Acetylene Chemistry. Part 31 [1]. Imidazoquinazolinones Derived from the Reaction Products of 2,4-Dichloroquinazoline and Acetylenic Amines

Johannes Reisch*

Institut für Pharmazeutische Chemie der Westfälischen Wilhelms-Universität Münster,
Hittorfstr. 58-62, 4400 Münster, Germany

Cyril Usifoh

Department of Pharmaceutical Chemistry,
School of Pharmacy, University of Benin,
Benin City, Nigeria

Received February 22, 1993

The reaction of 2,4-dichloroquinazolines with acetylenic amines afforded 2-chloro-4-(1,1-disubstituted-*N*-prop-2-inyl)quinazolines which on boiling in formic acid yielded the corresponding imidazoquinazolinones.

J. Heterocyclic Chem., **30**, 659 (1993).

Acetylenic amines have been used in the synthesis of potential biologically active heterocyclic compounds [2,3,4]. The interesting pharmacological activities exhibited by quinazolines cannot be over-emphasised [5].

2,4-Dichloroquinazoline is a versatile compound for the synthesis of various quinazoline based heterocyclic compounds [6]. The chlorine at the 4-position is more reactive than the one at the 2-position. This difference in reactivity between the two chlorine atoms provides the opportunity for selective nucleophilic substitution.

The desired 2-chloro-4-substituted quinazoline derivatives **3a-d** were obtained on reaction of 2,4-dichloroquinazoline with acetylenic amines [7]. The reactions were carried out in tetrahydrofuran (THF) at room temperature to minimize possible side reactions [7]. The compounds obtained were protected from light to avoid any possible breakdown. Cyclization to the imidazoquinazolinones was accomplished by boiling in formic acid due to a concomittant loss of the chlorine atom in the 2-position of **3**. However, no cyclization was observed when $R^1 = R^2 = H$ [4,8,9].

All compounds were unequivocally characterised by ir, nmr, ms and elemental analysis.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded at 200 MHz with tetramethylsilane as internal standard on a Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV.

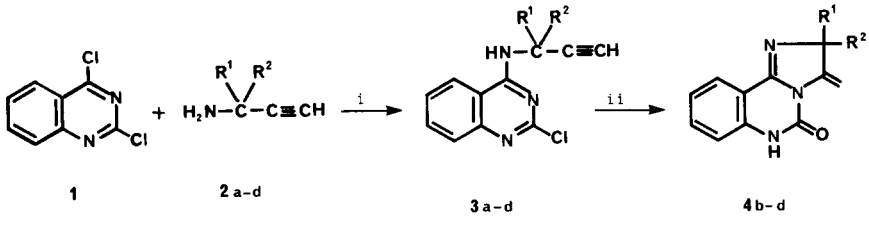
Reaction of 2,4-Dichloroquinazoline with Acetylenic Amines.

To a stirred solution of 2,4-dichloroquinazoline (0.5 g, 0.25 mmole) in 20 ml THF 3.0 ml of triethylamine was added. Acetylenic amine (0.5 mmole) was then added dropwisely for a period of 15 minutes and stirred at room temperature till tlc indicated complete disappearance of the 2,4-dichloroquinazoline. The hydrochloride salt formed was filtered off and washed with THF. Subsequent evaporation *in vacuo* and recrystallization of the resulting solid from dichloromethane-petroleum ether (40-60°) afforded the quinazolines **3a-d**.

2-Chloro-4-(*N*-prop-2-inyl)-quinazoline (**3a**).

Prop-2-inylamine (0.28 g, 0.5 mmole) was added to 2,4-dichloroquinazoline (0.5 g, 0.25 mmole) in THF and treated as above which gave colorless needles of 2-chloro-4-(*N*-prop-2-inyl)quinazoline 0.49 g (90%), mp 272-273°; ir (potassium bromide): ν 3400 (NH), 300, 1640, 1600, 1300, 960 cm^{-1}; ^1H nmr (deuteriomethanol): δ 2.37 (t, J = 2.6 Hz, 1H, 3'-H), 4.44 (dd, J = 2.6 Hz, 5.2

Scheme



a: $R^1 = R^2 = H$; b: $R^1 = R^2 = CH_3$; c: $R^1 = R^2 = CH_2CH_3$; d: $R^1 = R^2$ = ⬡; i: THF/$(CH_3)_3N$; ii: HCOOH.

Hz, 2H, 1'-H), 6.0 (s, 1H, NH), 7.47 (ddd, J = 1.7, 6.6, 8.3 Hz, 1H, 7-H), 7.62-7.78 (m, 2H, 6-H, 8-H), 8.02 (dd, J = 1.3, 8.3 Hz, 1H, 5-H); ^{13}C nmr (deuteriomethanol): δ 30.9 (C-1'), 71.7 (C-3'), 79.5 (C-2'), 113.8 (C-4a), 122.4 (C-8), 126.6 (C-6), 126.8 (C-5), 133.9 (C-7), 150.5 (C-8a), 157.6 (C-2), 161.2 (C-4); ms: m/z 217 (63, M$^+$), 216 (30, M$^+$ − 1), 182 (88), 163 (11), 143 (8), 129 (71), 116 (11), 102 (58), 90 (15), 75 (30), 63 (23), 54 (100).

Anal. Calcd. for $C_{11}H_8N_3Cl$: C, 60.71; H, 3.71; N, 19.30. Found: C, 60.66; H, 3.65; N, 19.32.

2-Chloro-4-(*N*-1,1-dimethylprop-2-inyl)quinazoline (**3b**).

1,1-Dimethylprop-2-inylamine (0.42 g, 0.5 mmole) was added to 2,4-dichloroquinazoline (0.5 g, 0.25 mmole) in THF. After 7 hours 2-chloro-4-(*N*-1,1-dimethylprop-2-inyl)quinazoline was isolated as colorless needles 0.53 g (86%), mp 129-130°; ir (potassium bromide): ν 3440 (NH), 2980, 1630, 1600, 1310, 980 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.91 (s, 6H, 2 x CH_3), 2.43 (s, 1H, 3'-H), 6.07 (s, 1H, NH), 7.48 (ddd, J = 2.4, 5.7, 7.2 Hz, 1H, 7-H), 7.75 (m, 3H, 5-H, 6-H, 8-H); ^{13}C nmr (deuteriochloroform): δ 28.9 (C-2 x CH_3), 50.0 (C-1'), 70.4 (C-3'), 87.1 (C-2'), 113.6 (C-4a), 121.1 (C-8), 126.6 (C-6), 128.4 (C-5), 133.8 (C-7), 151.3 (C-8a), 157.4 (C-2), 160.2 (C-4); ms: m/z 245 (57, M$^+$), 244 (82), 230 (45), 210 (74), 181 (11), 179 (31), 163 (21), 144 (100), 129 (21), 117 (28), 102 (85), 90 (33), 82 (25), 67 (42), 51 (74).

Anal. Calcd. for $C_{13}H_{12}N_3Cl$: C, 63.55; H, 4.92; N, 17.10. Found: C, 63.59; H, 4.93; N, 17.10.

2-Chloro-4-(*N*-1,1-diethylprop-2-inyl)quinazoline (**3c**).

1,1-Diethylprop-2-inylamine (0.56 g, 0.5 mmole) was added to 2,4-dichloroquinazoline (0.5 g, 0.25 mmole) in THF and treated as in the general procedure for 72 hours to give colorless needles of 2-chloro-4-(*N*-1,1-diethylprop-2-inyl)quinazoline, 0.51 g (74%), mp 122-123°; ir (potassium bromide): ν 3460 (NH), 2990, 1630, 1600, 1550, 1320, 990 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.05 (t, J = 7.4 Hz, 6H, 2 x CH_2CH_3), 2.05 (m, 2H, CH_2CH_3), 2.48 (s, 1H, 3'-H), 2.65 (m, 2H, CH_2CH_3), 5.88 (s, 1H, NH), 7.48 (ddd, J = 2.2, 6.0, 8.5 Hz, 1H, 7-H), 7.76 (m, 3H, 5-H, 6-H, 8-H); ^{13}C nmr (deuteriochloroform): δ 8.8 (C-2 x CH_2CH_3), 30.2 (C-2 x CH_2CH_3), 60.3 (C-1'), 72.6 (C-3'), 85.6 (C-2'), 113.5 (C-4a), 120.9 (C-8), 126.7 (C-6), 128.5 (C-5), 138.8 (C-7), 151.3 (C-8a), 157.5 (C-2), 160.0 (C-4); ms: m/z 273 (3, M$^+$), 245 (91), 244 (100), 230 (26), 210 (27), 193 (16), 179 (28), 163 (29), 144 (51), 129 (35), 102 (98), 71 (42), 55 (63).

Anal. Calcd. for $C_{15}H_{15}N_3Cl$: C, 66.06; H, 5.54; N, 15.40. Found: C, 65.91; H, 5.65; N, 15.38.

2-Chloro-4-(*N*-1-ethinylcyclohexyl)quinazoline (**3d**).

To 2,4-dichloroquinazoline (0.5 g, 0.25 mmole) in THF was added 1-ethinylcyclohexylamine (0.62 g, 0.5 mmole) to give after 10 hours colorless needles of 2-chloro-4-(1-ethinylcyclohexyl)quinazoline, 0.55 g (76%), mp 171-172°; ir (potassium bromide): ν 3460 (NH), 3000, 2960, 1640, 1600, 1320, 990 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.32-2.89 (m, 10H, cyclohexyl), 2.47 (s, 1H, 3'-H), 5.90 (s, 1H, NH), 7.42-7.79 (m, 3H, 6-H, 7-H, 8-H), 8.40 (dd, J = 1.3, 8.3 Hz, 5-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.2 (C-3'', 5''), 25.1 (C-4''), 36.5 (C-2'', 6''), 52.9 (C-1'), 72.9 (C-3'), 85.1 (C-2'), 113.9 (C-4a), 123.5 (C-8), 125.5 (C-6), 126.7 (C-5), 133.1 (C-7), 150.6 (C-8a), 156.2 (C-2), 160.2 (C-4); ms: m/z 285 (10, M$^+$), 270 (10), 256 (26), 250 (28), 244 (20), 231 (100), 196 (28), 179 (30), 163 (13), 144 (48), 129 (18), 117 (11), 102 (44), 91 (30), 77 (25).

Anal. Calcd. for $C_{16}H_{16}N_3Cl$: C, 67.25; H, 5.64; N, 14.70. Found: C, 67.07; H, 5.62; N, 14.67.

Synthesis of Imidazoquinazolinones.

2-Chloro-4-(1,1-disubstituted-*N*-prop-2-inyl)quinazoline was dissolved in 20 ml of formic acid and gradually heated to reflux (3-6 hours). Formic acid was removed *in vacuo*, water added and brought to *p*H 9 with sodium hydrogencarbonate. The resulting solid was washed with water and purified using column chromatography (dichloromethane). Recrystallization in dichloromethane-petroleum ether (40-60°) gave the imidazoquinazolinones.

2,2-Dimethyl-3-methylene-2,3,6-trihydroimidazo[1,2-*c*]quinazolin-5-one (**4b**).

2-Chloro-4-(*N*-1,1-dimethylprop-2-inyl)quinazoline was boiled in formic acid for 4 hours to yield colorless plates of **3b** (0.3 g, 80%), mp 174-175°; ir (potassium bromide): ν 3460 (NH), 1700, 1690 (C=CH_2, C=O), 1630, 1480, 1420 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.45 (s, 6H, 2 x CH_3), 4.72 (d, J = 1.2, 1H, =CH_{trans}), 5.99 (d, J = 1.2 Hz, =CH_{cis}), 7.00-7.20 (m, 2H, 7-, 9-H), 7.45 (ddd, J = 1.6, 6.5, 7.4 Hz, 1H, 8-H), 8.04 (dd, J = 1.4, 4.7 Hz, 1H, 10-H), 10.25 (br, s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 30.2 (C-2 x CH_3), 69.8 (C-2), 92.5 (C=CH_2), 111.9 (C-10a), 115.2 (C-8), 123.3 (C-9), 126.3 (C-10), 133.4 (C-8), 138.4 (C-6a), 149.3 (C-3), 150.3 (C-10b), 152.2 (C-5); ms: m/z 227 (8, M$^+$), 226 (6), 212 (100), 211 (72), 161 (3), 145 (10), 117 (8), 84 (6), 68 (15), 58 (10).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.48. Found: C, 68.52; H, 5.48; N, 18.34.

2,2-Diethyl-3-methylene-2,3,6-trihydroimidazo[1,2-*c*]quinazolin-5-one (**4c**).

2-Chloro-4-(*N*-1,1-diethylprop-2-inyl)quinazoline (0.40 g, 0.15 mmole) was refluxed in formic acid for 3 hours as in the general procedure to afford colorless plates of **3c** (0.23 g, 60%), mp 152-153°; ir (potassium bromide): ν 3500 (NH), 1710, 1700 (C=CH_2, C=O), 1620, 1600, 780 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.81 (t, J = 7.5 Hz, 6H, 2 x CH_2CH_3), 1.50-2.10 (m, 4H, 2 x CH_2CH_3), 4.62 (d, J = 1.1 Hz, 1H, =CH_{trans}), 6.16 (d, J = 1.1 Hz, 1H, =CH_{cis}), 7.05-7.25 (m, 2H, 7-H, 9-H), 7.52 (ddd, J = 1.5, 6.0, 7.2 Hz, 1H, 8-H), 8.15 (dd, J = 1.5, 7.2 Hz, 1H, 10-H), 10.4 (br, s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 8.2 (C-2 x CH_2CH_3), 35.0 (C-2 x CH_2CH_3), 77.9 (C-2), 93.5 (C=CH_2), 112.0 (C-10a), 115.4 (C-7), 123.5 (C-9), 126.6 (C-10), 133.5 (C-8), 138.6 (C-6a), 148.4 (C-3), 149.6 (C-10b), 151.1 (C-5); ms: m/z 255 (4, M$^+$), 226 (100, M$^+$-CH_2CH_3), 211 (3), 198 (3), 170 (2), 145 (12), 117 (8), 82 (12), 77 (2), 55 (17).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.57; H, 6.71; N, 16.45. Found: C, 70.47; H, 6.67; N, 16.42.

3'-Methylene-6'H-spiro-(cyclohexane-1,2'-imidazo[1,2-*c*]quinazolin)-5'-one (**4d**).

2-Chloro-4-(*N*-1-ethinylcyclohexyl)quinazoline was boiled for 3 hours in formic acid and worked-up as described in the general procedure to give colorless needles of **3d** (0.26 g, 70%), mp 216-218°; ir (potassium bromide): ν 3490 (NH), 1720, 1700 (C=CH_2, C=O), 1640, 1600, 780 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.40-2.20 (m, 10H, cyclohexyl), 4.68 (d, J = 1.1 Hz, 1H, =CH_{trans}), 5.98 (d, J = 1.1 Hz, 1H, =CH_{cis}), 7.10 (dd, J = 1.1, 7.4 Hz, 1H, 7-H), 7.17 (ddd, J = 1.1, 7.4, 8.3 Hz, 1H, 9-H), 7.47 (ddd, J = 1.1, 7.4, 8.3 Hz, 1H, 8-H), 8.14 (dd, J = 1.1, 8.3 Hz, 1H, 10-H), 9.41 (br, s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 22.3 (C-3', 5'), 25.9 (C-4'), 40.1 (C-2', 6'), 72.8 (C-2), 92.4 (C=CH_2), 112.5 (C-10a), 114.9 (C-7), 123.2 (C-9), 126.5 (C-10), 133.1 (C-8), 138

(C-6a), 149.1 (C-3), 149.4 (C-10b), 153.0 (C-5); ms: m/z 267 (65, M^+), 252 (13), 239 (41), 224 (100), 211 (78), 198 (20), 170 (11), 145 (28), 116 (21), 90 (17), 80 (27), 67 (18).

Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.71. Found: C, 71.90; H, 6.46; N, 15.80.

Acknowledgement.

We thank the "Deutscher Akademischer Austauschdienst" for a fellowship to C. O. Usifoh.

REFERENCES AND NOTES

[1] Part **30**: J. Reisch, J. Zappel, G. Henkel and N. Ekiz-Gücer, *Monatsh. Chem.*, in press.

[2] J. Reisch, C. O. Usifoh and J. O. Oluwadiya, *J. Heterocyclic Chem.*, **27**, 1953 (1990).

[3] J. Reisch, C. O. Usifoh and J. O. Oluwadiya, *Monatsh. Chem.*, **123**, 247 (1992).

[4] C. O. Usifoh, parts of the Dissertation, Universität Münster, 1992.

[5] S. Johne, *Prog. Drug. Res.*, **26**, 259 (1982).

[6] W. L. F. Armarego, Chemistry of Heterocyclic Compounds, Vol **24**, Part I, A. Weissberger, ed, Interscience Publishers, New York, 1967, p 225.

[7] F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.*, 1759 (1948).

[8] J. Reisch and M. Scheer, *J. Heterocyclic Chem.*, **25**, 677 (1988).

[9] J. Reisch, C. O. Usifoh and J. O. Oluwadiya, *J. Heterocyclic Chem.*, **27**, 287 (1990).