Electrosynthesis of 2-Alkyl-4(3H)-quinazolinones

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Electroreduction of 2-nitrobenzonitrile in a variety of alcohols leads to 2-alkyl-4(3H)-quinazolinones via incorporation of the alkyl chain of the alcohols under cyclization. Physical properties and spectroscopic data of the quinazolinones and a probable pathway of their formation are given.

In a study of the multistep reduction of ortho-substituted nitroarenes, we investigated the electroreduction of 2-nitrobenzonitrile 1. In alcohols as solvents, containing sulfuric acid as supporting electrolyte and proton donor, we unexpectedly obtained 2-alkyl-4(3H)-quinazolinones 2 as the main reaction products.

![Reaction scheme](image)

Since these compounds are of value as intermediates in the synthesis of pharmaceutical and agricultural drugs [1], we investigated the scope of this reaction.

The procedure is demonstrated with 2a (see Experimental): The electroreduction of 1 was performed in a one-compartment cell using a mercury pool cathode and a carbon-rod counter-electrode. As reference we employed SCE, and all potentials given hereafter refer to this electrode. The supporting electrolyte consisted of 2N sulfuric acid in ethanol (or the respective alcohol in the case of 2b–d). The reduction was carried out at controlled potential (-700 mV). This potential was chosen from cyclovoltammetric results on 1 which reveal 2 peaks at -730 and -1000 mV (EtOH, glassy carbon cathode). In the presence of acid (2 N H2SO4/EtOH, Pt-cathode), there is another strong peak at -390 to -400 mV.

The product obtained, 2-methyl-4(3H)-quinazolinone (2a), contains two carbon atoms more than the starting material. The only carbon source is the alcohol of the supporting electrolyte. In order to prove the participation of the solvent, further experiments were carried out using various primary alcohols R–CH2OH [ethanol, R=CH3; n-propanol, R=CH2CH3; n-butanol, R=CH(CH3)2; and isobutanol, R=CH(CH3)2]. In every case a 2-R-4(3H)-quinazolinone 2 could be isolated (see Table I). This proves the incorporation of the solvent in the reaction product.

Two mechanisms for the formation of 2 may be envisaged. In the first one, the nitro group of 1 is reduced to the hydroxylamine 3, presumably via the corresponding nitrosoarene. This is supported by the fact that 2,2'-dicyanoazobenzene [2] can be isolated after a change of the reaction conditions (lower concentration of 1, 0.12 N acid, less negative potential of -50 → -350 mV). Arylhydroxylamines are also reported as the first intermediates in the cathodic reduction of other ortho-substituted nitrobenzenes [3–12]. Simultaneously, a part of the alcohol R–CH2OH is oxidized to the corresponding aldehyde RCHO at the anode. Indeed, the yield of 2a is increased by about 10%, if acetaldehyde is added from the beginning. The hydroxylamine 3 as a N-nucleophile adds to the aldehyde to give 4. The adduct 4 is dehydrated to the carbenium ion 5. By cycloaddition of the carbenium center in 5 to the nitrile group and

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further dehydration, the ion 6 is formed, which adds water to 7 which is in equilibrium with its tautomer 2.

Recently, Tallec et al. [13] have shown that N-(2-nitrobenzoyl)acetamide can be cathodically reduced to 7a (R = Me). Since 7a is the tautomer of 2a, this observation would suggest an alternative mechanism for our reaction. The alcohol is oxidized to the carboxylic acid, which reacts with 1 to give that N-(2-nitrobenzoyl)acetamide mentioned above or with the phenylhydroxylamine 3a (or the corresponding aniline itself) to form other intermediates on the way to 2a. This is, however, less probable because, at least, 1 does not react with acetic acid in our reaction system. Moreover, we used a reduction potential of −700 mV, whereas 7a was formed from N-(2-nitrobenzoyl)acetamide only at a potential of −1000 to −1100 mV [12]. To our knowledge, there are only three reports that alcohols can add to intermediates of the reduction of orr/zo-disubstituted nitroarenes. The alcohol is added as a nucleophile to give side chain esters [13] or ring opened products [11]; only in one case, it is also involved in ring formation [14]. In all cases, however, reaction products different from 2 are formed by various mechanisms. It is thus interesting to see that similar substituted 1,2-difunctionalized aromatics, which are reduced by several successive or parallel electron-transfers, can form many different types of intramolecular reduction products via cycloaddition of the two functions in their different reduction states (eventually only after a reaction with solvent molecules had occurred), although the reaction conditions are not dramatically different. This may be also the reason for the observation that the experiments sometimes give only medium or low yields [13].

Yields as well as analytical and spectroscopic data are given in Tables I and II. All products were identified by their IR, NMR and mass spectra. The 1H and 13C NMR spectra of 2a were preliminarily assigned by treating the ring system as a substituted benzene and applying the usual substituent chemical-shift increment values. This assignment has been proven by the [1H, 1H] coupling pattern which could be treated as nearly first order in the

Table I. Analytical data of the 2-alkyl-4(3H)quinazolinones (2).

<table>
<thead>
<tr>
<th>No.</th>
<th>Yield [%]a</th>
<th>Solventb</th>
<th>M.p. [°C]</th>
<th>Formula (Mass)</th>
<th>MS ([m/e], rel. int.) and IR (KBr) data</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>22</td>
<td>CHCl3</td>
<td>205–209°</td>
<td>C6H6N2O2</td>
<td>159.1 (100%), 90.0 (25%), 62.9 (14%), 42.0 (17%) 785, 1140, 1630, 1700, 2900, 3150, 3300, 3500 cm⁻¹</td>
</tr>
<tr>
<td>b</td>
<td>28</td>
<td>EtOH</td>
<td>188–190°</td>
<td>C10H10N2O2</td>
<td>173.1 (100%), 90.1 (96%), 63.0 (87%) 1137, 1325, 1469, 1600, 1677, 3000, 3005, 3500 cm⁻¹</td>
</tr>
<tr>
<td>c</td>
<td>37</td>
<td>EtOH</td>
<td>208–210°</td>
<td>C12H12N2O2</td>
<td>189.0 (1%), 188.0 (12%), 187.1 (10%), 184.9 (1%), 173.0 (36%), 160.0 (100%), 118.9 (37%), 90.0 (24%) 1135, 1328, 1469, 1614, 1675, 2969, 3000, 3069, 3390 cm⁻¹</td>
</tr>
<tr>
<td>d</td>
<td>20</td>
<td>EtOH</td>
<td>183–185°</td>
<td>C13H12N2O2</td>
<td>188.1 (29%), 173.0 (100%), 160.0 (28%), 90.1 (19%) 1325, 1614, 1677, 2920, 2979, 3391 cm⁻¹</td>
</tr>
</tbody>
</table>

a After recrystallization; b solvent of recrystallization; c after two recrystallizations from CHCl₃; d elemental analysis: Calcd. C: 67.42, H: 4.99, N: 17.48; Found C: 67.58, H: 5.01, N: 17.23; e the compound sublimes.
Table II. NMR-Spectra of 2 (δ ppm vs TMS).

<table>
<thead>
<tr>
<th>No.</th>
<th>2-R</th>
<th>NH</th>
<th>H-5</th>
<th>H-6</th>
<th>H-7</th>
<th>H-8</th>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>2.34</td>
<td>12.1</td>
<td>8.06</td>
<td>7.45</td>
<td>7.50</td>
<td>7.65</td>
</tr>
<tr>
<td>s</td>
<td>s</td>
<td>br</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>1.46; 2.85</td>
<td>11.8</td>
<td>8.27</td>
<td>7.45</td>
<td>7.68; 7.80</td>
<td>7.68; 7.77</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>q</td>
<td>d</td>
<td>t</td>
<td>m</td>
<td>m</td>
</tr>
<tr>
<td>c</td>
<td>1.08; 1.94; 2.79</td>
<td>11.8</td>
<td>8.23</td>
<td>7.44</td>
<td>7.67; 7.78</td>
<td>7.67; 7.77</td>
</tr>
<tr>
<td>t</td>
<td>m</td>
<td>t</td>
<td>s</td>
<td>d</td>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>d</td>
<td>1.46; 3.04</td>
<td>11.0</td>
<td>8.23</td>
<td>7.44</td>
<td>7.68; 7.77</td>
<td>7.68; 7.77</td>
</tr>
</tbody>
</table>

a 13C NMR (CDCl3/DMSO: 100.6 MHz): 160.81 (C-4), 152.67 (C-2), 147.58 (C-8a), 132.55 (C-7), 125.05 (C-6, 7), 124.33, 124.24 (C-6, 7), 119.35 (C-4a), 20.20 (CH3); b in DMSO/CDCl3; 400.1 MHz; c in CDCl3; 300 MHz; d 13C NMR (CDCl3; 75.4 MHz): 164.13 (C-4), 156.62 (C-2), 149.38 (C-8a), 134.73 (C-7), 127.17 (C-8), 126.31, 126.19 (C-6, 7), 120.49 (C-4a), 37.77, 21.05, 13.75 (C-1, C-2, C-3 of propyl).

400 MHz spectrum, and by [1H, 13C] COSY and long-range COSY measurements. Although the signal at δ = 12 ppm would better correspond to a structure with an OH-group (7) than to a structure with a CO–NH group (2), the ketoform 2 is more compatible with the 13C NMR spectrum. The assignments of the NMR spectra of 2b–d follow that of 2a. Compound 2a is identical with the product 15,883-6 of Aldrich Chemical Co., Ltd. The difference in melting points of the two samples may be due to the fact that the Aldrich compound is the hydrate.

Experimental

2-Alkyl-4(3H)-quinazolinones (2)

500 mg (3.37 mmol) of ortho-nitrobenzonitrile were dissolved in 250 ml of ca. 2 N sulphuric acid/alcohol (prepared from 15.3 ml of concentrated 98% H2SO4 and 234.7 ml of the alcohol) and electrolyzed in a one-compartment cell, using a carbon rod as the counter electrode, SCE as the reference electrode and a mercury pool as the cathode. The electrolysis was carried out at 25 °C at a potential of −700 mV. The reaction time was 2 h. The progress of the reaction was followed by TLC and stopped at the exhaustion of the starting material. The solution was separated from the mercury and the alcohol partially removed in vacuo. Water was added, and the solution neutralized to pH 7 with 10% aqueous NaOH (under cooling). Inorganic salts were filtered off, and the organic layer was extracted with chloroform. The residue left after evaporation of the solvent was crystallized from the solvent given in Table I and identified as 2-alkyl-4(3H)-quinazolinone (2). There were also traces of other unidentified products.