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A Simple Indirect Route for the Synthesis of *N*-Alkyl-4-imino-1,4-dihydro-2*H*-3,1-benzoxazin-2-ones

Khosrow Jadidi[1,*], **Ramin Ghahremanzadeh**[1], **Morteza Mehrdad**[2], **Mohammad Ghanbari**[1], and **Hamid Arvin-Nezhad**[1]

[1] Department of Chemistry, Shahid Beheshti University, Tehran, Iran
[2] Department of Environmental Pollutants, Environmental Sciences Research Institute, Shahid Beheshti University, Tehran, Iran

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Summary. Novel *N*-alkyl-4-imino-1,4-dihydro-2*H*-3,1-benzoxazin-2-ones were synthesized in a single step by *Baeyer–Villiger* oxidation of *N*-alkyl-3-imino-2-indolinone derivatives in high yields. The structures of the products were determined by spectral data and by X-ray diffraction. Besides their novel structures, these compounds may have important biological activities and industrial applications.

Keywords. 3,1-Benzoxazin-2-ones; *Baeyer–Villiger* oxidation; 3-Imino-2-indolinone.

Introduction

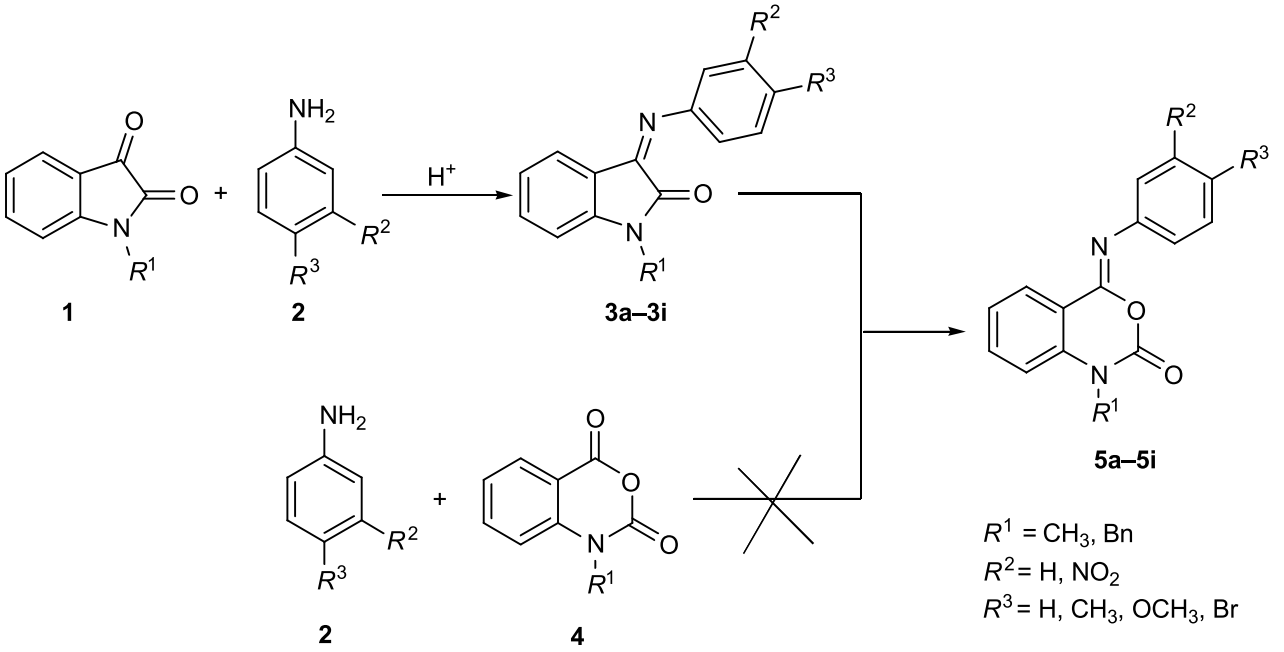
A literature survey reveals that 3,1-benzoxazin-2-ones and their homologue compounds have wide ranges of valuable pharmacological properties as well as industrial applications [1]. It is well known that similar compounds, such as 3-aryl-2,4-quinazolinediones are of current interest from both pharmacological and chemical aspects. These compounds have been tested against *Mycobacterium avium*, the most common systematic bacterial infection complicating *AIDS* [2]. On the other hand, *Baeyer–Villiger* oxidation is now a frequently used synthesis method for the conversion of cycloalkanones to lactones. The reaction can also be used in the synthesis of a wide variety of other chemicals, ranging from simple monomers used in the polyester industry to the more complex molecules used in the synthesis of pharmaceutical products [3].

As a continuation of our previous work and as part of our ongoing research program on the synthesis of various heterocyclic compounds [4], we wish to report the synthesis of novel derivatives **5** that may produce desired activity against *Mycobacterium avium* and may posses other antibacterial and antiviral activities [2b]. A new two-step method, which used the key *Baeyer–Villiger* oxidation reaction in the second step, was developed for the synthesis of novel compounds **5** since direct reaction of isatoic anhydride **4** with amines **2** did not afford them (Scheme 1).

Results and Discussion

Direct reaction of amines with isatoic anhydrides **4** produces anthranilic acid derivatives instead of *N*-alkyl-1,4-dihydro-4-imino-2*H*-3,1-benzoxazin-2-ones **5** (Scheme 1). Direct nucleophilic attack by amines on the oxazine ring of isatoic anhydrides results in loss of carbon dioxide and produces anthranilic acid derivatives [5]. To synthesize novel *N*-alkyl-4-imines **5** of the isatoic anhydrides **4** and to prevent the rearrangement of the oxazine ring, *N*-alkyl-3-imino-2-indolinones **3** were first synthesized from the reaction of anilines **2** with *N*-alkylisatin **1**. Then,

* Corresponding author. E-mail: k-jadidi@cc.sbu.ac.ir



Scheme 1

Table 1. The preparation of 3,1-benzoxazin-2-ones **5a**–**5i**

Product[a]	R^1	R^2	R^3	Yield/%
5a	*Me*	H	H	80
5b	*Me*	H	*Me*	85
5c	*Me*	NO_2	H	82
5d	*Me*	H	O*Me*	83
5e	*Me*	H	Br	83
5f	Bn	H	O*Me*	86
5g	Bn	H	Me	80
5h	Bn	H	Br	85
5i	Bn	H	H	80

[a] All compounds were recrystallized from methanol

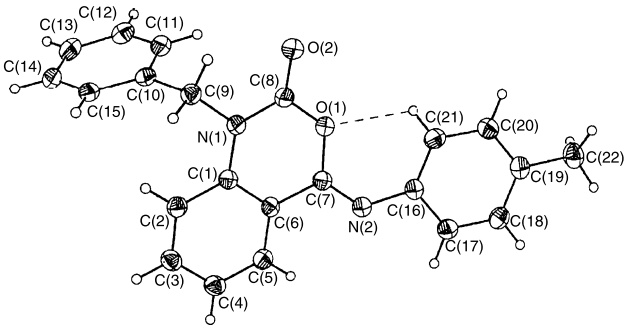


Fig. 1. X-Ray crystal structure of **5g**

the corresponding *N*-alkyl-3-imino-2-indolinones **3** were oxidized with *m*-chloroperbenzoic acid (*m-CPBA*) at 0°C in dichloromethane or methanol (Scheme 1). The *Baeyer–Villiger* oxidation products were easily purified by dry flash chromatography or by recrystallization in the appropriate solvent, and pure products **5a**–**5i** were obtained in high yields (Table 1).

The structural assignments of the products, which could not be concluded from NMR spectra and mass spectroscopy alone, were achieved by X-ray crystallographic analysis of **5g** (Fig. 1). For crystallization of **5g** *n*-hexane:ethanol (1:4) was used. Light-yellow crystals of **5g** were obtained by slow evaporation of the solvent.

According to geometrical parameters of **5g**, the backbone of this molecule is nearly flat. This can be also explained by existence of maximum tricyclic $\pi-\pi$ overlap. As a result of torsional angles of C16–N2–C7–O1 and C21–C16–N2–C7 which are nearly 0°, and existence of possible hydrogen bonding between O1 and H21, the imine moiety is forced to adopt the (*Z*)-configuration. Moreover, the only group nearly orthogonal with respect to the rest of the molecule is the *N*-benzyl substituent ring (N1–C9–C10–C15 = 122.7°).

In conclusion, a total of nine novel *N*-alkyl-4-imino substituted isatoic anhydrides **5** were synthesized from indirect *Baeyer–Villiger* oxidation of *N*-alkyl-3-imino-2-indolinones **3**. ^{1}H and ^{13}C NMR

spectra of the oxidation products could not confirm the exact structural assignment of these compounds. Therefore, X-ray diffraction was used to obtain the exact structural assignment of the compounds. Besides their novel structures, as mentioned earlier, these compounds may possess some important biological activities.

Experimental

Melting points were measured on a Mettler FP5. Mass spectra were recorded on a Shimadzu QP 1100 Ex mass spectrometer operating at an ionization potential of 70 eV. IR spectra were obtained with a Shimadzu IR-470 spectrometer (KBr). ^{1}H and ^{13}C NMR spectra were measured with a Bruker 500 DRX AVANCE instrument at 500 and 125 MHz. Isatin, anilines, and solvents used in the reactions were commercially available, and they were used after additional purification by distillation or crystallization. Educts **3a**–**3i** were prepared according to Ref. [4d].

X-Ray Crystallography

The room temperature diffraction measurements were carried out with a colorless $0.14 \times 0.14 \times 0.06\,mm^3$ plate of crystal of **5g** on a Bruker AXS area-detector diffractometer. The structure was solved by using SHELXS 97. The structure refinement and data reduction were carried out with SAINT (Bruker 1998). Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located by subsequent difference Fourier maps and were refined to a final *R* value of 0.045. Crystallographic data were deposited at the Cambridge Crystallographic Data Centre with the No. 673–953 and can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk, or http://www.ccdc.cam.ac.uk).

*Typical Procedure for the Preparation of (Z)-1-methyl-4-(phenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one as Exemplified with **5a***

A solution of 0.472 g **3a** (2.0 mmol) [4d] in 25 cm^3 CH_2Cl_2 was cooled to 0°C in an ice-bath. *mCPBA* (0.516 g, 3 mmol), which was dissolved in 25 cm^3 CH_2Cl_2, was added dropwise to the stirred solution of imine **3a**. After stirring 45 min at 0°C, product **5a** was formed (TLC). The crude product was poured into water and extracted with dichloromethane ($3 \times 20\,cm^3$). The organic layer was dried (Na_2SO_4) and evaporation of the solvent afforded the crude product **5a**. The latter was purified on silica gel by dry-flash chromatography using *n*-hexane/ethyl acetate or by recrystallization in methanol. Yield 80%; light-yellow crystals, mp 118–122°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H), 7.08–8.35 (m, 9H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.65$, 113.44–144.25 (12 signals arom), 144.50 (CN), 147.49 (CO) ppm; IR (KBr): $\bar{\nu} = 1675$ (CN), 1740 (CO), 2964, 3042 cm^{-1}; MS: m/z (%) = 252 (M^+, 50), 208 (M–CO_2, 100).

(Z)-1-Methyl-4-(4-tolylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5b**, $C_{17}H_{16}N_2O$)

Yellow crystals, mp 114–116°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.27$ (s, 3H), 3.42 (s, 3H), 6.96–8.22 (8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.58$, 31.15, 111.34–145.50 (12 signal arom), 142.10 (CN), 145.49 (CO) ppm; IR (KBr): $\bar{\nu} = 1652$ (CN), 1734 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: m/z (%) = 266 (M^+, 80), 221 (M–CO_2, 100).

(Z)-1-Methyl-4-(3-nitrophenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5c**, $C_{16}H_{13}N_3O_3$)

Light-brown crystals, mp 201–203°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (s, 3H), 7.09–8.31 (m, 8H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.77$, 113.64–139.82 (12 signals arom), 146.82 (CN), 148.76 (CO) ppm; IR (KBr): $\bar{\nu} = 1658$ (CN), 1739 (CO), 2330, 2357, 2848, 2949 cm^{-1}; MS: m/z (%) = 297 (M^+, 70), 253 (M–CO_2, 100).

(Z)-1-Methyl-4-(4-methoxyphenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5d**, $C_{17}H_{16}N_2O_2$)

Light-gray crystals, mp 206–210°C; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 3.40$ (s, 3H), 3.75 (s, 3H), 6.92–8.11 (8H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 31.56$, 55.46, 113.34–143.27 (12 signal arom), 147.69 (CN), 157.23 (CO) ppm; IR (KBr): $\bar{\nu} = 1654$ (CN), 1706 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: $m/z = 282$ (M^+, 100), 237 (M–CO_2, 50).

(Z)-1-Methyl-4-(4-bromophenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5e**, $C_{16}H_{13}BrN_2O$)

Light-orange crystals, mp 180–182°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.39$ (s, 3H), 6.94–8.13 (m, 8H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.69$, 113.56–143.33 (12 signals arom), 145.21 (CN), 147.23 (CO) ppm; IR (KBr): $\bar{\nu} = 1606$ (CN), 1734 (CO), 2964, 3042 cm^{-1}; MS: m/z (%) = 330 (M^+, 90), 332 ($M^+ + 2$, 90), 286 (M–CO_2, 100).

(Z)-1-Benzyl-4-(4-methoxyphenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5f**, $C_{23}H_{20}N_2O$)

Light-gray crystals, mp 148–150°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.88$ (s, 3H), 5.42 (s, 2H), 7.05–8.30 (m, 13H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.56$, 55.51, 111.56–151.79 (18 signal arom), 159.59 (CN), 162.09 (CO) ppm; IR (KBr): $\bar{\nu} = 1659$ (CN), 1708 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: m/z (%) = 358 (M^+, 100), 314 (M–CO_2, 20).

(Z)-1-Benzyl-4-(4-tolylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5g**, $C_{22}H_{17}BrN_2O$)

Light-yellow crystals, mp 156–158°C; ^{1}H NMR (300 MHz, CDCl3): $\delta = 2.32$ (s, 3H), 5.22 (s, 2H), 6.93–8.30 (m, 13H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.48$, 48.41, 114.44–140.45 (18 signal arom), 145.39 (CN), 147.68 (CO) ppm; IR (KBr): $\bar{\nu} = 1660$ (CN), 1731 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: m/z (%) = 342 (M^+, 100), 298 (M–CO_2, 40).

(Z)-1-Benzyl-4-(4-bromophenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5h**, $C_{22}H_{17}BrN_2O$)
Brown crystals, mp 144–145°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.23$ (s, 2H), 6.97–8.26 (13H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 48.24$, 114.41–143.20 (18 signal arom), 145.00 (CN), 147.68 (CO) ppm; IR (KBr): $\bar{\nu} = 1658$ (CN), 1747 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: m/z (%) = 407 (M^+, 100), 410 (M^++2, 30), 363 (M–CO_2, 40).

(Z)-1-Benzyl-4-(phenylimino)-1,4-dihydro-2H-3,1-benzoxazin-2-one (**5i**, $C_{22}H_{18}N_2O$)
Light-green crystals, mp 116–118°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.23$ (s, 2H), 6.97–8.26 (m, 13H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 48.24$, 114.41–143.20 (18 signal arom), 145.00 (CN), 147.68 (CO) ppm; IR (KBr): $\bar{\nu} =$ 1650 (CN), 1732 (CO), 2859, 2894, 2957, 3046 cm^{-1}; MS: m/z (%) = 327 (M^+, 100), 329 (M^++2, 30), 283 (M–CO_2, 40).

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