A ONE-POT SYNTHESIS OF 4-METHYLPYRANO[3,2-*C*]QUINOLIN-2,5[6*H*]-DIONES

N. Venkatesh Kumar and S.P. Rajendran*

Department of Chemistry, Bharathiar University, Coimbatore-46, Tamil Nadu, India.

Correspondence to *E-mail* : rajendrersp@yahoo.com

Abstract: 4-hydroxy-2-quinolone being endowed with both nucleophilic and electrophilic properties furnishes the dimeric quinoline in a base catalyzed self-condensation process. A one step synthesis, starting from 4-hydroxy-2-quinolone with ethyl acetoacetate and pyridine proceeded through the Michael addition, which was followed by cyclization, gave an angular isomer 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione. The reaction was then extended to synthesize further derivatives of angular pyrano quinolones. Structures of all the products have been established by spectral and elemental analysis data.

Keywords: One pot synthesis, 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-diones.

Introduction: Pyranoquinolines constitute the parent ring structure of pyranoquinoline alkaloids, which occur in the plant family Rutaceae. We have recently reported^{1,2,3} the synthesis of a series of 3,5-disubstituted pyrano[2,3-*b*]quinolin-2-ones starting from 2-chloro-3-formyl quinolines and 2-chloro-3-formyl-4-phenyl/methyl quinolines respectively. In continuation of our studies and in view of the pharmacological activities^{4,5} of pyranoquinolines, we herewith report the synthesis of new unreported derivatives of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione and its derivatives (Scheme 1).

Experimental: Melting points were determined on a Boetius Microheating table and are uncorrected. IR spectra were recorded on a perkin-Elmer-597 Infrared spectrophotometer as KBr Pellets. ¹H NMR spectra were recorded on a AMX 400 spectrometer in CDCl₃.

The coupling constants (*J*) were expressed in Hz. Mass spectra were recorded on a Jeol D 300 mass spectrometer. Carlo Erba 106 and Perkin-Elmer model 240B CHN analyzer performed elemental analyses and the values are within the permissible limits ($\pm 0.5\%$).

4-hydroxy-2-quinolones have been prepared by known procedures⁶. The hitherto unknown derivatives of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione synthesized were reported in Table 1.

Scheme 1:

Mechanism : Scheme 2 : Probable pathway for the formation of 2

General Procedure: Synthesis of 4-methylpyrano[3,2-c]quinolin-2,5[6H]-diones (2a-g):

A mixture of 4-hydroxy-2-quinolone (0.004 M) along with ethyl acetoacetate (0.004 M) and pyridine (6-8 drops) was refluxed for 8 h in an oil bath at 120-130°C. Excess of ethyl acetoacetate and pyridine was removed by distillation. The reaction mixture was cooled, added to ice-cooled water (50 ml) and acidified with HCl when 4-methylpyrano[3,2-c]quinolin-2,5[6H]-dione separated as yellow precipitate. The precipitated product was then filtered, washed with water, dried, and chromatographed over silica gel. The petrol-ethyl acetate (4:1) elute fractions furnished the pure compound, which was further recrystallized from petrol-chloroform mixture (Table 1). M.p., yield, ir and analytical data of (2a-g) are given in Table 1.

Results and Discussion: The OH group at 4th-position in the 4-hydroxy-2-quinolone activates the nucleophilic carbon at C-3 in the presence of a base and prompts it to react with a Michael type acceptor. Thus 4-hydroxy-2-quinolone⁶ (1a) upon refluxing with active methylene compound ethyl acetoacetate in the presence of pyridine for 8 h gave a product in 80 % yield, which melts at 246-248°C. Its IR spectra showed very sharp peaks. The peak at 1715cm⁻¹, was assigned to the pyrone ring. It possesses stronger absorption at 1666cm⁻¹(corresponds to an angular isomer) in the carbonyl region, which is attributable to amide-carbonyl stretching. 2-quinolones possess stronger carbonyl absorption at higher wavelength than 4-quinolones^{7,8}. The PMR spectra showed very sharp signals. The protons at C-7 and C-10 appear as a doublet at δ 7.40 and δ 7.67 of value J=7.9 Hz and J=8 Hz respectively (Indicates an angular isomer. The C-7 and C-10 protons of linear isomer would appear much downfield than the angular isomer)^{7,8}. The protons at C-8 and C-9 appear as a multiplet at δ 7.31-7.36. The proton at position C-3 appears as a singlet at δ 6.59. The signal due to methyl protons appears as a singlet at δ 2.75. A broad singlet is obtained at δ 12.01, which correspond to NH. The Mass spectra also showed intense molecular ion peak at m/e 227. Thus from the above spectral studies the product was confirmed as 4-methylpyrano[3,2-c]quinolin-2,5[6H]-dione (2a) an angular isomer. The reaction sequence leading to 2a was then extended to synthesize compounds (2b-g) and similar results were obtained.

Table – 1. Physical and Spectroscopic data of (2a–g) ^a:

Compd.	M.p. °C (Yield %)	Elemental analyses		IR ^b vmax (cm ⁻¹)	¹ H NMR ^c (δ) ppm	MS m/z 70ev (m+)
		Calcul. (%)	Found (%)			
2a	246-248 (80)	C 68.72 H 3.99 N 6.16	C 68.70 H 3.97 N 6.14	1715 1666	δ2.75 (s, 3H, C ₄ -CH ₃); δ6.59(s, 1H, C ₃ -H); δ7.40(d, 1H, J=7.9, C ₇ -H); δ7.67(d, 1H, J=8, C ₁₀ -H); δ7.31-7.36(m, 2H, C ₈ -H & C ₉ -H); δ12.01(bs, 1H, NH)	227
2b	236-238 (70)	C 69.79 H 4.60 N 6.14	C 69.68 H 4.59 N 5.80	1716 1666	δ2.72(s, 3H, C ₈ -CH ₃); δ2.75(s, 3H, C ₄ -CH ₃); δ6.58(s, 1H, C ₃ -H); δ7.38(s, 1H, C ₇ -H); δ7.66(d, 1H, J=7.8, C ₁₀ -H); δ7.25(d, 1H, J=8, C ₉ -H); δ11.72(bs, 1H, NH)	241
2c	227-229 (70)	C 69.70 H 4.60 N 5.81	C 69.67 H 4.58 N 5.80	1718 1658	δ2.72(s, 3H, C ₇ -CH ₃); δ2.76(s, 3H, C ₄ -CH ₃); δ6.61(s, 1H, C ₃ -H); δ7.68(d, 1H, J=7.2, C ₁₀ -H); δ7.29-7.33(m, 2H, C ₈ -H & C ₉ -H); δ11.72(bs, 1H, NH)	241
2d	247-249 (75)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.44	1725 1667	δ2.74(s, 3H, C ₄ -CH ₃); δ3.78(s, 3H, C ₉ -OCH ₃); δ6.58(s, 1H, C ₃ -H); δ7.47(d, 1H, J=7.4, C ₇ -H); δ7.71(s, 1H, C ₁₀ -H); δ7.40(d, 1H, J=7.9, C ₈ -H); δ11.75(bs, 1H, NH)	257

2e	263-265 (75)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.29 N 5.43	1722 1665	δ 2.75(s,3H,C ₄ -CH ₃); δ 3.77(s,3H,C ₈ -OCH ₃); δ 6.59(s,1H,C ₃ -H); δ 7.49(s,1H, C ₇ -H); δ 7.68(d,1H,J=7.7,C ₁₀ -H); δ 7.41(d,1H,J=7.9,C ₉ -H); δ 11.76(bs,1H,NH)	257
2f	258-260 (70)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.43	1725 1665	δ 2.77(s,3H,C ₄ -CH ₃); δ 3.77(s,3H,C ₇ -OCH ₃); δ 6.59(s,1H,C ₃ -H); δ 7.69(d,1H,J=8.2,C ₁₀ -H); δ 7.32-7.38(m, 2H,C ₈ -H & C ₉ -H); δ 11.72(bs,1H,NH)	257
2g	251-253 (70)	C 62.72 H 4.56 N 4.88	C 62.70 H 4.53 N 4.87	1717 1665	δ 2.76(s,3H,C ₄ -CH ₃); δ 3.76(s,3H,C ₇ -OCH ₃); δ 3.92(s,3H,C ₁₀ -OCH ₃); δ 6.58(s,1H,C ₃ -H); δ 7.38- 7.43(m, 2H,C ₈ -H &C ₉ -H); δ 11.74(bs,1H,NH)	287

a) recrystallized from Petrol-Chloroform mixture b) as KBr pellets
c) as CDCl₃ solvent

The plausible mechanism has been proposed for the formation of 4-methylpyrano[3,2-*c*]quinolin-2,5[6H]-dione(**2**) in **Scheme-2**. The expected Michael addition was followed by cyclization, involving the nucleophilic oxygen at C-4 and electrophilic carboxyl carbon in the side chain afforded the product **2**, which was isolated after chromatographic purification.

Conclusion: In conclusion, we have demonstrated the synthesis of newer derivatives of angular[3,2-*c*]pyranoquinolones in one pot method through Michael addition.

Acknowledgements: One of the author (NVK) thank Bharathiar University, Coimbatore for the award of University Research Fellowship, SIF, IISC, Bangalore and ICT, Hyderabad supported the spectral details.

References:

1. N. Venkatesh Kumar, L. Subramani and S.P. Rajendran, J. Ind.Chem.Soc. (2003) (in press).
2. N. Venkatesh Kumar and S.P. Rajendran, Asian.J.Chem. **Vol.15**, 111 (2003).
3. N. Venkatesh Kumar, N. Sampath Kumar and S.P. Rajendran, Asian.J.Chem. (2003) (in press).
4. M. Dean. ed: by L. Zchmeister, "Progress in the chemistry of Natural Products", **Vol.9**, (Verlag Chemic, Weinhein) 235 (1952).
5. H.T. Openshaw, The alkaloids, **Vol, IX**, edited by R.H.F. Manske (Academic press, New york). 223 (1967).
6. C. Balasubramaniam, Ph.D Dissertation, Bharathiar Univertsity., Coimbatore, India.
7. E.A. Clarke and M.F. Grundon, J.Chem.Soc. 4190 (1964).
8. Witcop, Patrick and Rosenblum, J.Amer.Chem.Soc., **73**, 2641 (1951)

Received on December 12, 2003.