HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 1341 - 1345. © The Japan Institute of Heterocyclic Chemistry
Received, 18th July, 2008, Accepted, 12th September, 2008, Published online, 18th September, 2008
DOI: 10.3987/COM-08-S(F)50

QUINOLINE DERIVATIVES BY CYCLOCONDENSATION OF *N*-(2-BROMOPHENYLMETHYLPHENYL)BENZENESULFONAMIDE WITH ENOL ETHERS AND ENAMINES[§]

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Abstract – The reaction of *N*-(2-bromophenylmethylphenyl)benzenesulfonamide (**1**) with electron rich alkenes (enol ethers (**2**), (**3**) and enamines (**4**)) gives quinoline derivatives **5** and ring fused quinoline **6**, **7** whose structures were assigned on the basis of analytical and spectroscopic data. The chemical behavior of adducts **5** and **7** is reported.

INTRODUCTION

In previous papers[1,2] we reported the use of benzyl bromides **1** as starting material for the preparation of different classes of heterocyclic systems. In continuation of our interest in this field and considering the significant applications of quinoline derivatives in synthetic organic-, bioorganic- and medicinal chemistry we describe an approach to the quinoline ring system.

RESULTS AND DISCUSSION

The treatment of **1** with **2**, **3**, **4** in DMF solution and sodium hydride at 0 °C, leads to the formation of cycloadducts **5**, **6**, **7** in good to fair yields[3] (**Scheme 1**). The structure of compounds **5**, **6**, **7** was assigned on the basis of analytical and spectroscopic data.

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§ This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

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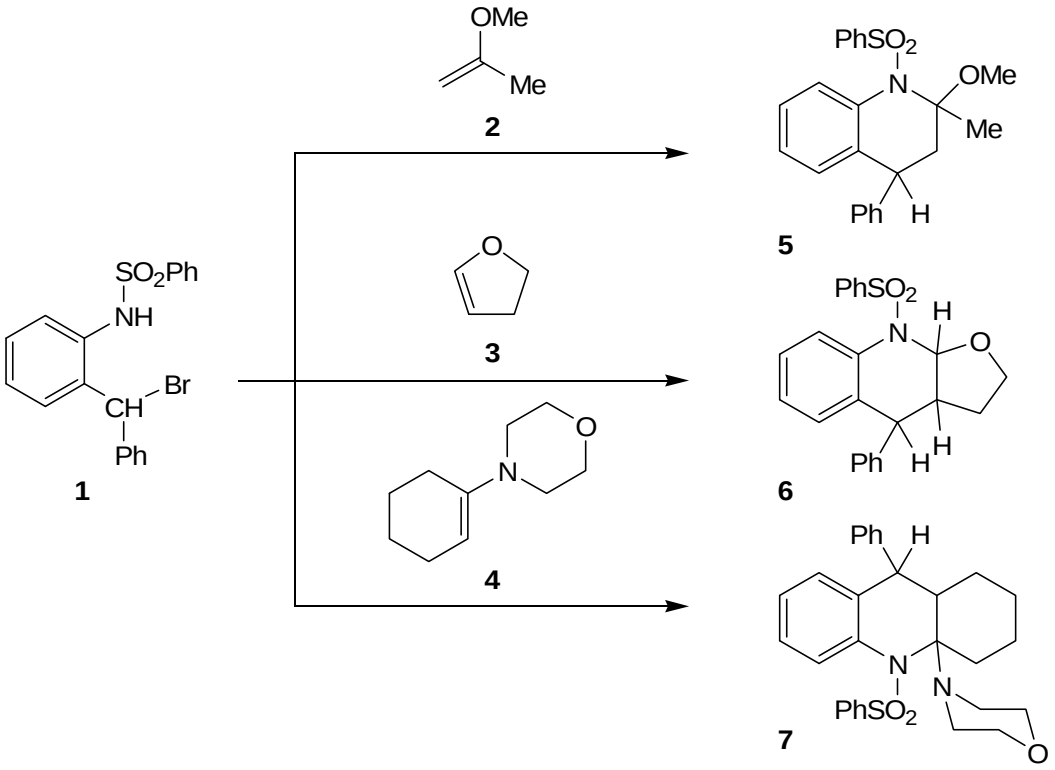
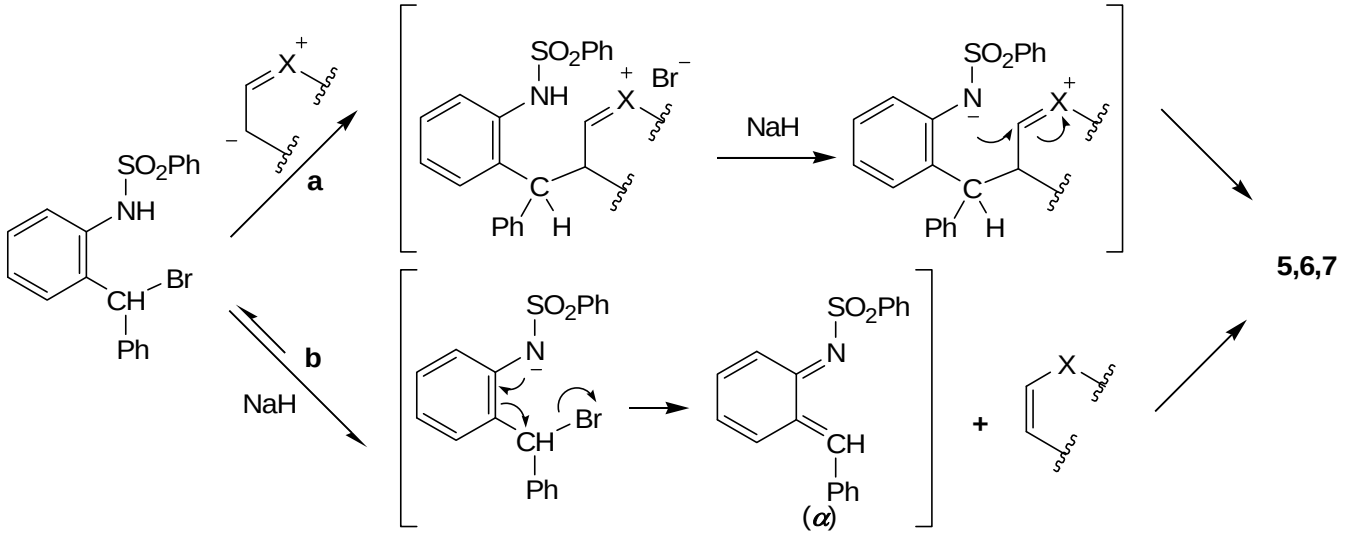
Scheme 1



The formation of adducts **5**, **6**, **7** can be rationalized assuming the behaviour of enol ethers and enamines (carbon anion in character) towards the *N*-(2-bromophenylmethylphenyl)benzenesulfonamide **1**, bearing an electrophilic center and a nucleophilic heteroatom (**Scheme 2 – pathway a**).

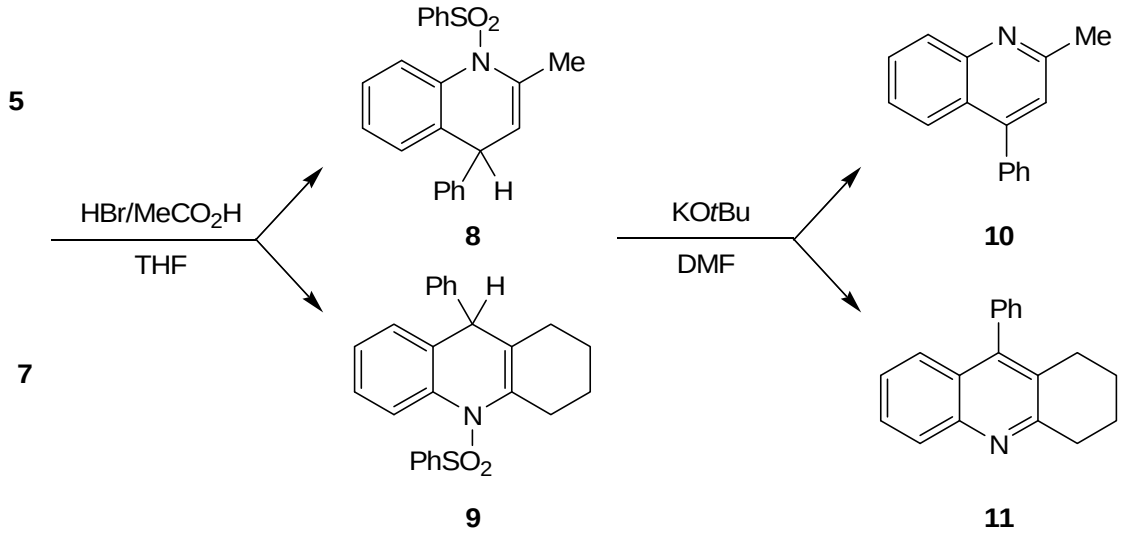
Scheme 2



Alternatively, the dehydrohalogenation of **1** by the enolate to *o*-azaxylylene (α), a highly reactive intermediate, cannot be ruled out. Starting from (α) it is possible a direct aza Diels-Alder cycloaddition with electron rich alkenes to give the final products. Some attempts to isolate (α) or detect its presence in the reaction mixture were unsuccessful as previously reported[4] for other cases of intermediate *o*-azaxylylenes.

The adducts **5** and **7** can be considered possible intermediate for the preparation of quinoline derivatives. With this purpose we treated **5** and **7** in THF solution with 40% HBr solution in acetic acid and observed their complete transformation into **8** and **9** respectively (**Scheme 3**).

Scheme 3



Finally, according to the known behaviour of *N*-phenylsulfonyl protected heterocycles under basic conditions, it is possible to eliminate this group with potassium *t*-butoxide in DMF solution and gain aromaticity to quinoline systems **10** and **11** in high yields.

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 (1)** was prepared according to the reported procedure.[2]

Enol ethers **2**, **3** and enamine **4** are commercially available.

Preparation of adducts (5, 6, 7): general procedure.

To a solution of **1** (3.0 mmol) and suitable **2, 3, 4** (6.0 mmol) in dimethylacetamide (10 mL) cooled to -10 °C NaH (3.0 mmol, 50% in oil) was added and the mixture was stirred at rt for 16 h. Treatment with water (20 mL), extraction with AcOEt (3 x 15 mL) and evaporation of the solvent gave the crude products. After column chromatography (SiO_2 – toluene/AcOEt : 90/10) were obtained:

2-Methoxy-2-methyl-4-phenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (5): Solid, mp 113-115 °C (*i*-Pr_2O). Yield 75%. ^{1}H NMR δ: 1.92 (s, 3H, CH_3); 2.20 (dd, 1H, *J* = 9.1 Hz, *J* = 14.0 Hz, H-3); 2.33 (dd, 1H, *J* = 7.8 Hz, *J* = 14.0 Hz, H-3); 3.15 (s, 3H, OCH_3); 3.20 (dd, 1H, *J* = 7.8 Hz, *J* = 9.1 Hz, H-1); 6.80-7.80 (m, 14H, Ar). MS (IE) *m/z* = 393 [M^+]. *Anal.* Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.19; H, 5.79; N, 3.47.

4-Phenyl-9-phenylsulfonyl-2,3,3a,4,9,9a-hexahydrofuro[2,3-*b*]quinoline (6): Solid, mp 164-166 °C (MeCN). Yield 71%. ^{1}H NMR δ: 1.60 (m, 1H, H-3); 1.98 (m, 1H, H-3); 3.18 (dq, 1H, *J* = 3.4 Hz, *J* = 8.6 Hz, H-3a); 3.40 (d, 1H, *J* = 3.4 Hz, H-4); 3.70 (m, 1H, H-2); 3.82 (dt, 1H, *J* = 3.6 Hz, *J* = 8.5 Hz, H-2); 6.35 (d, 1H, *J* = 8.1, H-9a); 6.75-7.85 (m, 14H, Ar). *Anal.* Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.52; H, 5.33; N, 3.60.

4a-Morpholin-4-yl-9-phenyl-10-phenylsulfonyl-1,2,3,4,4a,9,9a,10-octahydroacridine (7): Solid, mp 176-177 °C (MeOH). Yield 92%. ^{1}H NMR δ: 1.50-2.00 (m, 8H, cyclohexane); 2.75 (t, 4H, $N(CH_2)_2$); 3.75 (t, 4H, $O(CH_2)_2$); 4.50 (d, 1H, *J* = 7.2 Hz, H-4a); 5.50 (d, 1H, *J* = 7.2 Hz, H-9); 6.75-7.75 (m, 14H, Ar). MS (IE) *m/z* = 488 [M^+]. *Anal.* Calcd for $C_{29}H_{32}NO_3S$: C, 71.28; H, 6.60; N, 5.73. Found: C, 71.28; H, 6.51; N, 5.68.

Transformation of adducts (5, 7): general procedure.

To a solution of **5**/**7** (10.0 mmol) in THF (10 mL) 40% HBr solution in acetic acid (0.2 mL) was added and the mixture was stirred at 60 °C for 6 h. The solvent was evaporated off and the residue was taken up with water/AcOEt. The organic phase was separated, washed with 5% aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4) and evaporated off. The residue was purified by crystallization. In this way were obtained:

2-Methyl-4-phenyl-1-phenylsulfonyl-1,4-dihydroquinoline (8): Solid, mp 168-170 °C (toluene). Yield 84%. ^{1}H NMR δ: 2.22 (s, 3H, CH_3); 5.54 (d, 1H, *J* = 7.7 Hz, H-4); 6.30 (d, 1H, *J* = 7.7 Hz, H-3); 6.90-

7.80 (m, 14H, Ar). MS (IE) *m/z* = 361 [M^+]. *Anal.* Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 73.09; H, 5.21; N, 3.84.

9-Penyl-10-phenylsulfonyl-1,2,3,4,9,10-hexahydroacridine (9): Solid, mp 165-167 °C (AcOEt). Yield 81%. ^{1}H NMR δ: 1.50-2.50 (m, 8H, $(CH_2)_4$); 6.50 (s, 1H, H-9); 7.10-7.80 (m, 14H, Ar). MS (IE) *m/z* = 401 [M^+]. *Anal.* Calcd for $C_{25}H_{23}NO_2S$: C, 74.78; H, 5.77; N, 3.49. Found: C, 74.65; H, 5.68; N, 3.45.

Aromatisation of compounds (8, 9): general procedure.

To a solution of **8**/**9** (10 mmol) in DMF (10 mL), potassium *t*-butoxide (10 mL) was added and the mixture stirred at 65 °C for 4 h. The reaction was poured in water (20 mL), and the product was extracted with AcOEt (2x15 mL). The organic layer was washed with H_2O (10 mL), dried (Na_2SO_4) and the solvent was evaporated off. The residue was crystallized and afforded:

2-Methyl-4-phenylquinoline (10): Solid, mp 96-98 °C (*i*-Pr_2O). Yield 70%. Lit.,[5] 97-98 °C.

9-Penyl-1,2,3,4-tetrahydroacridine (11): Solid, mp 143-145 °C (*i*-Pr_2O). Yield 85%. Lit.,[6] 142-143 °C. The spectroscopic data (^{1}H NMR and MS) agree with those reported.

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