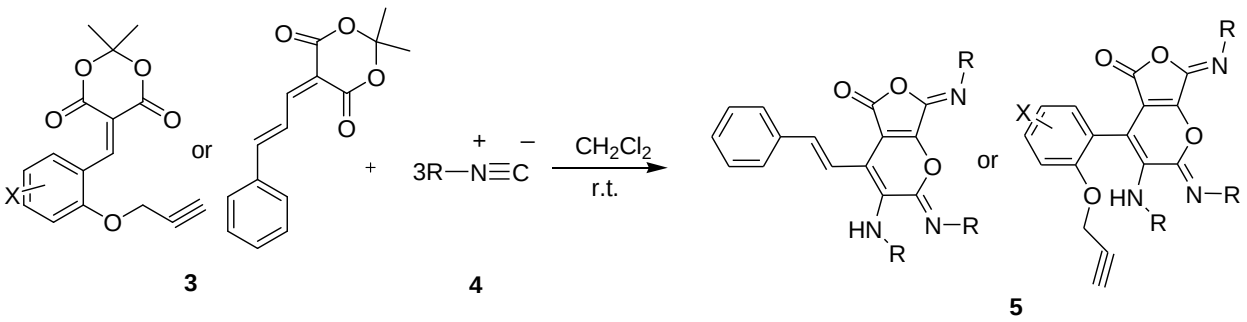
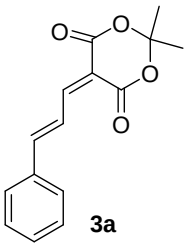
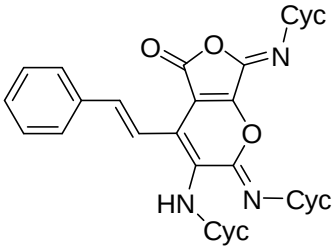
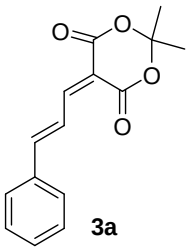
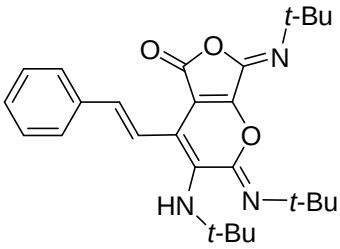


Scheme 2: The (3+1) multi-component reaction of **1** and **2**

Isolation and spectroscopic characterization of the separated solid indicated that, similar to previous work, three molecules of isocyanide react with one molecule of arylidene-substituted Meldrum's acid in one step and the desired (2*Z*,7*E*)-3-(alkylamino)-2,7-bis(alkylimino)-4-(2-aryl)-2*H*-furo[3,4-b]pyran-5(7*H*)-onewas obtained.

This result provoked us to investigate this strategy for the synthesis of a chemical library of furo-pyrans. Aiming at this objective, we performed reactions of cyclohexylisocyanide and *t*-butylisocyanide with several arylidene-substituted Meldrum's acid (Table 1). After compellation reaction the solvent was removed under reduced pressure.The product was precipitated by addition of methanol and standingfor a few hours, then collected by filtration and recrystallized from methanol.

Table 1**.** Synthesis offunctionalizedfuro-pyran derivatives **5a-e**

Entry	ArIsocyanide	Product	Yield (%)
1	 **3a**	**4a** (Cyc)[a]  **5a**	70
2	 **3a**	**4b** (*t*-But)[b]  **3b**	75

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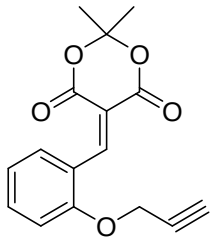
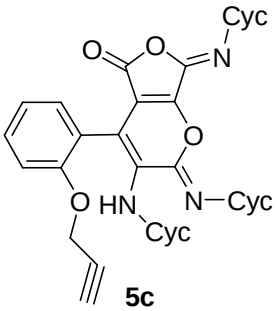
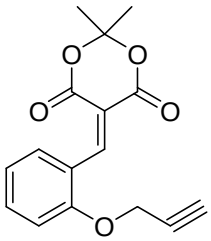
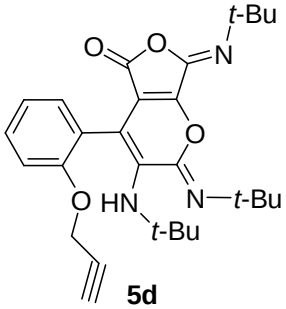
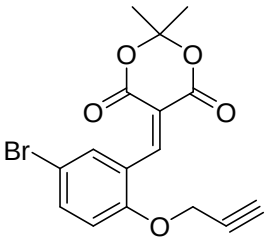
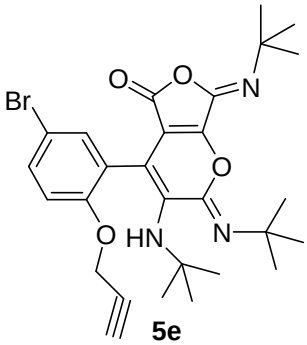
3	 **3b**	**4a** (Cyc)	 **5c**	65
4	 **3b**	**4b** (*t*-But)	 **5d**	68
5	 **3c**	**4b** (*t*-But)	 **5e**	65

a) Cyclohexylisocyanide
b) *t*-butylisocyanide

O-Propargyloxybenzaldehyde was used as starting material for the synthesis of products **5c-e**. We believe that this new functionality based multicomponent reactions have a huge potential in creating new molecules or simplifying the synthesis of existing compounds and the synthesized products have good potential for further reactions. The products **5a-e** could be used as starting material for some reactions such as: Click chemistry, Pauson-Khand reaction, and cyclization reaction.

The structures of compounds **5a–e** were deduced from their elemental analysis and their IR, ^{1}HNMR and ^{13}C NMR spectra. For example, the IR spectrum of **5e** shows several bands at 3338 (NH), 3304 (HC-Sp), 2211 (C-sp), 1808 (C=O), 1703 and 1690 (C=N) cm^{-1}.
The ^{1}H NMR spectrum of **5e** exhibited tree singlet (δ = 0.93, 1.40 and 1.44 ppm) for the tree *t*-butyl groups, a triplet (δ = 2.52 ppm) for acetylene CH and a doublet signal (δ = 4.70 ppm) for methylene protons along with NH (δ = 5.20 ppm) and aromatic protons. The proton-decoupled ^{13}C NMR

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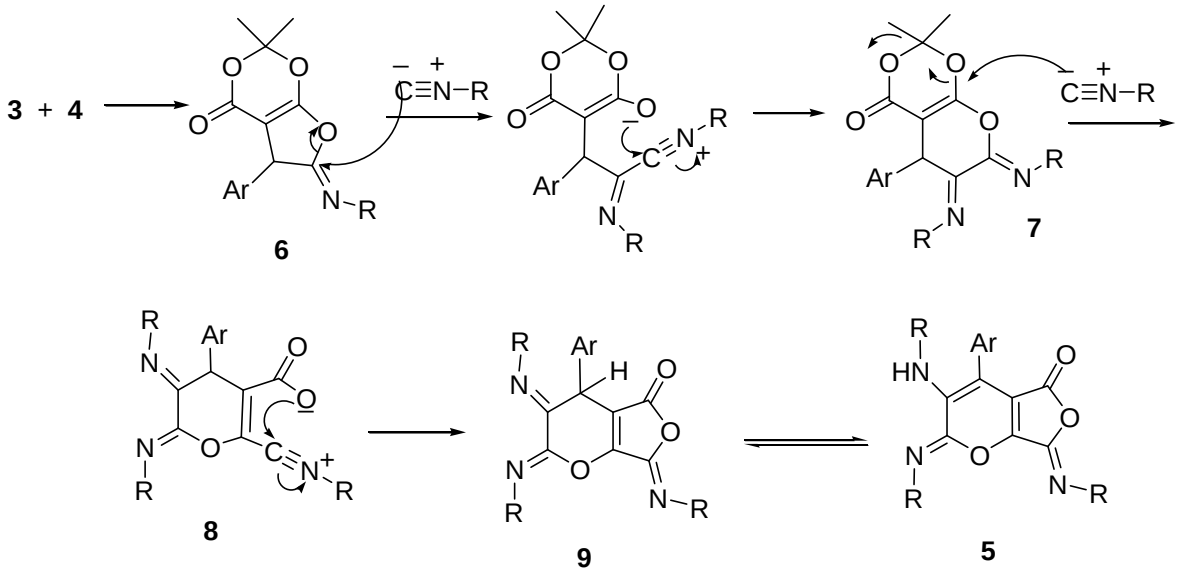
spectrum of **5e** exhibited distinct resonances in agreement with the furo-pyran structure. Partial assignments of these resonances are given in the experimental section. The spectral data of **5a–d** were similar to **5e** except for differences in the proton resonances of the substituents. We believe that this new functionality based multicomponent reactions have a huge potential in creating new molecules or simplifying the synthesis of existing compounds and the synthesized products have good potential for further reactions. These products could be used as starting material for some reactions such as: Click chemistry, Pauson-Khand reaction, and cyclization reaction.

Although the mechanism of this reaction has not been established experimentally, On the basis of the well-established chemistry of isocyanides (Dömling and Ugi 2000, Zhu 2003, Akritopoulou-Zanze 2008, Sadjadi and Heravi 2011, Banfi et al. 2008, Domling 2006), it is reasonable to assume that the furo-pyran **5** results from an initial [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of **3** with isocyanide **4** to produce an iminolactone intermediate **6**. Nucleophilic attack of a second isocyanide on the imine carbon of **6** followed by cleavage of the five-membered ring and subsequent cyclization gives di-iminopyran intermediate **7**. Addition of a third isocyanide to the carbonyl of intermediate **7** that easily loses an acetone molecule and gives unstable intermediate **8**. This intermediate cyclizes to give furo-pyran **9.** Inermediate **9** is an imine tautomer and rapidly interconverts to the enamine stable tautomer **5** (Scheme **3**).



Scheme 3: Proposed mechanism

In conclusion, the pseudo four-component reaction (3 + 1) of isocyanide and arylidene Meldrum's acid provide a simple one-pot entry for the synthesis of new furo-pyran derivatives in good yields. The neutral condition, room temperature and one-pot nature of the present method makes it an interesting alternative to multistep approaches for the synthesis of new functionalized derivatives of furo-pyran.

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