Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4667-4670, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00962-3

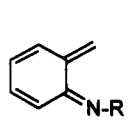
Generation and Reactions of Heteroanalogues of Aza-*ortho*-xylylenes

Krzysztof Wojciechowski* and Szymon Kosiński

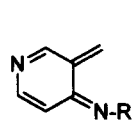
Institute of Organic Chemistry Polish Academy of Sciences
ul. Kasprzaka 44/52, PL. 01-224 Warszawa 42, P.O.Box 58, Poland.
e-mail: KRIS@ICHF.EDU.PL

Abstract: Intramolecular nucleophilic substitution of chlorine in 2-chloro-3-(alkanesulfonylamino)pyridines furnishes *N*-alkyl-1,3-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxides (pyridosultams, **8**), which undergo thermal extrusion of SO_2 giving heteroanalogues of aza-*ortho*-xylylenes **9**. These reactive 1-azadienes enter [4+2] cycloaddition with dienophiles leading to tetrahydro[1,5]naphthyridines **11**. With an excess of dienophile (*N*-phenylmaleimide) pyridoazocine derivatives **12** and **13** being 2:1 adducts are formed. © 1997 Elsevier Science Ltd.

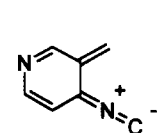
Ortho-quinodimethanes (*ortho*-xylylenes) reactive dienes have found numerous applications in organic synthesis, particularly for the construction of condensed carbocyclic systems.[1-3] In recent years also numerous examples of applications of hereroanalogues of *ortho*-xylylenes as building blocks for the synthesis of heterocycles have been described.[4] The aza-analogues of *ortho*-quinodimethanes, aza-*ortho*-xylylenes (6-methylene-2,4-cyclohexadien-1-imines, **1**), potential building blocks for the synthesis of fused heterocycles, are still less known and used in organic synthesis.[5,6] To our knowledge there are only three reports dealing with the generation and transformations of heteroanalogues of aza-*ortho*-xylylenes. Storr *et al.* have described intramolecular reactions of pyridine analogues of aza-*ortho*-xylylene **2** generated via 1,4-elimination of water from 4-amino-3-(hydroxymethyl)pyridine derivatives by flash vacuum pyrolysis at 600-800 °C.[7] Cumulated aza-*ortho*-xylylene **3** was generated via 1,5-elimination of hydrogen chloride from imidochloride derived from 4-amino-3-methylpyridine and cyclized to 2-phenyl-5-azaindole.[8] In mild conditions proceeded 1,4-elimination of hydrogen fluoride from 3-amino-4-(trifluoromethyl)quinoline led to heteroxylylene **4**, an intermediate for synthesis of condensed heterocycles in reaction with ketone enolates.[9]



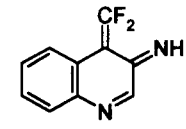
1



2



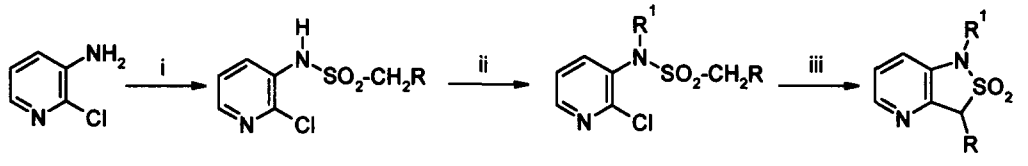
3



4

Recently we have developed the method of generation of aza-*ortho*-xylylenes via thermal extrusion of SO_2 from 2,1-benzisothiazoline 2,2-dioxides.[5] These aza-*ortho*-xylylenes entered Diels-Alder reaction with dienophiles or underwent [1,5]-hydrogen shift leading to *ortho*-vinylaniline derivatives.[6]

In this paper we would like to present the preliminary results of our studies on the generation of pyrido analogues of aza-*ortho*-xylylenes generated from previously unknown *N*-alkyl-1,3-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxides (pyridosultams, **8**). These pyridosultams **8** are readily accessible from 2-chloro-3-aminopyridine (**5**) which treated with methanesulfonyl chloride or α-tolunenesulfonyl chloride in the presence of triethylamine in dichloromethane gives corresponding sulfonamides **6**. Alkylation of **6** with alkyl halides (methyl iodide, *n*-propyl iodide, 1-bromo-4-pentene) in the presence of solid K_2CO_3 in DMF leads to *N*-alkyl derivatives **7**. Compounds **7** in the presence of *t*-BuOK (for R= H) or powdered NaOH (for R= Ph) in dimethylsulfoxide undergo intramolecular nucleophilic substitution of chlorine giving expected sultams **8** in good yields.

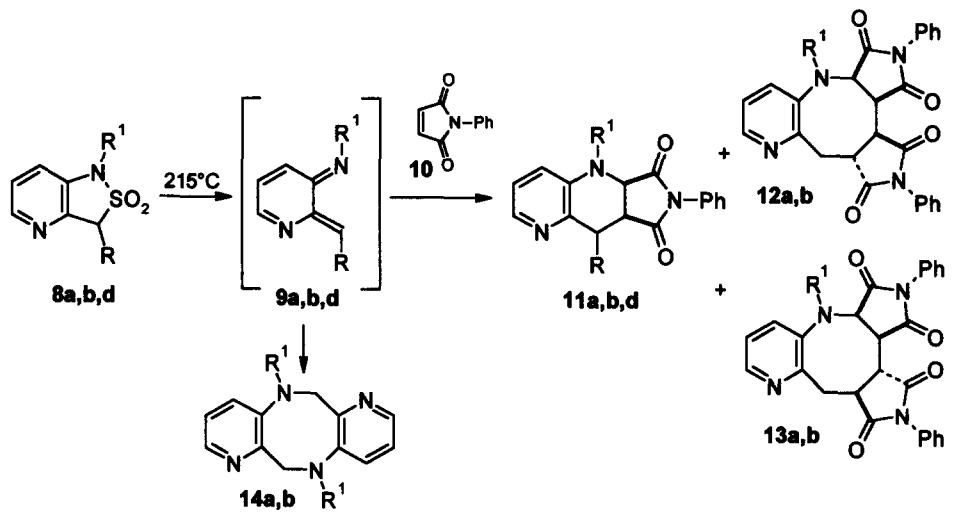


5 **6**, R= H, Ph **7** **8**

7a, 8a: R= H, R^1= Me
7b, 8b: R= H, R^1= *n*-C_3H_7
7c, 8c: R= H, R^1= $(CH_2)_3CH{=}CH_2$
7d, 8d: R= Ph, R^1= Me

i: $RCH_2SO_2Cl/Et_3N/CH_2Cl_2$/RT; ii: R^1-X/K_2CO_3/DMF; iii: t-BuOK (for **7a-c**) or NaOH (for **7d**)/DMSO/RT

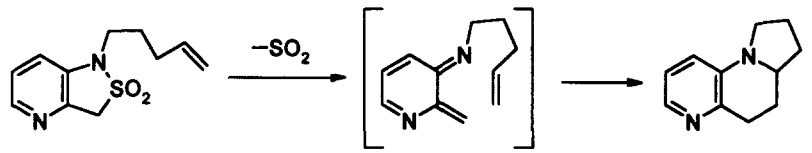
When the sultam **8a** was heated with 3 eqiuv. of *N*-phenylmaleimide (NPMI, **10**) in refluxing 1,2,4-trichlorobenzene (215°C, 0.5 hr) extrusion of SO_2 occured and the resulting intermediate pyridoazaxylylene **9a** entered Diels-Alder reaction leading to tetrahydro[1,5]naphthyridine derivative **11a** in 54% yield.[10]



8a,b,d **9a,b,d** **10** **11a,b,d** **12a,b** **13a,b** **14a,b**

Besides of the expected cycloadduct **11a** two additional products **12a** and **13a** were isolated in 18% yield. Molecular mass of the products **12a** and **13a** corresponded to the reaction of two molecules of NPMI with one molecule of xylylene **9a**. GC MS analysis of the crude reaction mixture has also revealed formation

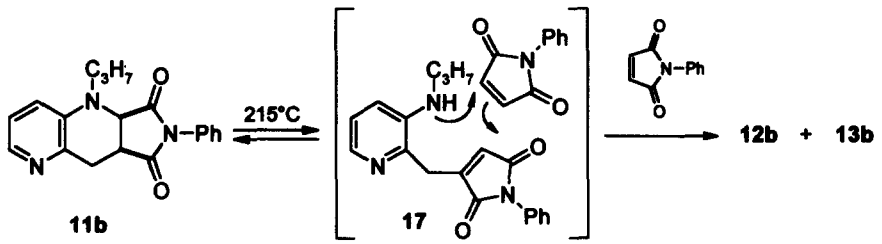
of dimerization product **14a** of xylylene **9a**.[11] The reaction of sultam **8b** proceeded similarly and the cycloadduct **11b** was obtained in 71% yield. Intramolecular cycloaddition of xylylene **15** generated in analogous conditions from 1-(4-pentenyl)sultam **8c** proceeded smoothly and the condensed tetrahydro[1,5]naphthyridine **16** was formed in 51% yield.[10] The extrusion of SO_2 from 3-phenylsultam **8d** occured at much lower temperature. In refluxing toluene it was complete in 1 hr, however the yield of cycloadditon product **11d** was only 23%, and large amounts of tars were produced.



8c **15** **16**

The formation of products **12b** and **13b** from sultam **8b** was studied in more details. When the sultams **8b** and NPMI were used in stoichiometric amount the formation of these 2:1 adducts was partly suppressed and the expected 1:1 cycloadduct **11b** was formed in 44% yield. In the reaction of 3 equiv. of NPMI with 1 equiv. of sultam **8b** in refluxing trichlorobenzene the sultam completly disappeared in 30 min and HPLC analysis showed presence of the [4+2] cycloadduct **11b** and products **12b** and **13b** also in 1:1 ratio. Increasing the reaction time to 4 hr assured the complete disappearance of the adduct **11b** and finally mixture of the products **12b** and **13b** in 1:1 ratio was formed in 84% yield. On the basis of ^{1}H NMR spectra for these compounds the structure of pyridoazocines **12b** and **13b** was assigned.[10] The *cis* configuration of hydrogen atoms in the "upper" five-membered ring was assigned on the basis of the coupling constants J = 8.5 Hz (for both **12b** and **13b**), while *trans* configuration in the "lower" ring was deduced from the coupling constants J = 2.4 Hz (**12b**) and 5.0 Hz (**13b**). We concluded that compounds **12b** and **13b** can differ only by the *cis* or *trans* configuration along C(3)-C(4) bond in the eight-membered ring. However, we are still unable to assign unambigously the actual structure for these compounds, since the difference in the coupling constants between H(3) and H(4) in both isomers J = 11.3 Hz (for **12b**) and 10.3 Hz (for **13b**) is too small, and attempts to obtain these compounds in the crystal form suitable for X-ray analysis were unsuccessful.

A plausible mechanism of formation of the 2:1 products consists of the base-induced ring opening in the adduct **11b** leading to **17** followed by Michael addition of amine to the next molecule of NPMI and ring closure. In an additional experiment the adduct **11b** was subjected to the reaction with NPMI in analogous conditions and also the 1:1 mixture of the products **12b** and **13b** was formed in 70%. We suppose that the 3-aminopyridine system present in the adduct is sufficiently basic to promote such ring opening in **11b**.



11b **17**

Formation of similar tetracyclic 2:1 adducts of NPMI with heteroxylylenes generated from pyrimidinothiophene dioxide was recently described by Storr *et al.*[12] Another example of such an unusual reaction involves quinoxalino-*ortho*-quinodimethanes with NPMI.[13]

The further studies of the scope of the reactions pyrido-aza-*ortho*-xylylenes are in progress.

Acknowledgement: This work was partly supported by the Committee for Scientific Research Grant No. 3 TO9A 073 08.

REFERENCES AND NOTES.

1. Michellys, P.; Pelissier, H.; Santelli, M. *Org. Prep. Proc. Intl.*, **1996**, *28*, 545-608.
2. Martin, N.; Seonae, C.; Hanack, M. *Org. Prep. Proc. Intl.*, **1991**, *23*, 239-272.
3. Charlton, J.L.; Alauddin, M.M. *Tetrahedron*, **1987**, *43*, 2873-2889.
4. Chou, T.-S. *Reviews on Heteroatom Chem.* **1993**, *8*, 65-104.
5. Wojciechowski, K. *Tetrahedron* **1993**, *49*, 7277-7286 and references cited therein.
6. Wojciechowski, K. *Tetrahedron* **1993**, *49*, 10017-10026.
7. Fishwick, C.W.G.; Storr, R.C.; Manley, P.W. *Chem. Commun.* **1984**, 1304-1305.
8. Randles, K.R.; Storr, R.C. *Tetrahedron Lett.* **1987**, *28*, 5555-5558.
9. Strekowski, L; Kiselyov, A.; Hojjat, M. *J. Org. Chem.* **1994**, *59*, 5886-5890.
10. Properties of the selected compounds: **11a**, m.p. 156-158 °C, ^{1}H NMR (200 MHz): δ= 3.21 (dd, *J*= 14.8, 6.8, 1H), 3.24 (s, 3H), 3.33 (dd, *J*= 14.8, 4.9, 1H), 3.71 (ddd, *J*= 9.2, 6.8, 4.9, 1H), 4.30 (d, *J*= 9.2, 1H), 7.02-7.10 (m, 3H), 7.15 (dd, *J*= 8.1, 4.7, 1H), 7.30-7-45 (m, 3H), 8.04 (dd, *J*= 4.7, 1.5, 1H); MS (EI 70 eV, *m/z*, %): 293 (M^+, 85), 200 (7), 172 (21), 146 (36), 145 (100), 129 (4), 120 (8), HRMS for $C_{17}H_{15}N_3O_2$ calcd. 293.1164, found 293.1162. **11d**, m.p. 221-223 °C, ^{1}H NMR (200 MHz): δ= 3.38 (s, 3H), 3.70, 4.40, 4.85 (AMX, *J*= 8.8, 6.9, 3H all *cis*), 6.41-6.47 (m, 2H), 7.15-7.35 (m, 10H), 8.02 (dd, *J*= 3.6, 2.3, 1H). MS (EI 70 eV, *m/z*, %): 369 (M^+, 100), 315 (5), 304 (10), 290 (18), 288 (17), 285 (20), 249 (18), 222 (23), 207 (30), 195 (80), 145 (55); HRMS for $C_{23}H_{19}N_3O_2$ calcd.369.1477, found 369.1484; **12b**, m.p. 175-177°C, ^{1}H NMR (500 MHz): δ= 0.98 (t, *J*= 7.4, 3H), 1.68-1.80 (m, 2H), 3.14 (dd, *J*= 17.9, 7.0, 1H), 3.17 (dd, *J*= 17.9, 8.7, 1H), 3.36 (dd, *J*= 11.3, 2.4, 1H), 3.57-3.73 (m, 2H), 3.80 (dd, *J*= 11.3, 8.5, 1H), 4.21 (ddd, *J*= 8.7, 7.0, 2.4, 1H), 4.45 (d, *J*= 8.5, 1H), 7.05 (dd, *J*= 8.3, 1.2, 1H), 7.16 (dd, *J*= 8.3, 4.7, 1H), 7.27-7.30 (m, 2H), 7.33-7.39 (m, 4H), 7.41-7.52 (m, 4H), 7.94 (dd, *J*= 4.7, 1.3, 1H); MS (EI 70 eV, *m/z*, %): 494 (M^+, 100), 465 (27), 374 (50), 373 (63), 344 (17), 320 (31), 304 (8), 292 (22), 276 (14), 173 (48), 131 (61); HRMS for $C_{29}H_{26}N_4O_4$ calcd. 494.1954, found 494.1949; **13b**, m.p. 206-210°C; ^{1}H NMR (500 MHz): δ= 1.01 (t, *J*= 7.4, 3H), 1.67-1.86 (m, 2H), 2.81 (dd, *J*=17.8, 5.4, 1H), 2.98 (dd, *J*= 17.8, 9.2, 1H), 3.31 (dd, *J*= 10.3, 8.5, 1H), 3.58-3.70 (m, 2H), 3.71 (dd, *J*= 10.3, 5.0, 1H), 3.76 (ddd, *J*= 9.2, 5.4, 5.0, 1H), 4.50 (d, *J*= 8.5, 1H), 7.05 (dd, *J*= 8.4, 1.3, 1H), 7.14 (dd, *J*= 8.4, 4.7, 1H), 7.23- 7.30 (m, 2H), 7.38-7.43 (m, 4H), 7.46-7.52 (m, 4H), 7.93 (dd, *J*= 4.7, 1.3, 1H); MS (EI 70 eV, *m/z*, %): 494 (M^+, 100), 465 (27), 374 (60), 373 (54) 320 (27), 292 (18), 276 (14), 173 (39), 131 (45); HRMS for $C_{29}H_{26}N_4O_4$: calcd. 494.1954 found 494.1954; **16**, oil, ^{1}H NMR (500 MHz): δ= 1.45-1.55 (m, 2H), 1.98 (dddd, *J*= 16.0, 12.4, 9.1, 6.9, 1H), 2.07-2.20 (m, 3H), 2.23 (dddd, *J*= 13.2, 3.5, 3.5, 3.5, 1H), 2.91-3.01 (m, 2H), 3.17 (ddd, *J*= 9.2, 9.2, 7.5, 1H), 3.27 (ddd, *J*= 9.0, 9.0, 2.1, 1H), 3.45 (dddd, *J*= 10.7, 10.7, 5.1, 3.1, 1H), 6.58 (dd, *J*= 8.1, 1.2, 1H), 6.95 (dd, *J*= 8.1, 4.7, 1H), 7.75 (dd, *J*= 4.7, 1.2, 1H); MS (EI 70 eV, *m/z*, %): 174 (M^+, 72), 173 (100), 145 (28), 131 (18), 119 (24); HRMS for $C_{11}H_{14}N_2$: calcd. 174.1157, found 174.1156.
11. When the sultam **8b** was refluxed in trichlorobenzene without a dienophile product **14b** was formed in 25% yield. ^{1}H NMR (500 MHz): δ= 0.68 (t, *J*= 7.4, 6H), 1.41-1.48 (m, 4H), 3.12 (t, *J*= 7.4, 4H), 4.59 (s, 4H), 7.08 (dd, *J*= 8.2, 4.5, 2H), 7.13 (d, *J*= 8.2, 2H), 7.98 (d, *J*= 4.5, 2H); MS (EI 70 eV, *m/z*, %): 296 (M^+, 100), 280 (7), 267 (43), 253 (87), 237 (40), 223 (15), 209 (10), 196 (13), 161 (34), 119 (42); HRMS for $C_{18}H_{24}N_4$: calcd 296.2001, found 296.2007.
12. a) Tomé, A.C.; Cavaleiro, J.A.S.; Storr, R.C. *Tetrahedron Lett.* **1993**, *34*, 6639-6642. b) Tomé, A.C.; Cavaleiro, J.A.S.; Storr, R.C. *Tetrahedron* **1996**, *52*, 1735-1746.
13. Chung, W.-S.; Liu, J.-H. *Chem. Commun.* **1997**, 205-206.

(*Received in UK* 21 *April* 1997; *revised* 9 *May* 1997; *accepted* 15 *May* 1997)