Pergamon

Tetrahedron Letters 41 (2000) 5265–5268

TETRAHEDRON LETTERS

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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Received 13 March 2000; accepted 16 May 2000

Abstract

Reaction of 3-arylimino-2-indolinones **1** with *m*-chloroperbenzoic acid in CH_2Cl_2 or methanol at 0°C leads to the corresponding 3-aryl-2,4(1*H*,3*H*)-quinazolinediones **4** and (2-arylcarbamoyphenyl)carbamic acid methyl ester **5**, respectively. These conversions proceed through 4-arylimino-(1*H*,4*H*)-3,1-benzoxazin-2-one **2** and its ring-opened isocyanate carboxamide isomer **3** as key intermediates.

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 CH_2Cl_2 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-arylcarbamoyphenyl)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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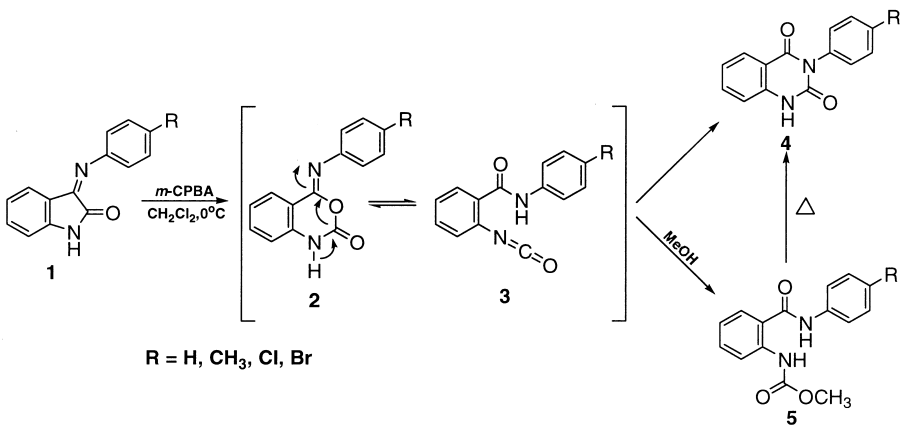
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00803-0



Scheme 1.

Table 1
The preparation and yield of 3-aryl-2,4(1*H*,3*H*)-quinazolinediones **4** and (2-arylcarbamoylphenyl)-carbamic acid methyl ester **5** and *N*-methyl-4-(*p*-tolylimino)-(1*H*,4*H*)-3,1-bezoxazine-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

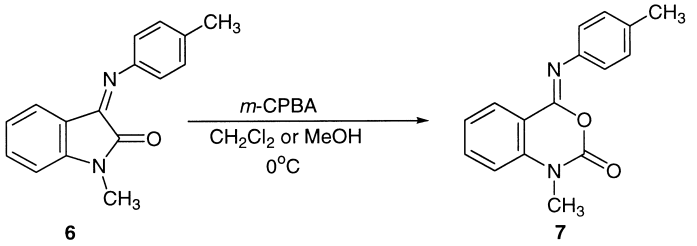
[a] All of the compounds are recrystallized from methanol.
[b] In literature, depending on the kind of recrystallization solvent, a wide range of melting points have been reported for 3-aryl-2,4-quinazolinediones.[2b,c] For example, the melting point ranges are **4a**: 210-306 °C; **4b**: 248-277 °C; **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-quinazolinedione **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 $SOCl_2$ or PCl_5 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 CH_2Cl_2 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 CH_2Cl_2 (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 Na_2SO_3, 2 M $NaHCO_3$) and dried (Na_2SO_4). 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 acetate[6] or the crude product was recrystallized from methanol.

Satisfactory mass and ^{13}C NMR spectra were obtained for **4**, in good agreement with the reported values.[14] The structures of **5a**–**d** and **7** are supported by ^{1}H and ^{13}C 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.

Acknowledgements

We thank the Vice President of research affairs at the Shahid Beheshti University for financial support. Professors I. Yavari and A. Shafiee are appreciated for their consultations. Finally, we gratefully acknowledge Professor A. Khodai for helpful suggestions.

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15. Compound **4a**: ^{1}H 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).
16. Compound **5a**: ^{1}H 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-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-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′-H), 3.67 (s, 3H, OCH_3). ^{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).
17. Compound **7**: ^{1}H 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-CH_3), 2.28 (s, 3H, Ph-CH_3). ^{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).