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Palladium-mediated total synthesis of 2-styrylbenzoic acids: a general route to 2-azachrysenes†

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Abstract—We describe a new total synthesis of 2-styrylbenzoic acids by Heck coupling of methyl *o*-iodobenzoates to styrenes. Additionally, in the first general synthesis of naphtho[2,1-*f*]isoquinolines, these acids were transformed into phenanthrenoic acids and thence into the target compounds by a six-step sequence including a Bischler–Napieralski cyclization.

Polycyclic aromatic hydrocarbons (PAHs) are widespread pollutants produced in the combustion of organic matter.[1,2] Some PAHs, such as chrysene (**9a**), are potent carcinogens, possibly because their rigid planar embedded 2-phenylnaphthalene subunit may facilitate interaction of their diol epoxide derivatives with DNA.[3,4] It has been suggested that structural modifications of PAHs may afford antineoplastic compounds. This is supported, for example, by the powerful anticancer activity of benzo[*c*]phenanthridines (**9**, Y = CH, Z = N-Me), such as nitidine and fagaronine, cases in which this activity has been attributed to perturbation of the charge distribution in the tetracyclic system of **9a** by the introduction of a nitrogen atom.[5] The introduction of alkoxy substituents at strategic positions may also interfere with the processes involved in the carcinogenic activity of **9a**. Although 2-azachrysenes (**9**, Y = N, Z = CH) have a structural relationship to chrysene that is similar to that of benzo[*c*]-phenanthridines, and therefore, like the latter, might show antineoplastic activity, the synthesis of these compounds has been almost completely overlooked,[6] and investigation of their properties[7] has practically been limited to studies on pollution by 2-azachrysene (**9d**). We report here a new, simple, efficient synthetic approach to 2-azachrysenes, starting from *o*-styrylbenzoic acids (**4**) and involving sequential construction of C and A rings of their tetracyclic framework.

Heck coupling[8] of methyl *o*-iodobenzoate **2a**[9] to styrene afforded the *E* isomer of *o*-styrylbenzoic acid (**4a**), together with a small amount of the corresponding α-coupling product **3a** (global yield 89%; α/β ratio 1:17) (Scheme 1). Subsequent photocyclization[10] of **4a** in 95:5 ether–dichloromethane containing 1 equiv. of iodine gave the phenanthrene ring system of the desired phenanthrenoic acid ester **5a**,[11] and the heterocyclic ring of 2-azachrysene was then added in five steps[12] as follows. Reduction of **5a** with $LiAlH_4$, followed by oxidation of the resulting phenanthrenylmethyl alcohol with MnO_2 afforded phenanthrene aldehyde **5b**. Reaction of compound **5b** with malonic acid gave phenanthrenyl acrylic acid **6a**, which upon treatment with $ClCO_2Et$ and then with NaN_3 afforded the corresponding acylazide **6b**. When a solution of **6b** in Ph_2O containing Bu_3N was refluxed for 1 h, the naphthoisoquinoline-1-one **8a** was obtained in 78% yield as a result of isomerization with respect to the double bond of **6b**, conversion of the resulting acylazide **7a** into the isocyanate **7b**, and Bischler–Napieralski cyclization of the latter. Finally, treatment of naphthoisoquinolinone **8a** with $POCl_3$ and subsequent removal of the chlorine atom of 1-chloronaphthoisoquinoline **9c** with Zn and AcOH gave the desired compound, **9d**.

The utility of this sequence was supported by the analogous synthesis of dimethoxylated 2-azachrysene **9f** from *o*-styrylbenzoic acid **4b**, via compounds **5c**, **5d**, **6c**, **6d**, **8b** and **9e**.

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† Preparation of an *o*-styrylbenzoic acid by Heck coupling reaction of iodobenzene to *o*-vinylbenzoic acid has recently been carried out by Kim, B. M.; Park, J. K. *Bull. Korean Chem. Soc.* **1999**, *20*, 744. As far as we know, neither nor any other *o*-styrylbenzoic acids have been obtained by similar procedures: see Refs. 12 and 13.

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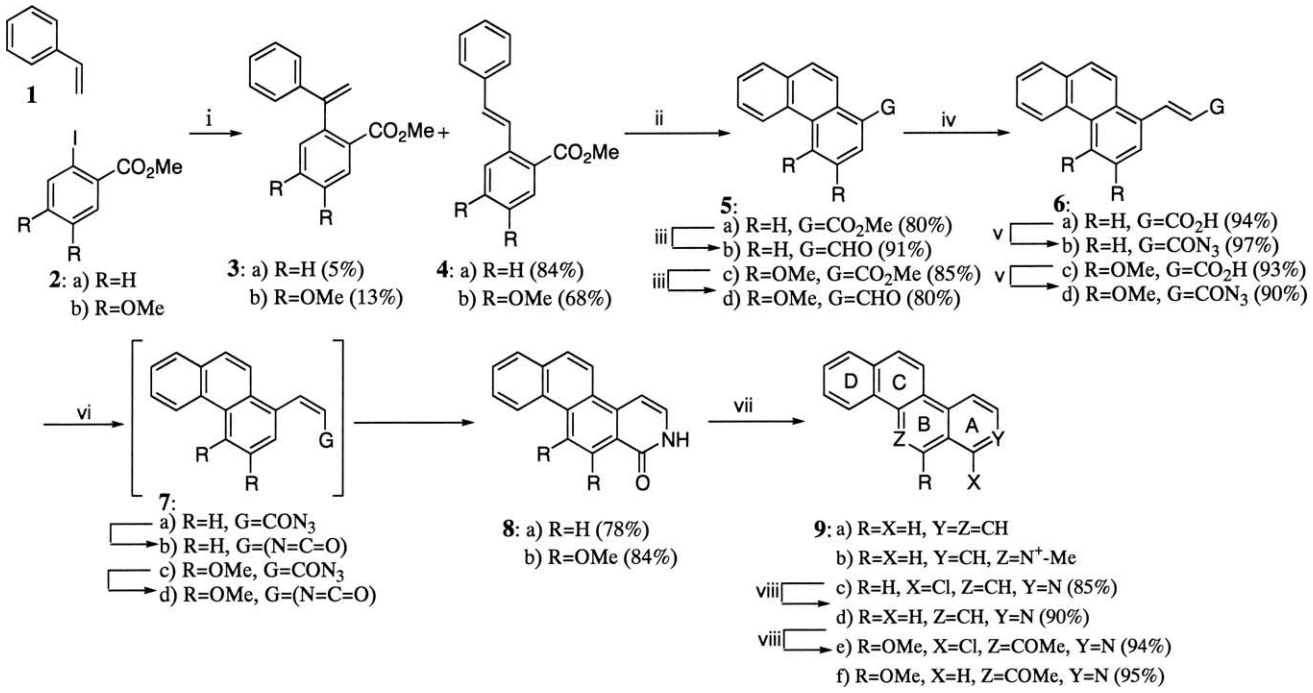

Scheme 1. (i) $Pd(OAc)_2$ (5% molar), Ph_3P, Et_3N, MeCN, argon, 80°C, 24 h. (ii) UV light, I_2, Et_2O, rt, 3 h. (iii) (a) $LiAlH_4$, THF, rt, 1.5 h; (b) MnO_2, $CHCl_3$, 40°C, 24 h. (iv) $CH_2(CO_2H)_2$, piperidine, pyr., 80°C, 2 h, then reflux, 1 h. (v) (a) $ClCO_2Et$, Et_3N, acetone, 0°C, 45 min; (b) NaN_3, H_2O, 0°C, 30 min. (vi) Bu_3N, Ph_2O, reflux, 1 h. (vii) $POCl_3$, reflux, 3 h. (viii) Zn, AcOH, reflux, 2 h.

To sum up, we describe here the first total synthesis of 2-azachrysenes, which includes new general syntheses of 2-styrylbenzoic acids and phenanthrenylbenzoic acids that are simpler and more efficient than previous ones.[13,14] Optimization of this route is now in progress in order to obtain a panel of 2-azachrysenes for a systematic study of their chemical and biological properties, antineoplastic activity included.

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References

1. (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*: *Chemistry and Carcinogenesis*; Cambridge University Press: Cambridge, UK, 1991; (b) Harvey, R. G. In *The Handbook of Environmental Chemistry*, Volume 3. Part I: *PAHs and Related Compounds*; Hutzinger, O. (Editor-in-Chief); Neilson, A. (Volume Ed.); Springer: Berlin, Heidelberg, 1997; Chapter 1, pp. 1–54.
2. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*: *Chemistry and Carcinogenesis*; Wiley–VCH: New York, 1997.
3. (a) Denisenko, M. F.; Pao, A.; Tang, M.; Pfeifer, G. P. *Science* **1996**, *274*, 430; (b) Pfeifer, G. P.; Denissenko, M. F. *Environ. Mol. Carcin.* **1998**, *31*, 197; (c) Denissenko, M. F.; Cheng, J. X.; Tang, M.; Pfeifer, G. P. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 3893; (d) Cheng, J. X.; Zheng, Y.; West, M.; Tang, M. *Cancer Res.* **1998**, *58*, 2170.
4. Cheng, C. C. In *Progress in Medicinal Chemistry*; Ellis, G. P.; West, G. B.; Eds. Structural aspects of antineoplastic agents—a new approach. Elsevier Science Publisher, B. V. (Biomedical Division): Amsterdam, 1988; Vol. 25, pp. 35–83.
5. (a) Zee-Cheng, K. Y.; Cheng, C. C. *J. Heterocycl. Chem.* **1973**, *10*, 867; (b) Zee-Cheng, K. Y.; Cheng, C. C. *J. Med. Chem.* **1975**, *18*, 66; (c) Stermitz, F. R.; Gillespie, L. G.; Amoros, L. G.; Romero, R.; Stermitz, T. A.; Larson, K. A.; Earl, S.; Ogg, J. E. *J. Med. Chem.* **1975**, *18*, 708; (d) Huang, A.-X.; Li, Z.-H. *Acta Chim. Sin.* **1980**, *38*, 535; (e) Fang, S.-D.; Wang, L.-K.; Hetch, S. M. *J. Org. Chem.* **1993**, *58*, 5025; (f) Taira, Z.; Matsumoto, M.; Ishida, S.; Icikawa, T.; Sakiya, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1556.
6. (a) Whaley, W. M.; Meadow, M. *J. Org. Chem.* **1954**, *19*, 661; (b) Galiazzo, G.; Bortolus, P.; Masetti, F. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1712; (c) Masetti, F.; Bartocci, G.; Mazzucato, U. *Gazz. Chim. Ital.* **1982**, *112*, 255; (d) Tanga, M. J.; Almquist, R. G.; Smith, T. H. *J. Heterocycl. Chem.* **1985**, *22*, 1597.
7. Chen, H.-Y.; Preston, M. R. *Environ. Sci. Technol.* **1998**, *32*, 577.
8. (a) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *46*, 4416; (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
9. Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804.
10. (a) Rubin, M. B.; Welner, S. *J. Org. Chem.* **1980**, *45*, 1847; (b) Koszyk, F. J.; Lenz, G. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1273.

11. (a) All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data follow. **Compound 4a**. ^{1}H NMR (δ, ppm, $CDCl_3$): 3.78 (s, 3H, -CO_2CH_3), 6.92 (d, J=16.3 Hz, 1H, -C*H*=CH-), 7.17–7.35 (m, 5H, 5×Ar-H), 7.47–7.51 (m, 2H, 2×Ar-H), 7.58 (d, J=7.7 Hz, 1H, Ar-H), 7.86 (dd, J=7.8 and 1.3 Hz, 1H, Ar-H), 8.02 (d, J=16.3 Hz, 1H, -C*H*=CH-). MS (m/z, %): 238 (M^+, 79), 178 (100). **Compound 5a**. ^{1}H NMR (δ, ppm, $CDCl_3$): 4.04 (s, 3H, -CO_2CH_3), 7.64–7.70 (m, 3H, 3×Ar-H), 7.87 (d, J=9.4 Hz, 1H, Ar-H), 7.93 (d, J=7.4 Hz, 1H, Ar-H), 8.22 (d, J=7.4 Hz, 1H, Ar-H), 8.70 (d, J=7.9 Hz, 1H, Ar-H), 8.78 (d, J=9.4 Hz, 1H, Ar-H), 8.92 (d, J=8.4 Hz, 1H, Ar-H). MS (m/z, %): 236 (M^+, 100). **Compound 4b**. Mp 86–88°C (MeOH). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.87 (s, 3H, -CO_2CH_3), 3.89 (s, 3H, -OCH_3), 3.94 (s, 3H, -OCH_3), 6.89 (d, J=16.2 Hz, 1H, -C*H*=CH-), 7.10 (s, 1H, Ar-H), 7.22–7.36 (m, 3H, 3×Ar-H), 7.44 (s, 1H, Ar-H), 7.51–7.54 (m, 2H, 2×Ar-H), 8.07 (d, J=16.2 Hz, 1H, -C*H*=CH-). MS (m/z, %): 298 (M^+, 100). **Compound 5b**. Mp 109–111°C (AcOEt). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.97 (s, 3H, -CO_2CH_3), 4.02 (s, 3H, -OCH_3), 4.06 (s, 3H, -OCH_3), 7.60–7.65 (m, 2H, 2×Ar-H), 7.69 (d, J=9.3 Hz, 1H, Ar-H), 7.84–7.88 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.65 (d, J=9.3 Hz, 1H, Ar-H), 9.62–9.66 (m, 1H, Ar-H). MS (m/z, %): 296 (M^+, 100). **Compound 9f**. Mp 152–154°C (MeOH). ^{1}H NMR (δ, ppm, $CDCl_3$): 4.04 (s, 3H, -OCH_3), 4.25 (s, 3H, -OCH_3), 7.68–7.74 (m, 2H, 2×Ar-H), 7.98–8.01 (m, 2H, 2×Ar-H), 8.45–8.46 (m, 1H, Ar-H), 8.63 (d, J=9.0 Hz, 1H, Ar-H), 8.77 (bs, 1H, Ar-H), 9.69 (bs, 1H, Ar-H), 9.77 (d, J=8.3 Hz, 1H, Ar-H). MS (m/z, %): 289 (M^+, 2), 58 (100).
12. Karmakar, A. C.; Kar, G. K.; Ray, J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1997.
13. For previous syntheses of *o*-styrylbenzoic acids, see Ref. 1. See also: (a) Kim, B. M.; Park, J. K. *Bull. Korean Chem. Soc.* **1999**, *20*, 744; (b) Noda, M. *Chem. Pharm. Bull.* **1998**, *46*, 1157; (c) Zehnter, R.; Gerlach, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2779; (d) Yoshikawa, M.; Harada, E.; Yagi, N.; Okuno, Y.; Muraoka, O.; Aoyama, H.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 721; (e) Mal, D.; Majumdar, G.; Pal, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1115; (f) Bowden, K.; Ghadir, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1333; (g) Lazer, E. S.; Wong, H. C.; Wegner, C. D.; Graham, A. G.; Farina, P. R. *J. Med. Chem.* **1990**, *33*, 1892; (h) Eicher, T.; Tiefensee, K.; Pick, R. *Synthesis* **1988**, 525; (i) Bellinger, G. C. A.; Campbell, W. E.; Giles, R. G. F.; Tobias, J. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2819; (j) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
14. (a) Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis* **1990**, 142; (b) Caluwe, P.; Pepper, T. *J. Org. Chem.* **1988**, *53*, 1786; (c) Rubin, M. B.; Welner, S. *J. Org. Chem.* **1980**, *45*, 1847.