Short Note

4-Aminoalkyl Quinolin-2-One Derivatives via Knorr Cyclisation of ω-Amino-β-Keto Anilides

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Abstract: In a high-yielding and solvent-free procedure N-ethoxycarbonyl protected ω-amino-β-keto anilides undergo Knorr cyclisation in neat polyphosphoric acid to provide straightforward route to 4-aminoalkyl quinolin-2-one derivatives with variable length of the alkyl chain.

Keywords: Knorr; quinolin-2-one; 2-quinolone; carbostyril; solvent-free

1. Introduction

The quinoline ring system is present in a vast number of natural [1,2] and synthetic [3,4] organic compounds with valuable properties. Among this large group, the subclass of quinolin-2-ones (also known as carbostyrils) stands out with many bioactive structures [5]. For example, the quinolin-2-one fragment is found in alkaloids such as Viridicatins [6–9], Aflaquinolones [10] and Yaequinolones [11], as well as in synthetic drug candidates with anti-inflammatory [12,13] and antibacterial [14] properties. The construction of the quinolin-2-one ring system is most commonly achieved via the classic Knorr cyclisation of β-keto anilides in acidic media [15,16]. The mechanism of this reaction has been studied in detail [17] and also an alternative approach based on N-aryl amides of 3-arylpropynoic acids has been developed [18]. In addition to this classical method, the scope of which is limited in the presence of acid-sensitive functionalities, there have been many recent developments. The modern approaches include Pd-catalysed formation of C-C or C-N bonds in the ring system [19–21], Pd-catalyzed synthesis from quinoline N-oxides and azodicarboxylates [22], Co-catalyzed cyclization of α-bromo-N-phenylacetamides [23], Intermolecular addition/cyclization of carbamoyl radicals under photoredox [24] or Ag [25] catalysis, hypervalent iodine(III)-mediated decarboxylative cyclization [26] and chemoenzymatic approaches [27,28].

Quinolin-2-ones with aminoalkyl substituent at position 4 are interesting as building blocks for complex natural products [29,30] and also in their own right as bioactive substances [12–14]. To date, all instances of these molecules in the literature are synthesised by either S_N2 amination of the corresponding 4-halogenoalkyl derivatives [12,13,31,32] or hydrogenation of the corresponding 4-cyano derivatives [14]—approaches that work mostly for the preparation of 4-aminomethyl derivatives and are not well suited for derivatives with a longer carbon chain between the amino functionality and the quinolin-2-one core. In this communication, we demonstrate that the Knorr reaction can be successfully carried out with N-ethoxycarbonyl protected ω-amino-β-keto anilides, leading directly to the corresponding 4-aminoalkyl quinolin-2-one derivatives with variable length of the alkyl chain.

2. Results

The problematic accessibility of ω-amino-β-keto anilides (I) by known methods is probably the main reason why these compounds have not been used as precursors to quinolin-2-ones until now. However, since a method developed recently in our laboratory...
provided easy access to these substrates [33], we decided to investigate their behaviour under Knorr-type conditions. After a quick screening of various acids and solvents, we arrived at polyphosphoric acid (PPA) as the optimal medium for the targeted cyclodehydration of 1 to 4-aminoalkylquinolin-2-ones 2. The cyclisation of 1 to 2 (Scheme 1, Table 1) proceeded for 90 min at 80 °C in neat PPA. The products 2 were isolated in 80–90% yield after easy workup, including only the addition of water to the reaction mixture and filtration of the precipitated product or, optionally, extraction in CH₂Cl₂. Although the extractive workup gave slightly cleaner products in case 2b and 2c, this synthesis could be carried out as a completely solvent-free procedure, depending on the operator preferences.

![Scheme 1. Knorr cyclisation of ω-amino-β-keto anilides to 4-aminoalkylquinolin-2-ones.](image)

### Table 1. Yields of 4-aminoalkylquinolin-2-ones 2, prepared according to Scheme 1.

| Product | n | Yield (%) |
|---------|---|-----------|
| 2a      | 1 | 90        |
| 2b      | 2 | 80        |
| 2c      | 3 | 85        |

3. Materials and Methods

The starting N-ethoxycarbonyl ω-amino-β-keto anilides (1) were prepared from the corresponding ω-amino acids and acetoacetanilide, according to our previously published procedure [33]. Polyphosphoric acid (115% H₃PO₄ basis, CAS No. 8017-16-1) was purchased from (Sigma-Aldrich, Darmstadt, Germany). NMR spectra were run on a Bruker Avance AV600 (600/150 MHz 1H/13C) or Bruker DRX 250 (250/62.5 MHz 1H/13C) spectrometers at BAS-IOCCP—Sofia and chemical shifts (δ, ppm) are downfield from TMS. High resolution mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer. TLC was conducted on aluminium-backed Silica gel 60 sheets (Merck) with KMnO₄ staining; Melting points were measured on Boetius hot stage apparatus and are not corrected.

**Synthetic Procedure**

4-aminoalkyl quinolin-2-ones (2a–c), general procedure: To the corresponding β-keto anilide 1a–c (200 mg) in a glass vial was added PPA (5–6 g, 2.5–3 mL). The mixture was heated to 80 °C and was stirred intensely until full homogenization (ca. 15–20 min). The homogenous mixture was left for a further 90 min at 80 °C, then the vial was cooled to r.t. with tap water and the contents were rinsed and poured into a glass with 50–70 mL of water. The isolation of the products 2a–c was conducted by filtration of the resulting suspension (2a) or by extraction with 2 × 30 mL CH₂Cl₂ (2b, 2c). The yields of 2b and 2c were practically unaffected by the type of workup procedure (filtration or extraction). For product 2a, filtration is recommended because of its poor solubility in CH₂Cl₂.

(2-Oxo-1,2-dihydro-quinolin-4-ylmethyl)-carbamic acid ethyl ester (2a): m.p. 173–174 °C; ¹H NMR (DMSO-d₆, δ ppm, J Hz): 1.19 (t, J = 7, 3H), 4.04 (q, J = 7, 2H), 4.42 (d, J = 5.9, 2H), 6.32 (s, 1H), 7.18–7.77 (m, 4H, ArH), 7.76 (br t, 1H, NH), 11.71 (br s, 1H, NH); ¹³C NMR
(DMSO-d$_6$, δ ppm): 15.1, 41.3, 60.6, 116.1, 118.1, 118.7, 122.2, 124.3, 130.9, 139.3, 148.9, 156.9, 162.1; HRMS (ES+): m/z [M + Na]$^+$ calcld for C$_{13}$H$_{14}$N$_2$NaO$_4^+$: 269.0897, found: 269.0896;

$[2$-$2$-$Ox o-1,2$-$dihydro$-$quinol ine$-$4$-$yl$]$ethyl$]$$-$car bamic acid ethyl ester (2b): m.p. 185–186 °C; 1H-NMR (250 MHz, DMSO-d$_6$, δ ppm, J Hz): 1.15 (t, 3H, J = 7), 2.95 (t, 2H, J = 7), 3.29 (m, 2H), 3.98 (q, 2H, J = 7), 6.36 (s, 1H), 7.17–7.84 (m, 5H) ArH +NH, 11.64 (s, 1H) NH; 13C-NMR (DMSO-d$_6$, δ ppm): 161.51, 156.31, 148.74, 138.96, 132.11, 123.82, 120.99, 118.80, 115.68, 59.60, 39.74, 31.82, 14.62; HRMS (ES+): m/z [M + Na]+$^+$ calcld for C$_{14}$H$_{16}$N$_2$NaO$_5^+$: 283.1053, found: 283.1055;

$[3$-$2$-$Ox o-1,2$-$ dihydro$-$quinol ine$-$4$-$yl$]$propyl$]$$-$car bamic acid ethyl ester (2c): m.p. 116–118 °C; 1H-NMR (250 MHz, CDCl$_3$, δ ppm, J Hz): 1.27 (t, 3H, J = 7), 1.97 (m, 2H), 2.94 (t, 2H, J = 8), 3.34 (m, 2H), 4.15 (q, 2H, J = 7), 4.98 (br s, 1H) NH, 6.66 (s, 1H), 7.23–7.74 (m, 4H) ArH, 12.67 (br s, 1H) NH; 13C-NMR (DMSO-d$_6$, δ ppm): 164.12, 156.85, 152.89, 138.42, 130.69, 124.02, 122.87, 119.78, 119.04, 117.11, 60.90, 40.63, 29.40. 29.20, 14.66; HRMS (ES+): m/z [M + Na]+$^+$ calcld for C$_{15}$H$_{18}$N$_2$NaO$_5^+$: 297.1210, found: 297.1206.

Supplementary Materials: The following are available online, S1.PDF—processed 1H and 13C NMR spectra. S2.zip—Raw NMR data, and mol files structure.

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