Synthesis of some Fused Triazoloquinolines [1]

T. Ramalingam*, M. S. R. Murty, Y. V. D. Nageswar and P. B. Sattur

Indian Institute of Chemical Technology,
Hyderabad-500 007, India

Received August 8, 1989

The reaction of 3-amino-1,2,4-triazolo[4,3-*a*]quinoline (**II**) with diethyl ethoxymethylenemalonate and ethyl acetoacetate/ethyl trifluoroacetoacetate afforded 10-carboethoxy-9-oxo-9*H*-pyrimido[1′,2′:1,5][1,2,4]triazolo-[4,3-*a*]quinoline (**III**) and 11-methyl/trifluoromethyl-9-oxo-9*H*-pyrimido[1′,2′:1,5][1,2,4]triazolo[4,3-*a*]quinoline (**IV/V**) respectively. 2-Chloropyridine-3-carboxylic acid chloride reacted with **II** to yield 5-oxo-5*H*-pyrido-[3″,2″:5′,6′]pyrimido[1′,2′:1,5][1,2,4]triazolo[4,3-*a*]quinoline (**VII**), a new ring system.

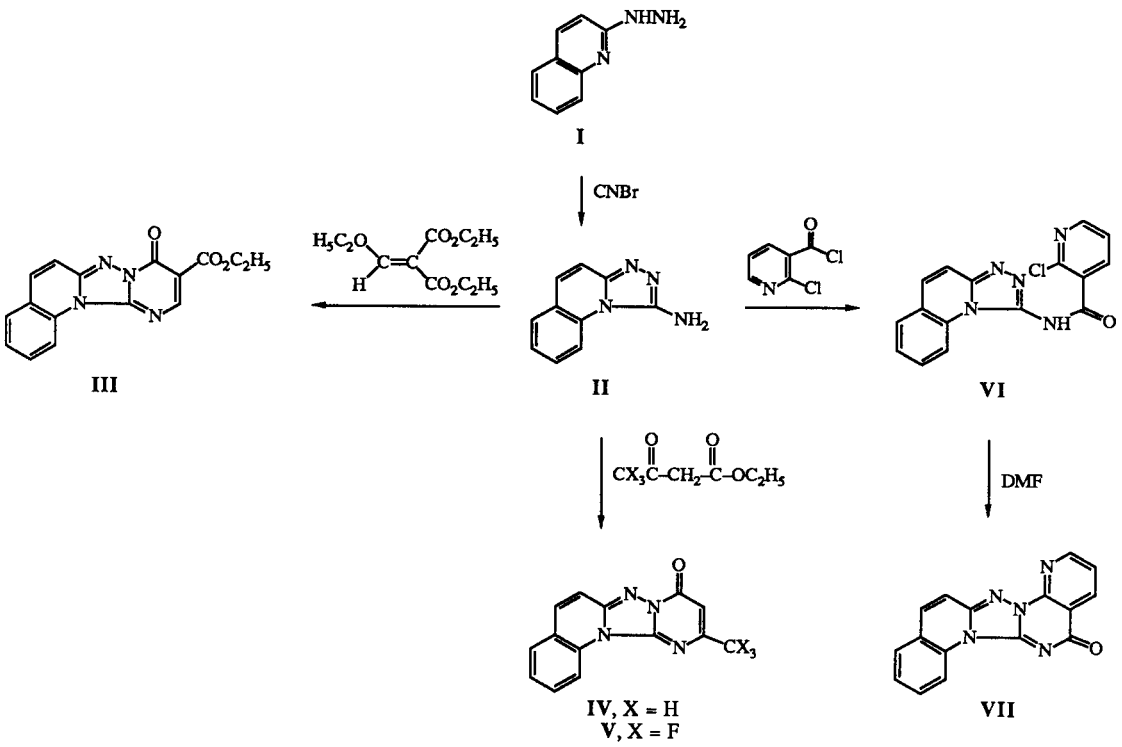
J. Heterocyclic Chem., **27**, 981 (1990).

The importance of quinoline, 1,2,4-triazole and pyrimidine nuclei is well established in pharmaceutical chemistry. Heterocycles bearing a trifluoromethyl group are of interest as intermediates for pharmaceuticals [2], but these have received fairly limited attention. In continuation of our studies on the synthesis of biologically active fused heterocycles [3,4], an extensive study on the reactions of 3-amino-1,2,4-triazolo[4,3-*a*]quinoline has been taken up.

We have come across the following literature references belonging to the related systems. Pyrimido[1′,2′:1,5][1,2,4]-triazolo[4,3-*a*]quinolin-8-ium salts have been prepared by the reaction of 3-amino-1,2,4-triazolo[4,3-*a*]quinoline with β-diketones [5]. Another literature report [6] mentions the synthesis of pyrimido[1′,2′:1,5][1,2,4]triazolo[3,4-*a*]isoquinolines by the cyclocondensation of 3-amino-1,2,4-triazolo-[3,4-*a*]isoquinoline with β-oxoesters.

The preparation of 3-amino-1,2,4-triazolo[4,3-*a*]quinoline (**II**) was reported in a U.S. patent [7] by the reaction of 2-hydrazinoquinoline (**I**) with a suitable acid or ester. In the present work, **II** was synthesised conveniently in a single step by condensing **I** with cyanogen bromide followed by neutralisation with aqueous potassium bicarbonate in 80% yield. Then **II** was reacted with diethyl ethoxymethylenemalonate, ethyl acetoacetate and ethyl trifluoroacetoacetate to obtain **III**, **IV** and **V** respectively in a single step. In our efforts to synthesise fused pentacyclic ring system with a bridgehead nitrogen atom, the reaction of **II** with 2-chloropyridine-3-carboxylic acid *via* its acid chloride was carried out for the first time in toluene and triethylamine which resulted in *N*-(1,2,4-triazolo[4,3-*a*]quinoline-3-yl)-2-chloropyridine-3-carboxamide (**VI**). The cyclisation of **VI** in dimethylformamide afforded **VII**, an entirely new

Scheme



class of heterocyclic system. The characterisation of **II-VII** is based on elemental analyses and spectroscopic data.

EXPERIMENTAL

Melting points were determined in Buchi 510 apparatus and are uncorrected, infrared (ir) spectra were recorded on a Perkin-Elmer 221 spectrophotometer. The ^{1}H nmr spectra have been obtained with a Varian FT-80A spectrometer using TMS as an internal standard. Mass spectra were recorded on a VG micromass 70-70H mass spectrometer at 70 eV.

3-Amino-1,2,4-triazolo[4,3-*a*]quinoline (**II**).

A solution of 2-hydrazinoquinoline (7.96 g, 0.05 mole) in ethanol (70 ml) and cyanogen bromide (5.83 g, 0.055 mole) was stirred for 5 hours at room temperature. After neutralisation of it with 10% aqueous potassium bicarbonate, the solid was filtered and recrystallised from ethanol to give 7.37 g (80%) of **II**, mp 175-177°; ir (potassium bromide): 3320, 1640, 1580 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.2-7.9 (m, 6H, aromatic protons), 6.4 (s, 2H, NH_2, deuterium oxide-exchangeable); ms: m/e 184 (M^+).

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.45; H, 4.41; N, 30.31.

10-Carboethoxy-9-oxo-9*H*-pyrimido[1′,2′:1,5][1,2,4]triazolo[4,3-*a*]-quinoline (**III**).

A mixture of **II** (1.84 g, 0.01 mole) and diethyl ethoxymethylenemalonate (2.16 g, 0.01 mole) in ethanol (25 ml) was refluxed for 3 hours. The solution was cooled and the solid obtained was filtered, recrystallised from ethanol to give 2.31 g (75%) of **III**, mp 250-253°; ir (potassium bromide): 1720, 1630, 1590 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.2 (s, 1H, 11-H), 7.6-8.8 (m, 6H, aromatic protons), 4.4 (q, 2H, CH_2, J = 7 Hz), 1.4 (t, 3H, CH_3, J = 7 Hz); ms: m/e 308 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.34; H, 3.92; N, 18.17. Found: C, 62.50; H, 4.01; N, 18.06.

11-Methyl-9-oxo-9*H*-pyrimido[1′,2′:1,5][1,2,4]triazolo[4,3-*a*]quinoline (**IV**).

A mixture of **II** (1.84 g, 0.01 mole), ethyl acetoacetate (1.43 g, 0.011 mole) and glacial acetic acid (25 ml) was refluxed for 4 hours. The solution was concentrated and the crude product obtained was recrystallised from chloroform-*n*-hexane (1:1) mixture to give 1.75 g (70%) of **IV**, mp 223-225°; ir (potassium bromide): 1650, 1560 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.4 (s, 1H, 10-H), 7.6-8.3 (m, 6H, aromatic protons), 2.7 (s, 3H, CH_3); ms: m/e 250 (M^+).

Anal. Calcd. for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.30; H, 4.12; N, 22.28.

11-Trifluoromethyl-9-oxo-9*H*-pyrimido[1′,2′:1,5][1,2,4]triazolo-[4,3-*a*]quinoline (**V**).

To a mixture of ethyl trifluoroacetoacetate (1.84 g, 0.01 mole) and freshly prepared polyphosphoric acid (10 ml) heated at 100°, was added **II** (1.84 g, 0.01 mole). The reaction mixture was stirred and heated at 130° for 2 hours. After cooling, ice water was added into the solution. The separated solid was filtered and recrystallised from chloroform to obtain 2.13 g (70%) of **V**, mp 183-185°; ir (potassium bromide): 1640, 1560 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.5 (s, 1H, 10-H), 7.8-8.5 (m, 6H, aromatic protons); ms: m/e 304 (M^+).

Anal. Calcd. for $C_{14}H_7F_3N_4O$: C, 55.27; H, 2.32; N, 18.41. Found: C, 54.99; H, 2.30; N, 18.51.

N-(1,2,4-Triazolo[4,3-*a*]quinoline-3-yl)-2-chloropyridine-3-carboxamide (**VI**).

2-Chloropyridine-3-carboxylic acid (1.57 g, 0.01 mole) and thionyl chloride (8 ml) were refluxed in benzene (20 ml) for 3 hours. The excess thionyl chloride distilled off, benzene (15 ml) was added and was distilled to remove the traces of thionyl chloride. The crude 2-chloropyridine-3-carboxyl chloride was dissolved in toluene (15 ml) and added slowly to a mixture of **II** (1.84 g, 0.01 mole) in toluene (20 ml) and triethylamine (1 ml). Then, the mixture was refluxed for 4 hours. The solid was filtered and the filtrate was concentrated to give 2.10 g (65%) of **VI**, mp 193-195°; ir (potassium bromide): 3100, 1630, 1560 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.3-8.3 (m, 9H, aromatic protons), 8.6 (broad, 1H, NH, deuterium oxide-exchangeable); ms: m/e 323 (M^+).

Anal. Calcd. for $C_{16}H_{10}ClN_5O$: C, 59.36; H, 3.11; N, 21.63. Found: C, 59.50; H, 3.12; N, 21.52.

5-Oxo-5*H*-pyrido[3″,2″:5′,6′]pyrimido[1′,2′:1,5][1,2,4]triazolo-[4,3-*a*]quinoline (**VII**).

A solution of **VI** (1 g, 0.003 mole) in dimethyl formamide (10 ml) was refluxed for 18 hours. After cooling, the solution was poured into ice cold water. The precipitate formed was filtered and recrystallised from ethanol to give 0.53 g (60%) of **VII**, mp 208-210°; ir: 1640 and 1580 cm^{-1}; ms: m/e 287 (M^+).

Anal. Calcd. for $C_{16}H_9N_5O$: C, 66.90; H, 3.16; N, 24.38. Found: C, 67.02; H, 3.20; N, 24.34.

Acknowledgement.

The authors are grateful to Prof. Kurt L. Loening, Chemical Abstracts Service for providing nomenclature of the ring systems.

REFERENCES AND NOTES

[1] IICT Communication No. 2412.

[2] R. Filler, *Chemtech*, **4**, 752 (1974).

[3] M. S. R. Murty, Y. V. D. Nageswar, A. V. N. Reddy, T. Ramalingam and P. B. Sattur, *J. Heterocyclic Chem.*, **26**, 473 (1989).

[4] A. R. Prasad, T. Ramalingam, A. B. Rao, P. V. Diwan and P. B. Sattur, *Eur. J. Med. Chem.*, **24**, 199 (1989).

[5] G. M. Golubushina, O. G. Ponomarenko, G. N. Poshtaruk and V. A. Chuiguk, *Khim. Geterotsikl. Soedin.*, 843 (1974); *Chem. Abstr.*, **81**, 152154p (1974).

[6] H. Reimlinger, W. R. F. Lingier, J. J. M. Vandewalle and R. Merenyi, *Chem. Ber.*, **104**, 3947 (1971); *Chem. Abstr.*, **76**, 72487f (1972).

[7] B. A. Dreikorn and K. E. Kramer, U. S. Patent 3,953,457 (1976); *Chem. Abstr.*, **85**, 29564c (1976).