SHORT COMMUNICATION

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Org. Commun. 12:4 (2019) 217-221

organic communications

Oxidation of some benzyl substituted fused quinazoline derivatives

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(Received November 04, 2019; Revised December 11, 2019; Accepted December 12, 2019)

Abstract: In this study, syntheses of some benzoyl substituted fused quinazoline derivatives **4a-d**, using Fieser's reagent, are reported. An unexpected product **5a** and **6** were isolated from the reaction mixture. Based on the experimental data, a possible oxidation mechanism of ketone **4a** with chromium trioxide is described. The synthesized compounds were characterized by ^{1}H, ^{13}C, ^{19}F NMR and LC-MS data.

Keywords: Oxidation; fused quinazoline derivatives; Fieser's reagent; benzyl to benzoyl; mechanism.

1. Introduction

Oxidation reactions are important tools in organic chemistry. This type of processes is particularly attractive for its versatile possibilities. It allows both to modify the molecule by introducing a new hydrophilic group and to carry out its degradation. Today, practically for each reaction the exact or approximate mechanism is known. Based on this, we can easily predict the reaction product.

Herein, an unusual oxidation of benzyl group is described and tested on other samples.

2. Background

Fused quinazoline derivatives were frequently described as a potential class of biologically active agents.[1-7] Thus, the chemical modifications of such compound are highly desirable.

Commonly used method for chemical modification is an oxidation reaction. Fieser's reagent[8] (a mixture of chromium trioxide in acetic acid) is one of the most accessible and effective oxidation system.[9,10] The aim of this research is to convert benzyl substituted fused quinazolines to the corresponding benzoyl-containing derivatives using chromium trioxide, during which an unexpected reaction took place.

3. Present Study

Chemical Material and Apparatus: Substances **1a-d** were synthesized according to the reported procedures.[11-13] Other chemicals and solvents were obtained from commercially available sources and

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The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © October-December 2019 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.70.19.11.1468

were used without additional purification. Melting points were determined in open capillary tubes and uncorrected. The reactions were monitored *via* silica gel coated aluminum TLC plate, with flourescent indicator F_{254} (Merck). Column chromatography was carried out using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 500 or 400 MHz, 125 MHz and 376 MHz, respectively. Chemical shifts were reported in ppm downfield from tetramethylsilane (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F), which were used as internal standards. Mass spectra were recorded with an LC-MS instrument using chemical ionization (CI). LC-MS data were acquired with an Agilent 1200 HPLS system equipped with a DAD/ELSD/LCMS-6120 diode matrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm; eluent A: acetonitrile/water, 99:1, with 0.1% of FA; eluent B: water with 0.1% of FA.

General Procedure: A mixture of the phenylacetic acid (4.4 mmol), CDI (4.8 mmol) and dioxane (20 mL) was stirred at 80 °C for 1 h. Then, the appropriate amine **1a-d** (4.4 mmol) was added and the mixture was refluxed for 3 h., after which H_2O (75 mL) was added. The precipitate was filtered,[a] washed thoroughly with H_2O and dried at 60 °C. The crude product was dissolved in AcOH (50 mL) and refluxed for 8 h. After that, the solvent was removed *in vacuo* and MeOH (10 mL) was added. The resulting precipitate was filtered and washed with cold MeOH and dried at 60 °C.[b] A solution of CrO_3 (4.2 mmol (~ three-fold excess)) in AcOH (40 mL) was added to a stirred solution of the crude product in AcOH (20 mL) over 30 min at 60-63 °C. The mixture was stirred for 3.5 h. at 60-63 °C, then, poured into a solution of Na_2SO_3 (2.8 mmol) in ice-water (100 mL). The residue was filtered,[c] washed thoroughly with H_2O and dried at 60 °C. The resulting material was purified to obtain the products (silica gel column chromatography EtOAc-$CHCl_3$-PE (6:2:2) **4a**[d] and **4b**. Crystallization from DMF-H_2O afforded **4c** and **4d**). (Please see the supporting information file to see the information of [a-d])

*N-(2-(1H-Benzo[d]imidazol-2-yl)phenyl)-2-phenylacetamide (**2a**):* Gray solid. M.p. 211 °C. Yield: 88.9%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 12.92 (s, 1H), 8.68 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 5.6 Hz, 1H), 7.54 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.27 – 7.20 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H), 3.81 (s, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d_6): 170.09, 153.03, 151.15, 148.73, 138.76, 135.88, 131.08, 130.87, 129.87, 129.00, 127.74, 127.32, 123.36, 120.37, 116.60, 115.89, 115.45, 110.56, 45.90. MS (CI): *m/z* 328.0 $[M + H]^+$.

*6-Benzylbenzo[4,5]imidazo[1,2-c]quinazoline (**3a**):* White solid. M.p. 199 °C (lit. 200-202 °C).[14] Yield: 70.0%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d_6): 8.58 (d, *J* = 7.9 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.47 – 7.28 (m, 5H), 7.25 (t, *J* = 6.7 Hz, 1H), 4.92 (s, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d_6): 149.96, 147.74, 144.31, 142.13, 135.54, 132.34, 129.30, 129.13, 129.04, 128.40, 127.93, 127.29, 125.79, 124.18, 123.36, 119.96, 118.26, 115.87, 41.53. MS (CI): *m/z* 310.2 $[M + H]^+$.

*Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(phenyl)methanone (**4a**):* Yellow solid. M.p. 183-185 °C (lit. 222-224 °C).[15] Yield: 22.8%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d_6): 8.67 (d, *J* = 7.6 Hz, 1H), 8.28 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.89 (t, *J* = 7.3 Hz, 1H), 7.86-7.79 (m, 2H), 7.65 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d_6): 188.22, 147.22, 144.30, 143.88, 141.12, 136.28, 134.00, 132.65, 131.49, 129.99, 129.79, 128.77, 128.00, 126.32, 124.44, 123.74, 120.40, 119.57, 113.83. MS (CI): *m/z* 324.0 $[M + H]^+$.

*(2-(4-Fluorophenyl)-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)(phenyl)methanone (**4b**):* White solid. M.p. 233-236 °C. Yield: 5.8%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d_6): 8.63 (d, *J* = 8.2 Hz, 1H), 8.24 (dd, 2H), 8.17 – 8.09 (m, 3H), 8.01 (t, *J* = 7.8 Hz, 1H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d_6): 186.41, 163.42, 152.72, 143.24, 142.01, 135.07 (d, *J* = 242.9 Hz), 133.25, 131.07, 130.47, 130.06 (d, *J* = 9.3 Hz), 129.69, 129.33, 126.70, 126.45, 124.09, 120.29, 118.54, 116.63 (d, *J* = 22.1 Hz). ^{19}F NMR (δ, ppm, 376 MHz, DMSO-d_6): -109.80. MS (CI): *m/z* 369.2 $[M + H]^+$.

*6-Benzoyl-3-phenyl-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (**4c**):* White needle crystals. M.p. 239-245 °C. Yield: 16.5%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d$_6$): 8.66 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 2H), 8.07 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.84 – 7.73 (m, 3H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d$_6$): 187.48, 159.88, 151.78, 150.28, 148.04, 143.34, 136.19, 135.82, 134.44, 131.9 , 131.76, 130.40, 130.31, 129.76, 129.46, 128.78, 128.56, 126.10, 120.62. MS (CI): *m/z* 379.2 [*M* + H]$^+$.

*6-Benzoyl-3-(4-fluorophenyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (**4d**):* White needle crystals. M.p. 218-223 °C. Yield: 13.7%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d$_6$): 8.66 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 2H), 8.08 (t, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.96 – 7.85 (m, 3H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d$_6$) δ 187.42, 164.43 (d, *J* = 250.5 Hz), 159.84, 151.78, 149.20, 147.95, 143.30, 136.23, 135.85, 134.40, 132.05 (d, *J* = 9.0 Hz), 130.41, 130.36, 129.77, 128.57, 128.22 (d, *J* = 2.4 Hz), 126.10, 120.56, 115.99 (d, *J* = 21.7 Hz). ^{19}F NMR (δ, ppm, 376 MHz, DMSO-d$_6$): -107.99. MS (CI): *m/z* 397.0 [*M* + H]$^+$.

*Benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**5a**):* Beige solid. M.p. >300 °C. Yield: 33.2%, ^{1}H NMR (δ, ppm, 500 MHz, DMSO-d$_6$): 11.95 (s, 1H), 8.36 (d, J = 7.9 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.55 – 7.29 (m, 4H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d$_6$): 148.13, 146.84, 143.98, 137.61, 132.73, 131.09, 125.46, 124.89, 124.10, 123.83, 119.58, 116.36, 115.20, 112.25. MS (CI): *m/z* 236.1 [M + H]$^+$.

*Benzoic acid (**6**):* White crystals. M.p. 118-120 °C (lit. 122.4 °C).[16] Yield: 8.1%. ^{1}H NMR (δ, ppm, 400 MHz, DMSO-d$_6$): 12.82 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (δ, ppm, 125 MHz, DMSO-d$_6$): 167.77, 133.32, 131.23, 129.72, 129.02. MS (CI): *m/z* 121.2 [*M* − H]$^-$.

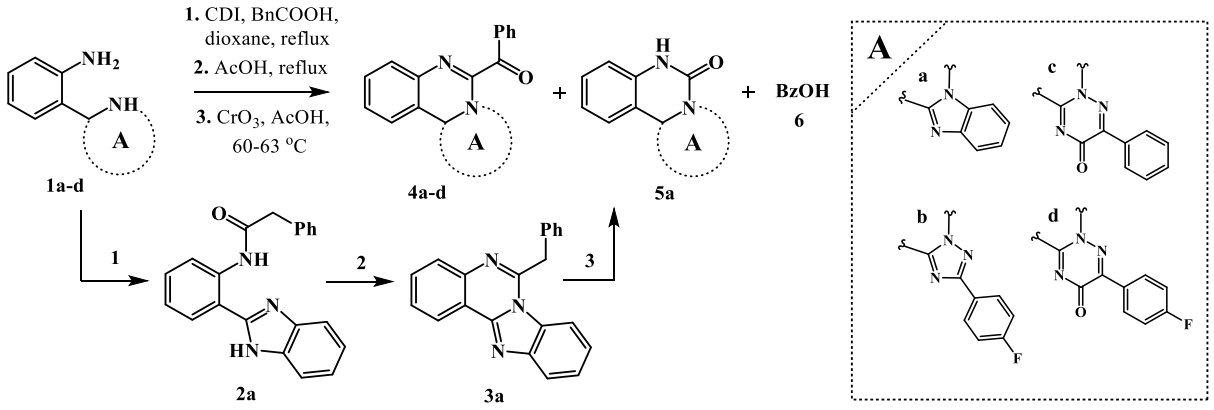

Figure 1. Synthesis and oxidation of some benzyl substituted fused quinazoline derivatives

Oxidation of benzyl substituted fused quinazoline derivatives produced solely one product. Namely, expected corresponding ketones **4b-d**, so the chemistry described herein is completely in accordance with the literature.[17,18] However, in the case of oxidation of **3a**, three products were isolated (Figure 1), which were identified as quinazolinone **5a** (main product), ketone **4a** and benzoic acid **6**. Thus, a novel oxidation process has been uncovered.

Mpreover, a combination of tertiary amine with vicinal carbonyl group was found to be resistant to the oxidation,[19] assuming the reaction is a Malaprade-like oxidation.[20] On the other hand, some tetra-substituted cyclobutanones can undergo a Baeyer-Villiger-like rearrangement to yield the

corresponding γ-lactones by chromic acid in a sulfuric acid-acetic acid mixture.[21] Nevertheless, it does not explain why ketones **4b-d** were not oxidized to the corresponding quinazolinones.

A plausible explanation could be that quinazolinone **5a** and benzoic acid **6** formations might be due to the less electron-withdrawing effect of imidazole in comparison with 1,2,4-triazole and 1,2,4-triazine heterocycles. It let to the supposedly favorable conditions for coordination of the lone pair of the sp^2 hybridized quinazoline nitrogen atom on the Cr^{VI} atom, resulting in the following degradation of ketone **4a** (Figure 2).

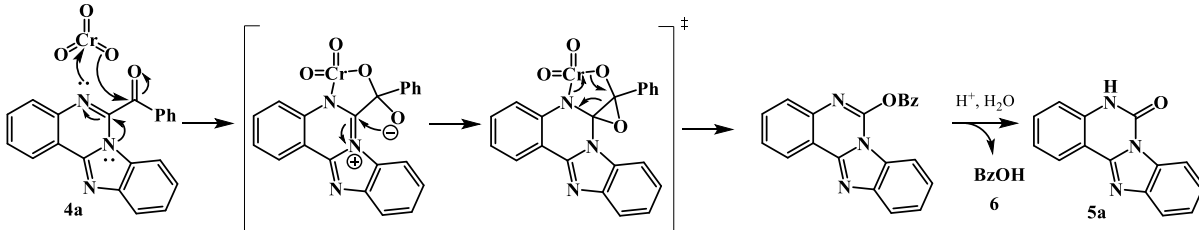

Figure 2. Possible oxidation mechanism of ketone **4a** by CrO_3

5. Conclusion

In this study, an unexpected interaction mechanism between ketone **4a** and chromium trioxide is disclosed. Besides, three new benzoyl substituted fused quinazoline derivatives **4b-d** were synthesized. The study showed that the level of electron-withdrawing effect of the fused heterocycle played a key role in the reaction. While the stronger one terminated the oxidation at the step of ketone formation, the weaker one yielded quinazolinone as a main product.

Acknowledgements

The author expresses his gratitude to Prof. Kovalenko S.I. and Dr. Voskoboinik O.Y. for providing some starting compounds and "Enamine Ltd." (Kiev, Ukraine) for financial support.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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