Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9549–9552
Tetrahedron Letters

Synthesis of 8-arylsulfoxyl/sulfonyl adenines

Laura Llauger, Huazhong He and Gabriela Chiosis*

Department of Medicine and Program in Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA

Received 24 September 2004; revised 1 November 2004; accepted 2 November 2004

Abstract—We report a method for the synthesis of 9-*N*-alkyl-8-arylsulfoxyl adenines and 9-*N*-alkyl-8-arylsulfonyl adenines. The approach starts with a tandem one-pot reaction that by using Mitsunobu conditions converts 8-arylsulfanyl adenines to the corresponding iminophosphorane protected 9-*N*-alkyl-8-arylsulfanyl adenines. These compounds were further subjected to selective OXONE®/alumina mediated oxidation followed by deprotection of the amine leading to the desired sulfoxides and sulfones.

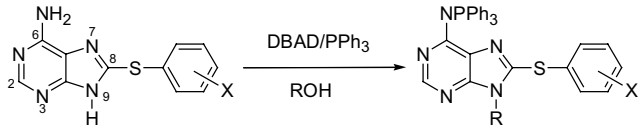
Purine derivatives have been shown to exhibit potent biological activities. Respectively, libraries of 2,6,9-purines have resulted in the identification of inhibitors of many biological processes including those regulated by cyclin-dependent kinases, sulfotransferases, and tubulin.[1] We have created libraries of 2,8,9-adenines in which the adenine is linked to an aryl ring through a methylene bridge at C8, and isolated selective inhibitors of the molecular chaperone Hsp90.[2] Our interest in exploring the C8 position of the purine ring is furthered by the strategic positioning of this carbon. Establishing a linker between C8 and another aromatic/heteroaromatic ring creates a biaromatic system in which the orientation of the two rings is regulated by the nature and length of the linker. Formation of a C–C, C–O, C–N, or C–S bond at this position is already documented in several publications.[3] To our knowledge however, no method on the formation of sulfoxides and sulfones has been previously reported.

A survey of the existing literature offers several synthetic procedures that exist on the oxidation of sulfides[4] however, none addresses the particular case of adenine containing derivatives. Oxidations that document the use of peroxides such as hydrogen peroxide,[4a] urea–hydrogen peroxide,[4b] hydrogen peroxide–$LiNbMoO_6$,[4c] *m*-chloroperbenzoic acid (*m*-CPBA),[4d] OXONE®,[4e–g] or *tert*-butylhydroperoxide,[4g] alone or in the presence of silica gel or alumina have been reported for alkyl- and arylsulfides. A convenient method described by Kropp and co-workers uses the magnesium salt of monoperoxyphtalic acid (MMPP) as oxidant.[5] This reagent is safer to handle compared to *m*-CPBA and does not require assaying for its stoichiometric addition. In our hands, its use towards the oxidation of 8-arylsulfanyl adenine derivatives led solely to recovery of starting material. Use of *m*-CPBA or OXONE®[6] at different temperatures (rt, −10 °C, −78 °C) and reagent ratios (2.2, 2, 1, and 0.5 oxidant/starting material) resulted in mixtures of sulfides, sulfoxides, sulfones, and hydroxylamino-derivatives (resulted by the oxidation of adenine's C6–NH_2). To avoid the later, we were compelled to protect the C6 amino functionality with a group that could withstand transformation under strong oxidizing conditions. Chern and co-workers have reported that in nucleosides this amine can be easily reacted under Mitsunobu conditions to form an iminophosphorane, group that can be ultimately removed under weak acidic conditions.[7] Subjecting 9-*N*-alkyl-8-arylsulfanyl adenine derivatives to triphenylphosphine (PPh_3)/di-*tert*-butylazodicarboxylate (DBAD) in CH_2Cl_2 or toluene/CH_2Cl_2 resulted indeed in the corresponding *N*-triphenylphosphoranylidene adenines.[8] Alternatively in a more direct method, the synthesis of C6–NH_2 protected 9-*N*-alkyl-8-arylsulfanyl adenine derivatives **1a–c** and **2a–c** could be achieved in a two-step one-pot reaction from the corresponding 8-arylsulfanyl adenines **1** and **2**[3g] using the Mitsunobu conditions previously described by Lucas et al.[9] however allowing for longer reaction times (Table 1).[10] The desired products were isolated in yields

Keywords: Oxidation; Alumina supported OXONE®; 8-Arylsufoxyl adenines; 8-Arylsufonyl adenines.
* Corresponding author. Tel.: +1 212 639 8929; fax: +1 212 717 3627; e-mail: chiosisg@mskcc.org

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.009

Table 1. Synthesis of the C6–NH_2 protected 9-*N*-alkyl-8-arylsulfanyl adenine derivatives **1a–c** and **2a–c**



1; X = 3-OMe
2; X = 3,4,5-OMe_3

1a-c
2a-c

Entry	Reactant[a]	R	Products[b]	Yield[c] (%)
1	**1**	Butyl	**1a**	30 (79)[d]
2		2-Isopropoxy-ethyl	**1b**	32
3		Pent-4-ynyl	**1c**	36
4	**2**	Butyl	**2a**	51
5		2-Isopropoxy-ethyl	**2b**	45
6		Pent-4-ynyl	**2c**	50

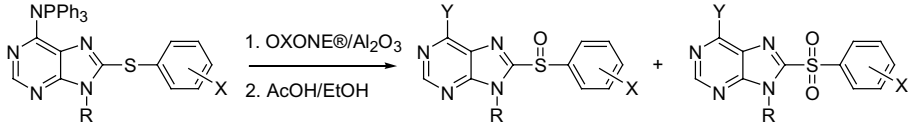
[a] Syntheses of **1** and **2** were described in Ref. 3g.
[b] Reaction conditions: DBAD (5 equiv), PPh_3 (2.2 equiv), ROH (1.3 equiv), CH_2Cl_2–toluene (1:5), overnight at room temperature.
[c] Yields isolated after chromatography.
[d] Yields by HPLC.

ranging from 35% to 70%. Formation of 3-*N* (5–30%) and 7-*N* (traces) alkylation products (separable by silica gel chromatography) was mostly responsible for the moderate yields whilst protection of the C6–NH_2 occurred quantitatively. The use of OXONE® in presence of alumina as reported by Kropp et al.[4g] allowed for monitoring the reaction to either sulfoxides (**3a–c** and **5a–c**) or sulfones (**4a–c** and **6a–c**). Mediation of oxidation by OXONE® involves activation by its being dispersed on the surface of the alumina adsorbent, providing contact between $KOSO_2OOH$, the active ingredient of OXONE®, and the sulfide. Formation of sulfoxide or sulfone relied on the stoichiometry of the reaction, and use of excess OXONE® over sulfide favored sulfone formation (Table 2).[11] In some cases, a mixture of sulfoxide and sulfone was obtained regardless of the excess OXONE® present in the reaction medium. Such instances were observed when alumina's water content was not carefully monitored. Prior to use, the alumina had to be activated (48 h/120 °C) and wetted for the reaction to occur; excessive wetting seemed to favor sulfoxide formation. Nevertheless, in the eventuality of sulfoxide and sulfone mixture formation, the two products are separable by silica gel column chromatography.

Synthesis of 9-*N*-alkyl-8-arylsulfoxyl adenines (**7a–c** and **9a–c**) and 9-*N*-alkyl-8-arylsulfonyl adenines (**8a–c** and **10a–c**) was completed with the deprotection of C6–NH_2 triphenylphosphine group. The reaction was conveniently conducted in refluxing AcOH/EtOH to result in complete deprotection (Table 2).[12,13] The use of stronger acidic conditions, such as HCl, resulted in compound decomposition via cleavage of the C–S bond. Due to the more labile nature of the C–S bond in 9-*N*-alkyl-8-arylsulfoxyl adenines compared to the corresponding sulfones, the reaction necessitated milder conditions and was carried out with 1 M[12] instead of 2 M AcOH.[13]

In summary, we present the first report on the synthesis of 9-*N*-alkyl-8-arylsulfoxyl/sulfonyl adenine derivatives.

Table 2. Oxidation of sulfides **1a–c** and **2a–c** to the corresponding sulfoxides **3a–c**; **5a–c**, and sulfones **4a–c**; **6a–c**, followed by deprotection of the triphenylphosphine group to result in sulfoxides **7a–c**; **9a–c**, and sulfones **8a–c**; **10a–c**, respectively



1a-c
2a-c

Y = $NPPh_3$ **3a-c** and **5a-c**
Y = NH_2 **7a-c** and **9a-c**

Y = $NPPh_3$ **4a-c** and **6a-c**
Y = NH_2 **8a-c** and **10a-c**

For:

1, **3**, **4**, **7** and **8** X = 3-OMe
2, **5**, **6**, **9** and **10** X = 3,4,5-OMe_3

Entry	Substrate	OXONE® (equiv)	Oxidation products[a]	Yield[c] (%) oxidation	Deprotection products[d]	Yield[c] (%) deprotection
1	**1a**	1	**3a**	61	**7a**	48
2	**1a**	4	**4a**	69	**8a**	59
3	**1b**	4	**3b**	19	**7b**	42
4	**1b**	4	**4b**	54	**8b**	70
5	**1c**	4	**3c**	17	**7c**	61
6	**1c**	4	**4c**	21	**8c**	61
7	**2a**	0.6	**5a**	40	**9a**	71
8	**2a**	4	**6a**	42	**10a**	65
9	**2b**	1.2	**5b**	34	**9b**	78
10	**2b**	4	**6b**	60	**10b**	69
11	**2c**	6[b]	**5c**	5	**9c**	—
12	**2c**	6[b]	**6c**	63	**10c**	60

[a] Reaction conditions: Al_2O_3 (2.5 g/mmol), H_2O (0.3 mL/mmol OXONE®), OXONE® (indicated), CH_2Cl_2 (5 mL/mmol), room temperature, 4 h (sulfoxide) and overnight (sulfone).
[b] Unreacted starting material was observed with only 4 equiv OXONE®.
[c] Yields isolated after chromatography.
[d] For sulfoxide: 1 M AcOH used, reaction refluxed for 1 h; for sulfones: 2 M AcOH used, reaction refluxed for 3 h.

The methodology can conveniently be applied to produce an array of such compounds containing the desired oxidation state on sulfur.

Acknowledgements

The work was funded in part by AACR-Cancer Research and Prevention Foundation, Mr. William H. Goodwin and Mrs. Alice Goodwin and the Commonwealth Cancer Foundation for Research and MSKCC Experimental Therapeutics Program and a generous donation from the Taub Foundation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.009. Supplementary data for the analytical characterization (^{1}H NMR, ^{13}C NMR, IR, and MS) of all presented compounds is available on line with the paper in ScienceDirect.

References and notes

1. (a) Arris, C. E.; Boyle, F. T.; Calvert, A. H.; Curtin, N. J.; Endicott, J. A.; Garman, E. F.; Gibson, A. E.; Golding, B. T.; Grant, S.; Griffin, R. J.; Jewsbury, P.; Johnson, L. N.; Lawrie, A. M.; Newell, D. R.; Noble, M. E.; Sausville, E. A.; Schultz, R.; Yu, W. *J. Med. Chem.* **2000**, *43*, 2797–2804; (b) Chapman, E.; Ding, S.; Schultz, P. G.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 14524–14525; (c) Perez, O. D.; Chang, Y. T.; Rosania, G.; Sutherlin, D.; Schultz, P. G. *Chem. Biol.* **2002**, *4*, 475–483.
2. Chiosis, G.; Lucas, B.; Huezo, H.; Solit, D.; Basso, A.; Rosen, N. *Curr. Cancer Drug Targets* **2003**, *5*, 371–376.
3. (a) Young, R. C.; Jones, M.; Milliner, K. J.; Rana, K. K.; Ward, J. G. *J. Med. Chem.* **1990**, *33*, 2073–2080; (b) Gonnella, N. C.; Nakanishi, H.; Holtwick, J. B.; Horowitz, D. S.; Kanamori, K. *J. Am. Chem. Soc.* **1983**, *105*, 2050–2053; (c) Draminsky, M.; Frass, E. *Pol. J. Chem.* **1987**, *61*, 901–904; (d) Chiosis, G.; Lucas, B.; Shtil, A.; Huezo, H.; Rosen, N. *Bioorg. Med. Chem.* **2002**, *11*, 3555–3564; (e) Camaioni, E.; Vittori, S.; Volpini, R.; Klotz, K.-N.; Cristalli, G. *Bioorg. Med. Chem.* **1998**, *6*, 523–533; (f) Klotz, K-N.; Kachler, S.; Lambertucci, C.; Vittori, S.; Volpini, R.; Cristalli, G. *Naunyn-Scmiedeberg's Arch. Pharmacol.* **2003**, *367*, 629–634; (g) He, H.; Llauger, L.; Rosen, N.; Chiosis, G. *J. Org. Chem.* **2004**, *69*, 3230–3232; (h) Kasibhatla, S. R.; Hong, K.; Zhang, L.; Biamonte, M. A.; Boehm, M. F.; Shi, J.; Fan, J. PCT Int. Appl., 2003, WO 2003037860.
4. (a) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469–2476; (b) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *2*, 189–191; (c) Choi, S.; Yang, J. D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* **2002**, *66*, 8192–8198; (d) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784–3793; (e) Greenhalgh, R. P. *Synlett* **1992**, 235–236; (f) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synlett* **1996**, 767–768; (g) Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122*, 4280–4285.
5. Foti, C. J.; Fields, J. D.; Kropp, P. J. *Org. Lett.* **1999**, *6*, 903–904.
6. OXONE® is a product of the Du Pont Company consisting of a 2:1:1 mixture of the active ingredient $KOSO_2OOH$, along with $KHSO_4$, and K_2SO_4, respectively.
7. Chien, T.-C.; Chen, C.-S.; Yeh, J.-Y.; Wang, K.-C.; Chern, J.-W. *Tetrahedron Lett.* **1995**, *36*, 7881–7884.
8. Synthesis of **1a** is representative: To a solution of 9-butyl-8-(3-methoxy-phenylsulfanyl)adenine[3h] (260 mg, 0.8 mmol) in toluene–CH_2Cl_2 (26:5), were added PPh_3 (674 mg, 2.5 mmol) and DBAD (240 mg, 1.0 mmol). The reaction mixture was stirred overnight at room temperature. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Subsequent to solvent removal, the crude was chromatographed on silica gel eluting with $CHCl_3$–hexanes–EtOAc at 2:2:1 to provide **1a** (360 mg, 70% isolated yield).
9. Lucas, B.; Rosen, N.; Chiosis, G. *J. Comb. Chem.* **2001**, *3*, 518–520.
10. Synthesis of **1a** is representative: To a solution of sulfide **1** (200 mg, 0.73 mmol) in toluene–CH_2Cl_2 (22:4.4 mL) (5:1), were added butanol (87 μL, 0.95 mmol), PPh_3 (425 mg, 1.6 mmol) and DBAD (860 mg, 3.7 mmol). The reaction was stirred at room temperature overnight. The product was purified by flash silica gel column chromatography, eluting with $CHCl_3$–hexanes–EtOAc at 2:2:1 to provide 130 mg of **1a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, H-2), 7.84 (m, 6H, *o*-PPh_3), 7.45 (m, 3H, *p*-PPh_3), 7.37 (m, 6H, *m*-PPh_3), 7.09 (t, $J = 8.0$ Hz, 1H), 6.83 (t, $J = 1.8$ Hz, 1H), 6.80 (m, 1H), 6.67 (dd, $J = 2.0$, 8.3 Hz, 1H), 4.00 (t, $J = 7.7$ Hz, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 1.54 (m, 2H), 1.17 (m, 2H), 0.75 (t, $J = 7.4$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 159.9, 152.1, 151.5, 142.3, 134.6, 133.2, 131.7, 129.9, 129.2, 128.3, 121.4, 114.6, 112.8, 55.2, 43.4, 31.5, 19.8, 13.5. MS (EIS) *m/z* 590.2 (M+1).
11. Syntheses of sulfoxide **3a** and sulfone **4a** are representative: Alumina (Fisher A540; 480 mg) was equilibrated with air at 120 °C for at least 48 h previous to use. The flask was stoppered and the contents allowed to cool to 25 °C. Water (0.06 mL) was added and the adsorbent was tumbled on a rotatory evaporator at atmospheric pressure until uniformly free flowing. A solution of sulfide **1a** (115 mg, 0.186 mmol) in CH_2Cl_2 (1 mL) was added with stirring, followed by OXONE® (120 mg, 0.194 mmol) or (480 mg, 0.776 mmol) if sulfoxide **3a** or sulfone **4a** were desired, respectively. The slurry was stirred for 4 h or overnight at 25 °C if sulfoxide **3a** or sulfone **4a** were desired, respectively. The adsorbent was then removed by vacuum filtration and washed first with EtOAc and then with a solution of $CHCl_3$–hexanes–EtOAc–MeOH–NH_4OH at 2:2:1:0.5:0.1. The combined organic fractions were washed with a saturated aqueous solution of $FeSO_4$ and dried over anhydrous Na_2SO_4. Following concentration under reduced pressure, the residue was chromatographed through silica gel by elution with CH_2Cl_2–EtOAc at 2:1 to afford 70 mg of sulfoxide **3a** or 76 mg of sulfone **4a**, respectively. Spectra of sulfoxide **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H, H-2), 7.82 (m, 6H, *o*-PPh_3), 7.46 (m, 3H, *p*-PPh_3), 7.36 (m, 6H, *m*-PPh_3), 7.29 (t, $J = 8.0$ Hz, 1H), 7.26 (m, 1H), 7.13 (br d, $J = 7.8$ Hz, 1H), 6.89 (dd, $J = 2.3$, 8.0 Hz, 1H), 4.18 and 3.97 (2m, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 1.62 and 0.85 (2m, 2H), 1.12 (t, $J = 7.0$ Hz, 2H), 0.68 (t, $J = 7.0$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 153.4, 151.9, 148.0, 143.2, 133.3, 132.0, 130.3, 128.9, 128.4, 127.9, 116.9, 116.7, 109.1, 55.6, 43.5,

31.4, 19.9, 13.5. MS (EIS) *m*/*z* 606.4 (M+1). Spectra of sulfone **4a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H, H-2), 7.80 (m, 6H, *o*-PPh_3), 7.54 (m, 2H), 7.45 (m, 3H, *p*-PPh_3), 7.36 (m, 7H), 7.07 (dd, J = 2.4, 8.2 Hz, 1H), 4.36 (t, J = 7.9 Hz, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 1.65 (m, 2H), 1.30 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 154.2, 151, 144.6, 140.8, 133.3, 132.1, 130.2, 128.9, 128.4, 127.9, 120.9, 120.7, 112.9, 55.8, 44.5, 32.4, 20.0, 13.6. MS (EIS) *m*/*z* 622.3 (M+1).

12. Synthesis of sulfoxide **7a** is representative: To a solution of **3a** (70 mg, 0.11 mmol) in EtOH (1.2 mL) was added 1 M aqueous AcOH solution (1.2 mL). The reaction mixture was refluxed for 1 h. Following cooling to room temperature, the solvent was removed under high vacuum and the crude taken up in CH_2Cl_2. The organic phase was washed with $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Subsequent to solvent removal, the residue was chromatographed on silica gel eluting with $CHCl_3$–hexanes–EtOAc–MeOH at 2:2:1:0.1 to afford 23 mg of **7a**. IR (film) ν_{max} 3321–2872, 1650, 1593, 1573, 1479, 1298, 1247, 1076 (SO), 1038 (SO). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, H-2), 7.35 (t, J = 8.0 Hz, 1H), 7.25 (m, 1H), 6.96 (dd, J = 2.0, 8.0 Hz, 1H), 6.26 (br s, 2H, NH_2), 4.25 and 4.14 (2m, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 1.65 (m, 1H), 1.18 (m, 3H), 0.77 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 156.0, 154.2, 151.6, 150.1, 142.3, 130.6, 119.3, 117.7, 116.8, 109.5, 55.6, 43.8, 31.6, 19.9, 13.5. MS (EIS) *m*/*z* 346.2 (M+1).

13. Synthesis of sulfone **8a** is representative: To a solution of **4a** (120 mg, 0.19 mmol) in EtOH (1.9 mL) was added 2 M AcOH aqueous solution (1.9 mL). The reaction mixture was refluxed for 3 h. Following cooling to room temperature, the solvent was removed under high vacuum and the crude taken up in CH_2Cl_2. The organic phase was washed with $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Subsequent to solvent removal, the residue was chromatographed on silica gel eluting with a gradient of $CHCl_3$–hexanes–EtOAc–MeOH at 2:2:1:0.1, followed by $CHCl_3$–MeOH at 98:2 to afford 46 mg of **8a**. IR (film) ν_{max} 3314–2873, 1650, 1595, 1574, 1480, 1321 (SO_2), 1246, 1154 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H, H-2), 7.55 (d, J = 7.9 Hz, 1H), 7.47 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.10 (dd, J = 2.0, 8.0 Hz, 1H), 6.70 (br s, 2H, NH_2), 4.41 (t, J = 7.9 Hz, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 1.68 (m, 2H), 1.31 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 156.9, 155.2, 151.0, 146.1, 139.9, 130.5, 121.0, 120.5, 118.9, 112.9, 55.7, 44.8, 32.3, 19.9, 13.5. MS (EIS) *m*/*z* 362.2 (M+1).