Metal-assisted Oxidative Cyclization of Arylamidrazones II [1].
Novel Synthesis of 1,4-Diaryl[1,2,4]triazino[6,5-h]quinolines

Monther A. Khanfar\textsuperscript{a}, Bassam A. Abu Thaher\textsuperscript{b}, Jalal A. Zahra\textsuperscript{a}, Raed A. AL-Qawasmeh\textsuperscript{a}, Mustafa M. El-Abadelah\textsuperscript{a}, and Wolfgang Voelter\textsuperscript{c}

\textsuperscript{a} Chemistry Department, Faculty of Science, The University of Jordan, Amman, Jordan
\textsuperscript{b} Chemistry Department, Faculty of Science, Islamic University of Gaza, Gaza Strip
\textsuperscript{c} Interfakultäres Institut für Biochemie, Universität Tübingen, Hoppe-Seyler Str. 4, D-72076 Tübingen, Germany

Reprint requests to Prof. Dr. W. Voelter. E-mail: wolfgang.voelter@uni-tuebingen.de or Dr. M.A. Khanfar. E-mail: m.khanfar@ju.edu.jo


New model 1,2,4-triazino[6,5-h]quinolines \(8\textsubscript{a}–\textsubscript{c}\) are prepared by oxidative cyclization of the respective \(N\)-(quinolin-8-yl)amidrazone precursors \(7\textsubscript{a}–\textsubscript{c}\) using copper(II) chloride. Interestingly, the cyclized products \(8\textsubscript{a}–\textsubscript{c}\) were found to be arylated at \(N\textsubscript{1}\) position. Analytical and spectral (MS, NMR) data of the title products are in compliance with the allocated structures.

Key words: \(\alpha\)-Acetyl-N-arylhydrazonoyl Chlorides, 8-Aminoquinoline, Arylamidrazones, CuCl\textsubscript{2}-catalyzed Cyclization, \(\alpha\texttextsubscript{a}\)-Triazino[6,5-h]quinolines

Introduction

The preparation and biological aspects of various isomeric 1,2,4-triazinoquinolines have been reported [2 – 18]. Examples of these tricyclic systems include 1,2,4-triazino[5,6-c]quinolines (1) [2 – 11], [1,2,4]triazino[6,5-c]quinolines (2) [12, 13], 5,10-dihydro-1,2,4-triazino[6,5-b]quinolines (3) [14], and 1,2,4-triazino[6,5-f]quinolines (4) [15]. Other related isomeric derivatives, namely 1,2,4-triazino[5,6-b]quinolin-3-ones [16], [1,2,4]triazino[4,3-a]quinolines [17] and [1,2,4]triazino[2,3-a]quinoline-3-ones [18], have also been tackled. Several derivatives of the aforementioned triazinoquinolines exhibit antiinflammatory [7, 9, 10, 13], bactericidal [4], antimicrobial [7, 10, 13], antymycotic [11], antifungal [2, 8], and analgesic [5, 7, 10] activities as well as binding interactions with central and peripheral-type benzodiazepine receptor sites [18] and inhibition of germination of Sinapis alba seeds [3].

To the best of our knowledge, the 1,2,4-triazine ring \([h]\)-fused onto a quinoline skeleton is hitherto undescribed in the literature. Accordingly, the present work has aimed at the synthesis of model 1,4-dihydro[1,2,4]triazino[6,5-h]quinolines \(9\textsubscript{a}–\textsubscript{c}\) which end up as the respective \(N\textsubscript{1}\)-arylated derivatives \(8\textsubscript{a}–\textsubscript{c}\), as outlined in Schemes 1 and 2 (vide infra).

Results and Discussion

8-Aminoquinoline (5), acting as a nitrogen nucleophile, readily adds to nitrile imines (the reactive 1,3-dipolar species, generated \textit{in situ} from their \(N\)-arylhydrazonoyl chloride \(6\textsubscript{a}–\textsubscript{c}\) precursors [19, 20] in the presence of triethylamine) to produce the corresponding \(N\)-(aryl)-2-oxo-\(N\textsuperscript{\prime}\textsuperscript{\prime}\)-(quinolin-8-yl)propanamide hydrazones \(7\textsubscript{a}–\textsubscript{c}\) (Scheme 1). The structures of the latter acyclic amidrazone adducts are in accordance
with their microanalyses, MS and NMR spectral data that are given in the Experimental Section.

Direct reaction of these acyclic adducts with copper(II) chloride dihydrate in ethanol gave dark brown solutions from which the major low-polarity products were isolated and identified as the respective 1,4-diaryl-1,2,4-triazino[6,5-h]quinolines 8a–c (Scheme 1). The microanalytical and spectral (MS, NMR) data of these cyclized products, given in the Experimental Section, are in agreement with the proposed structures. The mass spectra of 7 and 8 show the expected molecular ion peaks as suggested by their molecular formulas. The measured high-resolution (HRMS) data for M⁺ are also in good agreement with the calculated values.

The ¹H and ¹³C NMR signals were assigned to the different protons and carbons. This follows from DEPT and 2D (COSY, HMQC, HMBC) experiments which showed correlations consistent with these assignments. Thus, for compounds 7a–c, long-range correlations are observed between 4-H and each of C-2, C-5 and C-8a as well as between 7-H and each of C-5 and C-8a, and between the hydrazone N-H and each of C-1'′ and C-2'/C-6'. Likewise, strong 1,3-correlations in compounds 8a–c are observed between 6-H and each of C-4a and C-10a, between 5-H and C-6a, between 3'-H/5'-H and C-1', as well as between 2''-H/6''-H and C-4''. The cyclization of 7 into 8 is evidenced from the disappearance of the ¹H NMR signals at δ = 6.3 and 7.7 ppm (belonging to 7-H and 1'-NH, respectively) and of the ¹³C signal at δ = 111 ppm (belonging to CH-7 in the DEPT spectra). It is worth noting that substitution of the N(1)-position of the dihydrotriazinoquinoline (by an aryl group) has taken place as evident from a sizable increment of the molecular ion mass by a value equivalent to that of the N-aryl moiety. This interesting N(1)-aryl substitution is also substantiated by elemental analyses and NMR spectral data lacking the 8-NH proton singlet at ca. 8.4 ppm (present in 7). A possible mechanism for such unprecedented mode of aryl substitution at the N1 locus starts with initial coordination of copper ions by the presumed heterocyclic system 9, followed by cross-coupling at the N(4)-aryl bond to form the intermediate copper complex 10 which eventually leads to the production of 8.
(Scheme 2). Further investigations along this line are underway, and the results (if any) will be communicated separately.

Experimental Section

8-Aminoquinoline, 3-chloropentane-2,4-dione and CuCl₂·2H₂O were purchased from Acros. Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting temperature apparatus. ¹H, ¹³C NMR, DEPT, and 2D (H-H COSY, HMBC, HMQC) spectra were measured on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with reference to TMS as internal standard. Electron impact (EI) and high-resolution mass spectra (HRMS) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV and an ion source temperature of 200 °C. Microanalyses were performed at the Microanalytical Laboratory of the Hashemite University, Zarqa, Jordan.

I-(N-Arylhydrazono)-1-chloropropan-2-ones (6a–c)

These hydrazonoyl chlorides 6a–c [19, 20] have previously been characterized and were prepared in this study via the Japp-Klingemann reaction [21] which involves direct coupling of the appropriate arenediazonium chloride with 3-chloropentane-2,4-dione in aqueous pyridine, following standard procedures [19].

N-(4-Methylphenyl)-2-oxo-N²-(quinolin-8-yl)propanamide hydrazone (7a)

Triethylamine (3 mL) was added dropwise to a stirred and cooled (0 °C) solution of 1-chloro-1-[N-(4-methylphenyl)hydrazono]propan-2-one (6a) (2.1 g, 10 mmol) in THF (40 mL). To this solution was added dropwise 8-aminooquinoline (1.2 g, 12 mmol) in THF (10 mL), and the resulting mixture was allowed to stir at r. t. over night. Thereafter, the organic solvent was evaporated, and the residue was treated with cold water. The precipitated yellow solid product was collected, washed with cold ethanol (2 mL) and recrystallized from chloroform/petroleum ether. Yield: 1.6 g (50%), m. p. 148–149 °C (dec.). – ¹H NMR (300 MHz, CDCl₃): δ = 2.30 (s, 3H, CH₃Ph), 2.61 (s, 3H, CH₃CO), 6.28 (dd, 1H, J = 7.1, 2.5 Hz, 7-H), 7.04 (dd, 2H, J = 8.6 Hz, 2'-H + 6'-H), 7.10 (dd, 2H, J = 8.6 Hz, 3'-H + 5'-H), 7.24 (dd, 1H, J = 8.3, 4.2 Hz, 3-H), 7.30, 7.32 (center of two overlapped dd, 2H, 5-H + 6-H), 7.69 (s, 1H, 1'-NH), 8.11 (dd, 1H, J = 8.3, 1.7 Hz, 4-H), 8.39 (s, 1H, 8-NH), 8.82 (dd, 1H, J = 4.2, 1.7 Hz, 2-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 20.8 (CH₃Ph), 24.3 (CH₃CO), 110.9 (C-7), 114.0 (C-2' + C-6'), 118.9 (C-5), 121.8 (C-3), 126.9 (C-6), 128.8 (C-4a), 129.9 (C-3' + C-5'), 131.8 (C-4'), 135.7 (C-8a), 136.2 (C-4), 136.5 (C-8), 139.1 (C-1'), 140.6 (C-1'), 148.4 (C-2), 193.7 (CH₃CO). – EIMS (70 eV): m/z (%) = 318 (40) [M⁺], 276 (14), 198 (65), 169 (11), 155 (100), 144 (18). – HRMS (m/z): calcd. 318.14750 [M⁺]: 318.14804. – C₂₀H₁₄N₂O (318.37): calcd. C 71.68, H 5.70, N 17.60; found C 71.46, H 5.82, N 17.68.

N-(4-Chlorophenyl)-2-oxo-N²-(quinolin-8-yl)propanamide hydrazone (7b)

This compound was prepared from 1-chloro-1-[N-(4-chlorophenyl)hydrazono]propan-2-one (6b) (2.3 g, 10 mmol), following a similar procedure as noted above for the preparation of 7a. Yield: 2.0 g (59%), m. p. 177–178 °C (dec.). – ¹H NMR (300 MHz, CDCl₃): δ = 2.59 (s, 3H, CH₃Ph), 6.27 (dd, 1H, J = 6.2, 2.2 Hz, 7-H), 7.05 (d, 2H, J = 8.4 Hz, 2'-H + 6'-H), 7.23 (d, 2H, J = 8.4 Hz, 3'-H + 5'-H), 7.31, 7.33 (center of two overlapped dd, 2H, 5-H + 6-H), 7.43 (dd, 1H, J = 8.2, 4.1 Hz, 3-H), 7.67 (s, 1H, 1'-NH), 8.11 (dd, 1H, J = 8.2 Hz, 4-H), 8.42 (s, 1H, 8-NH), 8.67 (d, 1H, J = 4.2 Hz, 2-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 24.3 (CH₃CO), 111.1 (C-7), 115.1 (C-2' + C-6'), 119.2 (C-5), 121.8 (C-3), 126.9 (C-6), 126.9 (C-4'), 128.8 (C-4a), 129.4 (C-3' + C-5'), 136.1 (C-1'), 136.2 (C-4'), 136.4 (C-8a), 141.6 (C-1'), 148.5 (C-2'), 193.7 (CH₃CO). – EIMS (70 eV): m/z (%) = 338 (27) [M⁺], 295 (10), 259 (8), 198 (50), 169 (21), 155 (100), 144 (23). – HRMS (m/z): calcd. 338.09241 (338.09341 for C₁₉H₁₅ClN₄O, [M⁺]). – C₁₉H₁₅ClN₄O (338.79): calcd. C 63.81, H 4.46, N 16.54; found C 64.09, H 4.68, N 16.76.

N-(4-Fluorophenyl)-2-oxo-N²-(quinolin-8-yl)propanamide hydrazone (7c)

This compound was prepared from 1-chloro-1-[N-(4-fluorophenyl)hydrazono]propan-2-one (6c) (2.1 g, 10 mmol), following a similar procedure as noted above for the preparation of 7a. Yield: 1.3 g (40%), m. p. 159–160 °C (dec.). – ¹H NMR (300 MHz, CDCl₃): δ = 2.58 (s, 3H, CH₃Ph), 6.30 (dd, 1H, J = 7.0, 1.6 Hz, 7-H), 6.97 (m, 2H, 2'-H + 6'-H), 7.08 (m, 2H, 3'-H + 5'-H), 7.31, 7.33 (center of two overlapped dd, 2H, 5-H + 6-H), 7.42 (dd, 1H, J = 8.3, 4.2 Hz, 3-H), 7.83 (s, 1H, 1'-NH), 8.10 (dd, 1H, J = 8.2, 1.6 Hz, 4-H), 8.39 (s, 1H, 8-NH), 8.81 (dd, 1H, J = 4.2, 1.6 Hz, 2-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 24.3 (CH₃CO), 110.9 (C-7), 115.1 (d, Jᶜ–˒F = 7.8 Hz, C-2' + C-6'), 116.0 (d, Jᶜ–˒F = 22.8 Hz, C-3' + C-5'), 119.2 (C-5), 121.8 (C-3), 126.8 (C-6), 128.8 (C-4a), 136.0 (C-1'), 136.1 (C-4), 136.4 (C-8a), 139.0 (C-8a), 139.4 (d, Jᶜ–˒F = 2.4 Hz, C-1'), 148.3 (C-2'), 158.4 (d, Jᶜ–˒F = 240 Hz, C-4'), 193.6 (CH₃CO). – EIMS (70 eV): m/z (%) = 322 (31) [M⁺], 279 (12), 198 (50), 169 (19), 155 (100), 144 (21). – HRMS (m/z): calcd. 322.12368 (322.12297 for C₁₉H₁₅F₃N₄O, [M⁺]). – C₁₉H₁₅F₃N₄O (322.34): calcd. C 67.07, H 4.69, N 17.38; found C 66.79, H 4.58, N 17.63.
2-Acetyl-1,4-bis(4-methylphenyl)-1,4-dihydro[1,2,4]triazino[6,5-h]quinoline (8a)

To a solution of compound 7a (0.32 g, 1.0 mmol) in ethanol (10 mL) was added a solution of CuCl₂·H₂O (0.17 g, 1.0 mmol) in ethanol (5 mL). The dark brown solution was stirred over night at t. Thereafter, the organic solvent was evaporated, and the residue was treated with cold water. The precipitated solid product was collected and purified on preparative silica gel TLC plates, eluting with chloroform/methanol (95:5, v/v). Yield: 0.10 g (25 %), m.p. 68–69 °C (dec.). – ¹H NMR (300 MHz, CDCl₃): δ = 2.22 (s, 3H, CH₃-C⁴'), 2.41 (s, 3H, CH₃C⁴), 2.61 (s, 3H, CH₃CO), 6.97 (d, 2H, J = 8.4 Hz, 3'-H + 5'-H), 7.03 (d, 1H, J = 8.9 Hz, 5-H), 7.05 (d, 2H, J = 8.4 Hz, 2'-H + 6'-H), 7.25 (dd, 1H, J = 8.2, 4.4 Hz, 8-H), 7.28 (d, 2H, J = 8.1 Hz, 3''-H + 5''-H), 7.39 (d, 2H, J = 8.1 Hz, 2''-H + 6''-H), 7.47 (d, 1H, J = 8.9 Hz, 6-H), 8.01 (dd, 1H, J = 8.2, 1.7 Hz, 7-H), 8.90 (dd, 1H, J = 4.4, 1.7 Hz, 9-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 20.7 (CH₃-C⁴'), 21.1 (CH₃-C⁴'), 26.4 (CH₃CO), 115.0 (C-5), 120.2 (C-8), 120.3 (C-2' + C'-6'), 124.1 (C-2'' + C'-6''), 125.2 (C-6a), 126.1 (C-6c), 127.0 (C-4a), 129.5 (C-3' + C'-5'), 130.2 (C-3'' + C'-5''), 132.5 (C-4'), 136.0 (C-7), 136.8 (C-2''), 139.7 (C-1'), 143.0 (C-10a), 143.2 (C-2), 144.1 (C-10b), 144.6 (C-1''), 151.4 (C-9), 191.2 (CH₃CO). – EIMS (70 eV); m/z (%) = 466 (100) [M⁺], 390 (16), 362 (14), 322 (15), 315 (12). – HRMS (+)-EI; m/z = 466.17806 (calcd. 466.17936 for C₂₅H₂₅N₄O₂[M⁺]⁺). – C₂₅H₂₅N₄O₂ (466.48): calcd: C 76.83, H 5.46, N 13.78; found C 76.68, H 5.72, N 13.61.

2-Acetyl-1,4-bis(4-fluorophenyl)-1,4-dihydro[1,2,4]triazino[6,5-h]quinoline (8e)

This compound was prepared from 7e (0.32 g, 1.0 mmol) following a similar procedure as noted above for the preparation of 8a. Yield: 90 mg (22 %), m.p. 57–58 °C. – ¹H NMR (300 MHz, CDCl₃): δ = 2.47 (s, 3H, CH₃CO), 6.87 (m, 2H, 3'-H + 5'-H), 6.97 (d, 1H, J = 8.9 Hz, 5-H), 7.18 (m, 2H, 3''-H + 5''-H), 7.26 (m, 3H, 8'-H + 2'-H + 6'-H), 7.49 (m, 2H, 2''-H + 6''-H), 7.51 (d, 1H, J = 8.9 Hz, 6-H), 8.02 (dd, 1H, J = 8.2, 1.2 Hz, 7-H), 8.91 (dd, 1H, J = 4.0, 1.2 Hz, 9-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 26.4 (CH₃CO), 114.6 (C-5), 115.6 (d, 3JC-̲F = 22.5 Hz, C-3' + C'-5'), 116.6 (d, 3JC-̲F = 22.9 Hz, C-3'' + C'-3''), 120.4 (C-8), 123.5 (d, 3JC-̲F = 8.1 Hz, C-2'' + C'-6''), 126.5 (C-6a), 126.1 (d, 3JC-̲F = 8.4 Hz, C-2'' + C'-6''), 126.5 (C-6a), 127.1 (C-4a), 136.1 (C-7), 138.3 (d, 3JC-̲F = 3.0 Hz, C-1'), 142.7 (C-10b), 143.0 (d, 3JC-̲F = 2.6 Hz, C-1'), 143.5 (C-10a), 143.7 (C-2), 151.5 (C-9), 159.4 (d, 3JC-̲F = 243 Hz, C-4'), 161.2 (d, 3JC-̲F = 247 Hz, C-4''), 192.9 (CH₃CO). – EIMS (70 eV); m/z (%) = 414 (51) [M⁺], 399 (18), 344 (16), 319 (7), 279 (9), 167 (29), 149 (100). – HRMS (+)-EI; m/z = 414.12715 (calcd. 414.12919 for C₂₅H₂₃F₂N₄O₂[M⁺]⁺). – C₂₅H₂₁F₂N₄O₂ (414.41): calcd: C 69.56, H 3.89, N 13.52; found C 69.27, H 3.51, N 13.24.

Acknowledgement

We thank the Deanship of Scientific Research, Jordan University (Amman, Jordan), DFG and BMBF (Bonn, Germany) for financial support.


