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SHORT COMMUNICATIONS

# Cyclocondensation of 3-Acetylfuran-2(5*H*)-ones with Benzylidenemalononitrile. Synthesis of 3-(5-Amino-4,6-dicyanobiphenyl-3-yl)furan-2(5*H*)-ones

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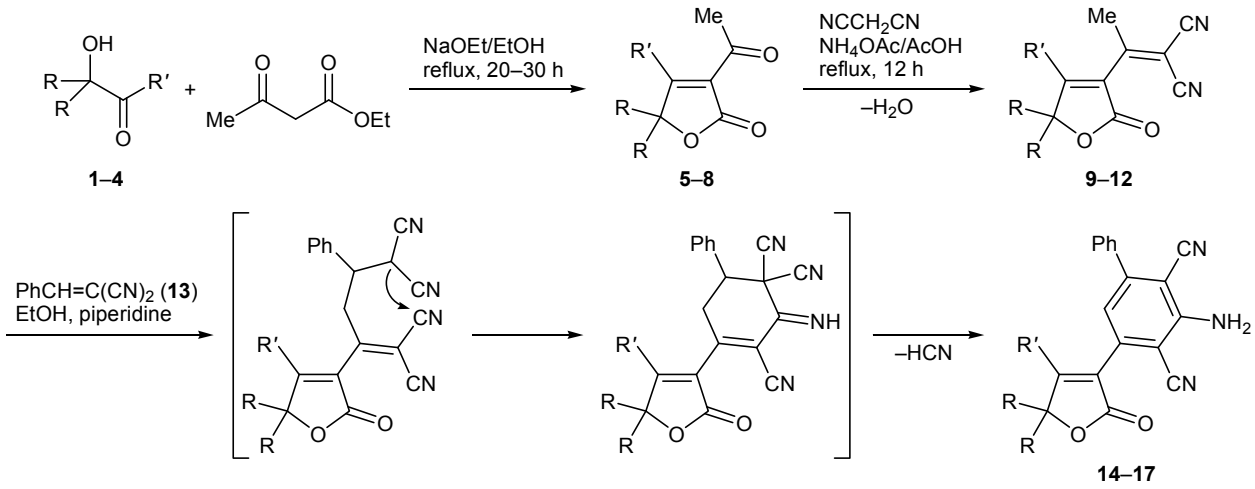
3,4-Disubstituted furan-2(5*H*)-one fragment is present in many natural biologically active compounds. In particular, furan-2(5*H*)-one derivatives containing nonidentical aromatic substituents in positions *3* and *4* of the furan ring exhibit various biological activities [1]. An example is the anti-inflammatory drug Rofecoxib [4-(4-methanesulfonylphenyl)-3-phenylfuran-2(5*H*)-one]. Eutypoid A isolated from the marine mangrove fungus *Eutypa* sp. (# 424) [2] and gymnoascolides [3] isolated from the Australian soil ascomycetes *Gimnoascus reessii* and *Malbranchea filamentosa* IFM41300 are naturally occurring 3,4-disubstituted furan-2(5*H*)-ones.

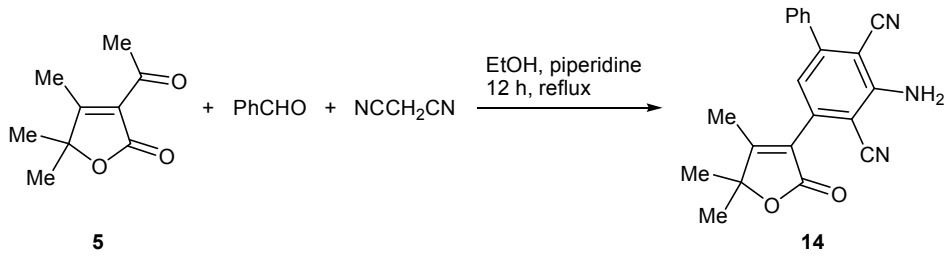
We have previously [4–8] synthesized unsaturated γ-lactones bearing heteroaromatic substituents in the 3-position of the lactone ring and revealed biological activity of benzimidazolyl-, benzothiazolyl-, and benzoxazolyl-substituted furan-2-ones. In the present article we report the synthesis of dihydrofuranones containing a 5-amino-4,6-dicyanobiphenyl-3-yl substituent on $C^3$. Cyclocondensation of α-hydroxy ketones **1–4** with ethyl acetoacetate in the presence of sodium ethoxide [9–11] gave the corresponding 4,5,5-trisubstituted 3-acetylfuran-2(5*H*)-ones **5–8** which reacted with malononitrile according to Knoevenagel (by heating in boiling benzene in the

**Scheme 1.**




**1**, **5**, **9**, R = R′ = Me; **2**, **6**, **10**, R = Me, R′ = Ph; **3**, **7**, **11**, RR = $(CH_2)_5$, R′ = Me; **4**, **8**, **12**, RR = $(CH_2)_5$, R′ = Ph.

**Scheme 2.**




**5** **14**

presence of ammonium acetate and glacial acetic acid with simultaneous removal of liberated water) [12] to afford 3-(1,1-dicyanoprop-1-en-2-yl) derivatives **9**–**12** in high yields (Scheme 1).

Ethylidenemalononitriles **9**–**12** possess an activated methyl group. It is known that ylidenemalononitriles can be converted into polyfunctionalized benzene derivatives [13, 14]. Compounds **9**–**12** were brought into reaction with benzylidenemalononitrile (**13**). The reaction involved initial Michael addition of the activated methyl group to the conjugated double bond of benzylidenemalononitrile, and the adduct thus formed underwent intramolecular cyclization, followed by aromatization via elimination of hydrogen cyanide. As a result, compounds **14**–**17** were obtained.

Ethylidenemalononitriles **9**–**12** and benzylidenemalononitrile (**13**) are formed in Knoevenagel reactions whose conditions are similar to those of the condensation of **9**–**12** with **13**. Therefore, we performed three-component reaction of 3-acetylfuranone **5** with benzaldehyde and 2 equiv of malononitrile in boiling ethanol in the presence of piperidine [17, 18] and isolated compound **14** in 32% yield (Scheme 2). The yield of **14** in the cyclocondensation of **9** with **13**, calculated on the initial 3-acetylfuranone **5**, was almost the same. Taking into account that the three-component procedure does not require preliminary preparation and isolation of **9** and **13**, it may by regarded as an alternative short-cut version of synthesis of **14**.

In summary, we have developed a convenient procedure for the synthesis of furan-2(5*H*)-ones with a 5-amino-4,6-dicyanobiphenyl-3-yl substituent in position *3* of the furan ring by reaction of 3-(1,1-dicyanoprop-1-en-2-yl)furan-2(5*H*)-ones with benzylidenemalononitrile or three-component condensation of 3-acetyl-4,5,5-trimethylfuran-2(5*H*)-one with benzaldehyde and malononitrile.

**Compounds 5–8 (***general procedure***).** A solution of equimolar amounts of hydroxy ketone **1**–**4** and ethyl acetoacetate and 0.1 equiv of sodium ethoxide in anhydrous ethanol was heated under reflux. When the reaction was complete, a part of the solvent was distilled off, and the residue was neutralized with dilute (1:1) hydrochloric acid and extracted with methylene chloride. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was distilled under reduced pressure to isolate 3-acetyl-4,5,5-trimethylfuran-2(5*H*)-one (**5**) [5], 3-acetyl-5,5-dimethyl-4-phenylfuran-2(5*H*)-one (**6**) [7], 3-acetyl-4-methyl-5,5-pentamethylenefuran-2(5*H*)-one (**7**) [6], or 3-acetyl-5,5-pentamethylen-4-phenylfuran-2(5*H*)-one (**8**) [6].

**Compounds 9–12 (***general procedure***).** 3-Acetylfuran **5**–**8** and 1.1 equiv of malononitrile were dissolved in toluene, 0.1 equiv of glacial acetic acid and 0.1 equiv of ammonium acetate were added, and the mixture was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. When the reaction was complete, a solution of sodium hydrogen carbonate was added, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3×25 mL). The extracts were combined with the organic phase and dried over sodium sulfate, the solvent was distilled off, and the residue crystallized and was washed with hexane–diethyl ether (3:1).

**2-[1-(4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene]malononitrile (9)** was synthesized from 3.66 g (0.02 mol) of **5** and 1.32 g (0.02 mol) of malononitrile in 20 mL of toluene in the presence of 0.2 g (0.0022 mol) of ammonium acetate and 0.6 mL of glacial acetic acid. Yield 2.4 g (56%), white crystals, mp 112–114°C; published data [12]: mp 115°C. IR spectrum, ν, $cm^{-1}$: 2215 (CN), 1740 (C=O), 1640 ($C^3$=$C^4$), 1569 (C=C). $^1$H NMR spectrum, δ, ppm: 1.53 s (6H, 5-$CH_3$), 2.13 s (3H, 4-$CH_3$), 2.52 s (3H, $CH_3$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 12.81 (4-$CH_3$), 21.54 ($CH_3$), 23.94 (5-$CH_3$), 86.36 ($C^5$), 88.64 [**C**$(CN)_2$], 110.82 (CN), 110.99 (CN), 122.82 ($C^3$), 166.19 ($C^4$), 167.39 (C=O), 171.97 ($CH_3$**C**=).

**2-[1-(5,5-Dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)ethylidene]malononitrile (10)** was synthe-

sized from 1.15 g (0.005 mol) of **6** and 0.33 g (0.005 mol) of malononitrile in 10 mL of toluene in the presence of 0.1 g (0.0011 mol) of ammonium acetate and 0.5 mL of glacial acetic acid. Yield 0.56 g (41%), light yellow crystals, mp 92–94°C. IR spectrum, ν, $cm^{-1}$: 2213 (CN), 1722 (C=O), 1605 (C=$C_{arom}$), 1562 (C=C). $^1$H NMR spectrum, δ, ppm: 1.65 s (6H, 5-$CH_3$), 2.48 s (3H, $CH_3$), 7.33–7.38 m (2H) and 7.49–7.55 m (3H) (Ph). $^{13}$C NMR spectrum, $\delta_C$, ppm: 22.07 ($CH_3$), 24.62 (5-$CH_3$), 86.80 ($C^5$), 89.05 [**C**$(CN)_2$], 110.56 (CN), 110.65 (CN), 124.16 ($C^3$), 127.09 (2C, $C_{arom}$), 128.79 (2C, $C_{arom}$), 129.46 and 130.20 ($C^i$, $C^p$), 165.57 ($C^4$), 167.32 (C=O), 171.61 ($CH_3$**C**=). Found, %: C 72.68; H 5.18; N 10.37. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.07; N 10.07.

**2-[1-(4-Methyl-2-oxo-1-oxaspiro[4.5]dec-3-en-3-yl)ethylidene]malononitrile (11)** was synthesized from 4.16 g (0.02 mol) of **7** and 1.4 g (0.033 mol) of malononitrile in 40 mL of toluene in the presence of 1.2 g (0.013 mol) of ammonium acetate and 2 mL of glacial acetic acid. Yield 3.95 g (77%), white crystals, mp 143–145°C. IR spectrum, ν, $cm^{-1}$: 2210 (CN), 1721 (C=O), 1625 ($C^3$=$C^4$), 1561 (C=C). $^1$H NMR spectrum, δ, ppm: 1.24–1.41 m (1H), 1.52–1.60 m (2H), and 1.63–1.90 m (7H) ($C_5H_{10}$); 2.11 s (3H, 4-$CH_3$), 2.51 s (3H, $CH_3$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 13.10 (4-$CH_3$), 21.27 (2C, $CH_2$), 21.62 ($CH_3$), 23.72 ($CH_2$), 32.53 (2C, $CH_2$), 88.01 ($C^5$), 88.62 [**C**$(CN)_2$], 110.88 (CN), 111.05 (CN), 123.01 ($C^3$), 166.33 ($C^4$), 167.53 (C=O), 171.95 ($CH_3$**C**=). Found, %: C 70.95; H 6.32; N 11.12. $C_{15}H_{16}N_2O_2$. Calculated, %: C 70.29; H 6.29; N 10.93.

**2-[1-(2-Oxo-4-phenyl-1-oxaspiro[4.5]dec-3-en-3-yl)ethylidene]malononitrile (12)** was synthesized from 2.7 g (0.01 mol) of **8** and 0.66 g (0.01 mol) of malononitrile in 10 mL of toluene in the presence of 0.08 g (0.00087 mol) of ammonium acetate and 0.5 mL of glacial acetic acid. Yield 1.76 g (55%), white crystals, mp 113–115°C. IR spectrum, ν, $cm^{-1}$: 2214 (CN), 1727 (C=O), 1620 (C=$C_{arom}$), 1562 (C=C). $^1$H NMR spectrum, δ, ppm: 1.14–1.30 m (1H) and 1.70–1.87 m (9H) ($C_5H_{10}$), 2.44 s (3H, $CH_3$), 7.27–7.32 m (2H) and 7.47–7.53 m (3H) (Ph). $^{13}$C NMR spectrum, $\delta_C$, ppm 21.35 (2C), 22.17, 23.66, 32.75 (2C), 88.48 ($C^5$), 89.03 [**C**$(CN)_2$], 110.42 and 110.65 (2C, CN), 125.03 ($C^3$), 126.93 (2C, $C_{arom}$), 128.58 (2C, $C_{aromr}$), 129.73 and 129.78 ($C^i$, $C^p$), 165.57 ($C^4$), 167.18 (C=O), 171.87 ($CH_3$**C**=). Found, %: C 73.21; H 5.52; N 8.95. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.45; H 5.70; N 8.80.

**Compounds 14–17 (*general procedure*).** A solution of equimolar amounts of compound **9**–**12** and benzylidenemalononitrile (**13**) and 0.05 mL of piperidine in anhydrous ethanol was heated for 4 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol.

**3-Amino-5-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)-1,1′-biphenyl-2,4-dicarbonitrile (14).** *a*. Compound **14** was synthesized according to the general procedure from 0.6912 g (0.0032 mol) of **9** and 0.5 g (0.0032 mol) of **13** in 16 mL of ethanol in the presence of 0.05 mL of piperidine. Yield 0.76 g (62%), light brown crystals, mp 235–237°C. IR spectrum, ν, $cm^{-1}$: 3480, 3381 ($NH_2$); 2200 (CN), 1721 (C=O), 1635 ($C^3$=$C^4$), 1520 (C=$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 1.56 s (6H, 5-$CH_3$), 2.09 s (3H, 4-$CH_3$), 6.57 br.s (2H, $NH_2$), 6.69 s (1H, $H_{arom}$), 7.46–7.60 m (5H, Ph). $^{13}$C NMR spectrum, $\delta_C$, ppm: 24.78 (2C, $CH_3$), 86.09 ($C^5$), 95.28 (**C**CN), 95.50 (**C**CN), 114.32 (CN), 114.98 (CN), 118.89 ($CH_{arom}$), 124.96 ($C^3$), 127.31 (2C), 127.96 (2C), 128.08 (2C), 128.34 (2C), 128.85 ($CH_{arom}$), 129.29 ($CH_{arom}$), 130.29, 136.90, 138.86 ($C^i$), 49.14 ($CNH_2$), 153.03 ($C^i$), 167.72 ($C^4$), 169.32 (C=O). Found, %: C 71.37; H 5.07; N 12.47. $C_{21}H_{17}N_3O_2$. Calculated, %: C 73.45; H 4.99; N 12.24.

*b*. A solution of 5 mmol (0.64 g) of **5**, 11 mmol (0.72 g) of malononitrile, 5 mmol (0.53 g) of benzaldehyde, and 0.3 mL of piperidine in 30 mL of anhydrous ethanol was heated for 12 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol. Yield 32%.

**3-Amino-5-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-1,1′-biphenyl-2,4-dicarbonitrile (15)** was synthesized from 0.278 g (0.001 mol) of **10** and 0.154 g (0.001 mol) of **13** in 5 mL of ethanol in the presence of 0.05 mL of piperidine. Yield 0.28 g (69%), yellow crystals, mp 212–214°C. IR spectrum, ν, $cm^{-1}$: 3415, 3325 ($NH_2$); 2200 (CN), 1702 (C=O), 1615 ($C^3$=$C^4$), 1525 (C=$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 1.67 s (6H, $CH_3$), 6.46 br.s (2H, $NH_2$), 6.70 s (1H, $H_{arom}$), 7.25–7.35 m (2H) and 7.38–7.45 m (3H) (Ph), 7.45–7.47 br.m (5H, Ph). Found, %: C 75.07; H 4.89; N 10.55. $C_{26}H_{19}N_3O_2$. Calculated, %: C 77.02; H 4.72; N 10.36.

**3-Amino-5-(4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-en-3-yl)-1,1′-biphenyl-2,4-dicarbonitrile (16)** was synthesized from 0.256 g (0.001 mol) of **11** and 0.154 g (0.001 mol) of **13** in 5 mL of ethanol in the presence of

0.05 mL of piperidine. Yield 0.22 g (57%), brown crystals, mp 255–257°C. IR spectrum, ν, $cm^{-1}$: 3451, 3345 ($NH_2$); 2205 (CN), 1720 (C=O), 1645 ($C^3$=$C^4$), 1515 (C=$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 1.26–1.44 m (1H) and 1.55–1.93 m (9H) ($C_5H_{10}$), 2.06 s (3H, 4-$CH_3$), 6.56 br.s (2H, $NH_2$), 6.66 s (1H, $H_{arom}$), 7.42–7.60 m (5H, Ph). $^{13}$C NMR spectrum, $\delta_C$, ppm: 12.36 ($CH_3$), 21.43 (2C, $CH_2$), 23.90 ($CH_2$), 32.73 (2C, $CH_2$), 87.01 ($C^5$), 95.17 (**C**CN), 95.63 (**C**CN), 114.40 (CN), 115.06 (CN), 118.59 ($CH_{arom}$), 123.72 ($C^3$), 127.99 (2C), 128.13 (2C), 128.87 ($CH_{arom}$), 137.03, 138.66 ($C^i$), 149.26 ($CNH_2$), 153.29 ($C^i$), 168.08 ($C^4$), 169.32 (C=O). Found, %: C 74.56; H 5.67; N 11.21. $C_{24}H_{21}N_3O_2$. Calculated, %: C 75.18; H 5.52; N 10.96.

**3-Amino-5-(2-oxo-4-phenyl-1-oxaspiro[4.5]dec-3-en-3-yl)-1,1′-biphenyl-2,4-dicarbonitrile (17)** was synthesized from 0.4 g (1.26 mmol) of **12** and 0.2 g (1.26 mmol) of **13** in 5 mL of ethanol in the presence of 0.05 mL of piperidine. Yield 0.26 g (47%), yellow crystals, mp 234–236°C. IR spectrum, ν, $cm^{-1}$: 3421, 3340 ($NH_2$); 2190 (CN), 1715 (C=O), 1625 ($C^3$=$C^4$), 1510 (C=$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 1.13–1.29 m (1H) and 1.73–1.91 m (9H) ($C_5H_{10}$), 6.46 br.s (2H, $NH_2$), 6.64 s (1H, $H_{arom}$), 7.20–7.29 m (2H) and 7.36–7.50 m (8H, Ph). Found, %: C 77.89; H 5.17; N 9.31. $C_{29}H_{23}N_3O_2$. Calculated, %: C 78.18; H 5.20; N 9.43.

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The $^1$H and $^{13}$C NMR spectra (including two-dimensional spectra) were measured on a Varian Mercury 300 VX spectrometer as 300 and 75 MHz, respectively, using DMSO-$d_6$–$CCl_4$ (1 : 3) as solvent and tetramethylsilane as internal standard. The elemental analyses were obtained using a Korshun–Klimova melting point apparatus (C, H) and by the Pregl–Dumas method (N). The melting points were determined on a Boetius hot stage.

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