HETEROCYCLES, Vol. 80, No. 2, 2010, pp. 1457 - 1461. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd July, 2009, Accepted, 11th September, 2009, Published online, 15th September, 2009
DOI: 10.3987/COM-09-S(S)72

TETRAHYDROQUINAZOLINE DERIVATIVES BY AZA DIELS-ALDER REACTION §

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Abstract – The reaction of *N*-(2-Chloromethylphenyl)benzenesulfonamides (**1**) with *N*-benzylideneamines (**2**) gives 1,2,3,4-tetrahydroquinazoline derivatives (**3**) *via* the highly reactive *o*-azaxylylene intermediates. The structure of (**3**) is fully assigned on the basis of analytical and spectroscopic data. The chemical behaviour of (**3**) has been studied.

Some our previous results concerned the reaction of **1** with enol ethers, enamines and enolates to obtain different classes of heterocyclic systems.[1,2] To explain the formation of heterocyclic derivatives we suggested the transformation of **1** into *o*-azaxylylenes,[3] a particular class of 1-aza-buta-1,3-dienes whose use on hetero Diels-Alder reactions is well known.[4] In continuation of our interest on reactivity of **1** towards dienophiles, we report a new approach to tetrahydroquinazoline ring system by reaction of **1** with *N*-benzylideneamines (**2**). Among the remarkable number of quinazoline synthesis[5] none deals with the direct preparation of its 1,2,3,4-tetrahydro-derivatives. The reported methods are based on the reduction of entirely or partly oxidized substrates.[5] Recent advances in quinazoline chemistry are concerned with the presence of this ring system in alkaloids[6] and in neuroprotective compounds, such as Dictyoquinazol B[7] with biological activity in neurodegeneration deseases.

The treatment of benzyl halides **1** with *N*-benzylideneamines (**2**), in dichloromethane solution in presence of cesium carbonate at -20 °C, leads to the formation of cycloadducts **3** in good to fair yields (**Scheme 1**). The structure of products **3** was assigned by means of analytical and spectroscopic data.

§ This paper is dedicated to Prof. Emeritus Akira Suzuki in the occasion of his 80th birthday.

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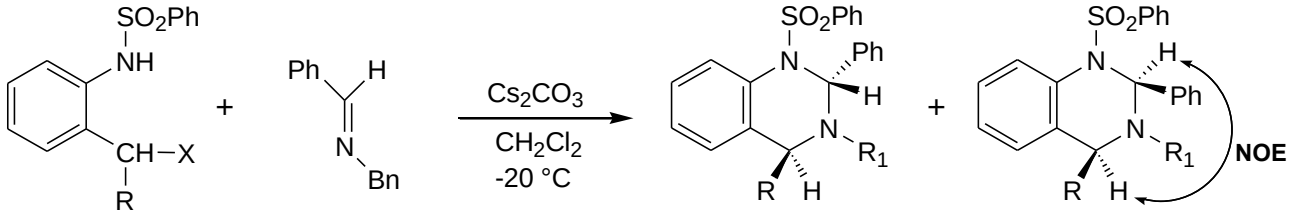
In the case of the reaction between **1b** and **2a** a careful NMR analysis of crude reaction mixture indicated the presence of two diastereomeric products **3e**/**3e'** in ratio 90:10. As it was not possible to separate them by means of chromatography on silica gel or crystallization, the mixture was submitted to NOESY analysis to determine their relative stereochemistry. The positive NOE effect observed in the minor diastereomer between the two protons H-2 and H-4, allowed us to assign to it the relative *cis* configuration, thereby the relative *trans* configuration was assigned to the major one.

Scheme 1



1a-b **2a-d** **3a-e** **3e'**

1a : R = H; X = Cl
1b : R = Ph, X = Br

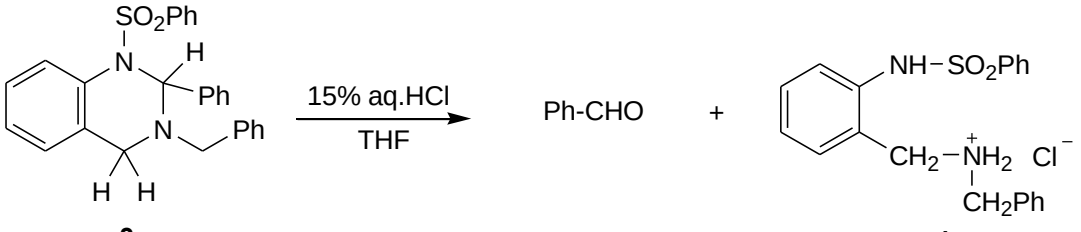
2a : R_1 = Bn
2b : R_1 = C_6H_{11}
2c : R_1 = Ph
2d : R_1 = 4-MeO-C_6H_4

3a	: R = H; R_1 = Bn	(72%)
3b	: R = H; R_1 = C_6H_{11}	(65%)
3c	: R = H; R_1 = Ph	(68%)
3d	: R = H; R_1 = 4-MeO-C_6H_4	(78%)
3e/3e'	: R = Ph; R_1 = Bn	(81%)

The formation of quinazoline derivatives (**3**) can be explained assuming an initially base promoted elimination of hydrogen halide from **1** giving to the highly reactive intermediate *o*-azaxylylenes.[1,2] Successively, these intermediates are readily trapped by electron rich imines (**2**)[8] to give tetrahydroquinazolines (**3**) *via* aza Diels-Alder type reaction. The stereochemical results observed in the reaction of **1b** with **2a** can be rationalized taking into account the two possible attacks of the *E*-imine to the dienic system with a preferential formation of the more stable *trans* diastereoisomer **3e**.

Compounds **3** can be structurally correlated to *N*,*N*-acetals therefore unstable under acid conditions and stable in basic medium. In order to confirm this prediction we treated **3** with 15% aq. HCl solution in THF solution and observed its complete transformation into **4** with elimination of benzaldehyde (**Scheme 2**). As expected no reaction occurs with potassium *t*-butoxide in DMF solution.

Scheme 2



3a **4**

EXPERIMENTAL

Melting points were determined on a *Büchi* B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department. ^{1}H NMR spectra were recorded in $CDCl_3$ solution using a *Bruker AMX 300 MHz* spectrometer, and chemical shifts are given in ppm relative to TMS. The MS spectra were determined using a *VG Analytical 7070 EQ* mass spectrometer with an attached *VG Analytical 11/250* data system.

***N*-(2-Bromophenylmethylphenyl)benzenesulfonamide (1b)**[9] and **imines** (**2a-d**)[10,11,12] were prepared according to the reported procedures.

***N*-(2-Chloromethylphenyl)benzenesulfonamide (1a)**. This compound was obtained following Corey's method,[3] reported for the tosyl analogue, starting from 2-aminobenzyl-alcohol and benzenesulfonyl chloride. Solid, mp 148-150 °C (toluene). Yield 98%. ^{1}H NMR δ: 4.33 (s, 2H, CH_2); 6.75 (s, 1H, NH); 7.20-7.98 (m, 9H, Ar). *Anal.* Calcd for $C_{13}H_{12}ClNO_2S$: C, 55.42; H, 4.29; N, 4.97. Found: C, 55.31; H, 4.21; N, 4.92.

Preparation of quinazoline derivatives (3): general procedure.

To a suspension of cesium carbonate (2.0 mmol) in CH_2Cl_2 (20 mL) containing **2** (2.0 mmol), cooled to -20 °C, **1** (1.0 mmol) in CH_2Cl_2 (20 mL) was added in 4 h and the mixture was then stirred at rt for 16 h. Treatment with water (20 mL), separation of organic layer and evaporation of the solvent gave the crude products. After column chromatography (Al_2O_3 – toluene/AcOEt : 85/15) were obtained:

1-Benzenesulfonyl-3-benzyl-2-phenyl-1,2,3,4-tetrahydroquinazoline (3a): Solid, mp 156-158 °C (toluene). Yield 72%. ^{1}H NMR δ: 3.25 (d, 1H, J = 17.2 Hz, H-4); 3.55 (d, 1H, J = 13.7 Hz, N-CH_2); 3.75 (d, 1H, J = 17.2 Hz, H-4); 4.00 (d, 1H, J = 13.7 Hz, N-CH_2); 6.60 (s, 1H, H-2); 6.80-8.00 (m, 19H, Ar). ^{13}C NMR δ: 46.0 (C-4); 58.0 (CH_2 of Bn); 78.5 (C-2); 120.0-140.6 (Ar). MS (IE) *m/z* = 440 [M^+]. *Anal.* Calcd for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.45; N, 6.36. Found: C, 73.54; H, 5.49; N, 6.34.

1-Benzenesulfonyl-3-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroquinazoline (3b): Solid, mp 128-130 °C (*i*-Pr_2O). Yield 65%. ^{1}H NMR δ: 1.10-2.50 (m, 11H, cyclohexyl); 3.50 (d, 1H, J = 17.0 Hz, H-4); 3.70 (d, 1H, J = 17.0 Hz, H-4); 6.50 (s, 1H, H-2); 6.80-7.85 (m, 14H, Ar). *Anal.* Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.19; H, 6.52; N, 6.48. Found: C, 72.08; H, 6.44; N, 6.50.

1-Benzenesulfonyl-2,3-diphenyl-1,2,3,4-tetrahydroquinazoline (3c): Solid, mp 164-165 °C (toluene). Yield 68%. ^{1}H NMR δ: 3.45 (d, 1H, J = 15.4 Hz, H-4); 4.05 (d, 1H, J = 15.4 H-4); 6.75 (s, 1H, H-2); 6.82-7.96 (m, 19H, Ar). MS (IE) m/z = 426 [M^+]. *Anal.* Calcd for $C_{26}H_{22}N_2O_2S$: C, 73.21; H, 5.20; N, 6.57. Found: C, 73.18; H, 5.18; N, 6.49.

1-Benzenesulfonyl-3-(4-methoxy-phenyl)-2-phenyl-1,2,3,4-tetrahydroquinazoline (3d): Solid, mp 168-170 °C (toluene). Yield 78%. ^{1}H NMR δ: 3.50 (d, 1H, J = 13.5 Hz, H-4); 3.75 (s, 3H, OMe); 4.10 (d, 1H, J = 13.5 H-4); 6.65 (s, 1H, H-2); 6.70-7.86 (m, 18H, Ar). ^{13}C NMR δ: 45.0 (C-4); 55.7 (Me-O); 71.4 (C-2); 113.8-141.6 (Ar). *Anal.* Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 71.05; H, 5.32; N, 6.11.

1-Benzenesulfonyl-3-benzyl-2,4-diphenyl-1,2,3,4-tetrahydroquinazoline (3e/3e'): Solid, mp 143-145 °C (MeOH). Yield 81%. ^{1}H NMR (mixture of two diastereoisomers **3e/3e'** in ratio 90:10 respectively) δ: 3.20 (d, 1H, J = 13.3 Hz, N-CH_2) (**3e**); 3.45 (d, 1H, J = 13.3 Hz, N-CH_2) (**3e**); 3.85 (d, 1H, J = 13.2 Hz, N-CH_2) (**3e'**); 4.03 (d, 1H, J = 13.2 Hz, N-CH_2) (**3e'**); 4.30 (s, 1H, H-4) (**3e'**); 4.95 (s, 1H, H-4) (**3e**); 6.20 (s, 1H, H-2) (**3e**); 6.54 (s, 1H, H-2) (**3e'**); 6.70-8.00 (m, 24H, Ar). ^{13}C NMR (mixture of two diastereoisomers **3e/3e'**) δ: 53.4 (CH_2) (**3e**); 59.6 (CH_2) (**3e'**); 63.5 (C-4) (**3e'**); 64.3 (C-4) (**3e**); 72.7 (C-2) (**3e**); 75.1 (C-2) (**3e'**); 124.2-142.7 (Ar). *Anal.* Calcd for $C_{33}H_{28}N_2O_2S$: C, 76.72; H, 5.46; N, 5.42. Found: C, 76.62; H, 5.49; N, 5.45.

***N*-[2-(Benzylamino-methyl)-phenyl]benzenesulfonamide hydrochloride (4).**

A solution of **3a** (1.0 mmol) in THF (20 mL) was treated with aq. HCl 15% solution (10 mL) and heated at 60 °C for 6 h. The organic solvent was evaporated off and the water residue extracted with toluene. The organic phase was separated, the aqueous layer was evaporated off and the residue treated with acetone. The solid was filtered and purified by crystallisation. Solid, mp 186-188 °C (AcOEt). Yield 75%. ^{1}H NMR δ: 3.45 (s, 2H, CH_2); 3.75 (s, 2H, CH_2); 7.00-7.82 (m, 14H, Ar). *Anal.* Calcd for $C_{20}H_{21}ClN_2O_2S$: C, 61.77; H, 5.44; N, 7.20. Found: C, 61.88; H, 5.41; N, 7.28.

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