ipso-Substitution of an Acyl group in Reactions of 3-Acyl-substituted Ethyl 7,8-Difluoro-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylates with Electrophilic Reagents

Yurii A. Azev, Sergei V. Shorshnev, Sergei G. Alexeev, Valerii N. Charushin and Oleg N. Chupakhin*

Chemico-Technical Department, Ural Technical University, Ekaterinburg, Russian Federation. Fax: +7 3432 44 1624

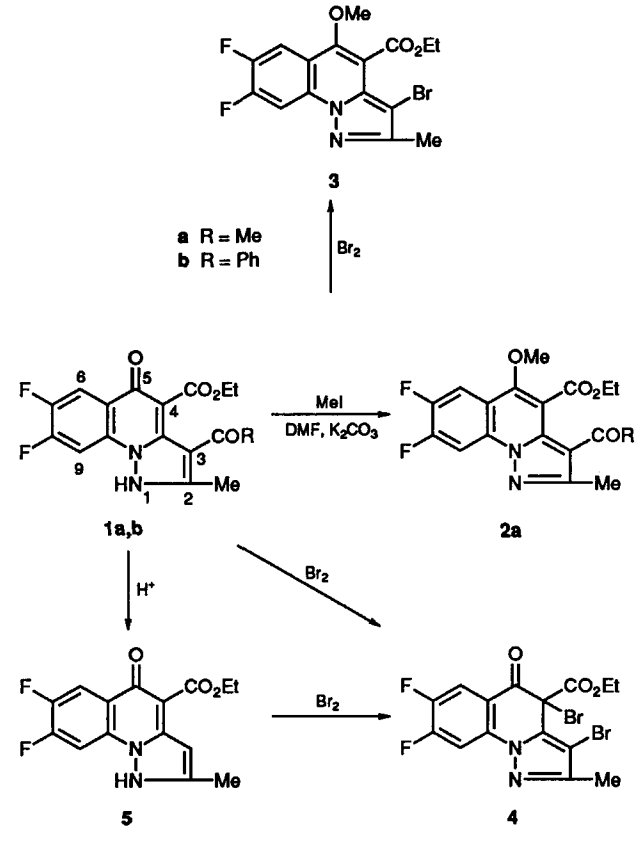
Reactions of 3-acetyl-(benzoyl-) substituted 7,8-difluoro-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylates **1a,b** with electrophilic reagents have been studied and reaction of **1a** with methyl iodide in dry DMF in the presence of potassium carbonate results in the corresponding 5-methoxy derivative **2**, in which the acetyl group at C–3 is easily substituted by a bromine atom. Treatment of **1a,b** with bromine causes *ipso*-substitution of the acetyl (benzoyl) group accompanied by addition of the second bromine atom at position 4; a similar *ipso*-substitution of the acetyl group at C-3 has been observed on protonation of **1a** with sulfuric acid.

We recently described a new synthetic route to tricyclic fluoroquinolones **1** by means of a cyclization reaction of 7-substituted ethyl 1-amino-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylates with β-diketones.[1] In this paper we wish to report on some features of electrophilic substitution reactions in these tricyclic ethyl 7,8-difluoro-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylates **1**.

Ethyl 3-acetyl-7,8-difluoro-2-methyl-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate **1a** has been found to undergo an *O*-alkylation reaction with methyl iodide in dry DMF (dimethyl formamide) in the presence of potassium carbonate yielding the corresponding 5-methoxy derivative **2**. Evidence for the structure of **2** is provided by the ^{1}H and ^{13}C NMR spectra in which both proton (δ 4.09 ppm) and carbon (δ 63.75 ppm) resonances of the methyl group indicate that it is attached to the oxygen atom.†

An unexpected feature of compounds **1a** and **2a** is the ability of the acetyl group at C–3 to undergo an *ipso*-substitution reaction by action of bromine or sulfuric acid (Table 1, Scheme 1). Indeed, when treated with bromine in acetic acid at room temperature compound **2a** is easily converted into 3-bromopyrazolo[1,5-*a*]quinoline **3** through a bromination–deacetylation reaction. Elimination of the acetyl group is evident from the ^{1}H NMR spectrum of the compound **3** which, unlike the ^{1}H NMR spectrum of the starting material, no longer contains signals due to acetyl protons.‡

Under the same conditions pyrazolo[1,5-*a*]quinolones **1a,b** react with bromine in a somewhat different manner giving rise to the product **4** containing two bromine atoms. Besides *ipso*-substitution of the acetyl or benzoyl group at C–3, addition of bromine at C–4 has been found to take place. Indeed, the tetrahedral character of C–4 bearing a bromine atom is substantiated by the ^{13}C chemical shift observed for this carbon resonance (δ 53.82 ppm).§



Scheme 1

† *Spectral data for* **2a**. ^{1}H NMR ($CDCl_3$): 1.42 t (3H, OCH_2CH_3, *J* 7.2 Hz), 2.54 s and 2.70 s (6H, 2–CH_3, $COCH_3$), 4.09 s (OCH_3), 4.54 q (2H, OCH_2CH_3, *J* 7.2 Hz), 7.81 d.d (H–6, *J* 10.6, *J* 7.9 Hz), 8.38 d.d (H–9, *J* 10.6, *J* 6.8 Hz). ^{13}C NMR ($CDCl_3$): 14.02 q.t (CH_2CH_3 ^1J 127.6, ^3J 2.4 Hz), 15.64 q (2–CH_3 ^1J 128.8 Hz), 30.29 q ($COCH_3$, ^1J 127.6 Hz), 61.89 t.q. (CH_2CH_3, ^1J 148.3, ^2J 4.3 Hz), 63.75 q (OCH_3, ^1J 146.2 Hz), 105.52 d.d. (C–9, ^1J 171.2, $^2J_{C,F}$ 23.2 Hz), 111.00 d.d.m. (C–6, ^1J 168.1, $^2J_{C,F}$ 20.1, $^3J_{C,F}$ 1.8 Hz), 115.54 d.d.m. (C–5a, $^3J_{C,F}$ 4.3, $^4J_{C,F}$ 1.8 Hz), 115.67 m (C–4), 116.00 m (C–3), 131.41 d.d.m. (C–9a, $^3J_{C,F}$ 9.8, $^4J_{C,F}$ 1.8 Hz), 136.85 s (C–3a), 149.04 d.d.m. (C–7, $^1J_{C,F}$ 250.6, $^2J_{C,F}$ 14.3 Hz), 152.23 q (C–2, ^2J 6.7 Hz), 152.76 d.d.m. (C–8, $^1J_{C,F}$ 256.7, $^2J_{C,F}$ 15.0 Hz), 153.64 d.m. (C–5, $^4J_{C,F}$ 3.1 Hz), 163.86 t (COO, ^3J 2.7 Hz), 192.65 q ($COCH_3$, ^2J 6.1 Hz).

‡ *Spectral data for* **3**. ^{1}H NMR ($CDCl_3$): 1.45 t (3H, CH_2CH_3, *J* 7.2 Hz), 2.46 s (3H, 2–CH_3), 4.06 s (3H, OCH_3), 4.52 q (2H, CH_2CH_3, *J* 7.2 Hz), 7.77 d.d. (H–6 *J* 10.6, *J* 8.0 Hz), 8.26 d.d. (H–9, *J* 11.0 *J* 7.1 Hz).

§ *Spectral data for* **4**. ^{1}H NMR ($CDCl_3$): 1.30 t (3H, CH_2CH_3, *J* 7.1 Hz), 2.34 s (3H, 2–CH_3), 4.38 q (2H, CH_2CH_3, *J* 7.1 Hz), 7.86 d.d. (H–6, *J* 9.5, *J* 7.7 Hz), 7.91 d.d. (H–9, *J* 10.6, *J* 6.6 Hz). ^{13}C NMR ($CDCl_3$): 12.12 q (2–CH_3, ^1J 128.8 Hz), 13.83 q.t. (CH_2CH_3, ^1J 127.6 ^2J 2.4 Hz), 53.82 s (C–4), 151.77 q (C–2, ^2J 7.0 Hz), 64.83 t.q. (CH_2CH_3, ^1J 149.5, ^2J 4.3 Hz), 100.30 q (C–3, ^3J 4.3 Hz), 105.80 d.d. (C–9, ^1J 172.1, $^2J_{C,F}$ 23.8 Hz), 114.17 d.d.m. (C–5a, $^3J_{C,F}$ 5.0, $^4J_{C,F}$ 3.5 Hz), 117.76 d.d.d. (C–6, ^1J 169.7, $^2J_{C,F}$ 19.8 Hz), 135.42 s (C–3a), 136.31 d.d.m. (C–9a, $^3J_{C,F}$ 10.4, $^4J_{C,F}$ 3.0 Hz), 148.77 d.d.m. (C–7, $^1J_{C,F}$ 252.1, $^2J_{C,F}$ 14.0 Hz), 156.18 d.d.m. (C–8, $^1J_{C,F}$ 262.1, $^2J_{C,F}$ 14.3 Hz), 161.86 t (COO, ^3J 2.7 Hz), 181.32 m (C–5, $^4J_{C,F}$ 3.4, $^5J_{C,F}$ 2.1 Hz).

Table 1 Products and yields obtained from reactions of 3-acyl-substituted ethyl 7,8-difluoro-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]-quinoline-4-carboxylates with some electrophilic reagents

Starting fluoro-pyrazo-loquino-lone	Reagent	Conditions: Solvent	Reac tion temp. /°C	Reac-tion time /h	Pro-duct	Yield (%)	M.p./ °C (recrys-tallized from)
1a	MeI	DMF	50	3	**2a**	35	166–167 (ethanol)
2a	Br_2	AcOH	25	2	**3**	35	184–185 (ethanol)
1a	Br_2	AcOH	25	0.25	**4**	50	149–151 (ethanol)
1b	Br_2	AcOH	25	0.25	**4**	50	149–151 (ethanol)
1a	H_2SO_4	AcOH	100	3	**5**	70	168–169 (acetic acid)
5	Br_2	AcOH	25	0.25	**4**	55	149–151 (ethanol)

The *ipso*-substitution of the acetyl group has also been found to occur on heating compound **1a** in acetic acid containing 5% of sulfuric acid, as indicated by the appearance of the H–3 resonance signal in the ^{1}H NMR spectrum of compound **5** at 6.53 ppm (in $CDCl_3$). In the ^{13}C NMR spectrum of the deacetylated pyrazoloquinolone **5** the C–3 resonance appears at δ 101.10 ppm as a double quartet with ^1J(C–3, H–3) = 180.7 Hz and ^3J(C–3, H–CH_3) = 3.1 Hz, thus providing a convincing argument for the structure of this deacetylation product.¶

The compound **5** reacts with bromine in acetic acid in a similar manner as do compounds **1a,b** with the formation of the authentic dibromo derivative **4** (Scheme 1, Table 1).

It is worth mentioning that the deacylation–protonation reaction described above takes place under milder conditions than similar *ipso*-substitutions in the series of pyrazoles, pyrroles and other azoles.[2–5] Indeed, *ipso*-substitution of the acetyl group in pyrazoles by a proton can be reached after many (24–48) hours of heating in the presence of glycols which enable one to convert the acyl group into a form of cyclic ketal, thus facilitating its elimination.[2,4]

We would also like to note that *ipso*-substitution reactions have never been used for chemical modification of condensed fluoroquinolones.[6–9]

¶ *An example of the experimental procedure used for the* ipso-*substitution reactions in 3-acyl-substituted ethyl 7,8-difluoro-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylates and spectral data for* **5**. Ethyl 3-acetyl-7,8-difluoro-2-methyl-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate **1a** (0.174 g, 0.5 mmol), was dissolved in acetic acid (3 ml) and then refluxed for 3 h with 5% aqueous sulfuric acid (0.5 ml). The reaction mixture was duiluted with water (3.5 ml) and cooled to room temperature. The precipitate formed was filtered off and recrystallized from acetic acid to yield 0.107 g (70%) of ethyl 7,8-difluoro-2-methyl-5-oxo-5,9a-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate **5**. ^{1}H NMR ($CDCl_3$): 1.52 t (3H, CH_2CH_3, *J* 7.2 Hz), 2.46 s (3H, 2–CH_3), 4.53 q (2H, CH_2CH_3, *J* 7.2 Hz), 6.53 s (H–3), 7.97 d.d. (H–6, *J* 10.4 Hz), 8.19 d.d. (H–9, *J* 11.0 *J* 7.0 Hz), 12.89, b.s. (NH). ^{13}C NMR ($CDCl_3$): 13.86 q (2–CH_3, ^1J 127.6 Hz), 14.16 q.t. (CH_2CH_3, ^1J 127.0, ^2J 2.4 Hz), 62.16 t.q. (CH_2CH_3, ^1J 148.9, ^2J 4.3 Hz), 96.13 m (C–4), 101.10 d.q. (C–3, ^1J 180.7 Hz), 104.44 d.d. (C–9, ^1J 170.3, $^2J_{C,F}$ 23.2 Hz), 112.67 m (C–5a), 112.82 d.d.d. (C–6, ^1J 169.1, $^2J_{C,F}$ 19.5, $^3J_{C,F}$ 1.5 Hz), 134.03 d.m. (C–9a, $^3J_{C,F}$ 10.4 Hz), 135.88 d (C–3a, ^2J 7.3 Hz), 147.86 d.d.m. (C–7, $^1J_{C,F}$ 247.8, $J_{C,F}$ 14.6 Hz), 152.47 d.k. (C–2, ^2J 6.1 Hz), 153.96 d.d.m. (C–8, $^1J_{C,F}$ 255.7, $^2J_{C,F}$ 14.0 Hz), 160.09 d.d.m. (C–5, $^4J_{C,F}$ 4.9, $^5J_{C,F}$ 1.8 Hz), 170.33 t (COO, ^3J 3.1 Hz).

References

1 O. N. Chupakhin, Yu. A. Azev, S. G. Alexeev, S. V. Shorshnev, E. Tsoy and V. N. Charushin, *Mendeleev Commun.*, 1992, 151.

2 K. M. Smith, M. Miura and H. D. Tabba, *J. Org. Chem.*, 1983, **48**, 4779.

3 K. M. Smith and K. C. Langry, *J. Chem. Soc., Chem. Commun.*, 1981, 283.

4 M. W. Moon and R. A. Wade, *J. Org. Chem.*, 1984, **49**, 2663.

5 T. Kametani, Y. Kigawa, T. Takahashi, H. Nemoto and K. Fukomoto, *Chem. Pharm. Bull.*, 1978, **26**, 1918.

6 D. Bouzard, *Recent Advances in the Chemistry of Quinolones*, in *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer–Verlag, Berlin, Heidelberg, 1990, 249–283.
The Quinolones, ed. V. T. Andriole, Academic Press, NY, 1988.
The Quinolones, ed. P. B. Fernandes, J. R. Prous Science Publishers, Barcelona, 1986.

7 G. A. Mokrushina, S. G. Alexeev, V. N. Charushin and O. N. Chupakhin, *Zh. Vses. Khim. O–va im. D. I. Mendeleeva*, 1991, 447 (in Russian).

Received: Moscow, 15th December 1992
Cambridge, 8th January 1993; Com. 2/06718H