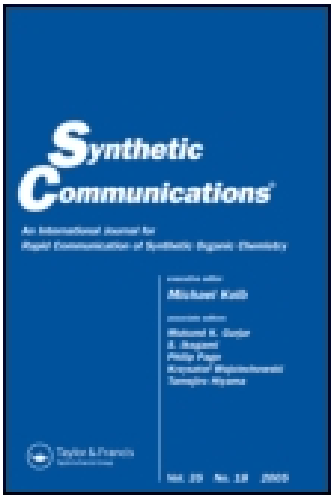

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Preparation of 5-Cyano-4,6-dimethyl-2H-pyran-2-one and 3-Cyano-5-methoxy-4-methyl-5H-furan-2-one via a One-Pot, Domino-Knoevenagel Process

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PREPARATION OF 5-CYANO-4,6-DIMETHYL-2*H*-PYRAN-2-ONE AND 3-CYANO-5-METHOXY-4-METHYL-5*H*-FURAN-2-ONE VIA A ONE-POT, DOMINO-KNOEVENAGEL PROCESS

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5-Cyano-4,6-dimethyl-2H-pyran-2-one* (1) *has been prepared via a simple one-pot domino-Knoevenagel reaction starting from ethyl acetoacetate* (2) *and cyanoacetone* (3). *Similarly, a new racemic 3-cyano-5-methoxy-4-methyl-5H-furan-2-one* (7) *has been prepared from 1,1-dimethoxyacetone* (6) *and cyanoacetic acid* (4). *The new alkylidene derivatives (Z/E)-ethyl-4-cyano-3-methylbut-3-enoate* (5), *(Z/E)-ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate* (9), *and (2,2-dimethoxy-1-methylethylidene)malononitrile* (11) *have been prepared via the Knoevenagel reactions. The easy access to these new compounds in good yields shows that ammonium acetate/acetic acid–catalyzed Knoevenagel reactions and domino-Knoevenagel reactions have a broad scope of application.

Keywords: (2,2-Dimethoxy-1-methylethylidene)malononitrile; (Z/E)-ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate; (Z/E)-ethyl 4-cyano-3-methylbut-3-enoate; NMR spectroscopy

INTRODUCTION

The 2*H*-pyran-2-ones (α-pyrones) and 5*H*-furan-2-ones (but-2-en-4-olides) are unsaturated lactones. They are components of several classes of bioactive natural compounds and exhibit a wide range of biological activity such as potent non-peptidic HIV protease inhibitory, antimicrobial, antifungal, androgen-like, and pheromonal effects.[1,2] 2*H*-Pyran-2-ones (α-pyrones) are also important synthetic intermediates for the preparations of various aromatic and heteroaromatic compounds. 2*H*-Pyran-2-ones undergo Diels–Alder reactions with acetylenes and olefin dienophiles to give addition products. These products give easy access to a whole range of substituted benzenes and cyclohexadiene derivatives under thermal expulsion of CO_2.[3–6]

α-Pyrones have been prepared by acid-catalyzed intermolecular condensation of two molecules of β-keto esters.[7] However, the 2*H*-pyran-2-one with a cyano

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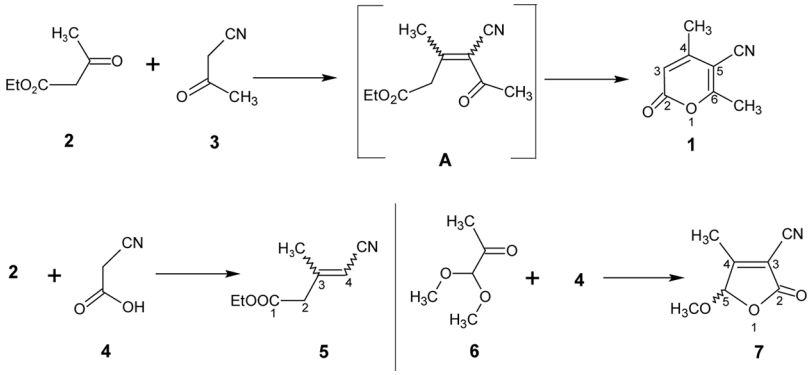
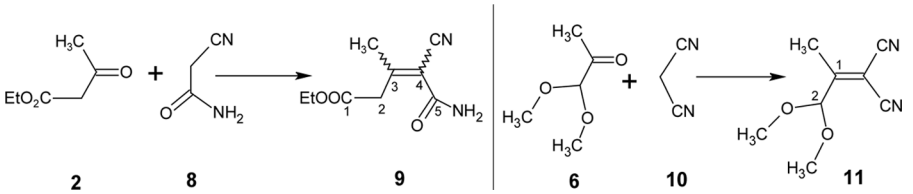


Scheme 1. Preparation of 5-cyano-4,6-dimethyl-2*H*-pyran-2-one (**1**) from ethyl acetoacetate (**2**) and 1-cyanoacetone (**3**); preparation of (Z/E)-ethyl 4-cyano-3-methylbut-3-enoate (**5**) from ethyl acetoacetate (**2**) and cyanoacetic acid (**4**); and preparation of (R/S)-3-cyano-5-methoxy-4-methyl-5*H*-furan-2-one (**7**) from 1,1-dimethoxyacetone (**6**) and cyanoacetic acid (**4**) via one-pot domino reactions under the Knoevenagel conditions.



Scheme 2. Preparation of alkylidene derivatives (Z/E) ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate (**9**) and (2,2-dimethoxy-1-methylethylidene)malononitrile (**11**).

substituent at position 5 was not known until the preparation of 5-cyano-4,6-dimethyl-2*H*-pyran-2-one via a complicated nickel-catalyzed conversion of propargyl halide and propargyl alcohol was reported.[8]

We have recently reported an efficient method to convert two bifunctional reagents into a single multifunctional system via the Knoevenagel condensation in which the total number of carbon atoms remains the same and which can be converted into a valuable heterocyclic compound in subsequent steps in a simple process.[9]

We now report ammonium acetate/acetic acid–catalyzed domino-Knoevenagel reactions and Knoevenagel reactions for the preparation of 5-cyano-4,6-dimethyl-2-*H*-pyran-2-one (**1**), (Z/E)-ethyl-4-cyano-3-methylbut-3-enoate (**5**), 3-cyano-5-methoxy-4-methyl-5*H*-furan-2-one (**7**), (Z/E)-ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate (**9**), and (2,2-dimethoxy-1-methylethylidene)malononitrile (**11**) in Schemes 1 and 2. Furthermore, the methodology employs an efficient and diverse synthesis of new compounds in simple and mild conditions.

RESULTS AND DISCUSSION

Ethyl acetoacetate (**2**; 6.50 g, 50 mmol) and 1-cyanoacetone (**3**; 4.14 g, 50 mmol) were condensed together in toluene (250 mL) for 5 h at 100–110 °C in the presence of

ammonium acetate (1.00 g) and acetic acid (5 mL) using the Dean–Stark trap. 1-Cyanoacetone can easily be prepared from commercially available 3-aminocrotononitrile by a known procedure.[10] This condensation afforded product **1** as a colorless powder (5.15 g, 69%) (Scheme 1). The mass spectrometry and other spectroscopic data are in agreement within experimental error for 5-cyano-4,6-dimethyl-2*H*-pyran-2-one (**1**).[8]

Previously, we reported the Knoevenagel reactions of 1,1-dimethoxyacetone (**6**) with 1-cyanoacetone (**3**) and 2-cyanoacetamide (**8**).[9] We anticipated that the Knoevenagel condensation of ethyl acetoacetate (**2**) with 1-cyanoacetone (**3**) should provide a general synthetic route to the intermediate α,β-unsaturated ketone (**A**), which is expected to be converted easily into 5-cyano-4,6-dimethyl-2*H*-pyran-2-one (**1**) by intramolecular cyclization.

It is interesting that both ethyl acetoacetate (**2**) and 1-cyanoacetone (**3**) have active methylene functions and both are possible keto donors. 5-Cyano-4,6-dimethyl-2*H*-pyran-2-one (**1**) is obtained in a very simple one-pot domino-Knoevenagel process in 69% yield. This result indicates that ethyl acetoacetate (**2**) reacts as a keto donor and 1-cyanoacetone (**3**) reacts as an active methylene compound. The reaction has occurred via the intermediacy of an E/Z mixture of ethyl 4-cyano-3-methyl-5-oxohex-3-enoate (**A**). The Z isomer of intermediate (**A**) has two functional groups, namely ethyl ester and carbonyl oxygen in close proximity, and leads to the cyclization (enol-lactonization) with the elimination of one molecule of ethanol to form an α-pyrone ring. The carbon–carbon double bond formed between two reactants in the intermediate (**A**) becomes the 4–5 bond in the final heterocycle. The E isomer can undergo an acid-catalyzed E/Z isomerization, leading to the thermodynamically stable product **1**. It is to be expected that this domino-Knoevenagel process has a broad scope to prepare a 5-cyano-2*H*-pyran-2-one system with different substituents at positions 3, 4, and 6 using various β-keto esters and cyanomethyl ketones.

The Knoevenagel reaction of ethyl acetoacetate (**2**; 6.50 g, 50 mmol) and cyanoacetic acid (**4**; 4.25 g, 50 mmol) afforded a Z/E (1:1) mixture of ethyl 4-cyano-3-methylbut-3-enoate (**5**) as a light yellow oil in 61% yield. The ^{1}H NMR of product **5** is in agreement with the proposed structure, which showed two signals for the CH_2 group corresponding to Z/E isomers at 3.17 and 3.43 ppm and CH signal at 5.29 ppm. Similarly, in ^{13}C NMR the CN and the C=O signals of product **5** are noticed at 115.9 and 168.3 ppm, respectively.

We conclude that (Z/E)-ethyl 4-cyano-3-methylbut-3-enoate (**5**) is obtained via the intermediate (Z/E)-2-cyano-5-ethoxy-3-methyl-5-oxopent-2-enoic acid, which undergoes decarboxylation faster than possible intramolecular cyclization. It has been mentioned that in the Knoevenagel condensation of carbonyl compounds and carboxylic acids, a decarboxylation may take place.[11]

The condensation of commercially available 1,1-dimethoxyacetone (**6**; 5.90 g, 50 mmol) and cyanoacetic acid (**4**; 4.25 g, 50 mmol) in toluene (250 mL) for 2 h at 120–130 °C in the presence of ammonium acetate (1.00 g) and acetic acid (5 mL) afforded a product **7** as a light yellow oil in 86% yield. Based on the spectral data, the structure of product **7** is assigned to 3-cyano-5-methoxy-4-methyl-5*H*-furan-2--one (**7**) (Scheme 1).

The *m*/*z* value of the parent peak of product **7** is 153.1350, which in agreement with the calculated value of 153.13538 for the formula $C_7H_7NO_3$. The ^{13}C NMR of

product **7** showed seven signals corresponding to 14.09 (CH_3), 57.95 (OCH_3), 103.8 (CH), 107.7 (NC−C=), 109.7 (CN), 164.1 (C=O), and 174.2 (CH_3−C=) ppm. The greater downfield shift ($\delta = 174$ ppm) of C-4 relative to the carbonyl carbon at $\delta = 164$ ppm is due to the extended conjugation with the two electron-withdrawing groups at the double bond in the product **7**. The ^{1}H NMR of product **7** is in compliance with the proposed structure, showing peaks at 2.31 ppm for CH_3 at position 4 and at 3.65 and 5.81 ppm for OCH_3 and CH at position 5. Also, ^{1}H NMR assignments were checked by ^{1}H–^{13}C correlation and ^{1}H correlation spectroscopy (COSY) spectra.

To our knowledge, the product **7** with a stereogenic center at position 5 has not been described previously in the literature. The reaction occurred via the intermediacy of the E/Z mixture of 2-cyano-3,3-dimethoxy-but-2-enoic acid. This is the expected intermediate in which an acid-catalyzed E/Z isomerization takes place. The intermediate Z isomer, with the dimethoxy acetal function and carboxylic acid function in close proximity, leads to the cyclization to form a butenolide ring with the elimination of one molecule of methanol. The excellent yield (86%) of the product **7** shows that the acid-catalyzed condensation of 1,1-dimethoxyacetone (**6**) and cyanoacetic acid (**4**) to obtain 3-cyano-5-methoxy-4-methyl-5*H*-furan-2-one (**7**) competes very well with the loss of CO_2 in the intermediate.

The number of known 5-methoxy substituted (5*H*)-furan-2-ones is very limited. (5*H*)-Furan-2-one derivatives often serve as useful synthetic intermediates in the stereoselective construction of substituted γ-butyrolactones via conjugated addition or catalytic hydrogenation of double bond.[12]

To test if other functional groups of active methylene compounds besides the carbonyl group will lead to a domino reaction during the Knoevenagel condensation, we treated ethyl acetoacetate (**2**) with 2-cyanoacetamide (**8**) and 1,1-dimethoxyacetone (**6**) with malononitrile (**10**) in Scheme 2. In all these cases, only the expected Knoevenagel alkylidene products (Z/E) ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate (**9**) and (2,2-dimethoxy-1-methylethylidene)malononitrile (**11**) were isolated and characterized. This result shows that under the normal Knoevenagel conditions the nitrile function and the amide function do not undergo further domino reactions. Alkylidene derivatives **9** and **11** have not been reported previously in the literature.

CONCLUSIONS

In this article, the preparation of 5-cyano-4,6-dimethyl-2*H*-pyran-2-one (**1**) from simple starting materials ethyl acetoacetate (**2**) and 1-cyanoacetone (**3**) catalyzed by ammonium acetate/acetic acid via a one-pot domino-Knoevenagel process has been described. It is to be expected that a whole range of 3, 4, and 6 trisubstituted 5-cyano-2*H*-pyran-2-ones can similarly be prepared via the domino reactions under Knoevenagel conditions using various substituted β-keto esters and cyanomethyl ketones. 2*H*-Pyran-2-one derivatives often used as building blocks in synthetic organic chemistry and their fruitful application in a variety of transformations has been mentioned in the literature.[13]

Similarly, a one-pot domino reaction for the preparation of a new racemic 3-cyano-5-methoxy-4-methyl-5*H*-furan-2-one (**7**) from 1,1-dimethoxyacetone (**6**) and cyanoacetic acid (**4**) has been described. The scope of the domino-Knoevenagel

condensation is very broad, because many different α,α-dimethoxy ketones and acetic acids with different electron-withdrawing groups are available that will lead to a 5-methoxy-5*H*-furan-2-one system with different substitutions at positions 3 and 4. There is also precedent for the reductive elimination of the substituent at position 5 in these systems that will allow easy access to prepare biologically active 3,4-disubstituted 5*H*-furan-2-ones.[14,15]

Moreover, a comparison of the reactions with 2-cyanoacetamide (**8**) and malononitrile (**10**) is presented in Scheme 2 that is informative in determining the relative importance of the α-carbonyl group in the active methylene compounds **3** and **4** for the cyclization under a domino process. As a result, new alkylidene derivatives (Z/E)-ethyl-4-cyano-3-methylbut-3-enoate (**5**), (Z/E)-ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate (**9**), and (2,2-dimethoxy-1-methylethylidene)-malononitrile (**11**) are obtained.

EXPERIMENTAL

General

Reactions were monitored by using thin-layer chromatography (TLC, on Merck F254 silica-gel 60 aluminium sheets, 0.2 mm): spots were visualized by treatment with an oxidizing spray (2 g of $KMnO_4$ and 4 g of $NaHCO_3$ in 100 ml of water). Column chromatography was performed on Merck silica gel 60. ^{1}H NMR spectra were recorded on Bruker WM-300 with tetramethylsilane (TMS: $\delta = 0.00$ ppm) as internal standard. ^{1}H noise-decoupled ^{13}C spectra were recorded on a Bruker WM-300 instrument at 75 MHz. Electron-impact (EI) mass spectrometry was carried out using a Jeol JMSSX/SX102A four-sector mass spectrometer, coupled to a Jeol MS-MP9021D/UPD system program. The sample was introduced via a direct insertion probe into the ion source. Perkin-Elmer Paragon 1000 Fourier transform (FT)–IR spectrophotometer was used for IR measurement. All other chemicals were purchased from Aldrich Fluka or Acros Chimica.

5-Cyano-4,6-dimethyl-2*H*-pyran-2-one (1)

A solution of ethyl acetoacetate (**2**) (6.50 g, 50 mmol), 1-cyanoacetone (**3**) (4.14 g, 50 mmol), ammonium acetate (1.00 g), and acetic acid (5 mL) in toluene (250 mL) was refluxed for 5 h at 100–110 °C using a Dean–Stark trap. The toluene layer was separated after washing with half-saturated NaCl, dried with $MgSO_4$, and evaporated in vaccuo to yield a colorless solid of **1** (5.15 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.17$ (s, CH_3), 2.39 (s, CH_3), 6.14 (CH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 18.26$ (CH_3), 20.04 (CH_3), 110.2 (=C−CN), 116.2 (CH), 116.4 (CN), 150.5 (C=C), 154.9 (C=C), 161.7 (C=O). FT-IR (neat): 2216, 1749, 1652, 1632, 1615 cm^{-1}. Ms (EI^+): m/z (%) = 148 (92), 119 (100), 105 (25), 93 (10).

Mixture of (3Z)- and (3E)-Ethyl-4-cyano-3-methylbut-3-enoate (5)

A solution of ethyl acetoacetate (**2**) (6.50 g, 50 mmol), cyanoacetic acid (**4**) (4.25 g, 50 mmol), ammonium acetate (1.00 g), and acetic acid (5 mL) in toluene

(250 mL) was refluxed for 7 h at 120–130 °C using the Dean–Stark trap. The toluene layer was separated after washing with half-saturated NaCl, dried with $MgSO_4$, and evaporated in vacuo to yield a light yellow oil of **5** (4.65 g, 61%) ^{1}H NMR (300 MHz, $CDCl_3$/TMS) (Z/E, 1:1): $\delta = 1.27$ (m, $2 \times CH_3$), 2.06, 2.34 (s, CH_3), 3.17, 3.43 (s, CH_2), 4.26 (m, $2 \times CH_2$), 5.30 (br, s, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS) (Z/E, 1:1): $\delta = 13.87$ ($2 \times CH_3$), 21.09, 23.04 (CH_3), 40.92, 43.14 (CH_2), 61.07 ($2 \times CH_2$), 99.10 (=C−CN), 115.9 (CN), 156.4 (=C−CH_3), 168.3 (C=O) ppm. HRMS calcd. for $C_8H_{11}NO_2$: 153.17838; found: 153.1759.

3-Cyano-5-methoxy-4-methyl-5*H*-furan-2-one (7)

Ammonium acetate (1.00 g) and acetic acid (5 mL) were added to a mixture of 1,1-dimethoxyacetone (**6**) (5.90 g, 50 mmol) and cyanoacetic acid (**4**) (4.25 g, 50 mmol) in toluene (250 mL). The mixture was refluxed for 2 h at 120–130 °C using a Dean–Stark trap. The organic solution was washed with half-saturated NaCl solution. The aqueous phase was again extracted with CH_2Cl_2 (3×100 mL). The extracted organic solvents were combined together and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow oil (6.57 g, 86%). The product was purified by column chromatography (silica gel 60, ethyl acetate/hexane, 1:3) to yield a light yellow oil of **7** (5.89 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 2.31$ (s, CH_3), 3.65 (s, OCH_3), 5.81 (s, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): $\delta = 14.09$ (CH_3), 57.95 (OCH_3), 103.8 (CH), 107.7 (NC−C=), 109.7 (CN), 164.1 (C=O), 174.2 (CH_3-C=) ppm. FT-IR: (neat) $\nu = 2226$, 1776, 1667, 1443, 1390 cm^{-1}. HRMS: calcd. for $C_7H_7NO_3$: 153.13538; found: 153.1350.

Mixture of (3Z)- and (3E)-Ethyl 5-amino-4-cyano-3-methyl-5-oxopent-3-enoate (9)

A solution of ethyl acetoacetate (**2**) (6.50 g, 50 mmol), 2-cyanoacetamide (**8**) (4.04 g, 50 mmol), ammonium acetate (1.00 g), and acetic acid (5 mL) in toluene (250 mL) was refluxed for 7 h at 160–170 °C using a Dean–Stark trap. The toluene layer was separated after washing with half-saturated NaCl, dried with $MgSO_4$, and evaporated in vacuo to yield a light yellow powder of **9** (7.45 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 1.29$ (t, $^3J_{H\text{-}H} = 7.12$ Hz, CH_3), 2.32 (s, CH_3), 3.86 (s, CH_2), 4.16 (q, $^3J_{H\text{-}H} = 7.12$ Hz, CH_2), 6.51 (br, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): $\delta = 13.95$ (CH_3), 25.96 (CH_3), 40.02 (CH_2), 61.35 (CH_2), 108.4 (=C−CN), 116.2 (CN), 162.7 (C=O), 164.0 (C=O), 168.7 (=C−CH_3). FT-IR (neat) $\nu = 3387$, 3170 (NH_2), 2222 (CN), 1728 (CO_2Et), 1695 (C=O), 1609 (C=C) cm^{-1}.

(2,2-Dimethoxy-1-methylethylidene)malononitrile (11)

A solution of 1,1-dimethoxyacetone (**6**) (5.90 g, 50 mmol), malononitrile (**10**) (3.34 g, 50 mmol), ammonium acetate (1.00 g), and acetic acid (5 mL) in toluene (200 mL) was refluxed for 2 h at 100–110 °C. The toluene layer was separated after washing with half-saturated NaCl, dried with $MgSO_4$, and evaporated in vacuo to yield a light brown oil of **11** (7.74 g, 93%). ^{1}H NMR (300 MHz,

$CDCl_3$/TMS): $\delta = 2.23$ (CH_3), 3.46 ($2 \times OCH_3$), 5.09 (CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): $\delta = 17.00$ (CH_3), 55.58 ($2 \times OCH_3$), 87.19 (=C−CN), 102.4 (CH), 110.4, 110.9 (CN), 174.7 (=C−CH_3). FT-IR (neat) $\nu = 2230$ (CN) cm^{-1}. HRMS calcd. for $C_8H_{10}N_2O_2$: 166.07428; found: 166.0752.

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