TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2014) 38: 121 – 126

doi:10.3906/kim-1306-58

On the peculiar reactivity of a C,N-annelated isoindole core

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Received: 24.06.2013 • **Accepted:** 11.07.2013 • **Published Online:** 16.12.2013 • **Printed:** 20.01.2014

Abstract: C-, N-, and/or O-methylation products were generated from 11*H*-isoindolo[2,1-a]quinazoline-5-one upon treatment with NaH followed by iodomethane under air, and possible recrystallization from methanol. Two products were fully characterized by NMR and X-ray diffraction analysis. In accordance with the HSAB principle, this soft methylating agent (MeI) leads mainly to the C,C-dimethylated product 11,11-dimethyl-11*H*-isoindolo[2,1-a]quinazoline-5-one, which was previously not observed, beside the N-methylated product, in a procedure using methyl tosylate as a hard methylating agent of the same substrate in the initial absence of a base. A mechanism is finally proposed for the formation of methyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)benzoate as an oxidation side product.

Key words: Isoindoles, methylation processes, oxidative ring opening, quinazolines

1. Introduction

The chemistry of isoindoles remains a blooming topic from both the standpoints of fundamental organic reactivity (aromaticity-driven processes)[1] and target-oriented synthesis of biologically active compounds (heterocyclic drug design). This is particularly prevalent in the annelated isoindole series, where derivatives of 11*H*-isoindolo[2,1-a]quinazoline-5-one (**1**) have been shown to exhibit various activities in vitro.[2] Examples of chemical variations of **1** were based on its treatment with a hard electrophile to give a quaternary ammonium salt, followed by addition of an alkali metal base leading to a locked N-methylated isoindole form.[3,4] The direct transformation of **1** into the isoindole form is hereafter addressed.

2. Results and discussion

Treatment of **1** with sodium hydride and then with iodomethane afforded 11,11-dimethyl-11*H*-isoindolo[2,1-a]quinazoline-5-one (**2**) as the major product in 43% yield (Scheme 1).

The structure of **2** was ascertained by NMR and IR spectroscopic analyses and mass spectrometry, and confirmed by X-ray diffraction analysis of a single crystal deposited from diethylether (Figure 1). Therefore, whereas methylation of various derivatives of **1** under hard (in the initial HSAB sense)[5] and harsh conditions (in the initial absence of a base with methyl tosylate, at 125–130 °C) afforded the N-methylated isoindole products, e.g., **4** from **1** itself,[3,4] the use of softer and milder conditions (in the presence of a base with MeI at room temperature) was found to afford the C-dimethylated iminoisoindole derivative **2** as the major product.

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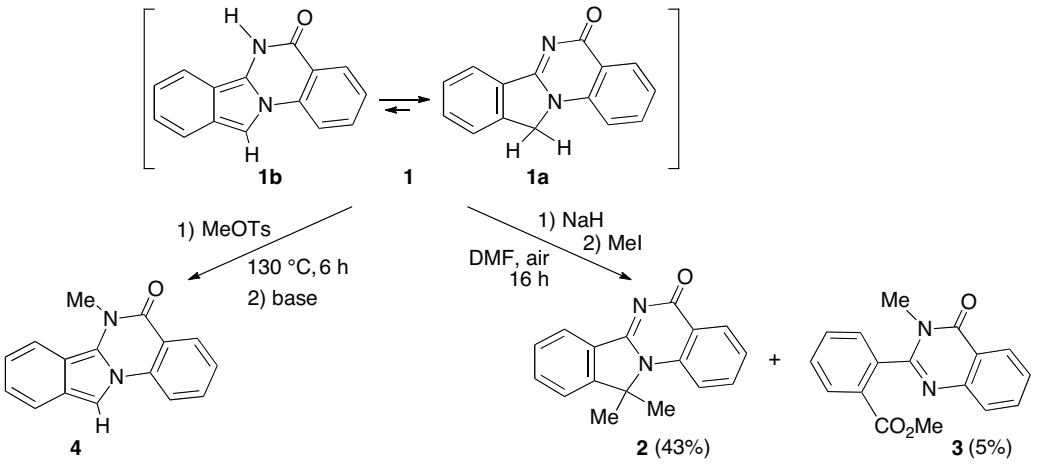


Scheme 1. Reaction of the C,N-annelated isoindole **1** with hard (*left*) and soft (*right*) methylating reagents.

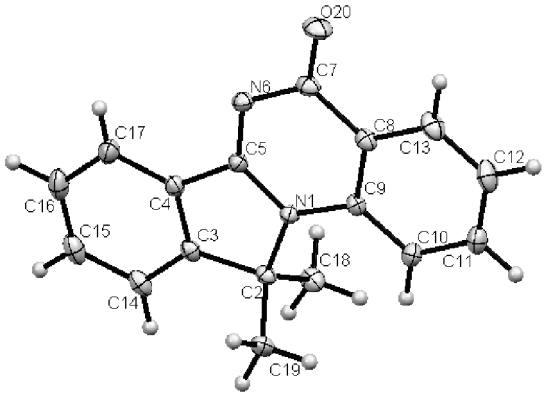


Figure 1. ORTEP view of the X-ray crystal structure of C,C-dimethylated product **2** (Scheme 1). $R = 4.2\%$. Selected bond lengths in Å: N1-C2: 1.5022(10), N1-C5: 1.3624(10), C2-C3: 1.5136(12), C4-C5: 1.4595(11), C5-N6: 1.3099(11), N6-C7: 1.3821(12), C7-O20: 1.2341(10).

Minor amounts of a side-product were isolated (in 5% yield) from the reaction mixture and assigned to the ester structure of methyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)benzoate **3** (Scheme 1), which was confirmed by X-ray diffraction analysis of a single crystal deposited from methanol (Figure 2).

The intense IR stretching vibration bands of the nonequivalent ester and amide carbonyl groups of **3** were observed at 1722 cm^{-1} and 1667 cm^{-1}, respectively. The presence of 2 different methyl groups was confirmed by ^{1}H (δ_{NCH3} = 3.33 ppm, δ_{OCH3} = 3.78 ppm) and ^{13}C (δ_{NCH3} = 32.8 ppm, δ_{OCH3} = 52.6 ppm) NMR spectroscopy. The amido-ester **3** formally results from concomitant oxidative opening of a ring of the pyrrole ring of **1** and N-,O-dimethylation.

In a previous report on the formation of such amido-esters, the proposed mechanism was based on oxidation of **1** by $SOCl_2$, followed by the formation of amino-hemi-ortho esters generated from aliphatic alcohols, and subsequent ring-opening to the corresponding esters.[6] In the present procedure, no oxidative auxiliary is added, except the oxygen of air. Although autoxidation by oxygen-derived hydroperoxide radicals cannot be ruled out, an alternative mechanism, based on previous reports on oxidative opening of a pyrrole ring (also annelated in an isoindole core),[7–9] is proposed (Scheme 2).

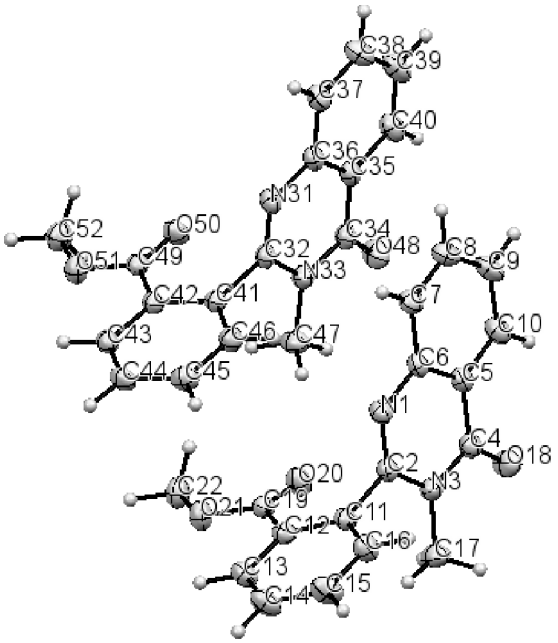
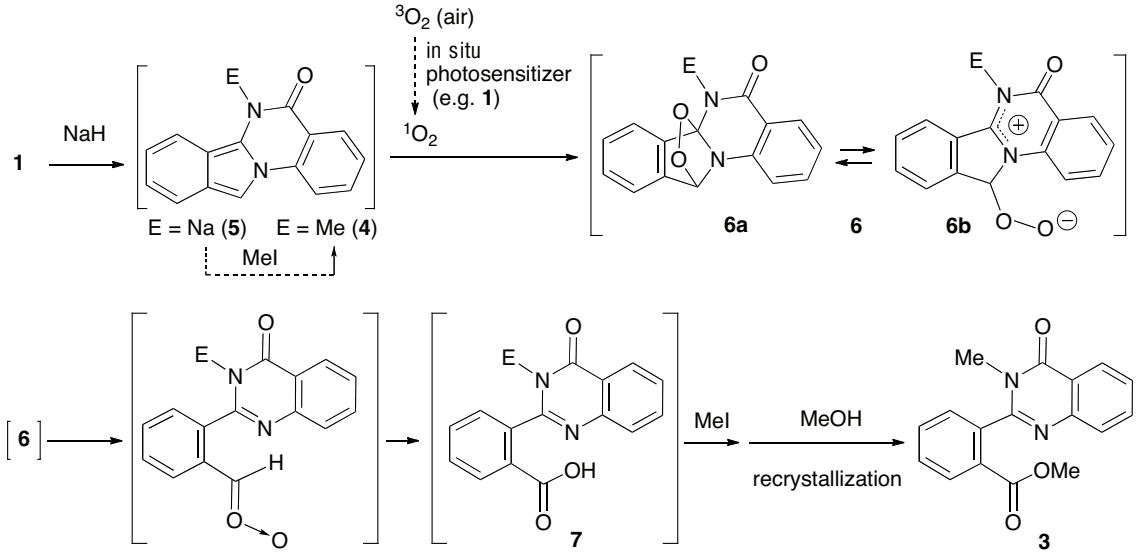


Figure 2. ORTEP view of the X-ray crystal structure of the amidoester **3**. R = 3.4%. Selected bond lengths in Å: N1-C2: 1.2943(11), N31-C32: 1.2901(11), C2-C11: 1.5067(11), C32-C41: 1.5050(11), C2-N3: 1.3750(11), C32-N33: 1.3801(11), N3-C4: 1.3979(11), N33-C34: 1.3954(11), C4-O18: 1.2230(11), C34-O48: 1.2257(11).



Scheme 2. Proposed mechanism for the oxidative conversion of **1** into the amidoester **3**.

After deprotonation of **1** with NaH, the anion of the sodium salt **5** might undergo either primary N-methylation to **4** (a rather slow process),[4] or oxidation by the aerobic atmosphere. Thus **4**, or more specifically **5**, would react with singlet oxygen that would be generated by some photosensitizer in situ, such as **1** or one of its heteroaromatic derivatives.[10] The process would thus consist of an allowed asynchronous [4 + 2] cycloaddition process leading to an endo-peroxide structure of type **6a**,[6–8] which would instantly rearrange into the zwitterionic peroxide **6b** (possibly even directly, without the intermediacy of any cyclo-adduct **6a** of

local minimum energy). The latter would then spontaneously evolve into a carboxylic acid of type **7** via a carbonyl oxide (and/or a putative dioxirane isomer).[11] The latter would finally react with MeI and MeOH (during recrystallization) to give **3** (not observed by TLC in the crude material).

3. Conclusion

The disclosed results and interpretations provide a further rationale in the scope of the versatile reactivity of isoindole cores, in particular of C,N-annelated representatives, and open new horizons for the design of either new structures or new preparative schemes in the field of hetero-aromatic chemistry.

4. Experimental

4.1. General

The following analytical instruments were used. ^{1}H and ^{13}C NMR: Bruker DPX 300, Avance 400 or Avance 500 spectrometers. Mass spectrometry: Quadrupolar Nermag R10-10H spectrometer. NMR chemical shifts (δ) are in parts per million, with positive values to high frequency relative to the tetramethylsilane reference; coupling constants (J) are in hertz. IR: 0.1 mm CaF_2 cell, PerkinElmer GX FTIR. 11*H*-isoindolo [2,1-a]quinazoline-5-one was prepared by a previously described procedure.[12,13]

4.2. Crystallographic data and structural refinement parameters for compounds 2 and 3 (Table).

Intensity data were collected at low temperature on an Agilent Gemini diffractometer or on a Bruker Apex2 diffractometer. Structures were solved by direct methods using SIR92[14] or SUPERFLIP,[15] and refined by full-matrix least-squares procedures using the programs of CRYSTALS.[16] Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[17] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were refined using a riding model. Absorption corrections were introduced using the program MULTISCAN.[18]

4.3. Synthesis procedure

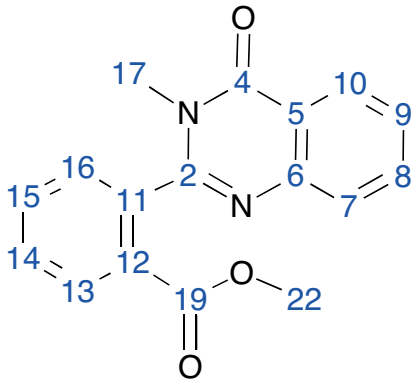
A solution of 11*H*-isoindolo[2,1-a]quinazoline-5-one (0.5 g, 2.1 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (100 mg, 2.5 mmol) in DMF (5 mL). The mixture was stirred for 30 min at 0°-before dropwise addition of iodomethane (0.15 mL, 2.35 mmol). Stirring was continued for another 16 h at room temperature; then chloroform (10 mL) and water (20 mL) were added, and the organic layer was collected, dried, and concentrated under reduced pressure. The crude residue was recrystallized from Et_2O to give **2** as a light yellow solid (0.24 g, 43%). The filtrate was then concentrated under reduced pressure and the residue was stirred in water for 16 h at room temperature. The precipitate was then recovered and recrystallized from methanol, to give **3** as a white solid (35 mg, 5%).

11,11-dimethyl-11*H*-isoindolo[2,1-a]quinazoline-5-one (**2**). mp 219–220°. IR: ν (cm^{-1}) 1649 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$)δ 1.99 (s, 6 H, 2 CH_3), 7.84–7.45 (m, 6 H, arom. C*H*), 8.27 (d, J = 7.6 Hz, 1 H, *H*7), 8.54 (d, J = 8.0 Hz, 1 H, *H*4). ^{13}C NMR (101 MHz, $CDCl_3$)δ 26.2 (–H_3), 69.6 (*C*Me_2), 115.0, 120.6, 124.7, 125.4, 129.3, 130.1, 133.3, 133.4 (arom *C*H), 120.2, 130.2, 138.1, 151.6 (quaternary arom.*C*), 159.7 (*C*=N), 170.5 (*C*=O). MS (DCI/NH_3): m/z 263.1 ($[MH]^+$), 280.1 ($[MNH_4]^+$). HRMS (DCI/CH_4): m/z calcd for $C_{17}H_{15}N_2O$ $[MH]^+$: 263.1184; found: 263.1190.

Table. Crystallographic data from X-ray diffraction analysis of **2** and **3**.

Compound nos.	**3**	**2**
Chemical formula	$C_{17}H_{14}N_2O_3$	$C_{17}H_{14}N_2O$
M (g mol^{-1})	294.31	262.31
Crystal system	Triclinic	Othorhombic
Space group	P-1	P_{bca}
a (Å)	10.4664(3)	14.2706(7)
b (Å)	11.1901(3)	12.7347(6)
c (Å)	12.5314(4)	14.7793(7)
α (°)	83.001(2)	90
β (°)	75.099(3)	90
γ (°)	88.381(2)	90
V(Å^3)	1407.75(8)	2685.9(2)
Z	4	8
ρ_{calcd}	1.389	1.297
μ (mm^{-1})	0.794	0.082
Θ_{max} (°)	71.71	33.30
Crystal size (mm)	0.20 × 0.20 × 0.25	0.20 × 0.20 × 0.25
λ (Å)	1.54180 (CuK$_\alpha$)	0.71073 (MoK$_\alpha$)
Scan mode	Φ and Ω scans	Φ and Ω scans
T (K)	180	100
Refl. measured	27,384	66,121
Refl. unique	5458	4989
R_{int}	0.014	0.031
Refl. with I > 3σ(I)	5182	3811
Nb. parameters	397	181
R	0.0345	0.0418
R_w	0.0472	0.0470
Residual electron density (ē Å^{-3})	–0.17/0.23	–0.18/0.51

Methyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)benzoate (**3**: see Scheme 3). mp 162–163°. IR: ν (cm^{-1}) 1722 (O=C(OMe)), 1667 (O=C(NH)). ^{1}H NMR (300 MHz, $CDCl_3$)δ 3.33 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 7.43–7.78 (m, 6 H, arom. CH), 8.20 (d, J = 7.7 Hz, 1 H, C$_{10}H$), 8.39 (d,



Scheme 3. Numbering of the carbon atoms for NMR assignment of the amidoester **3**.

J = 7.1 Hz, 1 H, $C_{13}H$). ^{13}C NMR (101 MHz, $CDCl_3$)δ 32.8 (NCH_3), 52.6 (OCH_3), 126.9 (2 C), 127.3, 129.0, 129.9, 131.0, 133.3, 134.1 (arom. CH), 120.8, 128.4, 136.7 (quaternary arom. C), 147.5 (C_6), 156.2 (C_2), 162.2, 165.8 (2 C=O). MS (DCI/NH_3): m/z 295.1 ($[MH]^+$). HRMS (DCI/CH_4):m/z calcd for $C_{17}H_{15}N_2O_3$ $[MH]^+$: 295.1083; found: 295.1072.

Acknowledgements

The purchase of supplies and costs of analyses were supported by the ANR (11-BS07-016-01). IB was supported by the French Embassy in Kiev, Ukraine, the investigations having been performed within the framework of the GDRI (Groupement Franco-Ukrainien en Chimie Moléculaire) funded by the CNRS. The ANR, the French Embassy in Kiev, and the CNRS are thus sincerely acknowledged.

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