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Three-step one-pot organobismuth-mediated synthesis of benzo[*b*]pyran compounds

Alexey V. Bolshakov,[a] Olga G. Ganina,[a] Andrew S. Shavirin,[b] Yury A. Kurskii,[b] Jean-Pierre Finet[c,*] and Alexey Yu. Fedorov[a,*]

[a]*Department of Organic Chemistry, Nizhny Novgorod State University, 23 Gagarin Avenue, 603950 Nizhny Novgorod, Russia*
[b]*Razuvaev Institute of Organometallic Chemistry, Russian Academy of Sciences, GSP-445, 49 Tropinin Street, 603600 Nizhny Novgorod, Russia*
[c]*UMR 6517 CNRS, Universités d'Aix-Marseille 1 et 3, Faculté des Sciences Saint-Jérôme, 13397 Marseille Cedex 20, France*

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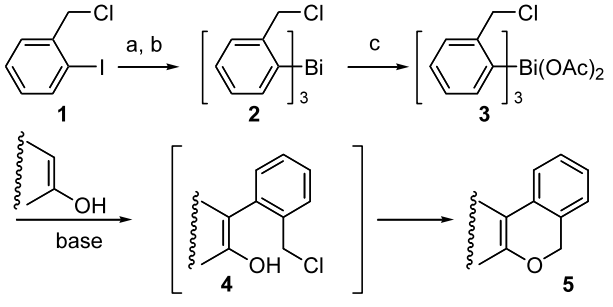
Abstract—Tris[*ortho*-chloromethylphenyl]bismuth diacetate reacted with phenols and enolisable substrates in the presence of a base to afford good yields of oxaphenanthrene derivatives.

The dibenzo[*b*,*d*]pyran nucleus constitutes the skeleton of a number of physiologically active natural products as well as of drugs.[1] Apart from the various classical strategies developed for their synthesis,[2–4] three recently reported pathways are based on direct one-pot methodologies: (a) organolead-mediated *ortho*-arylation–cyclisation sequence;[5] (b) intramolecular radical cyclisation[6] and (c) palladium-catalysed cross-coupling reactions.[7] However, the first method involves the use of toxic organolead reagents, the utility of the second route is limited by the low regioselectivity of the cyclisation, and the Heck-type reactions (c) are restricted to electron-rich phenols.[8]

In this letter, we report a new route to dibenzo[*b*,*d*]pyran derivatives, using organobismuth-mediated oxidation–*ortho*-arylation–cyclisation sequence in a one-pot reaction. Organobismuth derivatives are interesting candidates for their utilisation in 'green chemistry' as they are less toxic and less expensive than the analogous organolead reagents, and also than the palladium salts and phosphine or the related ligands that are needed for the palladium coupling.[9] The variety of organobismuth-mediated transformations (*C*-, *O*- and *N*-arylation reactions),[10–12] the high regioselectivity of these processes and the rather mild reaction conditions made these reagents attractive for a number of transformation of pharmacologically active products.[13–16] Moreover, these reactions are useful for the introduction of neutral, electron-poor, as well as electron-rich aryl groups,[17] the latter being frequently observed in natural products.

For the synthesis of oxaphenanthrene derivatives, the tris[*ortho*-chloromethylphenyl]bismuthane **2**, containing two electrophilic centres, was used as the key reagent. The synthetic procedure for the preparation of **2** involves the reaction of the functionalised aryl-Grignard reagent, recently reported by Cahiez and Knochel,[18,19] with bismuth trichloride (Scheme 1). This



Scheme 1. *Reagents and conditions*: (a) *i*-PrMgBr, THF, −10°C, 3 h; (b) $BiCl_3$, −10°C, 2 h, then rt overnight; (c) $PhI(OAc)_2$, CH_2Cl_2.

Keywords: arylation; cyclisation; dibenzo[*b*,*d*]pyran; ligand coupling.
* Corresponding author. Fax: 7 8312 65 85 92 (A.F.); fax: 33 4 91 98 85 12 (J.P.F.); e-mail: finet@srepir1.univ-mrs.fr; afnn@rambler.ru

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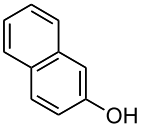
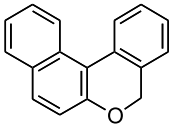
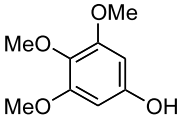
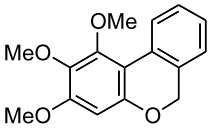
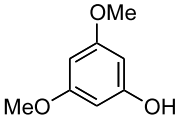
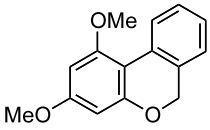
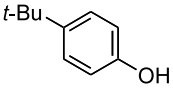
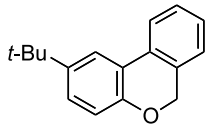
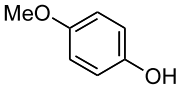
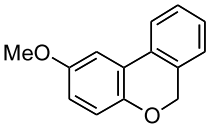
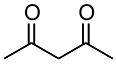
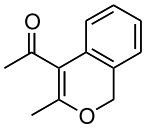
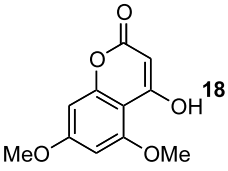
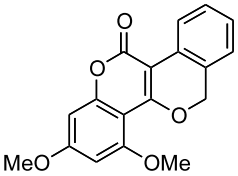
method afforded the trivalent organobismuth compound **2**[20] in moderate yield (27%). The following three steps for the synthesis of the dibenzo[*b*,*d*]pyran derivatives were performed in one pot. Oxidation of the Bi(III) derivative **2** by $PhI(OAc)_2$[21] led to the corresponding triarylbismuth diacetate **3**, which was treated directly with the various substrates. The *ortho*-arylation reaction afforded the arylation products **4**, which underwent a spontaneous intramolecular cyclisation to lead to the formation of **5**. Thus, this strategy permitted us to carry out a three-step synthesis in one-pot leading to the benzopyran derivatives.

In a typical procedure, a mixture of tris[*ortho*-chloromethylphenyl]bismuthane **2** (0.17–0.26 mmol, 1 equiv.) and iodobenzene diacetate (0.19–0.29 mmol, 1.1 equiv.) in CH_2Cl_2 (3–5 mL) was stirred at room temperature for 6–8 h. Then the substrate (0.17–0.26 mmol, 1 equiv.) and the base [triethylamine (0.51–0.78 mmol, 3 equiv.) or NaH (2 equiv.)] were added and the reaction mixture was stirred under the conditions described in Table 1. After completion of the reaction, distillation of the solvent under reduced pressure followed by purification of the residue by chromatography afforded the pure cyclisation products.[22]

Table 1. Synthesis of dibenzo[*b*,*d*]pyran derivatives, via one-pot oxidation–arylation–cyclisation sequence using tris[*ortho*-chloromethylphenyl]bismuthane **2**

Substrates	Reaction conditions[a]	Products	Yields (%)
 **6**	rt, 30h	 **7**	(55)
 **8**	reflux, 4h, rt, 30h	 **9**	(49)
 **10**	reflux, 3h, rt, 30h	 **11**	(48)
 **12**	rt, 30h	 **13**	(27)
 **14**	rt, 30h	 **15**	(5)
 **16**	reflux, 3h, rt, 30h[b]	 **17**	(35)
 **18**	reflux, 4h, rt, 30h	 **19**	(46)

a) All sequences were performed in two step one-pot reactions: 1- a mixture of **2** (1 molar equiv.) and iodobenzene diacetate (1.1 molar equiv.) in CH_2Cl_2 was stirred at room temperature for 6-8 hours; 2- the substrate (1 molar equiv.) and triethylamine (3 molar equiv.) were then added and the reaction performed as indicated.
b) NaH was used instead of triethylamine

Good overall yields of the benzopyran products were obtained with β-naphthol **6** and with electron-rich phenols (**8** and **10**). The less electron-rich 4-*tert*-butylphenol **12** afforded the oxaphenanthrene derivative **13** in a moderate yield and 4-methoxyphenol **14** gave the cyclisation product **15** in a poor yield in line with the general reactivity patterns of pentavalent organobismuth reagents towards phenols.[23] On the other hand, the phenols containing electron-withdrawing groups, for example 4-bromo-2-methylphenol, did not react with derivative **3**. The triarylbismuth diacetate **3** reacted not only with phenols, but also with β-dicarbonyl compounds. For example, the reaction of **3** with 2,4-pentanedione **16** afforded the bicyclic compound **17** in a good yield. It is interesting to note that the reaction with the cyclic β-ketoester **18** led to the tetracyclic compound **19** in a good yield. During the third step (cyclisation by nucleophilic substitution), the hydrochloric acid which is liberated could affect the yields of the reaction products. However, increasing the amount of triethylamine up to 6 equiv. did not improve the yields. By contrast, when pyridine was used instead of triethylamine, a significant reduction of the yields was then observed.

In conclusion, this new bismuth-mediated oxidation–*ortho*-arylation–cyclisation sequence for the synthesis of the dibenzo[*b*,*d*]pyran derivatives proved equal or even superior in terms of yield, but is environmentally more friendly than our recently reported method involving the use of the related organolead reagent.[5] It is interesting to note that different aryl derivatives of main group metal elements, containing good leaving groups or easily functionalisable substituents in the *ortho*-position of the aromatic moiety, have been involved in reductive coupling reactions.[5,24] The proximity of the metallocentre and the second electrophilic reaction centre could affect the routes and the speed of the chemical processes. Work in this direction is now underway and will be reported in due course.

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20. Tris[*ortho*-chloromethylphenyl]bismuthane (**2**): soft-gray crystals; mp 143°C; δ_H ($CDCl_3$, 200 MHz) 4.69 (2H, s, CH_2), 7.25 (1H, dt, *J* 7.4 and 1.6, 4-H), 7.36 (1H, dt, *J* 7.5 and 1.6, 5-H), 7.52 (1H, dd, *J* 7.6 and 1.4, 3-H), 7.77 (1H, dd, *J* 7.4 and 1.2, 6-H); δ_C ($CDCl_3$, 50 MHz) 51.2 (CH_2), 129.1 (C-3), 130.7 (C-4), 131.8 (C-5), 140.5 (C-6), 142.2 (C-2).

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22. ***Selected physical data***: ^{1}H NMR spectra ($CDCl_3$, 200.13 MHz), *J* values in hertz; ^{13}C NMR spectra ($CDCl_3$, 50.32 MHz). (**7**): PLC (eluent: hexane–ether, 9:1), colourless oil; δ_H 5.06 (2H, s, CH_2), 7.23–7.55 (6H, m), 7.70–7.87 (2H, m), 8.04 (1H, d, *J* 8), 8.56 (1H, d, *J* 10.1). (**9**): PLC (eluent: hexane–ether, 7:3), colourless plates; mp 70°C; δ_H 3.42, 3.86 and 3.88 (3×3H, 3s, OMe), 4.98 (2H, s, CH_2), 6.41 (1H, s), 7.15–7.41 (3H, m), 8.26 (1H, d, *J* 7.9); δ_C 55.9, 60.8, 61.2 (OMe), 69.1 (CH_2), 97, 109.8, 124.4, 125.2, 126.6, 128.5, 129.1, 130.9, 137.8, 152.2, 152.3, 153.8. (**11**): PLC (eluent: hexane–ether, 7:3), colourless oil; δ_H 3.81 and 3.92 (2×3H, 2s, OMe), 4.98 (2H, s, CH_2), 6.24 (2H, s), 7.13 (1H, d, *J* 7.4), 7.19 (1H, t, *J* 7.1), 7.32 (1H, dt, *J* 7.5 and 1), 8.25 (1H, d, *J* 7.9); δ_C 55.4 and 55.6 (OMe), 69.1 (CH_2), 93.6, 94.3, 124.2, 125.55, 126, 128, 129.4, 130.6, 157.7, 158.9, 160.7. (**13**): PLC (eluent: hexane–ether, 9:1), colourless oil; δ_H 1.37 (9H, s, CH_3), 5.10 (2H, s, CH_2), 6.93 (1H, d, *J* 8), 7.17 (1H, d, *J* 7.4), 7.23–7.41 (3H, m), 7.65–7.74 (2H, m); δ_C 29.7 ($\underline{C}Me_3$), 30.9 (Me), 68.5 (CH_2), 116.8, 119.9, 121.9, 124.7, 126.6, 127.5, 128.3, 122.1, 125.9, 131.6, 144.8, 152.5. (**15**): PLC (eluent: hexane–ether, 3:1), colourless oil; δ_H 3.87 (3H, s, CH_3), 4.99 (2H, s, CH_2), 7.34–7.57 (7H, m). (**17**): PLC (eluent: hexane–ether–chloroform, 7:2:1), colourless oil; δ_H 2.17 (3H, s, Me), 2.46 (3H, s, CO$\underline{Me}$), 5.01 (2H, s, CH_2), 7.05–7.35 (4H, m); δ_C 29.7 (Me), 31.6 (CO$\underline{Me}$), 69 (CH_2), 115.3, 127.4, 129.7, 122.4, 124.1, 126.4, 128.4, 160.4, 200.8. (**19**): PLC (eluent: hexane–ether–chloroform, 1:2:2), colourless powder; mp 202°C; δ_H 3.84 and 3.87 (6H, s, OMe), 5.28 (2H, s, CH_2), 6.29 (1H, d, *J* 2.3), 6.43 (1H, d, *J* 2.3), 7.09 (1H, d, *J* 7.3), 7.27 (1H, dt, *J* 7.3 and 1.1), 7.38 (1H, dt, *J* 7.9 and 1.3), 8.46 (1H, d, *J* 7.6); δ_C 55.7 and 56.3 (OMe), 69.5 (CH_2), 93, 95.8, 99.61, 99.63, 123.6, 124.3, 127.2, 128.7, 127, 156.3, 158.8, 160.1, 163.5, 164.1.
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