Supporting Information
for DOI: 10.1055/s-0035-1561640
© Georg Thieme Verlag KG Stuttgart · New York 2016
In-water Synthesis of Quinazolinones from 1,1-Dichloro-2-nitroethene and Anthranilamides

Fengjuan Zhu, Runjiang Song, Shen Li, Xusheng Shao*
Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai, 200237, China
Fax: +86-21-64252603; Tel: +86-21-64253967;
E-mail: shaoxusheng@ecust.edu.cn

Table of Contents

1. General information 1
2. General Procedure for the Synthesis of 2-(nitromethyl)quinazolin-4(1H)-ones (3a-3l) 2
3. Procedure for the Preparation of 2-(nitromethyl)benzofuro[3,2-d]pyrimidin-4(3H)-one (3m) 2
4. Procedure for the Preparation of N-(2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl)-2-nitroacetamide (3o) 2
5. Characterization data and Copies of $^1$H and $^{13}$C NMR spectra of products 2-33

1. General information

Melting points (m.p.) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AM-400 ($^1$H at 400 MHz, $^{13}$C at 100 MHz, $^{19}$F at 376 MHz) spectrometer with DMSO-$d_6$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution electron mass spectra (ESI-TOF) were performed on a Micromass LC-TOF spectrometer. High Resolution Mass Spectrometry (HRMS) EI were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254) and spots were visualized with ultraviolet (UV) light. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant (Hz) and integration.

Reagents: 2-Amino-4,5-dimethoxybenzamide, 2-amino-5-(trifluoromethyl)benzamide, 2-amino-3-methoxybenzamide, 2-amino-4-nitrobenzamide, 2-amino-3-bromobenzamide and 2-amino-6-chlorobenzamide were synthesized according to the reported procedures$^1$, 1,1-dichloro-2-nitroethene (DCNE) synthesis under the following steps: 36% hydrochloric acid (41.7 g, 0.411 mol) and 65% nitric acid (39.8 g, 0.411 mol) were add to round-bottom flask, drop add the 1,1-dichloroethylene (31.0 g, 0.315 mol) with Constant pressure hopper and keep temperature at 20-25°C , after reaction of 3 h, the mixture was continuously stirred for 1 h, washed with water, and extracted by chloroform, collect the organic phase, then add the chloroform layer to 235 mL 4% sodium hydroxide solution at the conditions of ice bath agitation, after simple separation and chloroform washing, concentrate the organic phase, dried with anhydrous magnesium sulfate, then obtain 29 g pale yellow oil. All other solvents and reagents
were purchased directly from commercial suppliers and used as received without further purification.


2. General Procedure for the Synthesis of 2-(nitromethyl)quinazolin-4(1H)-ones (3a-3l)

2-Aminobenzamides (1 mmol) and 1,1-dichloro-2-nitroethene (1.2 mmol) were added to 5 mL of water in a 25 mL round-bottom flask. Then stirred at corresponding temperature and corresponding reaction time, after completion, the product precipitated from the reaction mixture and can be easily separated by filtration, then give the pure products.

3. Procedure for the Preparation of 2-(nitromethyl)benzofuro[3,2-d]pyrimidin-4(3H)-one (3m)

3-Aminobenzofuran-2-carboxamide (176.1 mg, 1 mmol) and 1,1-dichloro-2-nitroethene (169.1 mg, 1.2 mmol) were added to 5 mL of water in a 25 mL round-bottom flask. Then stirred for 8 h at 10–15 °C, after completion, the mixture was purified by silica gel column chromatography (PE : EA = 3:2) to give the pure product (98.0 mg, 40% yield).

4. Procedure for the Preparation of N-(2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl-2-nitroacetamide (3o)

2-Amino-N-methylbenzamide (150.1 mg, 1 mmol) and 1,1-dichloro-2-nitroethene (169.1 mg, 1.2 mmol) were added to 2 mL of water in a 10 mL round-bottom flask. Then stirred for 4 h at 10 °C, after completion, the mixture was purified by silica gel column chromatography (DCM : EA = 9:2) to give the pure product (42.3 mg, 25% yield).

5. Characterization data of products
2-(nitromethyl)quinazolin-4(1H)-one (3a). Isolated as a yellowish powder; yield: 181 mg (88 %); m.p. 165.9–166.4 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\)\(H\): 10.82 (s, 1H), 7.87 (d, \(J = 8.0\) Hz, 1H), 7.80–7.64 (m, 2H), 7.43 (t, \(J = 7.2\) Hz, 1H), 5.67 (s, 2H); \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\)\(C\): 160.90, 138.73, 134.06, 133.53, 126.50 , 125.28, 116.35, 106.86, 78.68; HRMS (ESI) calc. for \(C_9H_6N_3O_3\) [M - H] 204.0409, found 204.0406.
8-methyl-2-(nitromethyl)quinazolin-4(1H)-one (3b). Isolated as a yellowish powder; yield: 182 mg (83 %) m.p. 158.8–159.3 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$: 10.65 (s, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 5.66 (s, 2H), 2.25 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 160.55, 136.84, 136.72, 135.62, 130.94, 127.99, 116.64, 111.20, 78.32, 17.45; HRMS (EI) calc. for C$_{10}$H$_{8}$N$_3$O$_3$ $^+$ 219.0644, found 219.0642.
8-methoxy-2-(nitromethyl)quinazolin-4(3H)-one (3c). Isolated as a yellowish powder; yield: 216 mg (92 %) m.p. 145.3–145.7 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_{HH}$: 10.54 (s, 1H), 7.46 (m, 3H), 5.63 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 160.59, 154.25, 129.00, 126.95, 124.28, 117.18, 116.24, 111.57, 78.33, 56.24; HRMS (EI) calc. for C$_{10}$H$_9$N$_3$O$_4$ $^+$ 235.0593, found 235.0594.
8-bromo-2-(nitromethyl)quinazolin-4(3H)-one (3d). Isolated as a yellowish powder; yield: 240 mg (85 %) m.p. 162.6–163.0 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$: 11.00 (s, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 5.69 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 160.72, 138.06, 137.31, 132.97, 129.83, 122.55, 115.59, 113.38, 78.24; HRMS (EI) calc. for C$_9$H$_6$BrN$_3$O$_3^+$ 282.9593, found 282.9597.
7-nitro-2-(nitromethyl)quinazolin-4(1H)-one (3e). Isolated as a yellowish powder; yield: 213 mg (85 %) m.p. 181.2–181.7 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta_H: 11.22\) (s, 1H), 8.60 (d, \(J = 0.8\) Hz, 1H), 8.20 (d, \(J = 2.0\) Hz, 2H), 5.73 (s, 2H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta_C: 161.54, 150.16, 140.20, 135.38, 120.49, 118.98, 115.00, 111.20, 78.71\); HRMS (EI) calc. for C\(_9\)H\(_6\)N\(_4\)O\(_5\)\(^+\) 250.0338, found 250.0337.
7-methyl-2-(nitromethyl)quinazolin-4(1H)-one (3f). Isolated as a yellowish powder; yield: 211 mg (96 %) m.p. 164.6–165.1 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$: 10.79 (s, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.52 (s, 1H), 7.24 (d, $J = 7.6$ Hz, 1H), 5.65 (s, 2H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 160.87, 144.89, 138.61, 133.26, 127.30, 125.70, 116.57, 103.96, 78.69, 21.29; HRMS (EI) calc. for C$_{10}$H$_9$N$_3$O$_3$ $^+$ 219.0644, found 219.0642.
6,7-dimethoxy-2-(nitromethyl)quinazolin-4(1H)-one (3g). Isolated as a yellowish powder; yield: 212 mg (80 %) m.p. 186.2–186.6 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$: 10.67 (s, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 5.62 (s, 2H), 3.82 (d, $J = 4.0$ Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 160.83, 152.70, 146.81, 133.63, 116.75, 114.37, 108.90, 98.20, 78.67, 56.06, 55.92; HRMS (EI) calc. for C$_{11}$H$_{11}$N$_3$O$_5$ $^+$ 265.0699, found 265.0700.
2-(nitromethyl)-6-(trifluoromethyl)quinazolin-4(1H)-one (3h). Isolated as a yellowish powder; yield: 254 mg (93 %) m.p. 127.9–128.4 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 11.12 (s, 1H), 8.39 (s, 1H), 8.12 (dd, $J = 8.8, 1.6$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 5.72 (s, 2H); $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$: -61.11 (s); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 162.55, 161.29, 142.40, (131.19, 131.15, 131.11, 131.07), (131.00, 130.96, 130.93, 130.90), (126.46, 125.18, 124.40, 121.70), (126.13, 119.41), 115.14, 106.54, 78.74; HRMS (EI) calc. for C$_{16}$H$_6$F$_3$N$_3$O$_3$ $^+$ 273.0361, found 273.0363.
6-chloro-2-(nitromethyl)quinazolin-4(1H)-one (3i). Isolated as a yellowish powder; yield: 220 mg (92 %) m.p. 144.2–144.8 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$H: 10.94 (s, 1H), 8.08 (s, 1H), 7.82 (d, $J = 7.2$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 5.68 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$C: 161.02, 137.84, 134.17, 132.84, 130.19, 126.75, 115.12, 108.22, 78.65; HRMS (EI) calc. for C$_9$H$_6$ClN$_3$O$_3$+ 239.0098, found 239.0102.
5-chloro-2-(nitromethyl)quinazolin-4(1H)-one (3j). Isolated as a yellowish powder; yield: 194 mg (81%) m.p. 177.1–177.6 °C, $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 11.00 (s, 1H), 7.76 (t, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 5.68 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 161.06, 140.84, 136.08, 135.02, 126.97, 123.89, 113.60, 107.60, 78.65; HRMS (EI) calc. for C$_9$H$_6$ClN$_3$O$_3$ $^{+}$ 239.0098, found 239.0102.
5-fluoro-2-(nitromethyl)quinazolin-4(1H)-one (3k). Isolated as a yellowish powder; yield: 194 mg (87 %) m.p. 158.8–159.6 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 11.01 (s, 1H), 7.81 (dd, $J = 15.2, 8.4$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.39 (t, $J = 9.2$ Hz, 1H), 5.69 (s, 2H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$: -106.74 (q, $J = 7.5$ Hz); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: (164.13, 161.59), 161.04, 161.14, 161.17, 135.96, 135.86, 120.77, 113.15, 112.95, 111.58, 96.05, 95.89, 78.67; HRMS (EI) calc. for C$_9$H$_6$FN$_3$O$_3$ $^+$ 223.0393, found 223.0394.
2-(nitromethyl)thieno[3,2-d]pyrimidin-4(3H)-one (3l). Isolated as a yellowish powder; yield: 200 mg (95 %) m.p. 172.8–173.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 11.31 (s, 1H), 8.02 (d, $J = 5.4$Hz, 1H), 7.60 (d, $J = 5.4$ Hz, 1H), 5.67 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 160.20, 143.87, 134.45, 122.79, 113.06, 93.98, 78.59; HRMS (EI) calc. for C$_7$H$_5$N$_3$O$_3$S$^+$ 211.0052, found 211.0054.
2-(nitromethyl)benzofuro[3,2-d]pyrimidin-4(3H)-one (3m). Isolated as a yellowish powder; yield: 98 mg (40 %) m.p. 183.0–183.5 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$H: 11.49 (s, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.66–7.626 (m, 1H), 7.497–7.462 (m, 1H), 5.78 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$C: 160.62, 153.48, 129.57, 127.44, 124.30, 121.41, 120.57, 117.49, 112.15, 111.81, 78.32; HRMS (EI) calc. for C$_{11}$H$_7$N$_3$O$_4^+$ 245.0437, found 245.0438.
1-methyl-2-(nitromethyl)quinazolin-4(1H)-one (3n). Isolated as a yellowish powder; HRMS (EI) calc. for C_{10}H_{8}N_{3}O_{3}^{+} 219.0644, found 219.0645.
**N-(2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl)-2-nitroacetamide (3o).** Isolated as a yellowish powder; yield: 42 mg (25%) m.p. 180.5–181.2 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$: 10.19 (s, 1H), 8.20 (d, $J = 6.8$ Hz, 1H), 7.88–7.79 (m, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.56–7.60 (m, 3H), 7.39 (t, $J = 7.6$ Hz, 1H), 5.42 (s, 2H), 3.27 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$: 161.70, 160.67, 153.62, 147.19, 134.12, 134.06, 130.29, 129.62, 128.48, 127.19, 126.90, 126.01, 125.61, 124.13, 120.62, 78.71, 32.74; HRMS (EI) calc. for C$_{17}$H$_{14}$N$_4$O$_4$ $^+$ 338.1015, found 338.1014.