Pergamon

Tetrahedron Letters 41 (2000) 5317–5320

TETRAHEDRON LETTERS

An intramolecular arylation route to the kinafluorenones

Ghassan Qabaja and Graham B. Jones*

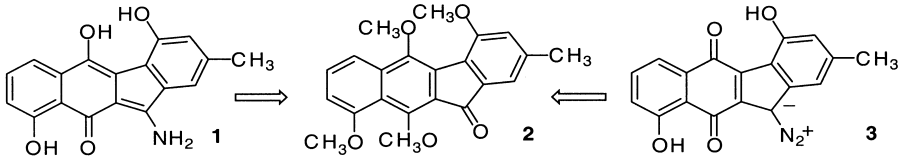
Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry and Barnett Institute, 102 Hurtig Hall, Northeastern University, 360 Huntington Avenue, Boston, MA 02115, USA

Received 13 April 2000; accepted 17 May 2000

Abstract

Intramolecular palladium-mediated arylation approaches to benzo[*b*]fluorenes have been investigated. The methodology has been applied in a short synthesis of kinafluorenone **2**, providing an effective alternative to Friedel–Crafts-based approaches.

The search for new antibiotics continues at a steady pace, and quinonoid derived systems have been the subject of a number of promising leads.[1] Of the benzo[*b*]fluorenone family, the natural products stealthin C, **1**[2]and prekinamycin **3**[3] have attracted considerable interest, and both are accessible from the benzo[*b*]fluorenone **2**.[4] Additionally, tetracycle **3** is a known intermediate in the biosynthesis of the kinamycin family of antibiotics produced by *Streptomyces murayamaensis*, and a number of these natural products show Gram positive and negative antibacterial properties, and antitumoral activity.[5]

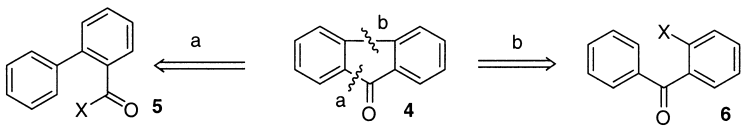


Though a number of different approaches to the basic benzo[*b*]fluorenone skeleton **4** have been reported, most involve variants of Friedel–Crafts type closures of acylbiphenyls **5** (Scheme 1).[6] Due to the versatility of transition metal-mediated arylations, we were interested to investigate the potential for a Pd mediated closure from **6**, which would offer a complimentary strategy for the production of analogs of the natural products.

To demonstrate the feasibility of the approach, appropriate model substrates were assembled, either by coupling arene **7** with 2-iodobenzoic acid, or in the case of **10**, acylation followed by Ti-catalyzed *ortho*-Fries rearrangement (Scheme 2). Palladium-mediated closures on substrates **8** and the methyl ether of **11** were conducted using a variety of methods with limited success, but

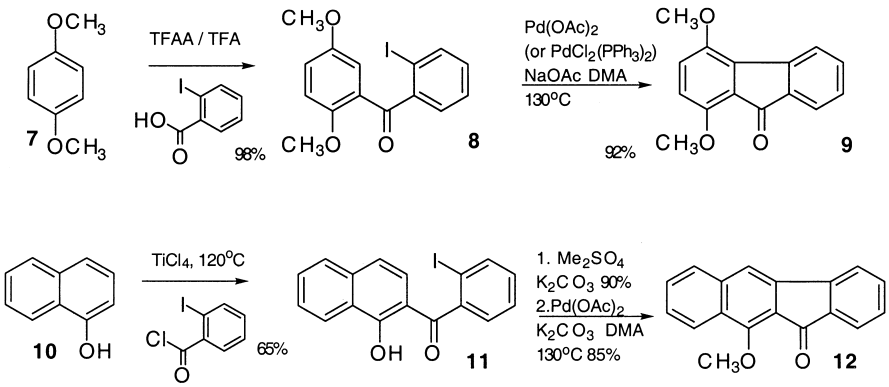
* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00848-0



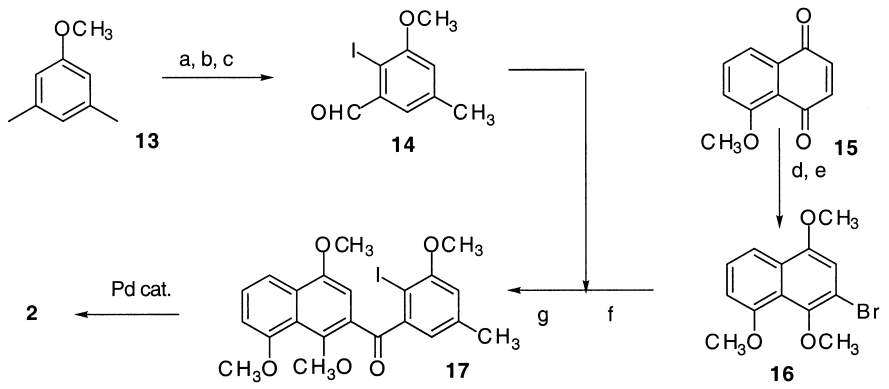
Scheme 1. Complimentary routes to the benzo[*b*]fluorene skeleton

optimal conditions were eventually found, involving high temperature closure with $Pd(OAc)_2$ in dimethylacetamide (DMA), as had been previously demonstrated by Ames and Opalko in the cyclization of substituted diphenylethers to dibenzofurans.[7]



Scheme 2. Model arylation route to benzo[*b*]fluorenones

With the model study complete, we sought application in the synthesis of key structure **2**. Accordingly, dimethylanisole **13** was converted to iodoaldehyde **14** which was subjected to 1,2 addition with the lithioarene derived from aryl bromide **16**, in turn prepared from methyljuglone **15**[8] (Scheme 3). The resulting benzylic alcohol was oxidized (**17**), and the Pd mediated closure attempted. Using identical conditions to the model substrates, low yields of **2** were isolated, suggesting either the *o*-methoxy group exerts a subtle electronic influence or else developing (repulsive) interactions between the aryloxy groups in **2** retard product formation.



Scheme 3. Convergent synthesis of kinafluorenone: (a) CCl_4, NBS, then K_2CO_3, dioxane, 40%; (b) *n*BuLi, hexanes, I_2 –78°C, 80%; (c) $COCl_2$, DMSO, 95%; (d) $Na_2S_2O_4$, ether then Me_2SO_4, K_2CO_3 85%; (e) CCl_4, Br_2 99% then K_2CO_3, Me_2SO_4 60%; (f) *t*BuLi, ether, –78°C (quant.); (g) PCC, CH_2Cl_2, 80%

Complicating the process was product decomposition which ensued at the higher temperatures and extended reaction times necessary to effect closure (Table 1). Since metal-catalyzed processes are often ideal candidates for acceleration using microwaves,[9,10] a reaction was conducted using microwave irradiation (mW). Additionally, DMA, which has a dielectric constant of 37.8 D would be expected to heat rapidly during the irradiation process. Accordingly, a sample of **17**, $PdCl_2(PPh_3)_2$ and sodium acetate dissolved in DMA, in a round-bottomed flask was placed in the center of a conventional microwave oven and irradiated for 60 sec.[11] During this period, the solution temperature reached 140°C, and gave a 53% yield of desired product **2**, along with traces of unreacted **17**. Efforts to improve the product yields by extended thermolysis were unsuccessful, and after 2 min the solution began to reflux, necessitating cessation of the reaction. Similarly, microwave accelerated closures to model substrates **9** and **12** were successful, in both cases giving comparable yields of product to the thermal process (Scheme 2) within 1 min.

Table 1
Attempted Pd-catalyzed arylation of **17**

Entry	Cat.	Solvent	Temp/°C	Time	%**2**
1	$Pd(OAc)_2$ /NaOAc	DMA	130	12h	0%
2	$PdCl_2(PPh_3)_2$/NaOAc	DMA	130	18h	29%
3	$Pd(OAc)_2(PPh_3)_2$/NaOAc	DMA	130	6h	31%
4	$Pd(OAc)_2/Et_3N$	CH_3CN	80	24h	0%
5	$Pd(PPh_3)_4$ /Et_3N	THF/CH_3CN	80	36h	<5%
6	$PdCl_2(PPh_3)_2$/NMI	NMI	170	24h	0%
7	$PdCl_2(PPh_3)_2$/NaOAc	DMA-mW	140	1 min.	53%
8	$Pd(OAc)_2(PPh_3)_2$/NaOAc	DMA-mW	160	1 min.	49%

The speed and efficiency of the mW accelerated coupling suggests additional applications in transition metal-mediated processes may be forthcoming. The described synthesis of kinafluorenone **2** is competitive with existing routes, and may allow development of additional analogs of the natural product. The scope and limitations of the arylation process, together with antitumoral and antibacterial data for synthetic analogs of **2** will be presented in a full account of this work.

Microwave accelerated route to ***2***: A heavy walled (5 mm) boiling tube (100 ml) equipped with a virgin septum and magnetic stir bar was flame dried under a stream of nitrogen gas. Ketone **17** (92 mg, 0.18 mmol), sodium acetate (46 mg, 0.54 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (20 mg, 0.027 mmol) in dimethylacetamide (50 ml) were introduced and the mixture degassed (N_2) for 2 h. The tube was placed in a 100 ml beaker within the cavity of a domestic microwave oven (450 W), and irradiated at full power for 60 sec. On cooling, the mixture was poured into ether (100 ml) and washed with HCl (1M, 3×30 ml). The combined organic extracts were dried ($MgSO_4$), condensed in vacuo, and the resulting residue purified by flash chromatography (5% EtOAc: 95% CH_2Cl_2) to give **2** (36 mg, 53%) isolated as an orange solid m.p. 110°C (dec.) and spectroscopically identical with authentic material.[3]

Acknowledgements

We thank the National Institute for General Medical Sciences (RO1GM57123) for generous financial support.

References

1. *CRC Handbook of Antibiotic Compounds*; Berdy, J., Ed.; CRC Press: Boca Raton, 1980.
2. Koyama, H.; Kamikawa, T. *Tetrahedron Lett*. **1997**, *38*, 3973; Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamaya, N. *J. Org. Chem*. **1996**, *61*, 5720; Gould, S. J.; Melville, C. R.; Cone, M. C.; Chen, J.; Carney, J. R. *J. Org. Chem*. **1997**, *62*, 320.
3. Cone, M. C.; Hassan, A. M.; Gore, M. P.; Gould, S. J.; Borders, D. B.; Alluri, M. R. *J. Org. Chem*. **1994**, *59*, 1923; Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem*. **1992**, *57*, 2774.
4. Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem*. **1991**, *56*, 2289.
5. Gould, S. J.; Melville, C. R. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 51.
6. For the phthalide annelation route, see: Hauser, F. M.; Zhou, M. *J. Org. Chem*. **1996**, *61*, 5722.
7. Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234.
8. Qabaja, G.; Perchellet, E.; Perchellet, J.; Jones, G. B. *Tetrahedron Lett*. **2000**, *41*, 3007–3010.
9. Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev*. **1991**, *20*, 1.
10. For pioneering examples in organic synthesis, see: Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett*. **1986**, *27*, 4945.
11. For previous reports from this laboratory, see: Huber, R. S.; Jones, G. B. *J. Org. Chem*. **1992**, *57*, 5778; Jones, G. B.; Huber, R. S.; Chau, S. *Tetrahedron* **1993**, *49*, 369; Jones, G. B.; Chapman, B. J. *J. Org. Chem*. **1993**, *58*, 5558.