



Rearrangement of 4-imino-(1*H*,4*H*)-3,1-benzoxazine-2-ones to 2,4-quinazolinediones via an isocyanate carboxamide intermediate

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Abstract

Reaction of 3-arylimino-2-indolinones **1** with *m*-chloroperbenzoic acid in CH₂Cl₂ or methanol at 0°C leads to the corresponding 3-aryl-2,4(1*H*,3*H*)-quinazolinediones **4** and (2-arylcarbamoylphenyl)carbamic acid methyl ester **5**, respectively. These conversions proceed through 4-arylimino-(1*H*,4*H*)-3,1-benzoxazine-2-one **2** and its ring-opened isocyanate carboxamide isomer **3** as key intermediates. © 2000 Elsevier Science Ltd. All rights reserved.

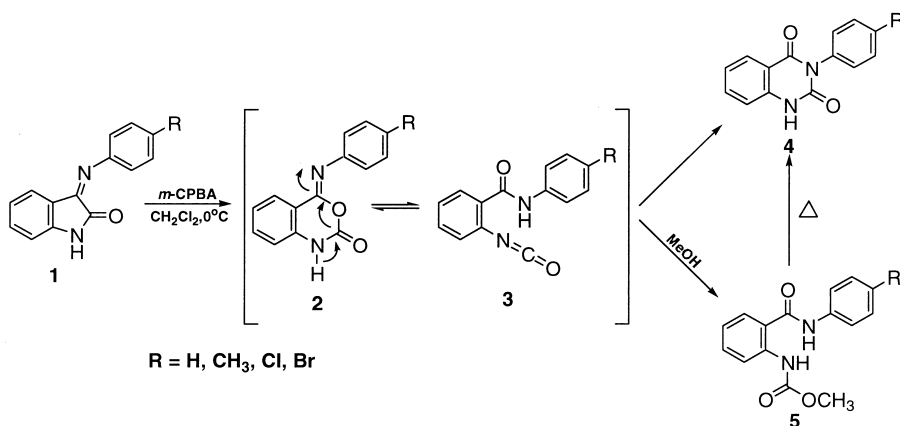
Keywords: benzoxazines; carbamates; quinazolinones; rearrangements.

The synthesis of 3-aryl-2,4-quinazolinediones are of current interest from both pharmacological and chemical aspects.¹ These compounds are prepared by various methods.² Most of these methods involve rearrangement of different starting materials.³

Recently, we have reported the preparation of 3-arylimino-2-indolinones **1** and their applications for the synthesis of several types of heterocyclic systems.⁴ As a continuation of this work, we wish to report the rearrangement and mechanism of the formation of 3-aryl-2,4(1*H*,3*H*)-quinazolinediones **4** from oxidation of isatin-3-imines **1** with *m*-chloroperbenzoic acid (*m*-CPBA).

When 3-arylimino-2-indolinones **1a–d** reacted at 0°C with *m*-CPBA in CH₂Cl₂ the expected *N*-aryl-2,4-quinazolinediones **4a–d** were obtained. This oxidation had been reported with hydrogen peroxide in alkaline solution.⁵ The product **4** was easily separated on silica gel from impurities by dry flash chromatography.⁶ The impurities were unstable compounds and decomposed during the separation process. However, when these impurities were heated in methanol, (2-arylcarbamoylphenyl)carbamic acid methyl ester **5** was obtained in low yield. When imine **1** was treated with *m*-CPBA in methanol, carbamate **5** was also obtained in high yield (Scheme 1). The results are summarized in Table 1. On the other hand, when carbamate **5** was heated to its melting point, ring closure occurred, and the quinazolinediones **4** were obtained.

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Scheme 1.

Table 1

The preparation and yield of 3-aryl-2,4(1*H*,3*H*)-quinazolin-2(1*H*)-ones **4** and (2-arylcarbamoylphenyl)-carbamic acid methyl ester **5** and *N*-methyl-4-(*p*-tolylimino)-(1*H*,4*H*)-3,1-benzoxazin-2-one **7**

Entry	Product	R	m.p./°C		Yield/%
			Found ^a	Lit. ^b	
1	4a	H	284	282 ^{c,8}	80
2	4b	CH ₃	270	267-8 ^{d,9}	93
3	4c	Cl	301-2	299-301 ^{e,10}	82
4	4d	Br	327-29	329-330 ^{f,1a}	83
5	5a	H	183-4	183-5 ¹¹	83
6	5b	CH ₃	172-3	-	76
7	5c	Cl	188-90	-	97
8	5d	Br	198	-	95
9	7	-	122-3	-	70

^a All of the compounds are recrystallized from methanol.

^b In literature, depending on the kind of recrystallization solvent, a wide range of melting points have been reported for 3-aryl-2,4-quinazolin-2(1*H*)-ones. ^{2b,c} For example, the melting point ranges are **4a**: 210-306 °C; **4b**: 248-277 °C; **4c**: 268-301 °C; **4d**: 299-330 °C.

^c Recrystallized from methanol.

^d Recrystallized from toluene.

^e Recrystallized from ethanol.

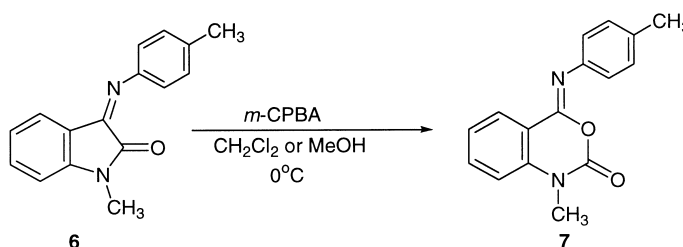
^f Recrystallized from aqueous acetone.

A possible mechanism for the conversion of **1** to **4** is through 4-imino-(1*H*,4*H*)-3,1-benzoxazin-2-one **2** as a product of Baeyer–Villiger oxidation followed by rearrangement of **2** to the isocyanate carboxamide intermediate **3** as proposed in Scheme 1. Recently, a similar rearrangement was reported for 4-imino-4*H*-3,1-benzoxazines to 4-quinazolinones via amidine carboxamides.⁷

The separation and purification of **2** was not possible; **2a** is the only example that has been reported as a likely intermediate; however, the authors were not sure of the actual structure of **2a**.¹² The formation of intermediates **3** by a ring-opening has not been reported. However, the intermediates have previously been obtained by a variety of methods. *N*-Aryl-2,4-quinazolin-2-one **4** has been obtained through this intermediate by: (i) the pyrolysis of 1-phenyl-5-(*o*-carboxyphenyl) tetrazole;^{13a} (ii) the reaction of isatoic anhydride with SOCl₂ or PCl₅ and then treatment

with 1 equivalent of amine;^{13b} (iii) the reaction of *N*-mesyloxy phthalimide with aniline and triethylamine;^{13c} and (iv) the reaction of imino-phosphorane with carbon dioxide.⁹ However, none of these authors have proved the structure of their intermediates. A hydrogen shift and formation of isocyanate **3** must be considered for the rearrangement of **2** into **4**. This isocyanate intermediate **3** can cyclize spontaneously to give **4**, or methanol attacks the isocyanate to generate carbamate **5**.

In support of the proposed mechanism, when *N*-methyl-3-(*p*-tolylimino)-2-indolinone **6** was treated in CH₂Cl₂ or MeOH with *m*-CPBA under the same reaction condition, the new compound *N*-methyl-4-(*p*-tolylimino)-(1*H*,4*H*)-3,1-benzoxazin-2-one **7** was obtained (Scheme 2). In this case, the formation of an isocyanate is impossible (Table 1).



Scheme 2.

The preparation of 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione **4a** from oxidation of **1a** is representative. The imine **1a** (2 mmol) in CH₂Cl₂ (25 ml) was cooled to 0°C in an ice-bath and *m*-CPBA (2.4 mmol) dissolved in the same solvent (25 ml) was added dropwise to a vigorously stirred solution. After 45 min at 0°C, some of the product **4** was precipitated and was filtered, and the filtrate was poured into water. Dichloromethane (50 ml) was added and the organic layer was separated, washed (1 M Na₂SO₃, 2 M NaHCO₃) and dried (Na₂SO₄). The rest of product **4** was obtained by evaporation of solvent at low pressure. The pure product **4a** was easily separated on silica gel by dry flash chromatography using hexane/ethyl acetate⁶ or the crude product was recrystallized from methanol.

Satisfactory mass and ¹³C NMR spectra were obtained for **4**, in good agreement with the reported values.¹⁴ The structures of **5a–d** and **7** are supported by ¹H and ¹³C NMR. HH COSY and CH COSY provided additional support for assignments of protons and carbons of structures **4**,¹⁵ **5**¹⁶ and **7**.¹⁷

Due to the simplicity of the experimental one-pot procedure and mild conditions, the synthesis of various compounds **4**, **5** and **7** by this method is efficient. Compounds **4** and **5** have been tested against *Mycobacterium avium*, which is the most common systematic bacterial infection complicating AIDS, but were not found to be active.^{1a} Recently, it was reported that the replacement of the oxygen in the heterocyclic ring resulted in a decrease or loss of antimycobacterial activity.^{1b} Therefore, the new compound **7** may be an active substance in this regard and will be tested in due course.

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- Compound **4a**: ^1H NMR (500 MHz, DMSO) δ (ppm), J (hertz): 11.55 (s, 1H, NH), 7.93 (dd, 1H, $J=8.0, 1.5$, 5-H), 7.67 (ddd, 1H, $J=8.5, 7.5, 1.5$, 7-H), 7.48 (dd, 2H, $J=7.5, 7.0$, 3', 5'-H), 7.41 (ddd, 1H, $J=7.0, 7.0, 1.5$, 4'-H), 7.32 (dd, 2H, $J=7.5, 1.5$, 2', 6'-H), 7.23 (dd, 1H, $J=8.5, 1.0$, 8-H), 7.20 (ddd, 1H, $J=8.0, 7.5, 1.5$, 6-H). ^{13}C NMR (125 MHz, DMSO) δ (ppm): 162.2 (C-4), 150.1 (C-2), 139.8 (C-8a), 135.7 (C-1'), 135.1 (C-7), 129.0 (C-2', 6'), 128.7 (C-3', 5'), 128.0 (C-4'), 127.5 (C-5), 122.4 (C-6), 115.2 (C-8), 114.3 (C-4a).
- Compound **5a**: ^1H NMR (500 MHz, DMSO) δ (ppm), J (hertz): 10.45 (s, 1H, NHCOOMe), 10.23 (s, 1H, NHCO-), 8.11 (d, 1H, $J=8.5, 6\text{-H}$), 7.84 (dd, 1H, $J=7.5, 2.0$, 3-H), 7.74 (d, 2H, $J=8, 1.0$, 2', 6'-H), 7.53 (ddd, 1H, $J=8.5, 7.0, 2, 5\text{-H}$), 7.36 (dd, 2H, $J=8.0, 7.5$, 3', 5'-H), 7.18 (dd, 1H, $J=7.5, 7.0$, 4-H), 7.13 (ddd, 1H, $J=7.5, 7.5, 1, 4'\text{-H}$), 3.67 (s, 3H, OCH₃). ^{13}C NMR (125 MHz, DMSO) δ (ppm): 167.1 (C-amide), 153.5 (C-carbamate), 138.6 (C-2), 138.5 (C-1'), 132.1 (C-5), 128.8 (C-3), 128.5 (C-3', 5'), 124.1 (C-4'), 122.2 (C-4), 122.2 (C-1), 120.9 (C-2', 6'), 119.7 (C-6), 52.0 (C-methyl).
- Compound **7**: ^1H NMR (500 MHz, DMSO) δ (ppm), J (hertz): 8.08 (dd, 1H, $J=8.0, 1.5$, 5-H), 7.66 (ddd, 1H, $J=8.5, 7.5, 1.5$, 7-H), 7.29 (dd, 1H, $J=8.5, 1.0$, 8-H), 7.26 (ddd, 1H, $J=8.0, 7.5, 1.0$, 6-H), 7.15 (d, 2H, $J=8.0$, 2', 6'-H), 7.04 (d, 2H, $J=8.0$, 3', 5'-H), 3.38 (s, 1H, N-CH₃), 2.28 (s, 3H, Ph-CH₃). ^{13}C NMR (125 MHz, DMSO) δ (ppm): 146.8 (C-2), 145.1 (C-4), 142.0 (C-8a), 139.6 (C-4'), 134.0 (C-7), 133.2 (C-1'), 129 (C-3', 5'), 126.9 (C-5), 123.5 (C-6), 122.4 (C-2', 6'), 114.4 (C-8), 114.1 (C-4a).