Russian Journal of General Chemistry, Vol. 74, No. 9, 2004, pp. 1467–1468. Translated from Zhurnal Obshchei Khimii, Vol. 74, No. 9, 2004, pp. 1579–1580.

LETTERS TO THE EDITOR

Formation of 6-Chloro-4-phenyl-2-quinolone in Reaction of Dimethyl Sulfate with 2-(Acetylamino)-5-chlorobenzophenone under Phase-Transfer Conditions

N. N. Popova, S. V. Kulikov, and L. B. Piotrovskii

KUPE Company, St. Petersburg, Russia

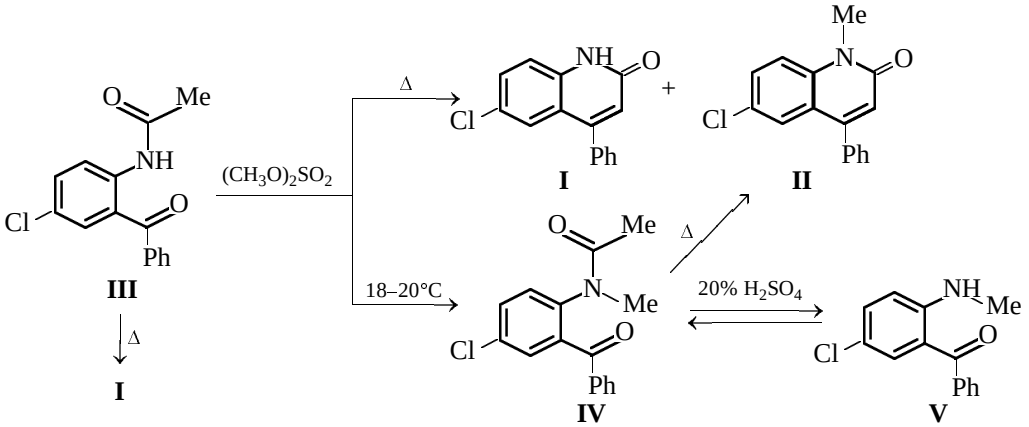
Research Institute of Experimental Medicine, Russian Academy of Medical Sciences, St. Petersburg, Russia

Received January 26, 2004

3-Substituted 4-phenyl-2-quinolones exhibit a conspicuous biologic activity [1], but the procedure of their synthesis, developed in the referred work, is unsuitable for preparing 3- unsubstituted derivatives, such as 6-chloro-4-phenyl-2-quinolone (**I**) and its *N*-methyl analog (**II**). At the same time, these compounds can be prepared from 2-(acetylamino)-5-chlorobenzophenone (**III**) [2] and 2-(*N*-acetyl-*N*-methylamino)-5-chlorobenzophenone (**IV**). To prepare compound **IV**, alkylation of ketone **III** with dimethyl sulfate under phase-transfer conditions at elevated temperatures was tried [3].

Under the conditions described in [3], i.e. by refluxing compound **III** [2] and dimethyl sulfate in toluene containing a mixture of NaOH and K_2CO_3, as well as tetrabutylammonium hydrosulfate as catalyst, no compound **IV** was formed. From the reaction mixture we isolated quinolone **II** as the major product (yield 85%) and quinolone **I** (yield 13%) [4]. The latter was also formed by refluxing ketone **III** in toluene with a mixture of NaOH and K_2CO_3 in the presence of a phase-transfer catalyst. The composition and structure of compounds **I** and **II** were confirmed by elemental analysis and ^{1}H NMR spectroscopy.

Ketone **IV** is prepared in quantitative yield by the procedure in [3] but at 18–20°C. Treatment of compound **IV** with a mixture of ethanol and 20% H_2SO_4 (1 : 2, v/v) provides 5-chloro-2-(methylamino)benzophenone (**V**) in 98% yield [2].



Thus, the reaction of benzophenone **I** with dimethyl sulfate, performed as described in [3], involves both N-methylation and cyclization and gives a mixture of 2-quinolones. Lowering the reaction temperature to 18–20°C allows substituted benzophenone **IV** to be prepared in quantitative yield.

2-(*N*-Acetyl-*N*-methylamino)-5-chlorobenzo-

1070-3632/04/7409-1467

phenone (IV). A solution of 4.9 ml of dimethyl sulfate was added dropwise with stirring to a suspension of 9.9 g of compound **III** [2], 4.9 g of NaOH, 9.86 g of K_2CO_3, and 1.22 g of tetrabutylammonium hydrosulfate in 50 ml of toluene, maintaining the temperature at 18–20°C. After 2-h stirring at the same temperature, the reaction mixture was filtered, and the precipitate was washed with toluene. The organic layer was washed with water (3×20 ml), dried with magnesium sulfate, and evaporated in a vacuum. The oily reaction product was dried in a vacuum over KOH–P_2O_5, yield 10.4 g (ca. 100%), R_f 0.33 (system **A**).

5-Chloro-2-(*N*-methylamino)benzophenone (V) [2]. Compound **IV**, 10.4 g, was refluxed in 150 ml of a mixture of 20% H_2SO_4 and ethanol (2 : 1, v/v). After cooling, the reaction product was filtered off, washed with water, and dried in a vacuum, yield 8.7 g (98%), mp 94–95°C, R_f 0.28 (system A). ^{1}H NMR spectrum, δ, ppm: 2.93 s (3H, CH_3), 6.74 d.d (1H, Ar–H, *J* 8 Hz) and 7.3–7.6 m (7H, Ar–H).

***N*-Methyl-6-chloro-4-phenyl-2-quinolone (II) and 6-chloro-4-phenyl-2-quinolone (I)** were prepared similarly to ketone **IV**, starting from 9.9 g of compound **III**, but in toluene under reflux. After 40 min, the reaction mixture was cooled, diluted with equal volume of toluene, and filtered. The filtrate was washed with water, dried with magnesium sulfate, and evaporated in a vacuum. The residue was recrystallized from ethanol to obtain 8.29 g (85%) of quinolone **II**, mp 143–146°C, R_f 0.64 (system B). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, CH_3), 6.63 s (1H, CH), 7.37–7.56 m (8H, Ar–H). Found, %: C 71.24; H 4.45; Cl 13.17; N 5.19. $C_{16}H_{12}ClNO$. Calculated, %: C 70.92; H 4.50; Cl 13.05; N 5.12.

Quinolone **I** was isolated from the mother liquor by preparative TLC in system B, yield 1.2 g (13%), mp 260–263°C. ^{1}H NMR spectrum, δ, ppm: 6.63 s (1H, CH), 7.44–7.60 m (8H, Ar–H), 12.22 br.s (1H, NH). Found, %: C 69.91; H 4.18; N 5.39. $C_{15}H_{10}ClNO$. Calculated, %: C 70.45; H 3.91; N 5.48.

The ^{1}H NMR spectra were measured on a Bruker CXP-300 spectrometer (300 MHz) in CD_2Cl_2. Thin-layer chromatography was performed on silica gel plates (Merck) in ethyl acetate–hexane, 1 : 4 (system A) and 1 : 1 (system B). The melting points were determined in an open capillary.

ACKNOWLEDGMENTS

The work was financially supported by INTAS (grant no. 01-0651).

REFERENCES

1. Hewawasam, P.P., Fan, W.W., Knipe, J.J., Moon, S.L., Boissard, C.G., Gribkoff, V.K., and Starrett, J.E., *Bioorg. Med. Chem. Lett.*, 2002, vol. 12, no. 13, p. 1779.
2. Sternbach, L.H., Frayer, R.I., Metlesics, W., Sach, G., and Stempel, A., *J. Org. Chem.*, 1962, vol. 27, no. 11, p. 3781.
3. Gajda, T. and Zwierzak, A., *Synthesis*, 1981, no. 12, p. 1005.
4. Bell, S.C., Sulkowski, T.S., Gochman, C., and Childress, S.J., *J. Org. Chem.*, 1962, vol. 27, no. 2, p. 562.