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3-Propynyl-2-substituted Carboxylic Acid Derivatives of Quinazolinone

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Abstract

Alkylation of quinazolinone-2-carboxylic acids with propargyl bromide in dimethylformamide in the presence of potassium carbonate afforded 3-prop-2-ynyl quinazolinone-2-substituted carboxylic acid derivatives. Further reaction of **4b-c** produced **5b-c**, which indicates that N-alkylation occurs before esterification with a propynyl moiety.

Keywords: Quinazolinone, Carboxylic acid, Prop-2-ynylester.

Introduction

The usefulness of acetylene moiety in some chemical transformations is well documented[1,2] . The ring opening of isatoic anhydride and N-methylisatoic anhydride with acetylenic amines and the subsequent conversion of the resulting amides to oxazoloquinazolinones and propynylquinazolinones have been reported[3,4]. Acetylenic amides have also been utilised as precursors for the synthesis of 3-propynylquinazolinones[5]. Recently, several acetylenic derivatives of quinazoline were prepared and screened for anticonvulsant activity[6].

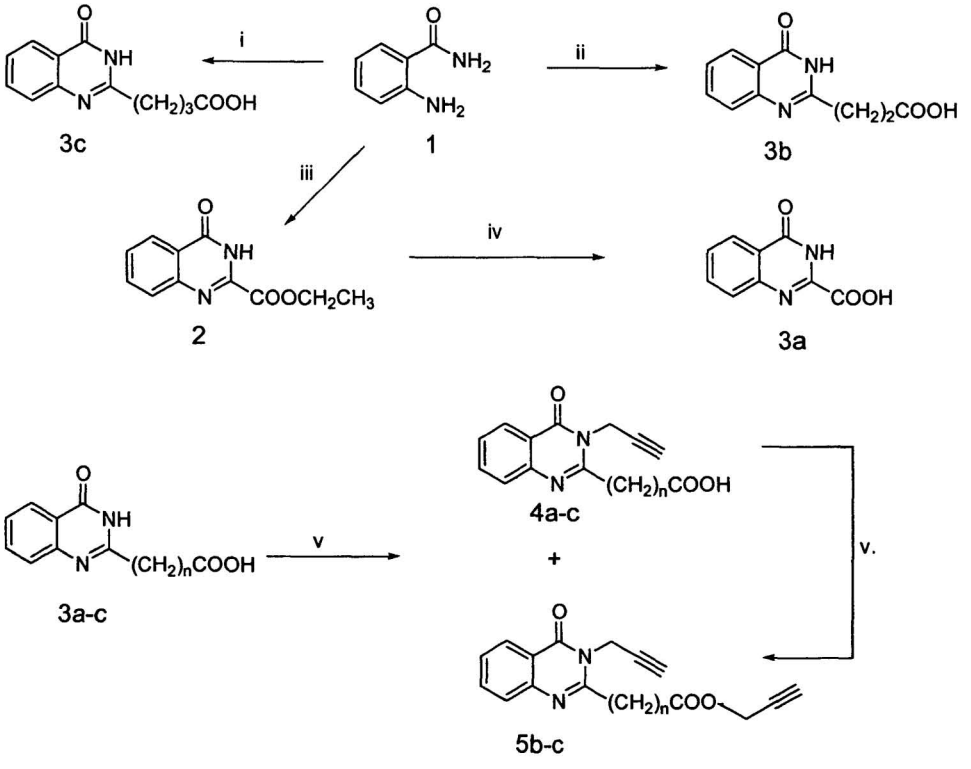
The continued interest in acetylene derivatives of quinazolinone prompted the investigation of the reaction of propargyl bromide and the quinazolinones **3a-c**. The biological usefulness of quinazolinones cannot be over-emphasized. Quinazolinones constitute a large class among the active chemical moieties and generally have little toxicity without serious side effects to the human body[7,8,9]. Quinazolinones are also versatile nitrogen heterocyclic compounds which exhibit a broad spectrum of biological activities in animals as well as in human systems[10,11,12].

Discussion

The reaction of **3a-c** with propargyl bromide was successfully carried out using potassium carbonate in dimethylformamide[13]. The use of sodium hydroxide in methanol-water (1:1) mixture instead of potassium carbonate in dimethylformamide gave a mixture of products and was therefore found unsatisfactory. The reaction utilising potassium carbonate proceeded smoothly at room temperature. When the quinazolinone **3a** with a carboxylic acid directly at position 2 was used, only one product of **4a** was obtained in good yield. However when the quinazolinones **3b** and **3c** were alkylated, additional less polar compounds **5b** and **5c** were isolated in addition to the expected products **4b** and **4c**, respectively. Initially, O-alkylated products along side with **4b** and **4c** (N-alkylated products) were suggested but the spectroscopic data indicated and confirmed prop-2-ynyl esters of the quinazolinones **4b** and **4c**. Esterification of the quinazolinone-2-carboxylic acids **4b** and **4c** under

basic conditions is plausible. This was confirmed by further reaction of **4a** and **4b** with propargyl bromide which gave **5b** and **5c** in good yield.

The compounds were unequivocally characterised by their spectroscopic data and elemental analysis. The proton signal of the carboxylic acid functional group was observed in the ^{1}H nmr of all the quinazolinone-2-carboxylic acids **4a, 4b** and **4c,** this functional group was also confirmed by the infra-red spectra. The presence of the single propynyl moiety was also evident in the ^{1}H nmr spectra for the quinazolinone-2-carboxylic acids. A long range coupling within the propynyl moiety as a doublet and triplet for -CH_2- and -CH respectively showed this. The structures of the quinazolinones **5b** and **5c** with two propynyl moieties are in full agreement with their ^{1}H nmr spectra and are confirmed by their mass spectra. Compounds **5b** and **5c** were generally less polar and their corresponding melting points were also lower than **4b** and **4c,** respectively.



i : Glutaric anhydride, toluene, reflux
ii : Succinic anhydride, toluene, reflux
iii : Diethyl Oxalate, 175-180°C
iv : 5% Sodium hydroxide
v : Propargyl bromide, K_2CO_3, DMF

Experimental

Melting points were determined with a Kofler hot stage microscope and were uncorrected. The reactions and purity of the products were monitored by tlc using pre-coated silica gel plates (Merck $60F_{254}$). Silica gel Merck 60 (70-230 mesh) was used for column chromatography. Nuclear Magnetic Resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 (TMS), infra-red spectra were measured on a Perkin-Elmer type 457 and the mass spectra were determined using a Varian MAT 44S, EI: 70 eV.

Synthesis of the Quinazolinones 3a-c

Ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylic acid 2

A mixture of anthranilamide (6.89g, 0.05mol) in diethyl-oxalate (50ml) was heated to 178°C, filtered after 15 minutes and cooled. The crystals formed were washed with ethanol to afford ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylic acid (7.1g, 65%); mp 178-180 °C [Lit[15] 179-180 °C]. MS m/z : 218[M^+]

3,4-Dihydro-4-oxoquinazoline-2-carboxylic acid 3a

A mixture of ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylic acid (1.0g, 4.6mmol) in 5% sodium hydroxide (20ml) was stirred at room temperature for 2.5h. The mixture was filtered and the filterate brought to pH 3 with 3N hydrochloric acid. The solid was collected by filteration and washed with water to give compound **3a** (0.7g, 81%), mp 213-215°C [Lit[15] 212-215 °C].

3,4-Dihydro-4-oxoquinazoline-2-propionic acid 3b

A mixture of anthranilamide (2.5g, 0.02mol) and succinic anhydride (1.85g, 0.02mol) in toluene (60ml) was refluxed for 4h. The solvent was removed *in vacuo* and 2N sodium hydroxide (25ml) added. The resulting solution was refluxed for another 2h, cooled to room temperature and acidified with acetic acid to pH 5. The solid was collected by filtration and washed with water (100ml) to give 3b (6.8g, 85%). mp 220-222°C [Lit[14,16] 221-224°C].

3,4-Dihydro-4-oxoquinazoline-2-butyric acid 3c

A mixture of anthranilamide (2.0g, 0.02mol) and glutaric anhydride (2.0g, 0.02mol) in toluene (80ml) was refluxed for 4h and the same synthetic procedure for **3b** was used for the isolation of **3c**. The yield was 1.35g (80%). mp >250°C [Lit[14,16] >250 °C]

General Synthetic Procedure for Quinazolinones 4a-c and 5b-c

To a mixture of quinazolinone **3** (4.6mmol, 1.0eq) and potassium carbonate (5.5 mmol, 1.1eq) in dimethylformamide (20ml) under nitrogen was added propargyl bromide (5.5 mmol; 1.1eq) and the reaction mixture stirred at room temperature until tlc indicated total disappearance of the quinazolinone (3-4 h). The reaction mixture was poured into water (50ml) and extracted with ethyl acetate (3x20ml).

The combined organic phase was washed with brine (2x10ml), dried over anhydrous sodium sulphate and evaporated to give a crude residue. Subsequent chromatography of the crude residue afforded the various compounds (**4a-c and 5b-c**) which were recrystallised from appropriate solvents.

3,4-Dihydro-4-oxo-3-prop-2-ynylquinazoline-2-carboxylic acid 4a
Column chromatography of the crude product gave **4a**, which was recrystallised from dichloromethane-hexane as colourless crystals. 0.8g (85%) mp 240-241°C. ir (KBr):= 3310, 3010, 1690, 1640, 1590, 770, 700 cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.46 (t, J = 2.4 Hz, 1H, 3'-H), 4.78 (d, J = 2.5Hz, 2H, 1'-H), 7.46-7.48 (d, J=7.6 Hz, 1H, 8-H), 7.66-7.75 (m, 2H, 6-H, 7-H), 8.25 (d, J = 7.8Hz, 1H, 5-H), 8.28 (brs, 1H, COOH). ^{13}C nmr: δ = 35.1, 75.1, 76.4, 121.7, 126.7, 127.4, 127.5, 134.5, 145.0, 147.7, 160.3, 170.4. MS: m/z = 184 [M^+- COOH] (100%), 155 (42), 142(4), 129(9), 115(30), 102(13), 92(3), 76(4), 51(3), $C_{12}H_8N_2O_3$ (228.21). Anal. Cal. C 63.16 H 3.53 N 12.28 : Found C 63.10 H 3.42 N 12.14.

The crude product of the reaction between **3b** and propargyl bromide on column chromatography (dichloromethane-ethyl acetate 6:1) yielded **5b** as the first eluate and later **4b**.

3-(3,4-Dihydro-4-oxo-3-prop-2-ynylquinazolin-2-yl)propionic acid 4b
Recrystallisation from methanol afforded **4b** as colourless needles. 0.83g (70%) mp 173-175°C. ir (KBr): = 3340, 3015, 1700, 1630, 1600, 1260, 770, 700 cm^{-1}. ^1H nmr (DMSO d_6): δ = 2.03 (t, J = 2.4Hz, 1H, 3'-H), 2.16 (t, J = 6.4Hz, 2H, 2"-H), 2.35 (t , J = 6.6Hz, 2H,1"-H), 4.14(d, J = 2.4Hz, 2H, 1'-H), 6.87 (t, J = 7.9Hz, 1H, 7-H), 7.60 (d, J = 8.0Hz, 1H, 8 -H), 7.17 (ddd, J = 1.2,7.9,8.0Hz, 1H, 6-H), 7.61(dd, J = 1.6, 8.0Hz, 1H, 5-H), 12.21(brs, 1H, OH). ^{13}C nmr : (DMSO d_6): δ = 28.8, 29.7, 51.6, 75.1, 120.8, 125.6, 126.3, 133.8, 148.1, 155.2, 162.1, 171.1.MS: m/z = 256 [M^+], 211[M^+- COOH] (21), 185 (2), 173(100), 155(6), 130(10), 119(16), 92(7), 77(4). $C_{14}H_{12}N_2O_3$ (258.26). Anal. Cal. C 65.65 H 4.72 N 10.93 : Found C 65.60 H 4.72 N 10.90.

3-(3,4-Dihydro-4-oxo-3-prop-2-ynylquinazolin-2-yl)propionic acid prop-2-ynyl ester 5b
Recrystallisation from dichloromethane-hexane afforded **5b** as needles 0.27g (20%), mp 95-96°C. ir (KBr): = 3005, 1710, 1630, 1600, 1280 ,1180 ,760, 710 cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.22 (t, J = 2.2Hz, 1H, 3'-H), 2.36 (t, J = 2.3Hz, 1H, 3"-H), 2.92 (t , J = 6.4Hz, 2H, 2'"-H), 3.22 (t, J = 6.4Hz, 2H, 1'"-H), 4.63 (d, J = 2.2Hz, 2H, 1' -H), 4.87(d, J = 2.2Hz, 2H, 1"-H), 7.34(t, J = 8.0Hz, 1H, 7-H), 7.50(d, J = 7.8Hz, 1H, 8-H), 7.59(t, J = 7.8Hz, 1H, 6-H), 8.15(d, J = 8.0Hz, 1H, 5-H). ^{13}C nmr: ($CDCl_3$): δ = 28.7, 30.1, 32.0, 52.1, 72.7, 74.9, 76.9, 77.6, 120.2, 126.7, 126.9, 127.2, 134.3, 146.7, 153.8, 161.3, 171.9. MS: m/z = 295 [M^+ +1](6), 294 [M^+] (5), 263(2), 249(48), 235(38), 221(100), 211(79), 179(148) 184(22), 173(28), 155(19), 130(21), 119(12). $C_{17}H_{14}N_2O_3$ (294.31). Anal. Cal. C 69.38, H 4.80, N 9.52 : Found C 69.30, H 4.82, N 9.48.

Column chromatography (dichloromethane-ethyl acetate 6:1) of the crude product from the reaction of **3c** with propargyl bromide gave **5c** and later **4c**. Recrystallisation of **4c** (methanol) and **5c** (dichloromethane-hexane mixture) afforded plates and needles, respectively.

4-(3,4-Dihydro-4-oxo-3-prop-2-ynylquinazolin-2-yl)butyric acid 4c
0.80g (65%), mp 139-140°C. ir (KBr): = 3400, 3000, 1690, 1640, 1600, 1585, 1260, 760, 700 cm^{-1}. ^1H nmr (DMSO d_6): δ = 1.96-2.02 (quint, J = 7.2Hz, 2H, 2"-H), 2.45 (t, J = 7.3Hz, 2H, 3"-H), 2.65 (t, J = 7.4Hz, 2H, 1"-H), 3.49 (s, 1H, 3'-H), 4.46(s,2H,1'-H),

7.43 (t, J = 8.0Hz, 1H, 7-H), 7.58 (d, J = 7.8Hz, 1H, 8-H), 7.75 (t, J = 7.8Hz,1H, 6-H), 8.06 (d, J = 8.0Hz, 1H, 5-H), 12.15 (brs, 1H, COOH). ^{13}C nmr (DMSO d_6): δ = 21.6, 32.4, 33.3, 51.6, 77.67, 78.5, 120.9, 125.7, 126.0, 126.8, 134.2, 148.8, 156.6, 161.8 (C=O), 171.9 (COOH). MS: m/z = 225 [M^+- COOH] (31), 210 (100), 195(32), 182(20), 167(24), 154(8), 141(7), 115(12), 89(8). $C_{15}H_{14}N_2O_3$ (270.29). Anal. Cal. C 66.66 H 5.22 N 10.37 : Found C 66.64, H 5.20, N 10.26.

4-(3,4-Dihydro-4-oxo-3-prop-2-ynylquinazolin-2-yl)butyric acid prop-2-ynyl ester 5c

0.28g (20%), mp 80-81°C. ir (KBr): = 3015, 1700, 1640, 1600, 1590, 1410, 770, 700 cm^{-1}. ^{1}H nmr ($CDCl_3$): δ = 2.19-2.32 (quint, J = 7.2Hz, 2H, 2'''-H), 2.48-2.57 (t, J = 7.3Hz, 2H, 3'''-H), 2.80 (t, J = 2.3Hz, 1H, 3'-H), 2.87(t, J = 2.3Hz, 1H, 3''-H), 2.96-2.99 (t, J = 7.3Hz, 2H,1'''-H), 4.61 (d, J = 2.4Hz, 2H, 1'-H), 4.88 (d, J = 2.4Hz, 2H, 1''-H), 7.36 (t, J = 7.8Hz,1H, 7-H), 7.55 (d, J = 8.0Hz, 1H, 8-H), 7.65 (t, J = 8.0Hz, 1H, 6-H), 8.17 (d, J = 7.8Hz, 1H, 5-H). ^{13}C nmr ($CDCl_3$): δ = 21.3, 32.6, 33.1, 51.8, 72.5, 74.9, 75.9, 77.5, 77.6, 120.1, 126.7, 126.9, 134.3, 146.8, 154.8, 161.2 (C=O), 172.2 (COOH). MS:m/z = 309 [M^++1](2), 308[M^+](1), 307[M^+](2), 263(5), 253(5), 235(16), 225(11), 211(24), 198(84), 194(100), 185(13), 169(12), 130(99),115(8). $C_{18}H_6N_2O_3$ (308.34). Anal. Cal. C 70.12 H 5.23 N 9.09 Found C 70.00 H 5.20 N 9.10.

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