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[1]Benzopyrano[2,3,4-*i*,*j*]isoquinolines: a new, versatile route from 1-bromoxanthones

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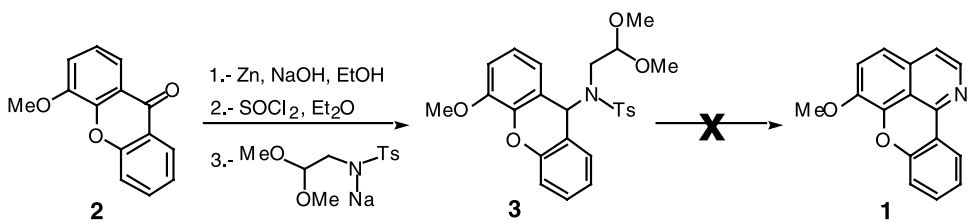
Abstract—[1]Benzopyrano[2,3,4-*i*,*j*]isoquinolines were synthesized from a bromoxanthone by assembly of the isoquinoline ring in three steps: vinylation, hydroamination and ring-closing reduction of the xanthone carbonyl.

In the course of research on tetracyclic xanthene derivatives we planned the synthesis of tetrahydroderivatives of [1]benzopyrano[2,3,4-*i*,*j*]isoquinolines **1**, to which little attention has hitherto been paid in the literature.[1] A classical approach to the isoquinoline ring is acid-catalyzed cyclization of imino, alkylamino or sulfonamido acetals derived from aminoacetaldehyde dimethylacetal; the degree of oxidation of the final product being determined by the type of compound subjected to cyclization. In particular, the use of *N*-tosyl acetals[2] delivers fully aromatized isoquinolines that can be reduced to tetrahydroisoquinolines, with or without prior *N*-alkylation. We therefore initially planned the synthesis of benzopyranoisoquinoline **1** by electrophilic cyclization of *N*-tosyl acetal **3**.

Reduction of the carbonyl group of xanthone **2**[3] with zinc powder in alkaline ethanol (92% yield),[4] followed by conversion of the resulting xanthydrol[4b] to the chloride ($SOCl_2$, Et_2O, reflux) and reaction with the sodium salt of *N*-tosyl aminoacetaldehyde dimethyl acetal,[2b] afforded compound **3** in 28% overall yield (Scheme 1). However attempts at cyclization using various acidic conditions (6N aq. HCl, dioxane, reflux; PPA, 100°C; $TiCl_4$, CH_2Cl_2, −78°C; $BF_3{\cdot}2AcOH$) afforded only products arising by nucleophilic displacement of the sulfonamide and subsequent disproportionation of the resulting xanthydrol, i.e. xanthene and xanthone.

The evident lability of the C9–N bond of **3** under acidic conditions prompted us to explore a route in which C9–N bond formation is the last step following introduction of the aminoethyl subunit on C1. Given the known hydroamination route from styrenes to phenethylamines,[5] the first step would be to obtain the 1-vinylxanthone derivative **5** (Scheme 2), which indeed was envisaged as being a better substrate than styrene for hydroamination because the electron-withdrawing carbonyl group *ortho* to the vinyl group ought to increase the electrophilicity of the double bond and stabilize the benzylic anion generated during the amination process.



Scheme 1.

Keywords: Xanthones; vinylation; amination; isoquinolines.

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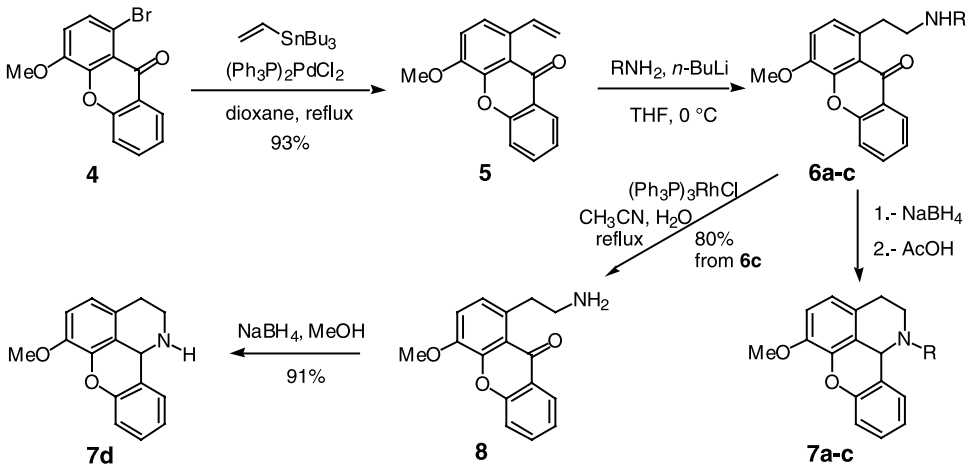

Scheme 2.

Table 1. Yields for hydroamination and ring closure

Compound	R	**6** (%)	**7** (%)
a	Bu	69	72
b	Bn	77	86
c	Allyl	85	83

Compound **5** was prepared in high yield by Stille coupling between vinyltributyltin and 1-bromoxanthone **4**,[6] which had been obtained regioselectively by bromination (Br_2, AcOH, NaOAc, 55°C, 88%) of 4-methoxyxanthone (**2**).[7,8] When compound **5**[6] was reacted in THF with the lithium salt of a primary amine,[9] the corresponding phenethylamine **6** (Table 1) was obtained in good yield.[6] $NaBH_4$ reduction of the keto group of **6** in ^{i}PrOH gave what ^{1}H NMR showed to be a 2:1 mixture of cyclized (**7**) and uncyclized (9-hydroxy) compounds, which upon treatment with glacial AcOH (rt, 60 min) afforded the isoquinoline **7** in good yield (Table 1).[6,10]

For the synthesis of **7d**, deallylation[11] of **6c** to the aminoethylxanthone **8** was followed by reduction with $NaBH_4$ in MeOH, which gave a 73% overall yield of the required product.[6]

In this way, 1,2,3,11b-tetrahydro-6-methoxy-[1]benzopyrano[2,3,4-*i*,*j*]isoquinolines **7a**–**d**, which have not previously been described in the literature, were synthesized in three steps and good overall yields from 1-bromo-4-methoxyxanthone.

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5. (a) For the base-catalyzed hydroamination of styrenes, see: Beller, M.; Breindl, C. *Tetrahedron* **1998**, *54*, 6359–6368; (b) For the stoichiometric addition of amides, see: Seijas, J. A.; Vázquez-Tato, M. P.; Entenza, C.; Martínez, M. M.; Onega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073–5076.
6. All new compounds were fully characterized spectroscopically and had satisfactory elemental analyses or HRMS data.
7. 4-Methoxyxanthone was prepared as described in Ref. 4b.
8. The starting 4-methoxyxanthone was chosen in order to allow for the regioselective bromination at the required C1-position. For the synthesis of isoquinolines with a different substitution pattern than **7a**–**d**, the present synthesis depends on the availability of the corresponding starting haloxanthone in order to allow for the vinylation at C1.
9. **Experimental procedure for 6b**: 1.6 M ^{n}BuLi (0.67 mL, 0.97 mmol) was added to a solution of benzylamine (0.10 g, 0.97 mmol) in 3 mL of dry THF at 0°C and the mixture was stirred for 5 min, treated with a solution of **5** (0.10 g, 0.39 mmol) in 2.5 mL of dry THF, left standing overnight without refrigeration and quenched with aq. NH_4Cl. After conventional work-up, chromatography of the solid residue on silica gel with 90/10 CH_2Cl_2/MeOH as eluent afforded 0.11 g (77%) of **6b** as a yellowish solid; mp 144–146°C; ^{1}H NMR ($CDCl_3$): δ 8.28 (dd, $J=7.8$ and

1.5 Hz, 1H), 7.71 (td, $J=7.5$ and 1.5 Hz, 1H), 7.58 (dd, $J=7.5$ and 1.2 Hz, 1H), 7.40–7.20 (m, 6H), 7.15 (d, $J=8.2$ Hz, 1H), 7.12 (d, $J=8.2$, 1H), 4.01 (s, 3H), 3.85 (s, 2H), 3.50 (t, $J=7.2$ Hz, 2H), 2.95 (t, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 178.9 (C), 155.4 (C), 148.3 (C), 147.6 (C), 140.8 (C), 134.8 (CH), 134.2 (C), 128.7 (2×CH), 128.5 (2×CH), 127.1 (CH), 127.0 (CH), 126.1 (CH), 124.3 (CH), 122.9 (C), 122.8 (C), 118.1 (CH), 115.1 (CH), 56.7 (OCH_3), 54.2 (CH_2), 51.2 (CH_2), 35.7 (CH_2); MS (m/z): 359 (M^+, 10), 340 (14), 268 (49), 240 (100), 225 (95), 120 (82), 91 (97). HRMS calcd for $C_{23}H_{21}NO_3$: 359.1534. Found: 359.1521.

10. **Experimental procedure for cyclization**: $NaBH_4$ (excess) was added to a solution of **6b** (0.40 g, 1.11 mmol) in 30 mL of isopropanol and the mixture was refluxed for 5 h. The solvent was partially evaporated, an aqueous saturated solution of NH_4Cl was slowly added at 0°C to destroy excess $NaBH_4$ and, after conventional work-up, the organic residue (0.38 g) was dissolved in 5 mL glacial AcOH and stirred at rt for 1 h. Toluene (20 mL) was added and the solvents evaporated to leave a solid, which was triturated with Et_2O and filtered to afford 0.33 g (86%) of **7b** as a brownish solid; mp 134–136°C; IR (CsI): 3030–2830, 1573, 1496, 1456, 1438, 1271, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.82 (d, $J=7.9$ Hz, 1H), 7.43–7.12 (m, 8H), 6.86 (s, 2H), 5.34 (s, 1H), 3.97 (s, 3H), 3.71 (d, $J=13.5$ Hz, 1H), 3.24–3.18 (m, 2H), 3.21 (d, $J=13.5$ Hz, 1H), 3.08–2.94 (m, 1H), 2.65–2.55 (dt, $J=16$ and 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 152.1 (C), 146.0 (C), 140.5 (C), 139.9 (C), 128.9 (2×CH), 128.7 (2×CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 127.0 (C), 123.8 (CH), 122.9 (CH), 121.5 (C), 118.8 (C), 117.5 (CH), 111.1 (CH), 56.7 (OCH_3), 54.6 (CH), 49.8 (CH_2), 46.2 (CH_2), 21.6 (CH_2); MS (m/z): 343 (M^+, 9), 342 (8), 252 (14), 224 (93), 209 (100), 91 (52). Anal. calcd for $C_{23}H_{21}NO_3$: C, 80.40; H, 6.16; N, 4.08. Found: C, 80.06; H, 6.30; N, 4.13%.
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