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Synthesis of 2-aryl-1,2,3,4-tetrahydroquinazolin-1-ols and their conversion to 7-aryl-9*H*-6-oxa-5,8-diaza-benzocycloheptenes

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Abstract—2-Aminobenzylamine was reacted with corresponding aromatic or heteroaromatic aldehydes to give 1,2,3,4-tetrahydroquinazolines **1** the oxidation of which with H_2O_2–tungstate in methanol led to the formation of the corresponding 1,2,3,4-tetrahydroquinazolin-1-ols **2**. A one-pot procedure involving the treatment of the in situ formed quinazoline **1** with H_2O_2–tungstate again led to the formation of **2**. Compounds **2** react with 2 equiv of aryl isocyanate in toluene at room temperature to produce compounds **3**. The probable mechanism of the ring-expanding carbamoylation of quinazolin-1-ols **2** to 6-oxa-5,8-diaza-benzocycloheptenes **3** is discussed.

1. Introduction

The quinazoline ring system is a part of many quinazoline alkaloids.[1–5] Luotonin A, tryptanthrin, febrifugine, rutaecarpine, peganidine, (+)-anisotine, (−)-vasicinone and vasisine are only a few examples of known quinazoline alkaloids.[3] There are examples of synthetic quinazoline derivatives used as pharmaceuticals.[6] Tomudex is a quinazoline derivative, which has demonstrated activity in colorectal, breast and pancreatic cancer.[6a] Many quinazolines can be prepared from 2-aminobenzaldehydes or anthranilic acids.[7] The ring-chain tautomerism of 2-aryl-1,2,3,4-tetrahydroquinazolines obtained from the reaction of 2-aminobenzylamine and the corresponding aldehydes was reported recently.[8]

Here we report the synthesis of tetrahydroquinazolines **1** and their oxidation with H_2O_2–tungstate to the corresponding quinazolin-1-ols **2**. The latter undergo interesting ring expansion to give novel 6-oxa-5,8-diaza-benzocycloheptenes **3** when treated with aryl isocyanates in toluene at room temperature. The probable mechanism of the ring-expanding carbamoylation of quinazolin-1-ols **2** is discussed.

2-Aminobenzylamine was stirred with an equimolar amount of an aldehyde in methanol at room temperature to give the corresponding tetrahydroquinazolines **1**. Compounds **1** could be isolated and characterized or used without isolation in the next step. Tetrahydroquinazolines **1** have an AB system between 3.40 and 3.90 ppm and a singlet near 5.20 ppm in their ^{1}H NMR spectra. All other peaks in their ^{1}H and ^{13}C NMR spectra are in agreement with the proposed quinazoline structure.

The treatment of isolated or in situ formed **1a–d** with H_2O_2 in the presence of catalytic amounts of Na_2WO_4 in methanol at room temperature led to the formation of MeOH insoluble compounds.[9] The elemental analyses and spectral data proved the structures to be quinazolin-1-ols **2** (see Scheme 1). There was again an AB system centred at δ 4.00, J = 16.7 Hz and an one proton singlet at 4.90 ppm. The signals at approximately 45.0 and 78.0 ppm in the ^{13}C NMR spectra corresponded to the benzylic and aminal carbons, respectively. The calculated values were in good agreement with the experimental ones.

Compounds **2** were treated with 2 equiv of an aryl isocyanate to give the corresponding 6-oxa-5,8-diaza-benzo cycloheptenes **3** (see Scheme 1) the structures of which

Keywords: Quinazoline; Quinazolin-1-ol; 6-Oxa-5,8-diaza-benzocycloheptenes; Benzo[*c*]oxadiazepine; Ring expansion; Oxidation with H_2O_2–tungstate; Rearrangement.
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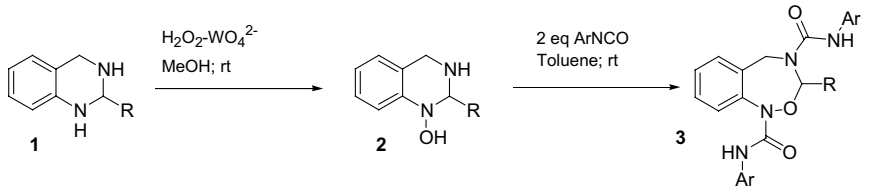


Scheme 1. Reagents: **1**–**3** (a) R = Ph, Ar = Ph; (b) R = 2-furyl, Ar = Ph; (c) R = 4-$MeOC_6H_4$, Ar = Ph; (d) R = 4-ClC_6H_4, Ar = Ph; (e) R = Ph, Ar = 2-$MeOC_6H_4$.

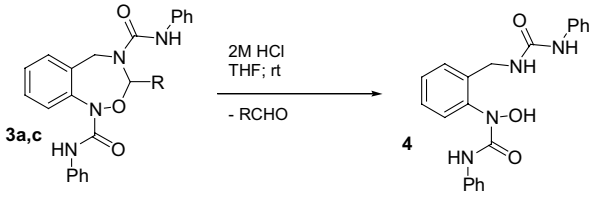
Table 1. Synthesis of compounds **1**, **2**, **3**

1–3	Yield (%)		Mp (°C)			IR **1**	IR **2**		IR **3** (cm^{-1})	
	2	**3**	**1**	**2**	**3**	ν_{NH}	ν_{NH}	ν_{OH}	ν_{NH}	$\nu_{C=O}$
a	31	70	96–97[a]	198	165	3251	3287	2750[d]	3287; 3333	1672; 1652
b	30	85	75–76	189	149	3306	3272	2750	3368; 3414	1670
c	31	60	104–105[b]	199.6	149–150	3241	3281	2750	3328; 3389	1671; 1650
d	30	62	87–90[c]	115.1	158–159	3251	3281	2750	3307; 3409	1667; 1654
e		62			162				3420	1674; 1698

[a] Lit.[8] mp 102–105 °C.
[b] Lit.[8] mp 105–107 °C.
[c] Lit.[8] mp 88–90 °C.
[d] Broad band due to intramolecular hydrogen bonding.

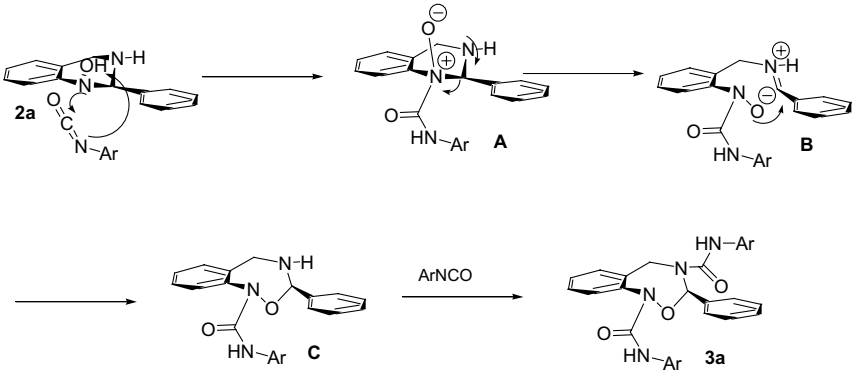
were deduced from their elemental analyses, IR (see Table 1) and NMR data. Compounds **3** have an AB system at approximately 4.50 ppm corresponding to the C-9 methylene and a singlet at 5.64 ppm.[10] The signal in the ^{13}C NMR corresponding to C-7 is at 90.0 ppm. The calculated values for structures **3** are in very good agreement with the experimental values.

To prove the location of hydroxylation in **2** and hence prove the position of the oxygen in structure **3** we hydrolyzed compounds **3** with 2 M HCl in THF and obtained the corresponding diphenylcarbamoylated *N*-(2-aminomethylphenyl)hydroxylamine **4** (see Scheme 2). The ^1H NMR of compound **4** showed a doublet for the benzylic hydrogens at 4.38 ppm $J = 5.9$ Hz, and a triplet for the proton of the benzylic nitrogen at 6.50 ppm, $J = 5.9$ Hz. The other urea type hydrogens gave signals at 8.69 and 9.33 ppm while the hydroxylamine OH appeared at 10.59 ppm. This unequivocally confirmed the position of hydroxylation in compounds **2** to be at nitrogen-1 and the bicyclic system to be 7-aryl-9*H*-6-oxa-5,8-diaza-benzocycloheptene.



Scheme 2.

It can be seen from the energy minimized model of compound **2a** as illustrated in Scheme 3 that the nitrogen not engaged in hydrogen bonding will be more appropriate to attack the isocyanate to give the unstable intermediate **A**, which undergoes ring opening to give **B** the recyclization of which leads to 6-oxa-5,8-diaza-benzocycloheptene **C**. Finally, carbamoylation of the latter gives the corresponding dicarbamoylated 6-oxa-5,8-diaza-benzocycloheptene **3**.



Scheme 3.

2. Experimental

2.1. Synthesis of 2-aryl-1,2,3,4-tetrahydroquinazolines 1. General procedure

To a solution of 2-aminobenzylamine (5 mmol, 0.611 g) in MeOH (20 mL) was added aldehyde (5 mmol) and the reaction mixture stirred for 1 h at room temperature. The solvent was evaporated and the compounds were recrystallized from ether (**1a**,**b**) or ethanol (**1c**,**d**).

2.1.1. 2-Furan-2-yl-1,2,3,4-tetrahydroquinazoline 1b. Prepared according to the general procedure and recrystallized from ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (1H, br s, NH), 3.92 (2H, AB system, $J = 16.8$), 5.23 (1H, s), 6.27 (3H, m), 6.49 (1H, d, $J = 8.0$), 6.63 (1H, t, $J = 7.6$), 6.83 (1H, d, $J = 7.4$), 6.95 (1H, t, $J = 7.6$), 7.32 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.91; 64.20; 107.05; 110.68; 115.73; 118.91; 121.83; 126.60; 127.74; 142.74; 143.25; 154.45.

2.2. 2-Aryl-1,2,3,4-tetrahydroquinazolin-1-ols 2. General procedure

To a solution of 2-aminobenzylamine (5 mmol, 0.611 g) in MeOH (20 mL), the aldehyde (5 mmol) was added and the reaction mixture stirred for 1 h at room temperature. H_2O_2 (20 mmol, 35%, 1.94 g, 1.7 mL) and $Na_2WO_4{\cdot}2H_2O$ (0.25 mmol, 0.075 g) were added and the mixture stirred at room temperature for 1 h. The precipitate formed was filtered and washed with methanol and dried under vacuum. Yield, mp and IR data are given in Table 1.

2.2.1. 2-Phenyl-1,2,3,4-tetrahydroquinazolin-3-ol 2a. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.03 (2H, AB system, $J = 16.7$), 4.92 (1H, s), 6.93 (1H, m), 7.05 (1H, m), 7.23 (2H, m), 7.47 (4H, m), 7.61 (2H, m), 8.89 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.85; 78.85; 118.23; 121.09; 125.53; 126.98; 127.25; 128.25; 128.68; 128.93; 142.49; 150.64. Anal. Calcd for $C_{14}H_{14}N_2O$ (226.27): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.32; H, 5.95; N, 12.30.

2.3. 7-Aryl-9*H*-6-oxa-5,8-diaza-benzocycloheptene-5,8-dicarboxylic acid bis-phenylamide 3. General procedure

Compound **2** (0.5 mmol) was suspended in toluene (15 mL), aryl isocyanate (1 mmol) was added and the mixture stirred for 18 h at room temperature. The precipitated product was filtered and dried under vacuum at room temperature. Yield, mp and IR data are given in Table 1.

2.3.1. 7-Phenyl-9*H*-6-oxa-5,8-diaza-benzocycloheptene-5,8-dicarboxylic acid bis-phenylamide 3a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52 (2H, AB system, $J = 17.7$), 6.35 (1H, s), 6.93 (1H, m), 7.02 (1H, m), 7.12–7.23 (10H, m), 7.37 (5H, m), 7.53 (2H, m), 7.67 (1H, s), 7.8 (1H, d, $J = 7.9$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.17; 90.22; 120.73; 121.03; 122.68; 124.33; 124.54; 126.20; 126.70; 127.40; 128.09; 128.72; 129.24; 129.26; 129.42; 130.00; 135.26; 137.70; 138.21; 139.36; 152.07; 155.80. Anal. Calcd for $C_{28}H_{24}N_4O_3$ (464.52): C, 72.40; H, 5.21; N, 12.06. Found: C, 72.35; H, 5.15; N, 12.00.

2.4. Synthesis of diphenylcarbamoylated *N*-(2-aminomethyl-phenyl)-hydroxylamine 4

To a solution of compound **3** (0.2 mmol) in THF (10 mL), hydrochloric acid (10 mL, 2 M) was added and the solution was stirred for 15 min. The solution was extracted with chloroform (3×10 mL) and the combined extracts were washed with water (2×10 mL) and dried over anhydrous Na_2SO_4. The organic solvent was removed under vacuum and the residue was triturated with ether to give compound **4** in quantitative yield. Mp 165–165.3 °C; IR (KBr) ν_{NH} 3358; ν_{OH} 3159; $\nu_{C=O}$ 1646 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.38 (2H, d, $J = 5.9$), 6.50 (1H, t, $J = 5.9$), 6.9 (1H, t, $J = 7.3$), 7.01 (1H, t, $J = 7.3$), 7.20–7.42 (10H, m), 7.7 (2H, d, $J = 6.5$), 8.69 (1H, s), 9.33 (1H, s), 10.59 (1H, s). Anal. Calcd for $C_{21}H_{20}N_4O_3$ (376.41): C, 67.01; H, 5.36; N, 14.88. Found: C, 67.10; H, 5.30; N, 14.80.

Acknowledgements

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9. In the case of compounds **1** having aliphatic R the precipitation of **2** were not observed. The products resulted from further oxidation of **2**.
10. The value is too high for an aminal proton in the unexpanded quinazoline structure. If this was the case, carbamoylation would occur at the oxygen, which should give a carbonyl frequency at approximately 1740 cm^{-1}.