Peculiarities of the tandem reaction between cyanoacetylenic alcohols and aminobenzoic acids: Synthesis of 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles

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Abstract
Tertiary cyanoacetylenic alcohols 1 reacting with 3-aminobenzoic acid (Et3N, MeCN, 20–25 °C, 28–30 h) afforded 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles 2 (77–85%). Under the same condition, 4-hydroxy-4-methylpent-2-ynenitrile 1a and 2-aminobenzoic acid gave 2-[(5-imino-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate 4 (39%). With 4-aminobenzoic acid, alcohol 1a was almost quantitatively converted into the ester 5.

Keywords: Aminobenzoic acids, cyanoacetylenic alcohols, 4,5-dihydrofurans, Knoevenagel condensation, nucleophilic addition, esterification

Introduction
4-Oxo-4,5-dihydrofurans occur widely in nature1 and are interesting pharmacological objects exhibiting anticancer,2 antiulcer,3 antiallergic4 and antifungal5 properties. Some their functional derivatives find application as non-steroidal anti-inflammatory drugs and analgetics6 as well as for the treatment of metabolic disorders.7 Therefore, exploration of the chemistry and pharmacology of 4-oxo-4,5-dihydrofurans has progressed with vigor. Particular attention has been paid to the search for general and expedient syntheses of these important compounds and their controlled functionalization.1f

Recently, we have briefly reported a novel general methodology for the synthesis of 5,5-dialkyl-2-aryl-4-oxo-4,5-dihydrofuran-3-carbonitriles by the tandem reaction between cyanoacetylenic alcohols and substituted benzoic acids (Scheme 1).8

Despite the large suite of substituted benzoic acids applied to this reaction, aminobenzoic acids have not been used, because when these were treated with cyanoacetylenic alcohols,9 the
reactions was shown to follow different courses. However, owing to the synthetic and pharmaceutical importance\(^\text{10}\) of aminobenzoic acid derivatives (e.g., Novocain, Anaesthesin, Dicain, Novocainamide), additional effort to find conditions for the aminobenzoic acid-based synthesis of 3(2\(H\))-furanones was felt justified. Here, we present the results of this research.

![Scheme 1](image1)

**Scheme 1**

**Results and Discussion**

We found that 3-aminbenzoic acid reacting with cyanoacetylenic alcohols 1a–c in the presence of an equimolar amount of Et\(_3\)N in MeCN at 20–25 °C does participate in the expected tandem sequence of reactions, leading to the formation of the desired 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles 2a–c in 77–85% yields (Scheme 2).

![Scheme 2](image2)

**Scheme 2**

The formation of 2 is assumed\(^\text{8}\) to proceed via the esters 3, which subsequently undergo Knoevenagel condensation. Catalysis by Et\(_3\)N brings about cyclization, forming 4-oxo-4,5-dihydrofurans 2 instead of the esters 3 that have been previously observed.\(^\text{9}\)

![Scheme 3](image3)

**Scheme 3**
By contrast, 2-aminobenzoic acid, also in the presence of Et$_3$N, reacted with cyanoacetylenic alcohol 1a in the same way as previously reported, forming chemo- and region-selectively 2-[(5-imino-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate (4) in 39% yield (74% without using the base catalyst) (Scheme 3).

Surprisingly, the reaction between 4-aminobenzoic acid and cyanoacetylenic alcohol 1a led neither to the corresponding 4-oxo-4,5-dihydrofuran nor to 4-[(5-imino-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate. In this case and under the above conditions (100 mol% Et$_3$N, MeCN, 20–25 °C, 28 h), the reaction stopped at the stage of ester 5 (96% yield) (Scheme 4).

![Scheme 4](image)

At a higher temperature (75–80 °C, other conditions being the same), ester 5 was partially converted into 2-(4-aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile 6, (by $^1$H NMR, GC-MS) in a mixture with the starting ester 5 (conversion 25%) (Scheme 5).

![Scheme 5](image)

Interestingly, under traditional Knoevenagel conditions (10 mol% piperidine, 20 mol% AcOH, benzene, 80 °C, 2 h$^{11}$ or 20 mol% β-alanine as catalyst, EtOH, 20–25 °C, 27 h$^{12}$) as well as in the presence of KOH (20 mol%, EtOH, 20–25 °C, 24 h), the cyclization of ester 5 to 4-oxo-4,5-dihydrofuran 6 did not take place at all; the starting ester 5 was almost completely recovered.

The observed peculiarities of the reactivity of 2-, 3-, and 4-aminobenzoic acids toward cyanocetylenic alcohols 1a–c are likely to be due to differences in the steric and electronic interaction between amino and carboxylic groups. For 2-aminobenzoic acid, the initial esterification should be significantly sterically hindered compared to its 3- and 4-isomers. Besides, the intramolecular H-bonding between NH$_2$ and COOH groups may also slow down the ester formation. Consequently, this acid takes the alternative pathway of nucleophilic addition of the amino substituent to the triple bond.
The π-electron-donating effect of the amino substituent toward the carboxylic group in 4-aminobenzoic acid is expected to decrease the electrophilicity of the carbonyl group, and hence hampers the Knoevenagel condensation with the CH₂CN moiety. This may explain the failure to form the 4-oxo-4,5-dihydrofuran derivative.

Conclusions

In summary, the tandem reactions of tertiary cyanoacetylenic alcohols 1a–c with 2-, 3-, and 4-aminobenzoic acids (Et₃N, MeCN, 20–25 °C, 28–30 h) follow different courses, respectively: (i) nucleophilic addition of the amino group across the triple bond yielded 2-[(5-imino-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylate (4), (ii) cyclization forming 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles (2a–c), (iii) formation of 4-cyano-2-methyl-3-oxobutan-2-yl 4-aminobenzoate (5). All products are prospective synthetic building blocks, potential drugs and/or rewarding precursors for their design.

Experimental Section

General. ¹H and ¹³C NMR spectra of the products were recorded in (CD₂)₂CO on a Bruker DPX-400 spectrometer (400.13 and 100.62 MHz, respectively). IR spectra of KBr pellets were measured on a Bruker Vertex-70 instrument. Mass spectra were recorded on an Agilent 5975C spectrometer. Sample introduction was carried out via an Agilent 6890N gas chromatograph: the column was an HP-5MS (0.25 mm x 30 m x0.25 μm); carrier gas helium, constant flow. All melting points were taken on a Kofler micro hot stage. The reaction was monitored by TLC on neutral Al₂O₃ (chloroform/benzene/ethanol, 20:4:1 as eluent).

Aminobenzoic acids are commercial reagents (Merck). Cyanoacetylenic alcohols 1a–c were prepared according to a published method.¹³ Commercially available starting materials were used without further purification.

5,5-Dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles (2a–c). General procedure

To a solution of 3-aminobenzoic acid (0.137 g, 1.0 mmol) and Et₃N (0.101 g, 1.0 mmol) in MeCN (5 mL), the appropriate cyanoacetylenic alcohols 1a–c (1.0 mmol) were added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28–30 h. The solvent was evaporated in vacuo, and the residue was purified by preparative TLC (SiO₂, CHCl₃/EtOAc, 1:1) to give products 2a–c.

2-(3-Aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (2a). Yellow powder (0.185 g, 81%); mp 186–188 °C. IR: νmax 1214 (C-O-C), 1566, 1647 (C=C), 1707 (C=O), 2234 (CN), 3249 (C=CH), 3372, 3458 (NH₂) cm⁻¹. ¹H NMR (400.13 MHz, acetone-d₆): δ 1.53 (6H, s,
CH$_3$), 7.07 (1H, m, H-6), 7.34 (1H, m, H-5), 7.41 (1H, s, H-2), 7.45 (1H, m, H-4). $^{13}$C NMR (100.61 MHz, acetone-$d_6$): δ 22.6 (CH$_3$), 87.7 (=q-CN), 91.1 [(CH$_3$)$_2$C], 113.1 (C-2), 113.3 (CN), 117.1 (C-6), 121.1 (C-4), 128.7 (C-1), 130.5 (C-5), 150.0 (H$_2$N-C), 187.4 (H$_2$N-C$_6$H$_4$-C=), 200.4 (C=O). MS: m/z (%) 228 (99) [M]$^+$, 143 (11), 142 (100), 120 (15), 115 (14), 114 (18), 92 (15), 65 (15). Anal. calc. for C$_{13}$H$_2$N$_2$O$_2$ (228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.15; H, 5.39; N, 12.53.

2-(3-Aminophenyl)-5-ethyl-5-methyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (2b). Yellow powder (0.186 g, 77%), mp 113–114 °C. IR: $\nu_{\text{max}}$ 1212 (C=O-C), 1589, 1632 (C=C), 1714 (C=O), 2225 (CN), 3233 (C=CH), 3372, 3460 (NH$_2$) cm$^{-1}$. $^1$H NMR (400.13 MHz, acetone-$d_6$): δ 0.87 (3H, t, $J = 7.5$ Hz, CH$_2$CH$_3$), 1.48 (3H, s, CH$_3$), 1.90 (2H, m, CH$_2$), 7.07 (1H, m, H-6), 7.33 (1H, m, H-5), 7.42 (1H, s, H-2), 7.43 (1H, m, H-4). $^{13}$C NMR (100.61 MHz, acetone-$d_6$): δ 7.2 (CH$_2$CH$_3$), 20.9 (CH$_3$), 21.0 (CH$_2$), 88.7 (q-CN), 93.8 (CH$_3$C), 113.1 (C-2), 113.3 (CN), 117.1 (C-6), 121.2 (C-4), 128.4 (C-1), 130.4 (C-5), 149.8 (H$_2$N-C), 188.0 (H$_2$N-C$_6$H$_4$-C=), 200.2 (C=O). MS: m/z (%) 242 (100) [M]$^+$, 227 (30), 214 (68), 142 (64), 120 (17), 115 (10), 114 (10), 92 (15), 65 (10). Anal. calc. for C$_{14}$H$_{14}$N$_2$O$_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.20; H, 6.03; N, 11.32.

2-(3-Aminophenyl)-4-oxo-1-oxaspiro[4.5]dec-2-ene-3-carbonitrile (2c). Yellow powder (0.229 g, 85%), mp 148–150 °C. IR: $\nu_{\text{max}}$ 1220 (C=O-C), 1589, 1606, 1628 (C=C), 1709 (C=O), 2223 (CN), 3240 (C=CH), 3374, 3457 (NH$_2$) cm$^{-1}$. $^1$H NMR (400.13 MHz, acetone-$d_6$): δ 1.40-1.90 [10H, (CH$_2$)$_2$], 7.05 (1H, m, H-6), 7.33 (1H, m, H-5), 7.45 (1H, s, H-2), 7.46 (1H, m, H-4). $^{13}$C NMR (100.61 MHz, acetone-$d_6$): δ 21.6, 24.6 and 31.8 [(CH$_2$)$_2$], 88.1 (q-CN), 92.7 [(CH$_2$)$_2$C], 113.2 (C-2), 113.4 (CN), 117.1 (C-6), 121.1 (C-4), 128.7 (C-1), 130.4 (C-5), 149.9 (H$_2$N-C), 187.3 (H$_2$N-C$_6$H$_4$-C=), 200.0 (C=O). MS: m/z (%) 268 (96) [M]$^+$, 267 (14), 227 (16), 226 (32), 214 (14), 213 (100), 200 (11), 142 (41), 120 (25), 115 (19), 114 (10), 92 (39), 65 (12). Anal. calc. for C$_{16}$H$_{16}$N$_2$O$_2$ (268.32): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.47; H, 6.16; N, 10.21.

2-[(5-Iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate (4). To a solution of 2-aminobenzoic acid (0.137 g, 1 mmol) and Et$_3$N (0.101 g, 1 mmol) in MeCN (5 mL), cyanoacetylenc alcohol 1a (0.109 g, 1 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28 h. The solvent was evaporated in vacuo, and the residue was washed with diethyl ether to give beige crystals 4 (0.096 g, 39%); mp 288–290 °C. IR, $^1$H and $^{13}$C NMR spectra correspond to literature data.

4-Cyano-2-methyl-3-oxobutan-2-yl 4-aminobenzoate (5). To a solution of 4-aminobenzoic acid (0.137 g, 1 mmol) and Et$_3$N (0.101 g, 1 mmol) in MeCN (5 mL), cyanoacetylenic alcohol 1a (0.109 g, 1 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28 h. The solvent was evaporated in vacuo, and the residue was washed with diethyl ether to give yellow crystals of ester 5 (0.236 g, 96%); mp 157–158 °C. IR, $^1$H and $^{13}$C NMR spectra correspond to literature data.

2-(4-Aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (6). A solution of ester 5 (0.121 g, 0.5 mmol) and Et$_3$N (0.05 g, 0.05 mmol) in MeCN (2 mL) was stirred at 75-80
°C for 30 h. The solvent was removed and the residue was dried in vacuo to give a 3:1 mixture (1H NMR and GC-MS) of ester 5 (0.121 g; 25% conversion) and 4-oxo-4,5-dihydrofuran-3-carbonitrile 6. 1H NMR (400.13 MHz, acetone-d$_6$): δ 1.46 (6H, s, CH$_3$), 6.83 and 8.00 (4H, m, $J = 8.9$ Hz, Ar). MS: m/z (%) 228 (32) [M]$^+$, 143 (11), 142 (100), 65 (12), 41 (12), 39 (16).

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