molbank

MDPI

Communication

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

Plamen Angelov *, Stilyana Velichkova and Pavel Yanev

Faculty of Chemistry, University of Plovdiv Paisii Hilendarski, 24 Tsar Asen Str., 4000 Plovdiv, Bulgaria; sv1415@abv.bg (S.V.); qnev@uni-plovdv.net (P.Y.)

* Correspondence: angelov@uni-plovdiv.bg; Tel.: +359-32-261349

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

Citation: Angelov, P.; Velichkova, S.; Yanev, P. 4-Aminoalkyl Quinolin-2-one Derivatives via Knorr Cyclisation of ω-Amino-β-Keto Anilides. *Molbank* **2021**, *2021*, M1266. https://doi.org/10.3390/M1266

Academic Editor: Raffaella Mancuso

Received: 14 June 2021
Accepted: 2 August 2021
Published: 5 August 2021

1. Introduction

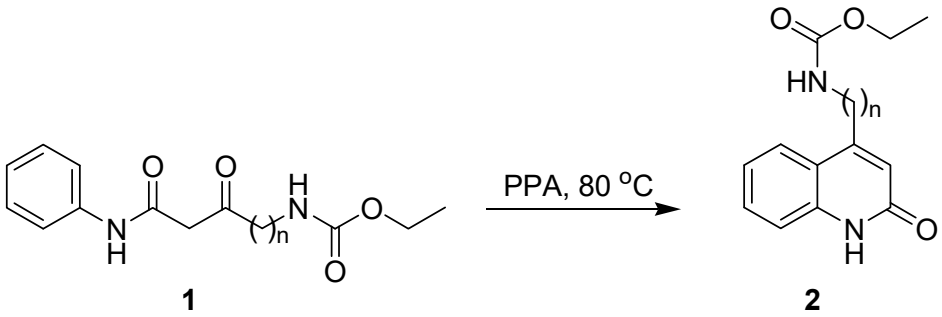
The quinoline ring system is present in a vast number of natural [1,2] and synthetic [3,4] organic compounds with valuable properties. Among this large group, the subclass of quinolin-2-ones (also known as carbostyrils) stands out with many bioactive structures [5]. For example, the quinolin-2-one fragment 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 (**1**) 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 cyclocondensation 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 CH_2Cl_2. 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.

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% H_3PO_4 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 $^1H/^{13}C$) or Bruker DRX 250 (250/62.5 MHz $^1H/^{13}C$) 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 $KMnO_4$ 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 CH_2Cl_2 (**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 CH_2Cl_2.

(2-Oxo-1,2-dihydro-quinolin-4-ylmethyl)-carbamic acid ethyl ester (**2a**): m.p. 173–174 °C; ^1H NMR (DMSO-d_6, 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); ^{13}C 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* $[M + Na]^+$ calcd for $C_{13}H_{14}N_2NaO_3^+$: 269.0897, found: 269.0896;

[2-(2-Oxo-1,2-dihydro-quinolin-4-yl)-ethyl]-carbamic acid ethyl ester (**2b**): m.p. 185–186 °C; ^{1}H 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; ^{13}C NMR (DMSO-d_6, δ ppm): 161.51, 156.31, 148.74, 138.96, 130.16, 124.32, 121.68, 120.99, 118.80, 115.68, 59.60, 39.74, 31.82, 14.62; HRMS (ES+): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}N_2NaO_3^+$: 283.1053, found: 283.1055;

[3-(2-Oxo-1,2-dihydro-quinolin-4-yl)-propyl]-carbamic acid ethyl ester (**2c**): m.p. 116–118 °C; ^{1}H 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; ^{13}C 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* $[M + Na]^+$ calcd for $C_{15}H_{18}N_2NaO_3^+$: 297.1210, found: 297.1206.

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

Author Contributions: Conceptualization, chemical synthesis and manuscript writing: P.A.; chemical synthesis: S.V. and P.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Bulgarian National Science Fund, grant number DN09-15/2016.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article and supporting Supplementary Materials.

Acknowledgments: The authors are grateful to the Faculty of Biology, Department of Plant Physiology and Molecular Biology for access to high resolution mass spectrometer, provided under the EC FP7/REGPOT-2009-1/BioSupport project.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Shang, X.-F.; Natschke, S.L.M.; Liu, Y.-Q.; Guo, X.; Xu, X.-S.; Goto, M.; Li, J.-C.; Yang, G.-Z.; Lee, K.-H. Biologically active quinoline and quinazoline alkaloids part I. *Med. Res. Rev.* **2018**, *38*, 775–828. [CrossRef] [PubMed]
2. Shang, X.-F.; Natschke, S.L.M.; Yang, G.-Z.; Liu, Y.-Q.; Guo, X.; Xu, X.-S.; Goto, M.; Li, J.-C.; Zhang, J.-Y.; Lee, K.-H. Biologically active quinoline and quinazoline alkaloids part II. *Med. Res. Rev.* **2018**, *38*, 1614–1660. [CrossRef] [PubMed]
3. Nainwal, N.M.; Tasneem, S.; Akhtar, W.; Verma, G.; Khan, M.F.; Parvez, S.; Shaquiquzzaman, M.; Akhter, M.; Alam, M.M. Green recipes to quinoline: A review. *Eur. J. Med. Chem.* **2019**, *164*, 121–170. [CrossRef] [PubMed]
4. Harry, N.A.; Ujwaldev, S.M.; Anilkumar, G. Recent advances and prospects in the metal-free synthesis of quinolines. *Org. Biomol. Chem.* **2020**, *18*, 9775–9790. [CrossRef]
5. Tashima, T. The structural use of carbostyril in physiologically active substances. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3415–3419. [CrossRef] [PubMed]
6. Kobayashi, Y.; Harayama, T. A Concise and Versatile Synthesis of Viridicatin Alkaloids from Cyanoacetanilides. *Org. Lett.* **2009**, *11*, 1603–1606. [CrossRef]
7. Tangella, Y.; Manasa, K.L.; Krishna, N.H.; Sridhar, B.; Kamal, A.; Babu, B.N. Regioselective Ring Expansion of Isatins with In Situ Generated α-Aryldiazomethanes: Direct Access to Viridicatin Alkaloids. *Org. Lett.* **2018**, *20*, 3639–3642. [CrossRef]
8. Liang, P.; Zhang, Y.Y.; Yang, P.; Grond, S.; Zhang, Y.; Qian, Z.-J. Viridicatol and viridicatin isolated from a shark-gill-derived fungus *Penicilliumpolonicum* AP2T1 as MMP-2 and MMP-9 inhibitors in HT1080 cells by MAPKs signaling pathway and docking studies. *Med. Chem. Res.* **2019**, *28*, 1039–1048. [CrossRef]
9. Einsiedler, M.; Jamieson, C.S.; Maskeri, M.A.; Houk, K.N.; Gulder, T.A.M. Fungal Dioxygenase AsqJ is Promiscuous and Bimodal: Substrate-Directed Formation of Quinolones versus Quinazolinones. *Angew. Chem. Int. Ed.* **2021**, *60*, 8297–8302. [CrossRef] [PubMed]
10. Neff, S.A.; Lee, S.U.; Asami, Y.; Ahn, J.S.; Oh, H.; Baltrusaitis, J.; Gloer, J.B.; Wicklow, D.T. Aflaquinolones A−G: Secondary Metabolites from Marine and Fungicolous Isolates of Aspergillus spp. *J. Nat. Prod.* **2012**, *75*, 464–472. [CrossRef]

11. Jia, W.-L.; Ces, S.V.; Fernández-Ibánez, M.A. Divergent Total Syntheses of Yaequinolone-Related Natural Products by Late-Stage C−H Olefination. *J. Org. Chem.* **2021**, *86*, 6259–6277. [CrossRef]
12. Kalkhambkar, R.G.; Kulkarni, G.M.; Kamanavalli, C.M.; Premkumar, N.; Asdaq, S.M.B.; Sun, C.M. Synthesis and biological activities of some new fluorinated coumarins and 1-aza coumarins. *Eur. J. Med. Chem.* **2008**, *43*, 2178–2188. [CrossRef] [PubMed]
13. Bonnefous, C.; Payne, J.E.; Roppe, J.; Zhuang, H.; Chen, X.; Symons, K.T.; Nguyen, P.M.; Sablad, M.; Rozenkrants, N.; Zhang, Y.; et al. Discovery of Inducible Nitric Oxide Synthase (iNOS) Inhibitor Development Candidate KD7332, Part 1: Identification of a Novel, Potent, and Selective Series of Quinolinone iNOS Dimerization Inhibitors that are Orally Active in Rodent Pain Models. *J. Med. Chem.* **2009**, *52*, 3047–3062. [CrossRef] [PubMed]
14. Skepper, C.K.; Armstrong, D.; Balibar, C.J.; Bauer, D.; Bellamacina, C.; Benton, B.M.; Bussiere, D.; De Pascale, G.; De Vicente, J.; Dean, C.R.; et al. Topoisomerase Inhibitors Addressing Fluoroquinolone Resistance in Gram-Negative Bacteria. *J. Med. Chem.* **2020**, *63*, 7773–7816. [CrossRef] [PubMed]
15. Yuan, Y.; Yang, R.; Zhang-Negrerie, D.; Wang, J.; Du, Y.; Zhao, K. One-Pot Synthesis of 3-Hydroxyquinolin-2(1H)-ones from NPhenylacetoacetamide via $PhI(OCOCF_3)_2$-Mediated α-Hydroxylation and H_2SO_4-Promoted Intramolecular Cyclization. *J. Org. Chem.* **2013**, *78*, 5385–5392. [CrossRef] [PubMed]
16. Liu, X.; Zhang, Q.; Zhang, D.; Xin, X.; Zhang, R.; Zhou, F.; Dong, D. PPA-Mediated C-C Bond Formation: A Synthetic Route to Substituted Indeno[2,1-c]quinolin-6(7H)-ones. *Org. Lett.* **2013**, *15*, 776–779. [CrossRef]
17. Sai, K.K.S.; Gilbert, T.M.; Klumpp, D.A. Knorr Cyclizations and Distonic Superelectrophiles. *J. Org. Chem.* **2007**, *72*, 9761–9764. [CrossRef] [PubMed]
18. Ryabukhin, D.S.; Gurskaya, L.Y.; Fukin, G.K.; Vasilyev, A.V. Superelectrophilic activation of N-aryl amides of 3-arylpropynoic acids: Synthesis of quinolin-2(1H)-one derivatives. *Tetrahedron* **2014**, *70*, 6428–6443. [CrossRef]
19. Guan, M.; Pang, Y.; Zhang, J.; Zhao, Y. Pd-Catalyzed sequential β-C(sp^3)–H arylation and intramolecular amination of δ-C(sp^2)–H bonds for synthesis of quinolinones via an N,O-bidentate directing group. *Chem. Commun.* **2016**, *52*, 7043–7046. [CrossRef]
20. Han, J.; Wu, X.; Zhang, Z.; Wang, L. Palladium-catalyzed arylation/cyclization/desulfonation cascades toward 4-aryl quinolin-2(1H)-ones with diaryliodonium salts. *Tetrahedron Lett.* **2017**, *58*, 3433–3436. [CrossRef]
21. Silva, V.L.M.; Silva, A.M.S. Palladium-Catalysed Synthesis and Transformation of Quinolones. *Molecules* **2019**, *24*, 228. [CrossRef]
22. Peng, J.-B.; Chen, B.; Qi, X.; Ying, J.; Wu, X.-F. Palladium-catalyzed synthesis of quinolin-2(1H)-ones: The unexpected reactivity of azodicarboxylate. *Org. Biomol. Chem.* **2018**, *16*, 1632–1635. [CrossRef]
23. Cheng, Y.-C.; Chen, Y.-Y.; Chuang, C.-P. Cobalt salt-catalyzed carbocyclization reactions of α-bromo-N-phenylacetamide derivatives. *Org. Biomol. Chem.* **2017**, *15*, 2020–2032. [CrossRef]
24. Petersen, W.F.; Taylor, R.J.K.; Donald, J.R. Photoredox-catalyzed procedure for carbamoyl radical generation: 3,4-dihydroquinolin-2-one and quinolin-2-one synthesis. *Org. Biomol. Chem.* **2017**, *15*, 5831–5845. [CrossRef] [PubMed]
25. Jin, C.; He, J.-Y.; Bai, Q.-F.; Feng, G. Silver-Catalyzed Decarboxylative Radical Addition/Cyclization of Oxamic Acids with Alkenes towards quinolin-2-ones. *Synlett* **2020**, *31*, 1517–1522. [CrossRef]
26. Fan, H.; Pan, P.; Zhang, Y.; Wang, W. Synthesis of 2-Quinolinones via a Hypervalent Iodine(III)-Mediated Intramolecular Decarboxylative Heck-Type Reaction at Room Temperature. *Org. Lett.* **2018**, *20*, 7929–7932. [CrossRef] [PubMed]
27. Kishimoto, S.; Hara, K.; Hashimoto, H.; Hirayama, Y.; Champagne, P.A.; Houk, K.N.; Tang, Y.; Watanabe, K. Enzymatic one-step ring contraction for quinolone biosynthesis. *Nat. Commun.* **2018**, *9*, 2826. [CrossRef]
28. Tang, H.; Tang, Y.; Kurnikov, I.V.; Liao, H.-J.; Chan, N.-L.; Kurnikova, M.G.; Guo, Y.; Chang, W.-C. Harnessing the Substrate Promiscuity of Dioxygenase AsqJ and Developing Efficient Chemoenzymatic Synthesis for Quinolones. *ACS Catal.* **2021**, *11*, 7186–7192. [CrossRef]
29. Selig, P.; Bach, T. Enantioselective Total Synthesis of the Melodinus Alkaloid (+)-Meloscine. *Angew. Chem. Int. Ed.* **2008**, *47*, 5082–5084. [CrossRef]
30. Selig, P.; Herdtweck, E.; Bach, T. Total Synthesis of Meloscine by a [2+2]-Photocycloaddition/Ring-Expansion Route. *Chem. Eur. J.* **2009**, *15*, 3509–3525. [CrossRef]
31. Brandes, S.; Selig, P.; Bach, T. Stereoselective Intra-and Intermolecular [2+2] Photocycloaddition Reactions of 4-(2′-Aminoethyl)quinolones. *Synlett* **2004**, 2588–2590. [CrossRef]
32. Selig, P.; Bach, T. Photochemistry of 4-(2¢-Aminoethyl)quinolones: Enantioselective Synthesis of Tetracyclic Tetrahydro-1aH-pyrido[4′,3′:2,3]-cyclobuta[1,2-c] Quinoline-2,11(3H,8H)-diones by Intra-and Intermolecular [2+2]-Photocycloaddition Reactions in Solution. *J. Org. Chem.* **2006**, *71*, 5662–5673. [CrossRef] [PubMed]
33. Yanev, P.; Angelov, P. Synthesis of functionalised β-keto amides by aminoacylation/domino fragmentation of β-enamino amides. *Beilstein J. Org. Chem.* **2018**, *14*, 2602–2606. [CrossRef] [PubMed]