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Graphical Abstract

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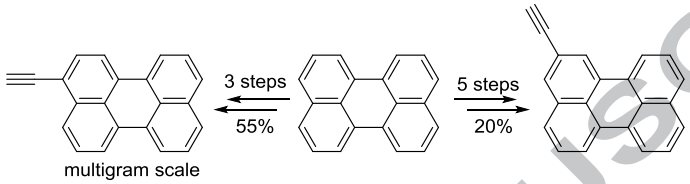

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2-Ethynylperylene and improved synthesis of 3-ethynylperylene

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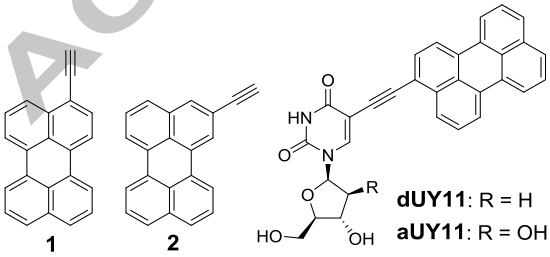
ABSTRACT

3-Ethynylperylene **1**, an important precursor for fluorescent dyes, fluorescent nucleosides, and potent nucleoside-based antivirals, has been prepared from perylene on a multigram scale (3 steps, 55% overall yield). A simple synthesis of 2-ethynylperylene **2** from perylene (5 steps, 20% yield) has been developed. UV and fluorescence spectra of the ethynylperylenes **1** and **2** are compared to those of perylene.

Introduction

3-Ethynylperylene **1**, initially studied as a suicide inhibitor of P450 metabolic enzymes;[1] later was used in syntheses of the bright emitting unit of light harvesting systems,[2] ferrocene-derived artificial receptor for nucleobases,[3] BODIPY[4] and other[5] fluorescent dyes, and fluorescent nucleosides.[6] Moreover, 5-(perylen-3-yl-ethynyl) uracil nucleosides, produced from 3-ethynylperylene via Sonogashira coupling, were recognized as antivirals.[7] However, reported procedures for the synthesis of **1**[2b,3,5c,7a,7d,8] were performed on a small scale, probably due to the limited solubility of perylene derivatives in organic solvents. 2-Ethynylperylene **2** was not previously reported.



1 **2**

In our studies of antiviral nucleosides we required multigram quantities of **1** for the synthesis of amphipathic compounds **dUY11** and **aUY11**, potent inhibitors[7b–e] of enveloped viruses with non-nucleoside mechanism of action. Therefore, our first aim was to develop a reliable and scalable synthetic procedure for **1**. We were also interested in the isomer **2** in light of its fluorescence properties and the potential antiviral activity of its nucleoside derivatives.

Results and discussion

The most convenient procedure for scale-up appeared to be that already used by our research group;[7a] the three-stage synthesis of **1** starting from perylene **3** (Scheme 1). The first step is the simple Friedel–Crafts acylation to afford ketone **4**. This transformation was initially reported in 1966 by Zieger in 54% yield[9] and later reproduced in 40%[10] and 56%[11] yields. In our attempts to increase the conversion of the starting perylene we obtained considerable amounts of undesired bis-acetylated product (non-separable mixture of 3,9- and 3,10-diacetylperylenes). However, the addition of $AlCl_3$ catalyst as a solution in nitromethane to perylene and acetyl chloride dissolved in chlorobenzene gave clean mono-acetylation and 91% yield of **4**. The reaction was easily performed on 100 mmol (25 g) scale. Apparently, nitromethane controls the reactivity of $AlCl_3$ and favors formation of the mono-acylated product.

The next two steps, **4**→**5**→**1** (Scheme 1), were previously performed on a 1.7 g scale (81% yield) and 200 mg scale (91% yield), respectively.[7a] However, yields decreased dramatically upon scale up. Nevertheless, the modification of the isolation step in the Vilsmeyer–Haak–Arnold **4**→**5** transformation allowed us to obtain an acceptable 66% isolated yield on a 107 mmol (31.5 g) scale. For the Bodendorf fragmentation **5**→**1** we succeeded in keeping the high yield through replacement of the solvent: a toluene–isopropanol mixture was used instead of dioxane. The reaction was performed on a 22 mmol (7.5 g) scale and gave a 92% yield of **1** (5.6 g). Thus, we report herein the multigram synthesis of 3-ethynylperylene **1** from perylene

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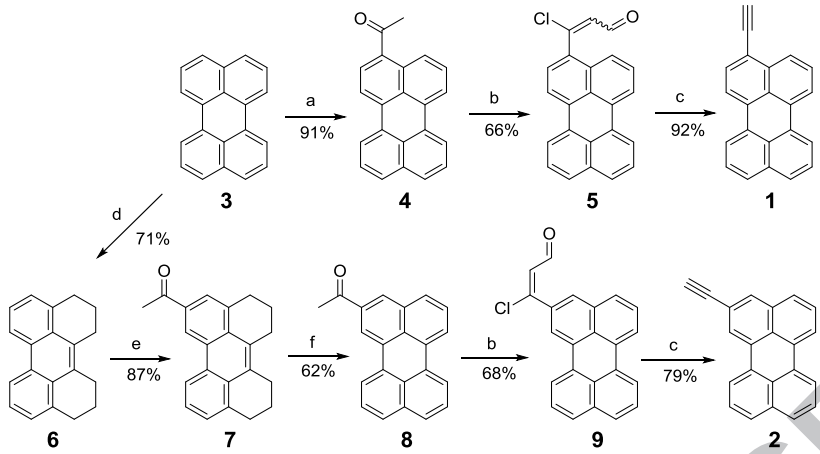

Scheme 1. Synthesis of 3- and 2-ethynylperylenes. Reagents and Conditions: (a) AcCl, $AlCl_3/CH_3NO_2$, chlorobenzene, 40 °C; (b) $POCl_3$, DMF, r.t.; (c) KOH, isopropanol/toluene, reflux; (d) H_2, 10% Pd/C, 17 bar, 60 °C; (e) AcCl, $AlCl_3$, CH_2Cl_2; (f) DDQ, toluene, reflux.

using inexpensive reagents and solvents.

For the preparation of 2-ethynylperylene **2** we used a similar approach (Scheme 1). Transformations **3**→**6**→**7** were already reported by Zieger.[9] Perylene hydrogenation was performed using 10% Pd/C catalyst and gave a similar yield of hexahydroperylene **6** to that obtained using copper chromite[9] or $Co_2(CO)_8$.[12] Acylation of **6** in dichloromethane gave 87% of ketone **7** vs. 64% by acylation in chlorobenzene as reported earlier.[9] Aromatization of **7** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) gave 2-acetylperylene **8** in 62% yield. Surprisingly, the compound was not reported previously. The ketone **8** was successively transformed to aldehyde **9** (remarkably, isolated as a single *E*-stereoisomer) and alkyne **2** using conditions similar to those used in the synthesis of the 3-isomer. The approach based on hydrogenation–acylation–aromatization followed by Vilsmeyer–Haak–Arnold formylation and Bodendorf fragmentation has already been used in the convenient synthesis of 2- and 4-ethynylpyrenes.[13]

Interestingly, the long-wavelength absorbance of 2-ethynylperylene is rather similar to that of parent hydrocarbon. In contrast, the absorbance of 3-ethynylperylene is red shifted by 16–18 nm (Fig. 1).

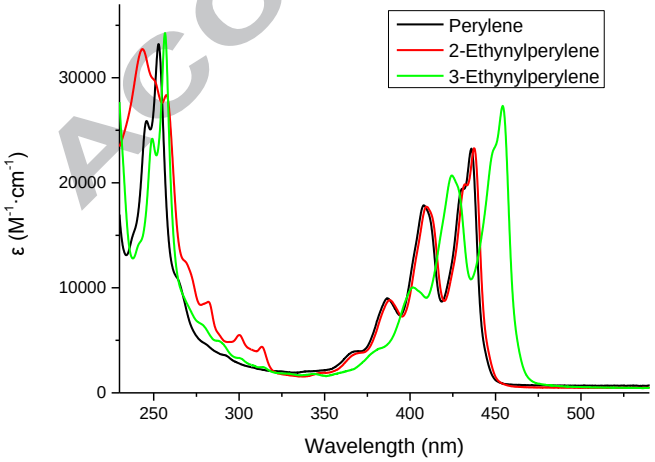

Figure 1. UV spectra of perylene, 2- and 3-ethynylperylene in cyclohexane.

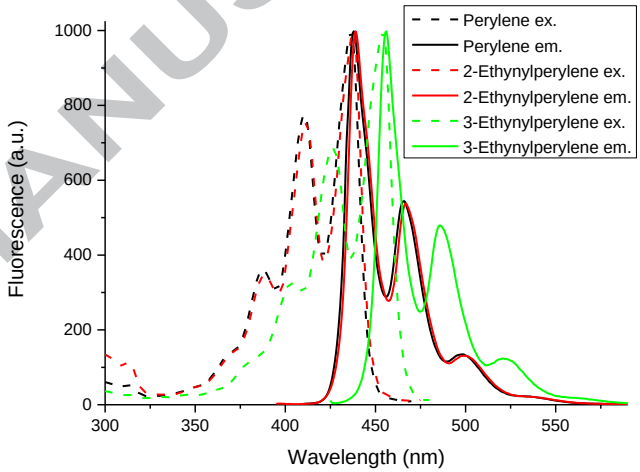

Figure 2. Normalized fluorescence spectra (excitation and emission) of perylene, 2- and 3-ethynylperylene in cyclohexane. Excitation wavelengths: 385 nm (perylene), 380 nm (**2**), and 420 nm (**1**).

Excitation and emission spectra of **2** are very similar to those of perylene, while **1** shows some red shift in both spectra (Fig. 2). Similar effects of differential conjugation was observed on 2- vs. 1(4)-phenylethynyl derivatives of pyrene.[13,14] Stokes shifts for perylene and both ethynylperylenes are about 2 nm.

Conclusion

To conclude, we report a simple and convenient multigram procedure for the three step transformation of perylene to 3-ethynylperylene **1**. The previously unknown 2-ethynylperylene **2** has been prepared from perylene in five steps and 20% total yield. The use of **2** in amphipathic antiviral nucleoside synthesis and click chemistry applications will be reported elsewhere.

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Supplementary data

Supplementary data (synthetic procedures, HRMS, NMR spectra) associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tetlet

References and notes

1. Hall, M.; Parker, D. K.; Grover, P. L.; Lu, J. L.; Hopkins, N. E.; Alworth, W. L. *Chem.-Biol. Interactions* **1990**, *76*, 181–192.
2. (a) Xu, Z.; Moore, J. S. *Acta Polym.* **1994**, *45*, 83–87; (b) Devadoss, C.; Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 9635–9644; (c) Pan, Y.; Lu, M.; Peng, Z.; Melinger, J. S. *J. Org. Chem.* **2003**, *68*, 6952–6958; (d) Atas, E.; Peng, Z.; Kleiman, V. D. *J. Phys. Chem. B* **2005**, *109*, 13553–13560.
3. Inouye, M.; Hyodo, Y.; Nakazumi, H. *J. Org. Chem.* **1999**, *64*, 2704–2710.
4. (a) Harriman, A.; Izzet, G.; Ziessel, R. *J. Am. Chem. Soc.* **2006**, *128*, 10868–10875; (b) Ulrich, G.; Goze, C.; Goeb, S.; Retailleau, P.; Ziessel, R. *New J. Chem.* **2006**, *30*, 982–986; (c) Goze, C.; Ulrich, G.; Ziessel, R. *J. Org. Chem.* **2007**, *72*, 313–322; (d) Goeb, S.; Ziessel, R. *Org. Lett.* **2007**, **9**, 737–740; (e) Goeb, S.; Ziessel, R. *Tetrahedron Lett.* **2008**, *49*, 2569–2574; (f) Alamiry, M. A. H.; Harriman, A.; Mallon, L. J.; Ulrich, G.; Ziessel, R. *Eur. J. Org. Chem.* **2008**, 2774–2782; (g) Harriman, A.; Mallon, L.; Ziessel, R. *Chem. Eur. J.* **2008**, *14*, 11461–11473; (h) Harriman, A.; Mallon, L. J.; Goeb, S.; Ulrich, G.; Ziessel, R. *Chem. Eur. J.* **2009**, *15*, 4553–4564; (i) Ziessel, R.; Rihn, S.; Harriman, A. *Chem. Eur. J.* **2010**, *16*, 11942–11953; (j) Ziessel, R.; Bura, T.; Olivier, J.-H. *Synlett* **2010**, 2304–2310; (k) Ulrich, G.; Goeb, S.; De Nicola, A.; Retailleau, P.; Ziessel, R. *J. Org. Chem.* **2011**, *76*, 4489–4505; (l) Huaulmé, Q.; Mirloup, A.; Retailleau, P.; Ziessel, R. *Org. Lett.* **2015**, *17*, 2246–2249.
5. (a) Diring, S.; Retailleau, P.; Ziessel, R. *J. Org. Chem.* **2007**, *72*, 10181–10193; (b) Rachford, A. A.; Goeb, S.; Ziessel, R.; Castellano, F. N. *Inorg. Chem.* **2008**, *47*, 4348–4355; (c) Beyer, C.; Wagenknecht, H.-A. *J. Org. Chem.* **2010**, *75*, 2752–2755; (d) Spaenig, F.; Olivier, J.-H.; Prusakova, V.; Retailleau, P.; Ziessel, R.; Castellano, F. N. *Inorg. Chem.* **2011**, *50*, 10859–10871; (e) Rihn, S.; Retailleau, P.; De Nicola, A.; Ulrich, G.; Ziessel, R. *J. Org. Chem.* **2012**, *77*, 8851–8863.
6. (a) Korshun, V. A.; Manasova, E. V.; Balakin, K. V.; Malakhov, A. D.; Perepelov, A. V.; Sokolova, T. A.; Berlin, Y. A. *Nucleosides Nucleotides* **1998**, *17*, 1809–1812; (b) Skorobogatyj, M. V.; Pchelintseva, A. A.; Ustinov, A. V.; Korshun, V. A.; Malakhov, A. D. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 931–934; (c) Skorobogatyi, M. V.; Malakhov, A. D.; Pchelintseva, A. A.; Turban, A. A.; Bondarev, S. L.; Korshun, V. A. *ChemBioChem* **2006**, *7*, 810–816; (d) Kumar, P.; Østergaard, M. E.; Baral, B.; Anderson, B. A.; Guenther, D. C.; Kaura, M.; Raible, D. J.; Sharma, P. K.; Hrdlicka, P. J. *J. Org. Chem.* **2014**, *79*, 5047–5061; (e) Kim, K. T.; Heo, W.; Joo, T.; Kim, B. H. *Org. Biomol. Chem.* **2015**, *13*, 8470–8478; (f) Kundu, R. *Chem. As. J.*, **2016**, *11*, in press (DOI: 10.1002/asia.201500996).
7. (a) Andronova, V. L.; Skorobogatyi, M. V.; Manasova, E. V.; Berlin, Y. A.; Korshun, V. A.; Galegov, G. A. *Russ. J. Bioorg. Chem.* **2003**, *29*, 262–266; (b) St.Vincent, M. R.; Colpitts, C. C.; Ustinov, A. V.; Muqadas, M.; Joyce, M. A.; Barsby, N. L.; Epand, R. F.; Epand, R. M.; Khramyshev, S. A.; Valueva, O. A.; Korshun, V. A.; Tyrrell, D. L. J.; Schang, L. M. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 17339–17344; (c) Colpitts, C. C.; Ustinov, A. V.; Epand, R. F.; Epand, R. M.; Korshun, V. A.; Schang, L. M. *J. Virol.* **2013**, *87*, 3640–3654; (d) Vigant, F.; Hollmann, A.; Lee, J.; Santos, N. C.; Jung, M. E.; Lee, B. *J. Virol.* **2014**, *88*, 1849–1853; (e) Orlov, A. A.; Chistov, A. A., Kozlovskaya, L. I.; Ustinov, A. V.; Korshun, V. A.; Karganova, G. G.; Osolodkin, D. I. *Med. Chem. Commun.*, **2016**, *6*, in press (DOI: 10.1039/C5MD00538H).
8. Yamaji, M.; Maeda, H.; Nanai, Y.; Mizuno, K. *Chem. Phys. Lett.* **2012**, *536*, 72–76.
9. Zieger, H. E. *J. Org. Chem.* **1966**, *31*, 2977–2981.
10. Sarobe, M.; Kwint, H. C.; Fleer, T.; Havenith, R. W. A.; Jenneskens, L. W.; Vlietstra, E. J.; van Lenthe, J. H.; Wesseling. J. *Eur. J. Org. Chem.* **1999**, 1191–1200.
11. Markovic, V.; Villamaina, D.; Barabanov, I.; Daku, L. M. L.; Vauthey E. *Angew. Chem. Int. Ed.* **2011**, *50*, 7596–7598.
12. Friedman, S.; Metlin, S.; Svedi, A.; Wender, I. *J. Org. Chem.* **1959**, *24*, 1287–1289.
13. Filichev, V. V.; Astakhova, I. V.; Malakhov, A. D.; Korshun, V. A.; Pedersen, E. B. *Chem. Eur. J.* **2008**, *14*, 9968–9980.
14. Astakhova, I. V.; Korshun, V. A. *Russ. J. Bioorgan. Chem.* **2008**, *34*, 510–512.