Tetrahedron Letters 54 (2013) 4512–4514

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

13*H*-Quinazolino[3,4-*a*]quinazolin-13-one: synthesis and structural revision ☆

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ARTICLE INFO

Article history:
Received 24 April 2013
Revised 11 June 2013
Accepted 13 June 2013
Available online 20 June 2013

Keywords:
Nitrogen heterocycles
Quinazolines
Fused quinazolinoquinazolinones
Dehydrogenation
Structural revision

ABSTRACT

13*H*-Quinazolino[3,4-*a*]quinazolin-13-one has been synthesized from 2-aminobenzamide via 11b, 12-dihydro-13*H*-quinazolino[3,4-*a*]quinazolin-13-one in four steps. However, the spectroscopic data did not match with those of literature data. Thus, the published structure from the reaction of 2-aminobenzonitrile and triethyl orthoformate is not 13*H*-quinazolino[3,4-*a*]quinazolin-13-one and has been revised as 8*H*-quinazolino[4,3-*b*]quinazolin-8-one.

Quinazoline and its derivatives are a class of heteroaromatic compounds that have drawn much attention because of their biological and pharmaceutical importance and their synthesis has been extensively investigated.[1,2] Among these, 4-(phenylamino)quinazolines were found to be potent and selective ATP competitive tyrosine kinase inhibitors for the treatment of EGFR-associated cancer types (e.g., Iressa™-gefitinib and Tarceva™-erlotinib are being used for the treatment of nonsmall cell lung cancer).[3] 8*H*-Quinazolino[4,3-*b*]quinazolin-8-ones (**1**) and 13*H*-quinazolino[3,4-*a*]quinazolin-13-ones (**2**) are two isomeric angularly fused quinazolinoquinazolinones (Fig. 1). Although, a number of methods[4–7] were reported for the synthesis of **1**, synthetic studies on the isomeric compound **2** are rather limited.[8–10] In view of the important biological activities of the fused quinazolinones and in continuation of our interest in this chemistry,[11] we required an efficient synthesis of 13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**2**).

Only two methods were reported for the synthesis of 6-unsubstituted 13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**2**).[8,9] The first Letter described the formation of compound **2** as a minor product during the reaction of 2-[4-imino-2-thioxa-1,4-dihydro-3(*2H*)-quinazolinyl]benzonitrile with $Mn(OAc)_3$.[8] A recent report[9] has described the synthesis of **2** in two steps starting from 2-aminobenzonitrile via 13*H*-quinazolino[3,4-*a*]quinazolin-13-imine acid salt (Scheme 1).

Our initial efforts[11b] to make **2** by dehydrogenation of 11b, 12-dihydro-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**3**) failed and instead gave a rearranged product **1**. Among the several known dehydrogenation reagents,[12] DDQ was chosen for the aromatization reaction. The requisite intermediate **3** was prepared starting from 2-aminobenzamide in three steps (Scheme 2).

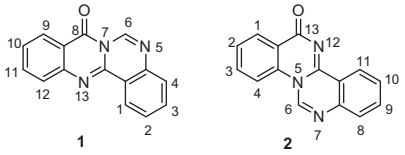
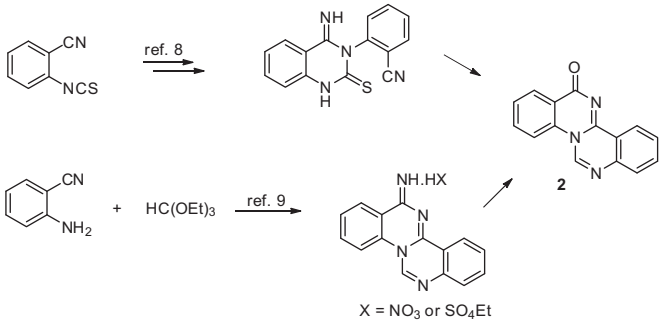


Figure 1. 8*H*-Quinazolino[4,3-*b*]quinazolin-8-one (**1**) and 13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**2**).



Scheme 1. Known methods to prepare 13*H*-quinazolino[3,4-*a*]quinazolin-13-one.

☆ In memories of Professor A. Srikrishna (1955–2013), Department of Organic Chemistry, Indian Institute of Science, Bangalore, India.

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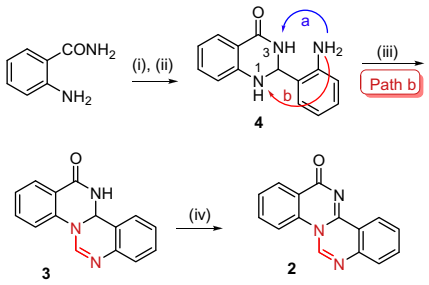
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.06.060



Scheme 2. Reagents and conditions: (i) 2-Nitrobenzaldehyde, water/AcOH, reflux, 5 h, 88% (ii) Fe/HCl, NH_4Cl, MeOH, reflux, 0.5 h, 86% (iii) DMF–DMA, AcOH, toluene, reflux, 2 h, 82% (iv) DDQ, dioxane, rt, 16 h, 85%.

Table 1
Dehydrogenation of **3** with DDQ

S. no.	Conditions[a]	Yield[b] (%)	
		1	**2**
1	Dioxane, rt, 16 h	0	85
2	Dioxane, 80 °C, 4 h	20	50
3	Dioxane, reflux, 2 h	43	30
4	THF, rt, 16 h	0	80
5	THF, reflux, 8 h	24	49

[a] All the reactions were performed with **3** (0.5 mmol), DDQ (0.6 mmol) and solvent (20 mL).
[b] Isolated yields.

Thus 2-aminobenzamide was condensed with 2-nitrobenzaldehyde to give 2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one[13] in 88% yield, which was reduced to **4** using iron powder/HCl in 86% yield. Selective cyclization of 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**4**) on to N_1-nitrogen via path b with dimethylformamide–dimethylacetal (DMF–DMA) in toluene/acetic acid at refluxing temperature gave **3** in 82% yield (Scheme 2). Compound **3** was then treated with DDQ under various conditions and the results are summarized in Table 1. Dehydrogenation of **3** with 1.2 equiv of DDQ in dioxane at rt gave selectively **2** in 85% yield (entry 1). However, the same reaction at 80 °C and at refluxing conditions resulted in the formation of **1** and **2** in good yield (entries 2 and 3). As expected dehydrogenation of **3** with DDQ in THF at rt gave selectively **2**, while at refluxing temperature gave both **1** and **2** (entries 4 and 5). These results indicated that the dehydrogenation of **3** at lower temperature gave kinetic isomer **2**, whereas at higher temperature thermodynamically stable product **1** is formed. This might be due to better stability of the system **1** (having complete π-conjugation from the carbonyl group to the carbon-6, which is absent in **2**). All the structures have been deduced from their spectroscopic data.[14]

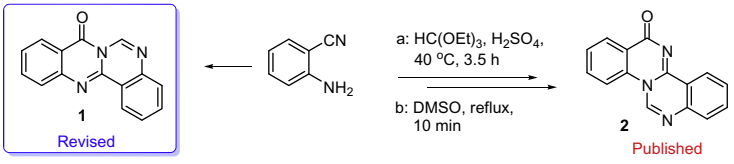
Calestani et al. reported[8] **2** (mp 112–114 °C) with very limited spectroscopic data while Marinho et al. reported[9] the synthesis of **2** (mp 181–183 °C) starting from *o*-aminobenzonitrile as shown in Scheme 3. The differences reported for **2**, prompted us to investigate further. The physical and spectroscopic data of **2** from our synthesis and that reported are presented in Table 2.

The carbonyl absorption of **2** is at 1656 cm^{-1}, whereas for **2** (published) it was reported at 1703 cm^{-1}. In proton NMR, the H-6 proton in **2** gave a singlet at δ 9.67 and the same proton in **2** from the published work resonated at δ 9.28. The other chemical shifts of published **2** are also inconsistent with the synthetic **2** (Table 2). Further, in carbon NMR, the carbonyl carbon in **2** resonated at δ 166.05 and the same carbon in published **2** resonated at δ 157.75. The other carbon values (^{13}C NMR) of published **2** are also inconsistent with **2** (Table 2). Obviously, the structure published for the product from the reaction of 2-aminobenzonitrile is not 13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**2**). In light of this observation, we carefully reanalyzed the spectroscopic data of published structure **2** by Marinho et al. and found that the data were well in agreement with an isomeric structure **1**. The spectroscopic data of isomeric compound **1** are reported in $CDCl_3$ from our group[15] as well as others,[5,6] since the compound is freely soluble in $CDCl_3$. To compare unambiguously, the spectroscopic data of **1** are recorded in DMSO-d_6 and presented in Table 2. The carbonyl absorption in IR for published **2** was reported at 1703 cm^{-1}, which is in good agreement with those of **1** (1705 cm^{-1}). Further, the singlet at δ 9.28 in the ^1H NMR data of published **2** agrees well with the chemical shift of **1** (δ 9.31). From Table 2, it is clearly evident that the mp, IR, proton and carbon NMR data reported for published **2** are in good agreement with those of **1**. From the above

Table 2
Physical and spectroscopic data of **2**, published **2** and revised **1**

Data	**2**[a]	Published **2**[b]	Revised **1**[c]
Mp (°C)	>300	181–183	190–192
IR (cm^{-1})	1656 (C=O)	1703 (C=O)	1705 (C=O)
^1H NMR	9.67 (1H, s)	9.28 (1H, s)	9.31 (1H, s)
	8.70 (1H, d, 7.6)	8.72 (1H, dd, 7.8, 1.2)	8.75 (1H, d, 7.6)
	8.65 (1H, d, 8.8)	8.32 (1H, dd, 8.1, 1.2)	8.34 (1H, d, 8.0)
	8.29 (1H, d, 7.6)	7.95 (1H, td, 6.9, 1.2)	7.99 (1H, t, 7.6)
	7.99 (2H, t, 7.4)	7.89 (1H, td, 6.9, 1.2)	7.92 (1H, t, 7.6)
	7.88 (1H, d, 8.0)	7.84 (1H, dd, 8.1, 1.2)	7.84–7.87 (2H, m)
	7.77 (1H, t, 7.2)	7.82 (1H, dd, 8.1, 1.5)	7.75 (1H, t, 7.4)
	7.75 (1H, t, 7.2)	7.72 (1H, td, 6.9, 1.5)	7.62 (1H, t, 7.6)
		7.59 (1H, td, 8.1, 1.2)	
^{13}C NMR	166.05	157.75	158.73
	150.71	147.13	147.15
	143.94	144.49	144.49
	139.28	142.89	142.91
	136.84	138.18	138.13
	134.92	135.97	135.93
	133.94	133.85	133.81
	128.77	128.90	128.87
	128.21	127.73	127.72
	127.68	127.37	127.37
	127.37	127.00	126.97
	126.39	126.50	126.47
	120.46	125.41	125.41
	120.35	121.24	121.25
	115.81	118.74	118.75

[a] ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) in DMSO-d_6, chemical shifts are expressed in ppm and *J* values in parentheses are in Hz.
[b] ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) in DMSO-d_6 are taken from Ref.9.
[c] The compound was synthesized by a known method (Ref.15) and ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) are recorded in DMSO-d_6.



Scheme 3. Synthesis of **2** by Marinho et al.[9] and structure of **1**.

observation it is safe to conclude that the structure of the product from the reaction of 2-aminobenzonitrile with triethyl orthoformate is 8*H*-quinazolino[4,3-*b*]quinazolin-8-one (**1**), a known fused quinazolinoquinazoline.[5,6]

In summary, we have accomplished the synthesis of 13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**2**) from 2-aminobenzamide in four steps with an overall yield of 53%. The physical (mp) and spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR) did not match with those published for **2**. The reported data for 13*H*-quinazolino[3,4-*a*]quinazolin-13-one from the reaction of 2-aminobenzonitrile and triethyl orthoformate have been reassigned to that of an isomeric compound, 8*H*-quinazolino[4,3-*b*]quinazolin-8-one.

Acknowledgments

We sincerely thank Sri G. Ganga Raju, Chairman, and Mr. G. Rama Raju, Director, Laila Impex, for support and encouragement.

Supplementary data

Supplementary data (general experimental procedures, copies of ^{1}H, ^{13}C NMR spectra of **1**–**3** and HPLC chromatogram of **1** and **2**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.060.

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14. Procedure and spectroscopic data of **3**: To a suspension of **4** (717 mg, 3.0 mmol) in toluene (20 mL) were added successively DMF–DMA (0.8 mL, 6.0 mmol) and acetic acid (0.16 mL, 3.0 mmol) at rt and refluxed for 2 h. The reaction mixture was allowed to rt and the precipitated product was filtered, washed with toluene and dried. The crude product was recrystallized from excess of chloroform–methanol to give **3** as a white solid (615 mg, 82% yield), mp 296–302 °C. IR (KBr) ν_{max} 3447, 3162, 1686, 1620, 1603, 1356, 1303, 1254, 1181, 746 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (1H, s, exchangeable with D_2O), 7.98 (1H, d, J = 7.6 Hz), 7.78 (1H, s), 7.69 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.36–7.41 (3H, m), 7.25 (1H, t, J = 7.4 Hz), 7.20 (1H, d, J = 8.0 Hz), 6.50 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 143.6, 140.8, 139.8, 133.5, 129.9, 128.1, 127.6, 125.8, 125.2, 125.1, 123.1, 118.5, 118.2, 62.0; LC–MS (positive ion mode): m/z 250 (M+H)$^+$; HRMS-(EI) (m/z): (M+H)$^+$ calcd for $C_{15}H_{11}N_3OH$ 250.0980, found 250.0977.
Procedure and spectroscopic data of **2**: To an ice cold suspension of **3** (125 mg, 0.50 mmol) in dioxane (20 mL) was added DDQ (136 mg, 0.60 mmol) and stirred at rt for 16 h. The reaction mixture was filtered, washed with dioxane to remove excess reagent. The residue was suspended in 0.1% aqueous sodium bicarbonate (100 mL) and sonicated for 15 min. The solid was filtered, washed with water (20 mL) and dried, which was further recrystallized from excess of chloroform/methanol (1:1) to give the product as a pale yellow solid (105 mg, 85% yield), mp >300 °C. IR (KBr) ν_{max} 1656, 1601, 1529, 1352, 1270, 1238, 1142, 1120, 1034, 910 cm^{-1}; ^{1}H and ^{13}C NMR: see Table 2; LC–MS (positive ion mode): m/z 248 (M+H)$^+$; HRMS-(EI) (m/z): (M+Na)$^+$ calcd for $C_{15}H_9N_3ONa$ 270.0643, found 270.0645; HPLC: 99.9%.
Spectroscopic data of **1**: mp 190–192 °C (lit.[5] mp 194–196 °C). IR (KBr) ν_{max} 1705, 1625, 1379, 1326, 1265, 1211, 1179, 1136, 902, 878, 777 cm^{-1}; ^{1}H and ^{13}C NMR: see Table 2; LC–MS (positive ion mode): m/z 248 (M+H)$^+$; HPLC: 99.8%.
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