Transformation of 3-Nitroanilines into Dioxoisothiazolo[5,4,3-*k,l*]acridines

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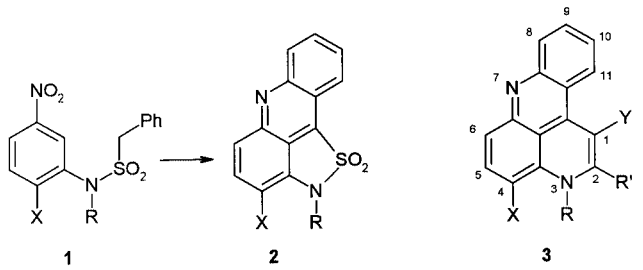
Received 24 August 2001

Abstract: *N*-Methyl-*N*-3-nitroaryl benzyl sulfonamides on treatment with *t*-BuMe$_2$SiCl in the presence of DBU formed silylated oxime derivatives which were photocyclized to the dioxoisothiazolo[5,4,3-*k,l*]acridine systems. In one example the latter was converted to pyridoacridine derivative.

Key words: benzyl nitroarylsulfonamides, cyclization, silylation, nucleophilic aromatic substitution, photochemistry

Recently, we reported a 3-step conversion of 3-nitroanilines into tricyclic 1*H*-1-alkyl-8-X-2,2-dioxoisothiazolo[5,4,3-*d,e*]quinolines via intramolecular cyclization of *N*-alkyl-*N*-3-nitroaryl prop-3-enyl sulfonamides in the presence of base and Lewis acid.[1] These tricyclic products were further converted to 2,2-dioxoisothiazolo[5,4,3-*d,e*]quinolines[2] as well as to 1*H*-benzo[*i,j*][2,7]naphthyridines.[3]

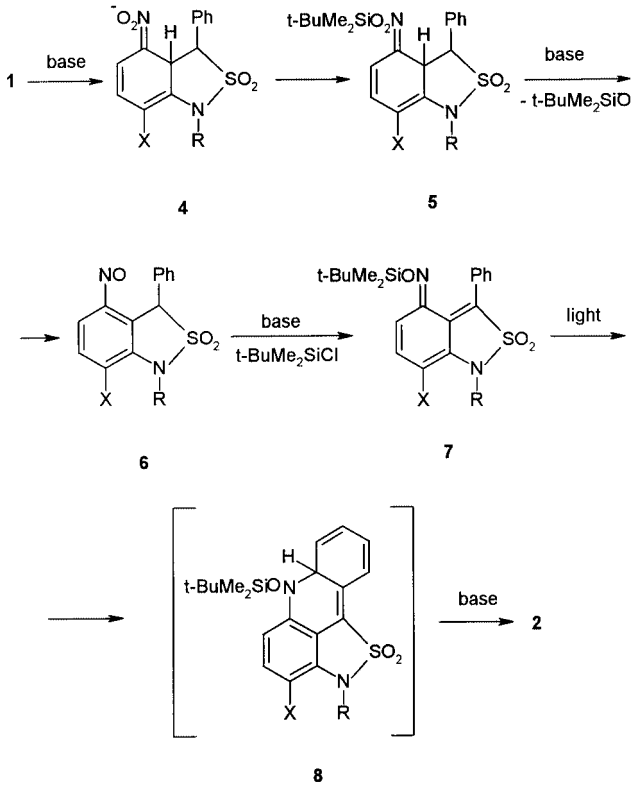
As we were looking for the intermediate in the synthesis of some pyridoacridine marine alkaloids **3**[4] we used the phenyl ring as the equivalent of the vinyl group (**1** as a starting material), expecting the formation of a fused tetracyclic system **2** (Scheme 1).



Scheme 1

Preliminary attempts to convert directly *N*-methyl-*N*-(3-nitrophenyl) benzylsulfonamide **1a** (prepared from 3-nitroaniline via sulfonylation with commercial benzylsulfonyl chloride followed by alkylation with methyl iodide)[5] to **2a** in the presence of DBU and Lewis acids such as $MgCl_2$, $Ti(O\text{-}iPr)_4$, Me_3SiCl or bis-trimethylsilylacetamide[2] in various solvents were discouraging.

Unexpectedly, when **1a** was treated with an excess of *t*-BuMe$_2$SiCl and DBU in dry acetonitrile solution, a deep red compound precipitated which turned out to be the silylated oxime form **7a** of nitroso compound **6a** (Scheme 2).[6]



Scheme 2

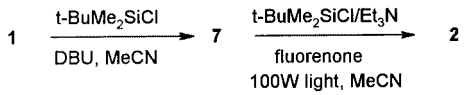
This compound was comparatively stable for aqueous work-up or crystallization and (to some extent) even for column chromatography. Its isolation supported the previously presented idea that similar reactions may proceed via nitroso compounds as intermediates.[2] The proposed structure of **7a** agrees with its ^{1}H NMR spectrum. It seems that **7a** exists as a single, presumably *anti* isomer.

Some efforts were undertaken in order to transform **7a** into **2a**. Refluxing **7a** in xylene produced **2a** in a low 20% yield. Further attempts to improve the yield of **2a** by changing the solvent, addition of acids or bases, photochemical conditions (mercury lamp or sunlight in MeCN, AcOEt, PhH or DCM, addition of some sensitizers) were discouraging. The best result was obtained when the diluted acetonitrile solution of **7a** containing *t*-BuMe$_2$SiCl/Et_3N system and fluorenone as sensitizer was exposed to light of an ordinary 100W bulb for several days. After col-

Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1927,1928,ftx,en;G18601ST.pdf.

ISSN 0936-5214

umn chromatography **2a** was isolated in 68% yield.[7] Other *N*-alkyl-*N*-(3-nitroaryl) benzylsulfonamides were found to undergo the same transformations (Equation,Table).



Equation

Table Conversion of **1** to **7** and Photocyclization of **7** to **2**

1	X	R	**7**	Yield[%][a]	**2**	Yield[%][a]
a	H	Me	**a**	88	**a**	68
b	H	allyl	–	–[b]	**b**	22[c]
c	H	Bn	–	–[b]	**c**	25[c]
d	Cl	Me	**d**	82	**d**	88[d]
e	Cl	allyl	**e**	–[b]	**e**	23[d]

[a] Isolated yield.
[b] Conversion to **2** performed on crude mixture resulted from silylation of **1** after addition of *t*-BuMe$_2$SiCl and fluorenone.
[c] Yield after two steps based on **1**.
[d] 150 W bulb.

In the cases where **7** was difficult to separate, the cyclization step was conducted on the crude silylation mixture after addition of more *t*-BuMe$_2$SiCl and fluorenone.

The nature of cyclization remained unclear so far. It seems that the photochemical conrotation might be favoured over the thermal disrotation process for steric reasons. Addition of a base and silylating agent would facilitate elimination of *t*-butyldimethylsilanol from the cyclized intermediate **8** to form aromatized system.

As an illustration of the versatility of dioxoisothiazolo[5,4,3-*k,l*]acridines as intermediates in synthesis of pyridoacridine systems **2a** was converted to **3a** (X = H, R = R' = Me, Y = CO_2Me)[8] on treatment with methyl acetoacetate in K_2CO_3/DMF system.[3]

Acknowledgement

This study was funded by the State Committee of Scientific Research Grant No. PBZ 6.01.

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(4) For example: (a) Delfourne, E.; Roubin, C.; Bastide, J. *J. Org. Chem.* **2000**, *65*, 5476. (b) Nakahara, S.; Matsui, J.; Kubo, A. *Tetrahedron Lett.* **1998**, *39*, 5521. (c) Kitahara, Y.; Tamura, F.; Nishimura, M.; Kubo, A. *Tetrahedron* **1998**, *54*, 8421. (d) Ozturk, T.; Mc Killop, A. *Can. J. Chem.* **2000**, *78*, 1158.
(5) Typical conditions: (a) : Sulfonylation: 3-Nitroaniline (1.38 g, 10 mmol); benzylsulfonyl chloride (2.30 g, 12 mmol); dry pyridine (20 mL); 0 °C to r.t.; 6 h; 75%; (b) : Methylation to **1a**: (1.17g, 4 mmol); K_2CO_3 (2.7 g, 20 mmol); MeI (excess, 1 mL); dry DMF (10 mL); r.t.; 3 h; 90%.
(6) Typical procedure: **1a** (306 mg, 1 mmol); *t*-BuMe$_2$SiCl (452 mg, 3 mmol); DBU (746 μL, 5 mmol); dry MeCN (20 mL); 8 days at r.t.; 130 mg of **7a** (85%); mp 191–192 °C (PhCH$_3$-hexane); δ_H (200 MHz, $CDCl_3$): –0.12 (s, 6 H), 0.78 (s, 9 H), 3.16 (s, 3 H), 5.51 (d, *J* = 6.6 Hz, 1 H), 6.45 (dd, *J* = 10.0, 6.6 Hz, 1 H), 6.69 (dd, *J* = 10.0, 0.6 Hz, 1 H), 7.39-7.50 (m, 3 H), 7.56-7.66 (m, 2 H); *m/z* (EI, int.%): 403 (27.9), 402 (100.0), 401 (11.8), 346 (10.9), 345 (46.4), 297 (8.5), 282 (21.6), 281 (87.6), 280 (22.1), 272 (23.6), 271 (43.9); UV ($CHCl_3$): 465.8 nm.
(7) Typical procedure: **7a** (50 mg, 0.125 mmol); *t*-BuMe$_2$SiCl (19 mg, 0.125 mmol), Et_3N (20 μL, 0.130 mmol); fluorenone (20 mg); dry MeCN (25 mL); 100 W bulb; 2 days; yield: 23 mg of **2a** (68%): δ_H (500 MHz, DMSO-d_6): 3.44 (s,3 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 7.76 (d, *J* = 9.0 Hz, 1 H,), 7.94 (dd, *J* = 9.0, 7.2 Hz, 1 H), 7.96-8.00 (m, 1 H), 8.10 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1 H), 8.33 (app d, *J* = 8.4 Hz, 1 H), 8.44 (d, *J* = 8.8 Hz, 1 H); δ_c (125 MHz, DMSO-d_6): 150.1 (Cq), 146.0 (Cq), 136.5 (Cq), 134.3, 132.8 (Cq), 131.9, 130.6, 130.4, 122.1, 119.3, 117.4 (Cq), 112.5 (Cq), 102.9, 27.0 (CH_3); *m/z* (EI, int.%): 271 (9.6), 270 (100.0), 223 (7.55), 222 (41.7), 221 (11.0), 206 (8.4), 205 (42.4), 179 (27.0), 178 (19.9); HRMS: calcd. for $C_{14}H_{10}O_2N_2S$ [270.0463], found: 270.0458.
(8) Following procedure:[3] **2a** (68 mg, 0.25 mmol), methyl acetoacetate (0.56 mL, 5 mmol) and K_2CO_3 (345 mg, 2.5 mmol) were stirred in DMF (5 mL) for 20 h at r.t. After evaporation of the solvent and the excess of methyl acetoacetate the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (1:5) mixture as eluent to give **3** as red crystals (35 mg; 45%): δ_H (500 MHz, DMSO-d_6): 2.45 (s, 3 H), 3.49 (s, 3 H), 3.85 (s, 3 H), 6.65 (d, *J* = 7.8 Hz, 1 H, H-8), 7.23 (ddd, *J* = 8.7, 6.6, 1.3 Hz, 1 H, H-9), 7.32 (dd, *J* = 8.6, 0.7 Hz, 1 H, H-4), 7.56 (app d, *J* = 8.6 Hz, 1 H, H-11), 7.59 (ddd, *J* = 8.6, 6.6, 1.3 Hz, 1 H, H-10), 7.63 (t, *J* = 8.6 Hz, 1 H, H-5), 7.71 (dd, *J* = 8.6, 0.7 Hz, 1 H, H-6); *m/z* (EI, int.%): 305 (21,6), 304 (100.0), 290 (3.7), 289 (15.7), 274 (10.3), 273 (5.47), 258 (3.1), 248 (6.3), 245 (10.1), 229 (11.3); HRMS: calcd. for $C_{19}H_{16}O_2N_2$ [304.1212], found: 304.1205.