Synthesis of 2-ethynyl-4(3*H*)quinazolinone and 2-(1,3-butadienyl)-4(*3H*)quinazolinone

Jan Bergman* and Ivan Romero

Department of Biosciences and Nutrition, Karolinska Institute, SE 141 57 Huddinge, Sweden
E-mail: jan.bergman@ki.se

In honor of Prof. Henk van der Plas on the occasion of his 80th anniversary

Abstract
2-Ethynyl-4(3*H*)quinazolinone and 2-(1,3-butadienyl)-4(3*H*)quinazolinone have been synthesized by cyclizations from appropriate precursors. These two molecules are of interest as analogues of the known p-53 reactivator 2-vinyl-4(3*H*)quinazolinone.

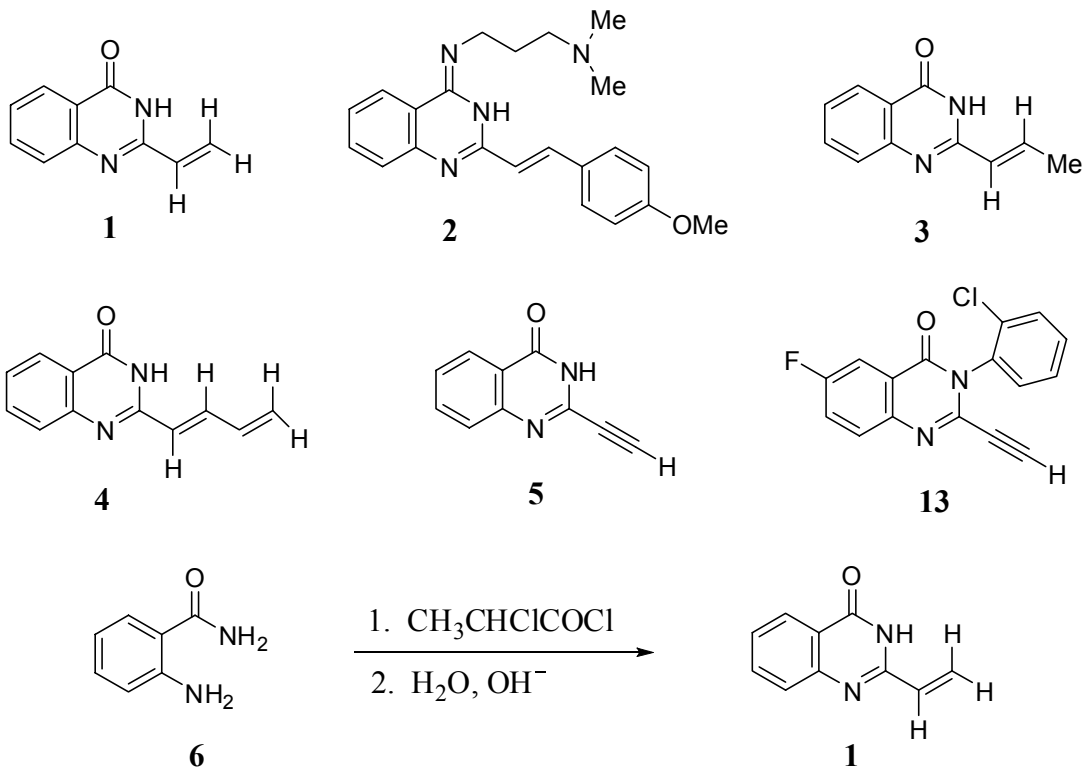
Keywords: 2-Vinyl-4(*3H*)quinazolinone, cyclizations, Michael additions

Introduction

The tumor suppressor protein p-53 is expressed at low levels in most cells and tissues under normal conditions. Cellular stress such as DNA damage, oncogene activation induces p-53 protein levels, leading to an array of biological responses. The high frequency of p-53 mutations in human tumors, and the high levels of mutant p-53 expression in tumors makes p-53 an attractive target for novel cancer therapy.[1] Several studies have demonstrated ways to restore normal function to mutant p-53.[2]

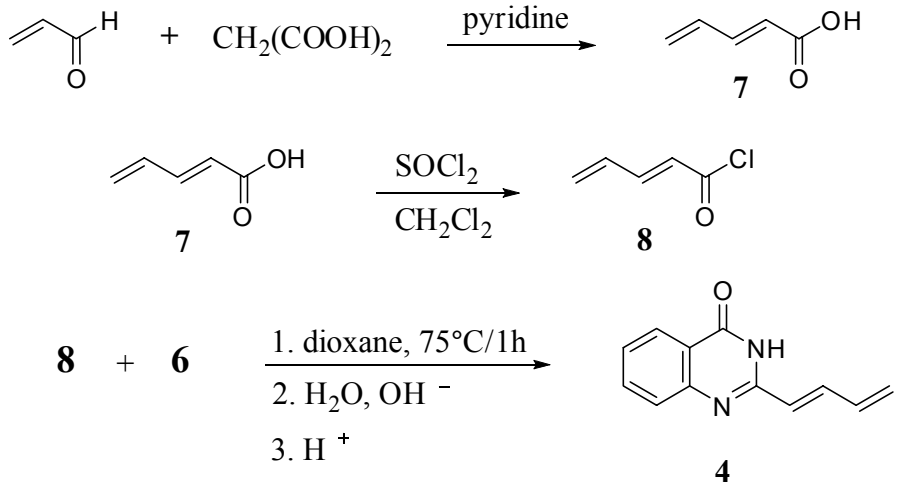
Results and Discussion

We have recently demonstrated that 2-vinyl-4(3*H*)quinazolinone (**1**) is a particularly interesting reactivator of p-53.[2] The effect is similar to, but stronger than, that of CP-31398, **2**. More substituted derivatives of **1**, such as **3**, are considerably less active. With this background we considered it of interest to synthesize some related molecules, with a similarly low level of substitution, namely, **4** and **5**.



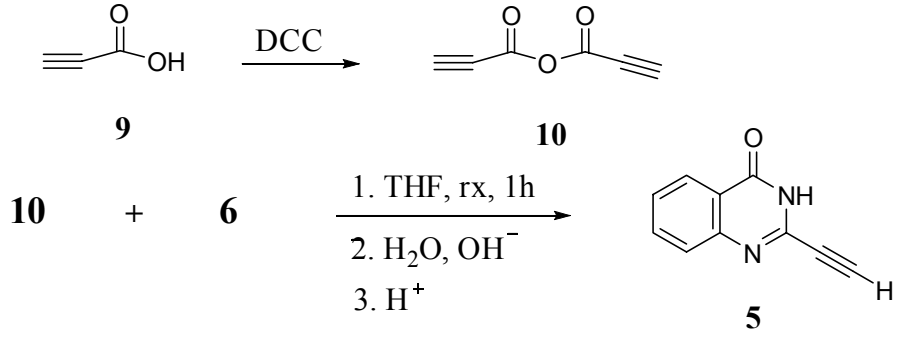
Scheme 1

As compound **1** can be readily synthesized from 2-aminobenzamide, **6**, on a large scale, as outlined in Scheme 1,[3] this molecule was considered as an attractive precursor to **5**. However, treatment of **1** with chlorine or bromine followed by conventional dihydrohalogenation was tried, but the outcome was erratic. At this point it was decided to prepare compound **4** before any approach to **5** would be tried. The required and known [4,5] conjugated acid **7** and acid chloride **8** were prepared as outlined in Scheme 2. The final step leading to **4** was unproblematic.



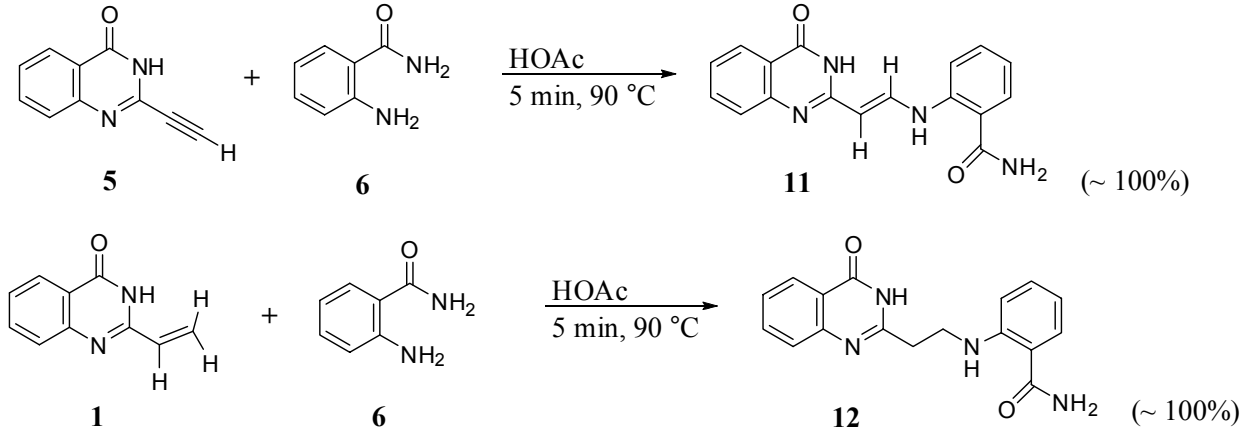
Scheme 2

Compound **5**, was then finally prepared similarly from propiolic acid **9**, as outlined in Scheme 3. During the development of this procedure it was found that 2-aminobenzamide readily added to **5** in Michael fashion to give the adduct **11**. In fact, this molecule could be obtained quickly, in quantitative yield, by heating equimolecular amounts of **5** and **6** in acetic acid. The vinyl derivative **1** gave the adduct **12** similarly (Scheme 4).



Scheme 3

The ethynyl derivative **5** is a new compound, and the only known somewhat- related molecule is the AMPA receptor inhibitor[6] **13**.[7] The atoms in the side-chain of molecule **5** feature some interesting couplings in the 2D- NMR HMBC spectrum which are as follows: $^{1}J_{CH}$=256.3 Hz and $^{2}J_{CH}$=56.2 Hz.



Scheme 4

Conclusions

Convenient procedures for 2-ethynyl-4(3*H*)quinazolinone **5** and 2-(1,3-butadienyl)-4(3*H*)quinazolinone, **4**, have been developed that will make them available for biological evaluations. Both compounds were found to be efficient acceptors for Michael additions.

Experimental Section

2,4-Pentadienoic acid (7). Malonic acid (21.1 g, 0.2 mol) was stirred in pyridine (25 mL) at 40 °C until a clear solution was obtained, whereupon acrolein (10 mL) was added dropwise. The temperature rose to 60 °C and carbon dioxide was formed. A second addition of acrolein (10 mL) was made when the evolution of gas has subsided and the temperature kept at 70-75 °C for 30 min. The reaction was then poured into ice/water and the mixture was acidified with ortho-phosphoric acid, which resulted in partial precipitation of the title acid **7** as a solid, 8.5 g, mp. 71-71 °C (lit.[4] mp. 71-72 °C). The mother liquor was extracted with methylene chloride (3x) which upon drying and evaporation gave a second crop of **7**, 5.5 g. Total yield 14.0 g (72%). IR 2900-2500 (br), 1693, 1627, 1599, 1433, 1300, 1272, 1216, 1158, 1006, 928, 864 cm^{-1}; ^{13}C NMR δ: 123.1 (d), 125.5 (t), 132.7 (d), 143.9(d), 167.3 (s).

2-(1,3-Butadienyl)-4(3*H*)quinazolinone (4). 2,4-Pentadienoic acid (8.2 g, 0.1 mol) was dissolved in methylene chloride (60 mL), and thionyl chloride (4.5 mL) was added. After a period at reflux the solvent was evaporated and the residue dissolved in dioxane (30 mL); 2-aminobenzamide (13.6 g, 0.1 mol) was added, and the mixture heated (75 °C, 1h). After concentration, the residue was treated with water which resulted in the formation of an oil, which was dissolved in sodium hydroxide (aq, 8%, 60 mL) and kept at 80 °C for 1h. This solution was allowed to cool and then acidified with acetic acid, to give the title compound as a white solid, 18.2 g (92%) mp. 136-137 °C. IR 3184-2900 (br), 1661, 1602, 1460, 1002, 766 cm^{-1}; ^{13}C NMR δ 121.0 (s), 124.3 (t), 124.9 (d), 125.7 (d), 126.3 (d), 127.0 (d), 134.3 (d), 135.6 (d), 139.0 (d), 148.8 (s), 151.2 (s), 161.7 (s). Anal: Calc. for $C_{12}H_{10}N_2O$, C; 72.71; H, 5.09; N, 14.13, Found C, 72.30; H, 5.00; N, 14.22.

2-Ethynyl-4(3*H*)quinazolinone (5). Propiolic acid (5.4g, 0.1mol) was added to dicyclohexyl-carbodiimide (20.6 g, 0.1 mol) in tetrahydrofuran (100 mL). A precipitate was formed and 2-aminobenzamide (13.6 g, 0.1 mol) was added. After a period at reflux (30 min) the mixture was allowed to cool, the precipitate of dicyclohexylurea was removed, and the residue was concentrated, and a solution (8%) of sodium hydroxide (60 mL) was added. After heating at 80 °C for 1 min, the mixture was allowed to cool. Acidification with acetic acid gave the title compound, 11.5 g (68%), mp 160 °C dec. IR 3220-2700 (br), 2114, 1672 (s), 1587, 1465, 1273, 1256, 994, 869, 769 cm^{-1}; ^{1}H NMR δ 4.69 (s), 7.511 (dd), 7.63 (d), 7.95 (dd), 8.11 (dd), 12.8 (s, br), ^{13}C NMR δ 77.0 (d), 82.4 (s), 122.2 (s), 125.8 (d), 127.2 (d), 127.5 (d), 134.5 (d), 137.6 (s),

148.1 (s), 160.9 (s). Anal: Calc. for $C_{10}H_6N_2O$, C, 70.57; H, 3.55, N, 16.46; Found C, 70.30; H, 3.68, N, 16.26.

The adduct 11. 2-Ethynyl-4(3*H*)quinazolinone (170 mg, 1 mmol) and 2-aminobenzamide (136 mg, 1 mmol) in acetic acid (8.0 mL) were heated on a water-bath for 5 min. The precipitate obtained was collected, washed with methanol, and dried, 306 mg (100%) mp. >260 °C. IR 3368, 3110-2970, 1672, 1634, 1605, 1582, 1519, 1274, 966, 838, 766, 743 cm^{-1}; ^1H NMR δ: 5.19 (d, 1H, CH, J=8.75), 6.99 (m, 1H, CH, J_1=8.75, J_2=12.5), 7.35 (dd, 1H, CH), 7.45-8.20 (m, 10H, 8CH+NH_2), 11.9 (s, 1H, NH), 12.7 (d, 1H, NH, J=12.5). ^{13}C NMR δ: 90.9 (d), 114.2 (d), 119.6 (s), 120.6 (d), 121.1 (s), 124.5 (d), 125.4 (d), 126.7 (d), 129.0 (d), 132.1 (d), 133.9 (d), 138.3 (d), 141.2 (s), 149.6 (s), 153.5 (s), 161.7 (s), 170.0 (s). Anal: Calc. for $C_{17}H_{14}N_4O_2$, C, 66.65; H. 4.61; N, 18.29, Found C, 66.35; H, 4.73, N, 18.08.

The adduct 12. 2-Vinyl-4(3*H*)quinazolinone (172 mg, 1 mmol) and 2-aminobenzamide (136 mg, 1 mmol) in acetic acid (8.0 mL) was heated on a water-bath for 5 min. the precipitate obtained was collected, washed with methanol and dried, 308 mg (100%) mp. > 260 °C. IR 3429, 3296, 3040, 2760, 1690, 1672, 1647, 1611, 1578, 1515, 1470, 1281, 1186, 911, 878 cm^{-1}; ^1H NMR δ: 2.91 (t, 2H, CH_2), 3.60 (m, 2H, CH_2), 6.53 (dd, 1H, CH), 6.79 (d, 1H, CH), 7.15 (br, s, 1H, NH), 7.25 (dd, 1H, CH), 7.46 (dd, 1H, CH), 7.57 (dd, 1H, CH), 7.65 (m, 2H, CH+NH), 7.75 (m, 2H, CH+NH), 8.07 (d, 1H, CH), 8.33 (t, 1H, NH), 12.3 (br, s, 1H, NH). ^{13}C NMR δ 34.2 (t), 39.6 (t), 111.1 (d), 114.1 (s), 114.2 (d), 120.9 (s), 125.7 (d), 126.1 (d), 126.9 (d), 129.1 (d), 132.6 (d), 134.3 (d), 148.8 (s), 149.4 (s), 155.5 (s), 161.8 (s), 171.5 (s).

References and Notes

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