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SYNTHESIS AND SINGLE CRYSTAL X-RAY STRUCTURE OF 2,6-DI-*TERT*-BUTYL-4-(3-(4-CHLOROPHENYL)-4-METHYL-4,5-DIHYDROISOXAZOL-5-YL)PHENOL 1,4-DIOXANE HEMISOLVATE

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The title compound (2,6-di-*tert*-butyl-4-(3-(4-chlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl)phenol is synthesized and studied by the single crystal X-ray diffraction method. The structure of the product was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. The crystal structure of 1,4-dioxane hemisolvate of the product is solved in the monoclinic space group $P2_1/c$ with $a = 17.713(6)$, $b = 9.529(3)$, $c = 13.972(4)$ Å, $\beta = 94.09(4)°$, $V = 2352.3(13)$ Å^3, $Z = 4$, $T = 120(2)$ K.

K e y w o r d s: single crystal X-ray structure, quinone methide, isoxazoline, oxime, DDQ.

Isoxazoline moieties represent a class of unique pharmacophores, which are observed in many therapeutic agents and are versatile intermediates for the synthesis of complex natural products and are found in GPII/IIIa inhibitors [1]. They are also known to exhibit interesting biological activities in the agricultural field [2] and possess medicinal properties, including anticancer, antibiotic [3] or antiviral and anti-HIV activities [4]. Quinone methides are interesting compounds and play an important role in biosynthesis and in the biological activity of many quinonoid antitumor compounds [5]. However, synthetic methodologies to produce such quinone methides and their applications are limited because *in situ* generated *o*-quinone methides act as heterodynes in Diels-Alder reactions [6]. *p*-Quinone methides have been proposed as intermediates in enzyme inhibition [7], insect cuticle chemistry [8], wood lignin chemistry [9], and release mechanisms in photographic processes [10].

EXPERIMENTAL

Typical experimental procedure. 3-[3,5-Di-*tert*-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one oxime **5**: to the mixture of hydroxylamine hydrochloride (1 g) and sodium acetate trihydrate (2 g) in water (1 ml) a solution of 3-[3,5-di-*tert*-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one (0.5 g, 1.3 mmol) in EtOH (5 ml) was added, and the mixture refluxed for 1 h. After the removal of EtOH, water (5 ml) was added and stirred in an ice bath until oxime crystallization was complete. The precipitate was filtered and recrystallized from EtOH (96 %) to give the product as white needles (0.4 g, 81 %), m.p. 97—98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (d, 3H in one isomer, $J = 7.2$ Hz), 1.33 (d, 3H in other isomer, $J = 6.9$ Hz), 1.39 (s, 18H in one isomer), 1.42 (s, 18H in other isomer), 2.50—3.00 (m, 2H in both isomers), 3.39—3.62 (m, 1H in both isomers), 5.06

(s, 1H, D_2O exchangeable), 5.10 (s, 1H, D_2O exchangeable), 6.90 (s, 2H in one isomer), 6.92 (s, 2H in other isomer), 7.06 (d, 2H in one isomer, J = 8.1 Hz), 7.12 (d, 2H in other isomer, J = 7.8 Hz), 7.23 (d, 2H in one isomer, J = 8.1 Hz), 7.35 (d, 2H in other isomer, J = 7.8 Hz), 8.21 (bs, 1H in one isomer, D_2O exchangeable), 8.37 (bs, 1H in other isomer, D_2O exchangeable). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 17.03, 18.30. 30.29, 30.34, 34.19, 34.24, 36.80, 39.19, 40.81, 41.84, 47.86, 125.37, 125.58, 127.24, 127.43, 127.55, 128.05, 128.16, 128.32, 128.80, 129.11, 130.24, 130.58, 134.43, 135.13, 135.68, 152.07, 161.66, 162.95. IR (KBr, cm^{-1}): 3627, 3228, 3005, 2965, 2915, 2874, 1593, 1488, 1432, 1392, 1232, 1148, 1º94, 996, 933, 832, 821, 769.

2,6-Di-*tert*-butyl-4-(3-(4-chlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl)phenol **7**: to a solution of 3-[3,5-di-*tert*-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one oxime **5** (0.401 g, 1 mmol) in dry DCM (10 ml), DDQ (0.25 g, 1.1 mmol) was added and the mixture stirred at room temperature for 5 min. The contents were filtered using Celite as filter aid, then the filtrate was washed with water (3×20 ml) and dried over Na_2SO_4. The removal of the solvent gave a yellow solid that was recrystallized from hexane to give the title compound as white needles (0.24 g, 60 %), m.p. 201—202 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43 (d, 3H, 7.2 Hz), 1.45 (s, 18H), 3.70 (quin, 1H, J = = 6.9 Hz), 5.21 (d, 1H, J = 6.6 Hz), 5.26 (s, 1H, D_2O exchangeable), 7.15 (s, 2H), 7.40 (d, 2H, J = = 8.4 Hz), 7.64 (d, 2H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 17.94, 30.19, 34.38, 50.02, 91.31, 122.63, 127.68, 128.24, 129.06, 130.78, 135.74, 136.25, 153.95, 159.51. IR (KBr, cm^{-1}): 3632, 3010, 2968, 2915, 2871, 1587, 1494, 1456, 1436, 1401, 1367, 1213, 1160, 1096, 918, 899, 878, 843, 831, 650.

Single crystals of **7** were prepared from a mixture of *n*-hexane/dioxane (10:1) at 46 °C during two weeks using the branch tube method [11]. The colorless crystals were filtered off, washed with a cold mixture of *n*-hexane/dioxane (20:1, 10 ml), and dried in vacuum over P_4O_{10}.

X-Ray crystal structure determination of 7·0.5($C_4H_8O_2$). The crystallographic measurement was performed on a κ-geometry automated four-circle Xcalibur PX diffractometer with graphite-monochromatized MoK_α radiation. The data for the crystal were collected at 120(2) K using the *Oxford-Cryosystems* cooler. A summary of conditions for the data collection and the structure refinement parameters are given in Table 1. The data were corrected for Lorentz and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the Xcalibur PX software (Oxford Diffractiod Ltd.): CrysAlis CCD and CrysAlis RED respectively [12]. The structure was solved by direct methods with the SHELXS-97 program [13] and refined by a full-matrix least-squares technique with SHELXL-97 [13] and anisotropic thermal parameters for non-H atoms. All H atoms were found in difference Fourier maps and refined isotropically. In the final refinement cycles, the H atoms were treated as riding atoms in geometrically optimized positions, with C—H = 0.95—1.00 Å and O—H = 0.84 Å, and with U_{iso}(H) = 1.2U_{eq}(C) for CH and CH_2, or 1.5U_{eq}(C,O) for CH_3 and OH. Figures were made with the XP program [14]. Puckering parameters were calculated using the PLATON program [15]. CCDC-827546 contains the supplementary crystallographic data for **7·0.5($C_4H_8O_2$)**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

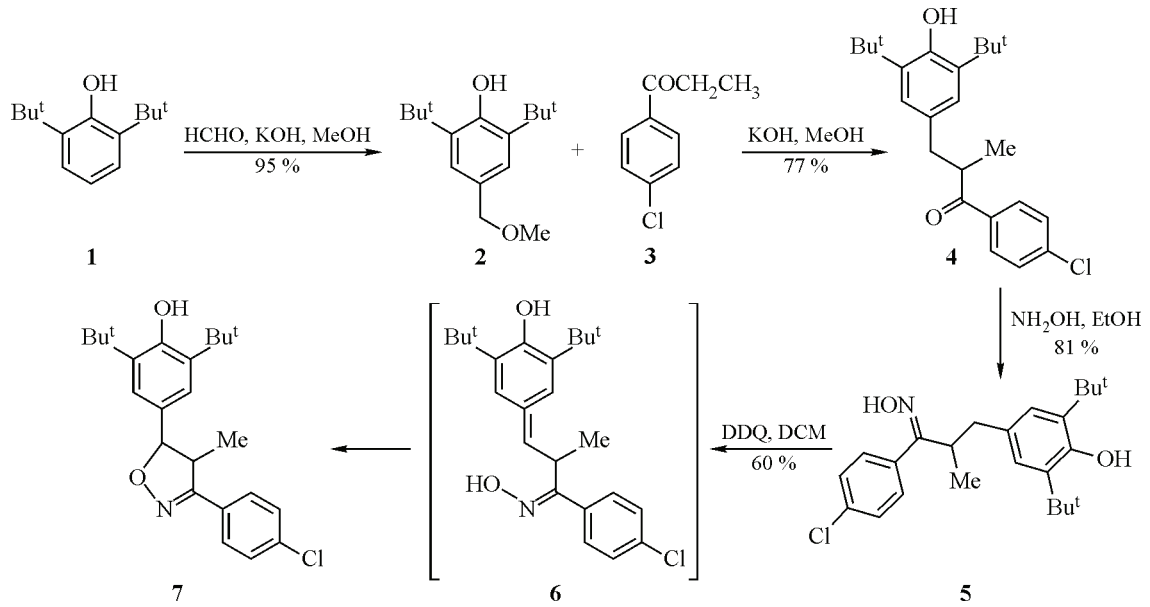
The conventional method of the preparation of isoxazolines involves a 1,3-dipolare cycloaddition of nitrile oxide to alkenes [16]. Herein, we report the random synthesis of isoxazoline derivative **7** from 3-[3,5-di-*tert*-butyl-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one oxime **5** by novel C—O bond formation via *in situ* generated *p*-quinone methide (Scheme 1). 2,6-Disubstitution imparts increased stability to quinone methide [17], so the subsequent cyclization would require an internal nucleophile (cyclization terminator). To the best of our knowledge, there are no reports in the literature on the formation of isoxazoline derivative **7**. Treatment of 3-[3,5-di-*tert*-butyl-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one oxime **5** with DDQ. 2,6-di-*tert*-butyl-4-methoxymethylphenol **2** is required to generate quinone methide, which allows a subsequent nucleophilic attack to give 3-[3,5-di-*tert*-butyl-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one **4** (Scheme 1). 2,6-Di-*tert*-butyl-4-methoxymethylphenol **2** was prepared from the KOH catalyzed condensa-

Table 1

Crystal data and structure refinement details for **7·0.5($C_4H_8O_2$)**

Crystalized from	*n*-hexane/$CHCl_3$	Scan type	ω and φ
Empirical formula	$C_{24}H_{30}ClNO_2 \cdot 0.5(C_4H_8O_2)$	Radiation type, λ, Å	MoK_α, 0.71073
M_r	443.99	Index ranges	$-27 \le h \le 28$
Crystal color, habit	Colorless, parallelepiped		$-13 \le k \le 12$
Crystal dimensions, mm	0.22×0.17×0.09		$-22 \le l \le 22$
Temperature, K	120(2)	Measured reflections	25074
Crystal system	Monoclinic	Independent reflections	9409
Space group	$P2_1/c$	Reflections with $I > 2\sigma(I)$	5036
Z	4	R_{int}	0.051
θ range, deg.	4.18—35.00	Completeness to θ = 25.0°	0.98
Unit cell parameters:		Refinement on	F^2
a, Å	17.713(6)	Data, restraints, parameters	9409, 0, 288
b, Å	9.529(3)	R ($F_0^2 > 2\sigma(F_0^2)$)	$R1$ = 0.046
c, Å	13.972(4)		$wR2$ = 0.072
β, deg.	94.09(4)	R (all data)	$R1$ = 0.106
V, Å^3	2352.3(13)		$wR2$ = 0.077
d_x (calc.), g·cm^{-3}	1.254	Goodness-of-fit = S	1.001
μ, mm^{-1}	0.19	Weighting parameter a/b	0.0190/0.0
F(000), e	952	Δρ(max; min), e·Å^{-3}	0.38; –0.33

$R1 = \sum||F_0| - |F_c||/\sum|F_0|$; $wR2 = \sqrt{\sum[w(F_0^2 - F_c^2)^2]/\sum[w(F_0^2)^2]}$; weighting scheme: $w = 1/[\sigma^2(F_0^2) + (aP)^2 + b]$, where $P = (F_0^2 + 2F_c^2)/3$.



Scheme 1. Synthesis of 2,6-di-*tert*-butyl-4-(3-(4-chlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl)phenol **7**

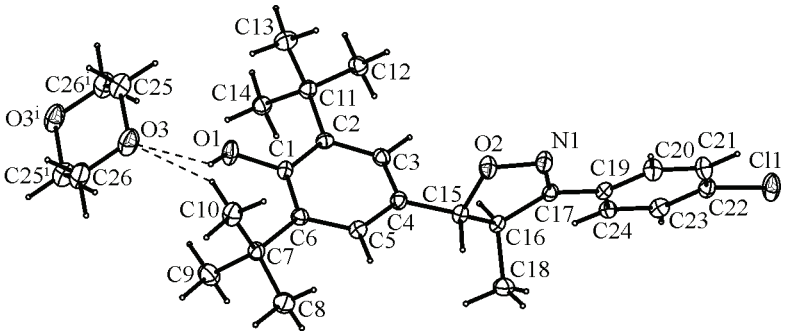


Fig. 1. Molecular structure of compound **7** along with 1,4-dioxane co-crystallizing in a **7·0.5($C_4H_8O_2$)** crystal, showing the X-ray atom numbering scheme and intermolecular O/C—H···O hydrogen bonds (dashed lines). Displacement ellipsoids represent the 50 % probability level. Symmetry code: (*i*) –*x*, –*y*+1, –*z*+1

tion of formaldehyde with 2,6-di-*tert*-butylphenol **1** in methanol [18]. 2,6-Di-*tert*-butyl-4-methoxymethylphenol **2** was treated with KOH followed by the addition of *p*-chloropropiophenone **3** to afford 3-[3,5-di-*tert*-butyl-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one **4** in good yield [19]. Ketone **4** was condensed with hydroxylamine [20] in EtOH to give 3-[3,5-di-*tert*-butyl-4-hydroxyphenyl]-1-(4-chlorophenyl)-2-methyl-propan-1-one oxime **5**, which was obtained as two *Z* and *E* isomers in a 60:40 ratio. The formation of oxime **5** in two different ratios was confirmed with its ^{1}H NMR spectrum by the appearance of two signals for each proton of oxime **5**. Finally, oxime **5** was treated with DDQ in dry DCM and stirred at room temperature affording 2,6-di-*tert*-butyl-4-(3-(4-chlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl)phenol **7** as a white solid in 60 % yield (Scheme 1) [20]. The cyclization was indicated by the absence of the OH proton of oximes as broad singlets at δ 8.37 and 8.21 in the ^{1}H NMR spectrum. Product **7** was characterized by ^{1}H and ^{13}C NMR and IR analysis. The structure of substituted isoxazoline **7** was elucidated the by X-ray single crystal determination (Fig. 1).

T a b l e 2

Selected interatomic distances (Å), *valence* (deg.) *and torsion angles* (deg.) *of* **7·0.5($C_4H_8O_2$)**

Bond lengths			
Cl(1)—C(22)	1.7487(12)	N(1)—C(17)	1.2853(14)
O(1)—C(1)	1.3803(13)	C(4)—C(15)	1.5093(15)
O(2)—N(1)	1.4170(12)	C(16)—C(17)	1.5109(15)
O(2)—C(15)	1.4648(14)	C(17)—C(19)	1.4798(15)
Valence angles			
N(1)—O(2)—C(15)	108.53(8)	C(4)—C(15)—C(16)	118.22(9)
C(17)—N(1)—O(2)	109.16(9)	C(17)—C(16)—C(18)	116.70(9)
O(2)—C(15)—C(4)	108.90(9)	C(17)—C(16)—C(15)	99.80(9)
O(2)—C(15)—C(16)	104.73(8)	C(18)—C(16)—C(15)	111.24(9)
Torsion angles			
C(15)—O(2)—N(1)—C(17)	11.75(11)	C(4)—C(15)—C(16)—C(18)	–97.74(12)
C(1)—C(6)—C(7)—C(8)	174.60(11)	O(2)—N(1)—C(17)—C(19)	176.59(9)
C(1)—C(2)—C(11)—C(12)	–176.62(10)	O(2)—N(1)—C(17)—C(16)	0.39(12)
N(1)—O(2)—C(15)—C(4)	–145.80(9)	C(18)—C(16)—C(17)—N(1)	–131.29(11)
N(1)—O(2)—C(15)—C(16)	–18.44(10)	C(15)—C(16)—C(17)—N(1)	–11.39(12)
C(3)—C(4)—C(15)—O(2)	68.01(13)	C(18)—C(16)—C(17)—C(19)	52.84(15)
C(3)—C(4)—C(15)—C(16)	–51.25(15)	C(15)—C(16)—C(17)—C(19)	172.73(10)
O(2)—C(15)—C(16)—C(17)	17.04(10)	N(1)—C(17)—C(19)—C(20)	16.51(16)
C(4)—C(15)—C(16)—C(17)	138.46(10)	C(16)—C(17)—C(19)—C(20)	–167.79(10)
O(2)—C(15)—C(16)—C(18)	140.84(9)		

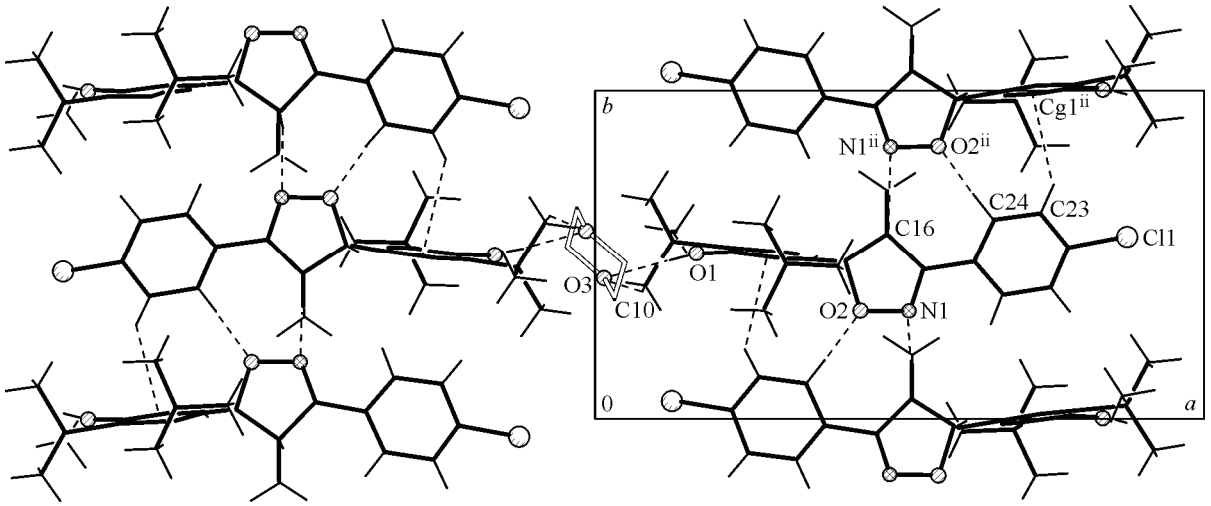


Fig. 2. Arrangement of the ribbons of **7** (running down the *b* axis) and 1,4-dioxane molecules in the crystal lattice of **7·0.5($C_4H_8O_2$)**. O/C—H···O/N/π contacts are shown with dashed lines. Symmetry codes are given in Table 3

Crystal structure of 7·0.5($C_4H_8O_2$). The centrosymmetric space group shows that the crystal contains racemic compound **7**. The *RR* isomer is shown in Fig. 1. Compound **7** crystallizes with 1,4-dioxane molecules (1/0.5) lying on the inversion centre.

In the molecule of compound **7**, the central 4,5-dihydroisoxazole ring is puckered in an *envelope* (*E*) manner on the C(15) atom, as confirmed by the pseudorotation parameters [21] $P = 234.4(2)°$ and $\tau_m = 18.9(1)°$ (reference C(17)—C(16) bond), as well as by the Cremer and Pople [22] puckering parameters $q_2 = 0.181(1)$ Å and $\varphi_2 = 142.6(4)°$. The chlorophenyl ring is in the equatorial position, while the remaining substituents (at C(15) and C(16) atoms) are in bisectional positions (being in relative *trans* configuration). The chlorophenyl ring is almost coplanar with the 4,5-dihydroisoxazole reference plane (defined by O(2), N(1), C(17), C(16) atoms), as reflected in the value of the N(1)—C(17)—C(19)—C(20) torsion angle (Table 2). In contrast, the ring of another aromatic substituent is almost perpendicular to the dihydroisoxazole reference plane, as indicated by an angle of 87.6(1)° between the two planes: C(1) ~ C(6) and O(2) ~ C(16).

The crystal packing in **7·0.5($C_4H_8O_2$)** is determined mainly by C—H···O and C—H···N interactions resulting in the arrangement of the molecules of **7** into ribbons running down the *b* axis, as shown in Fig. 2 (Table 3). Additional stabilization of the ribbon is provided by weak C—H···π con-

T a b l e 3

Geometry of Proposed Hydrogen Bonds and Close Contacts for **7·0.5($C_4H_8O_2$)**

D—H···A	D—H, Å	H···A, Å	D···A, Å	D—H···A, deg.	Offset, Å
O(1)—H(1)···O(3)	0.84	2.16	2.800(2)	133	—
C(10)—H(10C)···O(3)	0.98	2.43	3.309(2)	149	—
C(13)—H(13B)···O(1)	0.98	2.39	3.014(2)	121	—
C(14)—H(14B)···O(1)	0.98	2.25	2.905(2)	123	—
C(16)—H(16)···N(1)^{ii}	1.00	2.58	3.360(2)	135	—
C(24)—H(24)···O(2)^{ii}	0.95	2.41	3.327(2)	162	—
C(23)—H(23)···*Cg*(1)^{ii}	0.95	2.81	3.570(2)	137	0.41

Symmetry codes: (*ii*) –*x*+1, *y*+1/2, –*z*+1/2; *Cg*(1) is the centroid of the C(1) ~ C(6) ring.

tacts formed between the aromatic rings. The adjacent ribbons interact with each other mainly through 1,4-dioxane molecules acting as the acceptors of two O—H···O and two C—H···O bonds from two different ribbons each (Fig. 2).

In conclusion, we have demonstrated a novel quinone methide mediated synthesis of new fully substitued isoxazoline **7** from treatment of substituted propan-1-one oxime **5** with DDQ in DCM. The simple procedure at room temperature of this chemical process provides a very straightforward route to construct various fully substituted isoxazolines.

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