Chemistry of Heterocyclic Compounds, Vol. 44, No. 6, 2008

4-HYDROXY-2-QUINOLONES

145*. *p*-TOLUENESULFONYLHYDRAZIDE AS A TOSYLATING AGENT

I. V. Ukrainets[1], A. A. Tkach[1], V. V. Kravtsova[1], and S. V. Shishkina[2]

The reaction of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate with p-toluenesulfonylhydrazide in anhydrous solvents in the presence of triethylamine results in the tosylation of position 4 of the quinolone. Features of the steric structure of the tosyl-substituted compound are discussed.

Keywords: 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate, *p*-toluenesulfonylhydrazide, X-ray structural analysis, tosylation.

p-Toluenesulfonylhydrazide is well known as a chemical reagent in organic chemistry. It is quite often used in laboratory practice for converting aliphatic, aromatic, and heteroaromatic carboxylic acids to the corresponding aldehydes *via* the McFayden-Stevens reaction [2]. Aldehydes or ketones can be transformed to diazo compounds which, in turn, decompose to olefins upon treatment with bases [3]. As examples of preparatively important reactions occurring with the participation of p-toluenesulfonylhydrazide mention should be made of interesting rearrangements of the carbon skeleton in pinacol, camphor, and a series of other compounds, the synthesis of cyclopropenes from α,β-unsaturated aldehydes, identification of sugars, and the dehalogenation of activated hetaryl halides [3, 4].

A characteristic of all of the reactions listed above is that the p-toluenesulfonylhydrazide itself is used in them only at the intermediate stages of formation of β-N-acyl(hetaryl)tosylhydrazides or tosylhydrazones. In the final step this residue is generally completely removed. An exception is diazo compounds, the diazide group of which consists of nitrogen atoms initially occurring in the p-toluenesulfonylhydrazide. On the other hand we were unable to find examples where the *p*-toluenesulfonylhydrazide would, in fact, serve as a source of a *p*-toluenesulfonyl group, i.e. behave in the role of a tosylating agent.

A further example of the "utilization" of the nitrogen atoms of the starting reagent in the final product are the 5-alkyl substituted 3-hydroxy-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-ones prepared by reaction of ethyl 4-chloro-1-R-2-oxo-1,2-dihydroquinoline-3-carboxylates with p-toluenesulfonylhydrazide in refluxing ethanol [5]. It was suggested that one of the basic factors influencing the direction of this reaction is the presence of water in the alcohol. Hence it was certainly of interest to carry out the synthesis in an anhydrous solvent.

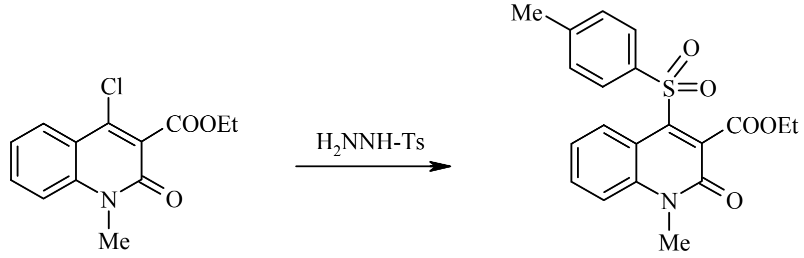
---

* For Communication 144 see [1].

---

[1] National Pharmaceutial University, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2] STC Institute for Single Crystal, Ukraine National Academy of Sciences, Kharkiv 61001; e-mail: sveta@xray.isc.kharkov.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 847-852, June, 2008. Original article submitted June 8, 2007.

As a result of the experiments carried out by us it was shown that the this modification to the reaction conditions basically changes the direction of the reaction of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) with p-toluenesulfonylhydrazide in anhydrous acetonitrile or THF such that it occurs quite differently. Firstly the ^{1}H NMR spectrum clearly shows the presence of a *p*-toluenesulfonyl fragment in the formed product. In the second no signal at all is found which might be identified as belonging to an NH group proton of a hydrazide fragment. The recorded mass spectroscopic fragment ions with *m/z* 340 and 312 correspond to successive loss of ethoxy and carbonyl groups from the molecular ion confirming the NMR data regarding the presence of a ethoxycarbonyl group in the sample studied. However, more important for proving the structure of the product, was the peak with *m/z* 385 which can evidently be assigned as due to the molecular ion. This being so the overall spectroscopic parameters for the product of the reaction of the 4-chloro-substituted ester **1** with *p*-toluenesulfonylhydrazide in anhydrous acetonitrile or THF point to it being the ethyl 1-methyl-2-oxo-4-tosyl-1,2-dihydroquinoline-3-carboxylate (**2**).



1 **2**

In the mass spectrum, fragment ion peaks which might be regarded as due to the loss of a toluenesulfonyl substituent from the molecular ion or its derivative are absent. None the less, the X-ray structural analysis carried out by us fully confirms the initial conclusion regarding the structure of the material

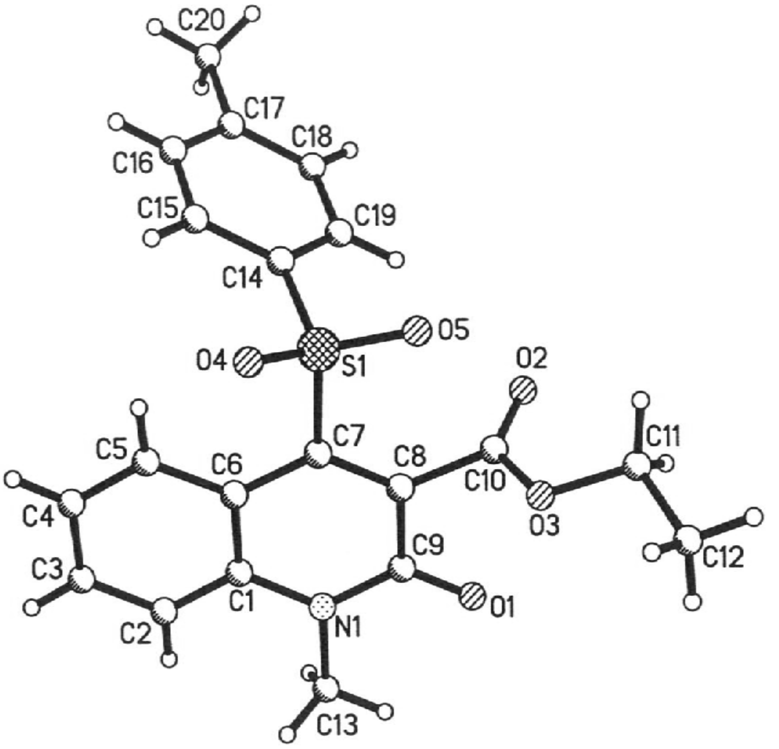


Fig. 1. Structure of the tosylquinoline **2** molecule with atomic numbering.

prepared (see Figure 1 and Tables 1 and 2). It was found that the bicyclic fragment and atoms $O_{(1)}$, $S_{(1)}$, and $C_{(10)}$ of the tosylquinoline **2** lie in a single plane to within 0.03 Å. The toluenesulfonyl substituent is located such that the $S_{(1)}-O_{(5)}$ bond is virtually coplanar with the endocyclic $C_{(7)}-C_{(8)}$ bond and the $S_{(1)}-O_{(4)}$ has an -*ac*-orientation relative to it (torsional angles $O_{(5)}-S_{(1)}-C_{(7)}-C_{(8)}$ -7.8(2)° and $O_{(4)}-S_{(1)}-C_{(7)}-C_{(8)}$ -137.5(2)°C). The tolyl group has an -*ac* orientation relative to the $C_{(7)}-C_{(8)}$ bond (torsional angle $C_{(14)}-S_{(1)}-C_{(7)}-C_{(8)}$ 107.0(2)°) and is strongly twisted relative to the $C_{(7)}-S_{(1)}$ bond (torsional angle $C_{(7)}-S_{(1)}-C_{(14)}-C_{(15)}$ 110.1(2)°). Such a position for the

TABLE 1. Bond Lengths (*l*) in the Tosylquinoline Structure **2**

Bond	*l*, Å	Bond	*l*, Å
$S_{(1)}-O_{(4)}$	1.421(3)	$S_{(1)}-O_{(5)}$	1.423(4)
$S_{(1)}-C_{(14)}$	1.744(5)	$S_{(1)}-C_{(7)}$	1.787(3)
$N_{(1)}-C_{(9)}$	1.348(4)	$N_{(1)}-C_{(1)}$	1.403(5)
$N_{(1)}-C_{(13)}$	1.466(3)	$O_{(1)}-C_{(9)}$	1.232(4)
$O_{(2)}-C_{(10)}$	1.196(4)	$O_{(3)}-C_{(10)}$	1.311(4)
$O_{(3)}-C_{(11)}$	1.446(4)	$C_{(1)}-C_{(2)}$	1.370(4)
$C_{(1)}-C_{(6)}$	1.403(3)	$C_{(2)}-C_{(3)}$	1.371(5)
$C_{(3)}-C_{(4)}$	1.363(4)	$C_{(4)}-C_{(5)}$	1.348(4)
$C_{(5)}-C_{(6)}$	1.406(5)	$C_{(6)}-C_{(7)}$	1.426(4)
$C_{(7)}-C_{(8)}$	1.358(5)	$C_{(8)}-C_{(9)}$	1.456(4)
$C_{(8)}-C_{(10)}$	1.491(4)	$C_{(11)}-C_{(12)}$	1.479(5)
$C_{(14)}-C_{(19)}$	1.379(4)	$C_{(14)}-C_{(15)}$	1.382(5)
$C_{(15)}-C_{(16)}$	1.368(5)	$C_{(16)}-C_{(17)}$	1.370(4)
$C_{(17)}-C_{(18)}$	1.380(5)	$C_{(17)}-C_{(20)}$	1.489(5)
$C_{(18)}-C_{(19)}$	1.364(5)		

TABLE 2. Valence Angles (ω) in the Tosylquinoline Structure **2**

Angle	ω, deg	Angle	ω, deg
$O_{(4)}-S_{(1)}-O_{(5)}$	119.3(2)	$O_{(4)}-S_{(1)}-C_{(14)}$	108.8(2)
$O_{(5)}-S_{(1)}-C_{(14)}$	109.0(2)	$O_{(4)}-S_{(1)}-C_{(7)}$	108.6(2)
$O_{(5)}-S_{(1)}-C_{(7)}$	106.6(2)	$C_{(14)}-S_{(1)}-C_{(7)}$	103.4(1)
$C_{(9)}-N_{(1)}-C_{(1)}$	124.1(2)	$C_{(9)}-N_{(1)}-C_{(13)}$	117.0(2)
$C_{(1)}-N_{(1)}-C_{(13)}$	118.9(2)	$C_{(10)}-O_{(3)}-C_{(11)}$	116.1(3)
$C_{(2)}-C_{(1)}-N_{(1)}$	121.1(2)	$C_{(2)}-C_{(1)}-C_{(6)}$	120.0(2)
$N_{(1)}-C_{(1)}-C_{(6)}$	118.8(2)	$C_{(1)}-C_{(2)}-C_{(3)}$	121.1(3)
$C_{(4)}-C_{(3)}-C_{(2)}$	119.9(3)	$C_{(5)}-C_{(4)}-C_{(3)}$	119.8(3)
$C_{(4)}-C_{(5)}-C_{(6)}$	122.5(2)	$C_{(1)}-C_{(6)}-C_{(5)}$	116.6(3)
$C_{(1)}-C_{(6)}-C_{(7)}$	118.1(2)	$C_{(5)}-C_{(6)}-C_{(7)}$	125.3(2)
$C_{(8)}-C_{(7)}-C_{(6)}$	121.5(2)	$C_{(8)}-C_{(7)}-S_{(1)}$	118.2(2)
$C_{(6)}-C_{(7)}-S_{(1)}$	120.3(2)	$C_{(7)}-C_{(8)}-C_{(9)}$	120.3(3)
$C_{(7)}-C_{(8)}-C_{(10)}$	128.0(2)	$C_{(9)}-C_{(8)}-C_{(10)}$	111.6(2)
$O_{(1)}-C_{(9)}-N_{(1)}$	122.8(2)	$O_{(1)}-C_{(9)}-C_{(8)}$	120.3(3)
$N_{(1)}-C_{(9)}-C_{(8)}$	116.9(2)	$O_{(2)}-C_{(10)}-O_{(3)}$	125.6(3)
$O_{(2)}-C_{(10)}-C_{(8)}$	122.5(2)	$O_{(3)}-C_{(10)}-C_{(8)}$	111.7(3)
$O_{(3)}-C_{(11)}-C_{(12)}$	107.5(3)	$C_{(19)}-C_{(14)}-C_{(15)}$	120.4(2)
$C_{(19)}-C_{(14)}-S_{(1)}$	118.3(3)	$C_{(15)}-C_{(14)}-S_{(1)}$	121.3(2)
$C_{(16)}-C_{(15)}-C_{(14)}$	119.4(2)	$C_{(15)}-C_{(16)}-C_{(17)}$	121.4(3)
$C_{(16)}-C_{(17)}-C_{(18)}$	118.1(3)	$C_{(16)}-C_{(17)}-C_{(20)}$	121.7(3)
$C_{(18)}-C_{(17)}-C_{(20)}$	120.2(2)	$C_{(19)}-C_{(18)}-C_{(17)}$	122.1(2)
$C_{(18)}-C_{(19)}-C_{(14)}$	118.7(3)		

toluenesulfonyl substituent is likely additionally stabilized by a weak intramolecular hydrogen bond ($C_{(5)}$–$H_{(5)}\cdots O_{(4)}$, H···O 2.38 Å. C–H···O 123°) and results in a shortened intramolecular contact $H_{(5)}\cdots C_{(15)}$ 2.78 Å (sum of van der Waal radii 2.87 Å [6]). A marked repulsion between the rather bulky substituents at atoms $C_{(7)}$ and $C_{(8)}$ (shortened intramolecular contact $O_{(5)}\cdots C_{(10)}$ 2.55 Å (3.00 Å)) results in an increase in the valence angle $C_{(7)}$–$C_{(8)}$–$C_{(10)}$ to 128.0(2)° and twists the ester substituent practically perpendicular to the quinolone plane (torsional angle $C_{(7)}$–$C_{(8)}$–$C_{(10)}$–$O_{(2)}$ -85.6(3)). The ethyl group has an *ap*-orientation relative to the $C_{(8)}$–$C_{(10)}$ bond (torsional angle $C_{(11)}$–$O_{(3)}$–$C_{(10)}$–$C_{(8)}$ 177.1(2)°) and the $C_{(11)}$–$C_{(12)}$ bond an *ap*-conformation relative to the $C_{(10)}$–$O_{(3)}$ bond (torsional angle $C_{(10)}$–$O_{(3)}$–$C_{(11)}$–$C_{(12)}$ -169.7(2)°).

A marked repulsion between the N-methyl substituent, the neighboring carbonyl group, and the benzene ring atoms of the quinolone (shortened intramolecular contacts $H_{(2)}\cdots C_{(13)}$ 2.47 (2.87), $H_{(2)}\cdots H_{(13c)}$ 2.15 (2.34), $H_{(13b)}\cdots O_{(1}$ 2.28 (2.46), and $H_{(13c)}\cdots C_{(2)}$ 2.63 Å (2.87 Å)) leads to some deviation of the N-methyl group from the bicyclic fragment plane (torsional angle $C_{(13)}$–$N_{(1)}$–$C_{(1)}$–$C_{(2)}$ -6.0(3)°) with preservation of the trigonal planar configuration of the nitrogen atom.

Hence the investigation we have carried out has broadened the boundaries of the practical use of *p*-toluenesulfonylhydrazide and adds a tosylating ability to its already known properties. Even though the mechanism of the unusual reaction we report remains unclear its theoretical and perhaps wider practical use is not in doubt.

EXPERIMENTAL

The ^1H NMR spectrum of the tosylquinoline **2** was recorded on a Varian Mercury VX-200 instrument (200 MHz) using DMSO-d_6 solvent and TMS as internal standard. Mass spectra were registered on a Varian 1200L spectrometer in full scan mode in the range 35-700 *m/z* with EI ionization of 70 eV and with direct sample introduction. Commercial p-toluenesulfonylhydrazide and anhydrous acetonitrile were used from the Aldrich company and anhydrous THF from Riedel-de Haën.

Ethyl 1-Methyl-2-oxo-4-tosyl-1,2-dihydroquinoline-3-carboxylate (3). A solution of the 4-chloro-substituted ester **1** (2.65 g, 0.01 mol), *p*-toluenesulfonylhydrazide (1.86 g, 0.01 mol, triethylamine (1.4 ml, 0.01 mol), and anhydrous acetonitrile (or THF) (30 ml) was refluxed for 48 h. The reaction mixture was cooled and diluted with cold water. The precipitate was filtered off, washed with water, and dried. Yield 2.66 g (69%); mp 249-251°C (DMF). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.35 (1H, d, $J = 8.3$, H-5); 7.99 (2H, d, $J = 8.4$, H-2',6'); 7.66 (2H, m, H-7,8); 7.47 (2H, d, $J = 8.4$, H-3',5'); 7.32 (1H, td, $J = 7.6$, 1.6, H-6); 4.38 (2H, q, $J = 7.0$, OCH_2); 3.65 (3H, s, NCH_3); 2.35 (3H, s, CH_3); 1.33 (3H, t, $J = 7.0$. $OCH_2C\underline{H}_3$). Mass spectrum, *m/z* (I_{rel}, %): 385 $[M]^+$ (92), 340 $[M\text{-}OEt]^+$ (91), 312 $[M\text{-}OEt\text{-}CO]^+$ (32), 292 (24), 276 (51), 262 (55), 248 (55), 234 (100). Found, %: C 62.32; H 4.97; N 3.63. $C_{20}H_{19}NO_5S$. Calculated, %: C 62.24; H 4.86; N 3.69.

X-ray Structural Investigation. Crystals of the tosylquinoline **2** are monoclinic (DMF), at 20°C: a = 8.91(2), b = 13.54(4), c = 15.36(2) Å. β = 101.5(2)°, V = 1804(8) Å^3, M_r = 385.42, Z = 4, space group $P2_1/c$, d_{calc} = 1.419 g/cm^3, μ(MoKα) = 0.212 mm^{-1}, $F(000)$ = 808. The parameters of the unit cell and intensities of 12554 reflections (5099 independent, R_{int} = 0.084) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω scanning to $2\theta_{max}$ = 60°).

The structure was solved by a direct method using the SHELXTL program package [7]. The positions of the hydrogen atoms were revealed using electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ (n = 1.5 for a methyl group and n = 1.2 for remaining hydrogen atoms). The structure was refined in F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.114 for 5099 reflections (R_1 = 0.051 for 2007 reflections with $F > 4\sigma(F)$, S = 0.849). The full crystallographic information has been placed in the Cambridge structural database (reference No. CCDC 650599). Interatomic distances and valence angles are given in Tables 1 and 2.

REFERENCES

1. I. V. Ukrainets, I. A. Tugaibei, N. L. Bereznyakova, V. N. Kravchenko, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 718 (2008). [*Chem. Heterocycl. Comp.*, **44**, 565 (2008)].
2. D. H. R. Barton and W. D. Ollis, *Comprehensive Organic Chemistry* [Russian translation], Vol. 2, Khimiya, Moscow (1982), p. 716.
3. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis* [Russian translation], Vol. 3, Mir, Moscow (1970), p. 357.
4. G. Berecz, J. Reiter, and J. Csaszar, *J. Heterocycl. Chem.*, **36**, 1199 (1999).
5. I. V. Ukrainets, V. V. Kravtsova, A. A. Tkach, and G. Sim, *Khim. Geterotsikl. Soedin.*, 233 (2008). [*Chem. Heterocycl. Comp.*, **44**, 173 (2008)].
6. Yu. V. Zefirov, *Kristallografiya,*, **42**, 936 (1997).
7. G. M. Sheldrick, *SHELXTL PLUS. PC Version. A System of Computer Programs for the Determination of Crystal Structure from X-ray Diffraction Data,*, Rev. 5.1 (1998).