An Expedient and Short Synthesis of a 6-Iodo Isocoumarin Building Block for the Rubromycin Family and its First Palladium-Catalyzed Couplings

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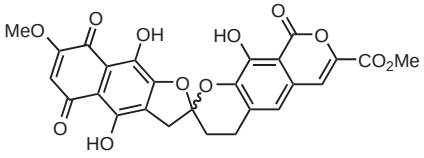
Abstract: An efficient six-step synthesis of 6-iodo substituted isocoumarin **6** is presented, which is a suitable building block for the preparation of rubromycin type compounds. Key transformations of the sequence were achieved by directed *ortho*-lithiation, Horner–Wadsworth–Emmons olefination and condensation processes. The protected isocoumarin **7** was successfully employed in first Heck and Sonogashira coupling reactions.

Key words: rubromycins, isocoumarins, *ortho*-lithiation, olefination, palladium catalysis

Natural products from the known rubromycin family[1] display various biological activities. γ-Rubromycin[2] may serve as a representative example for the remarkable molecular architecture consisting of a 5,6-spiroketal core fused to hydroxynaphthoquinone and isocoumarin units (Figure 1).

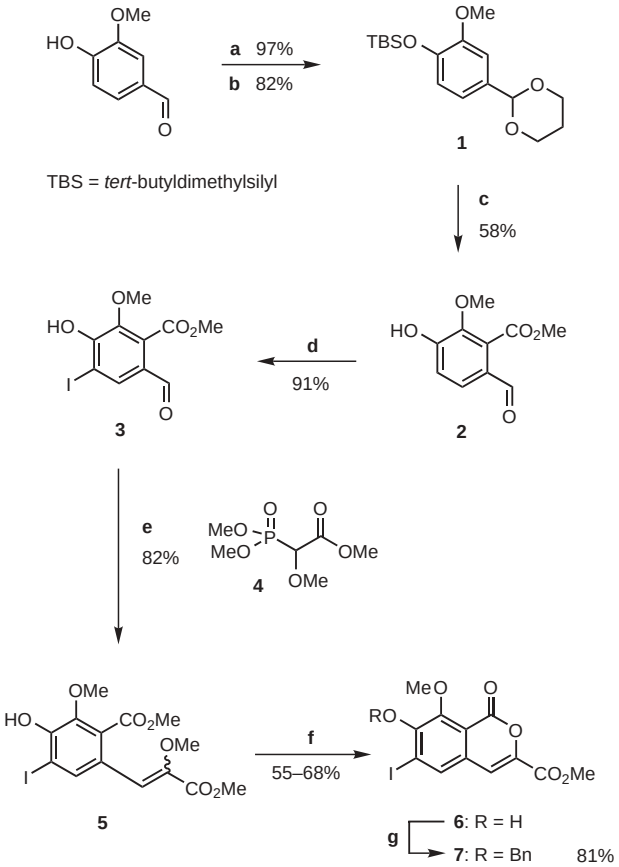


γ-rubromycin

Figure 1

To date, only one total synthesis of a rubromycin compound, namely heliquinomycinone, has been reported.[3] Versatile building blocks for their syntheses thus remain desirable targets.[4] In this letter, we report a concise preparation of a 6-iodo-substituted isocoumarin fragment designed for insertion into rubromycin syntheses. We also present first C,C-coupling reactions of our building block with several substrates, which is planned to be a key step in a future synthesis of rubromycin type compounds.

Our six-step protocol for the synthesis of the 6-iodo isocoumarin derivative **6** is depicted in Scheme 1. Vanillin was first protected as TBS ether (97% yield), which furnished an intermediate with two differentiated hydroxyl groups. Its conversion into the 1,3-dioxane derivative **1** was performed under mild conditions using tetra-*n*-butylammonium tribromide as catalyst[5] (82% yield). The directed *ortho*-lithiation and carboxylation of acetal **1** was optimized and finally performed with *n*-butyllithium in cyclohexane.[6] After 3 hours of metallation at ambient temperature, methyl chloroformate was added and direct deprotection of the crude carboxylation product provided ester **2**[7] in satisfactory 58% yield. The iodination of **2** proceeded smoothly using tetramethylammonium dichloroiodate[8] as source of electrophilic iodine. Iodide **3** was formed regioselectively[9] and in excellent 91% yield. Enol ether **5** could be obtained from aldehyde **3** without previous protection of the free hydroxyl group. Two equivalents of NaHMDS were used in the Horner–



Scheme 1 *Reagents and conditions:* a) TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 24 h; b) 1,3-propanediol, *n*-Bu_4NBr_3, $HC(OMe)_3$, CH_2Cl_2, r.t., 2.5 h; c) *i*: 1.2 equiv *n*-BuLi, cyclohexane, r.t., 3 h; *ii*: $ClCO_2Me$, 0 °C → r.t., overnight; *iii*: 37% HCl (aq), KF, THF, r.t., 6–24 h; d) Me_4NICl_2, $NaHCO_3$, CH_2Cl_2, r.t., 4 h; e) **4**, 2 equiv NaHMDS, THF, –78 °C → r.t.; f) 47% HBr (aq):MeOH = 1:1, reflux, 12 h; g) BnBr, *i*-Pr_2NEt, DMF, 65 °C, 24 h.

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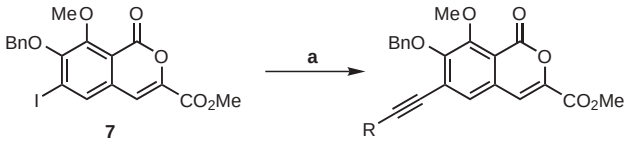
Wadsworth–Emmons reaction of **3** with phosphonate **4**[10] resulting in a 35:65 mixture of diastereoisomers (82% yield), (*Z*)-**5** being the major product.[11]

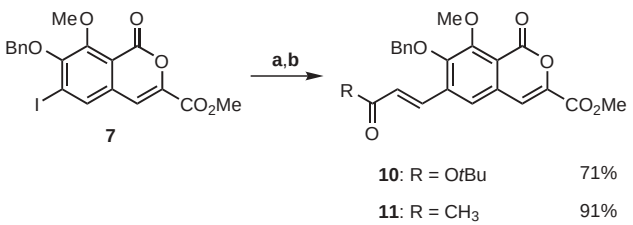
The acid-promoted intramolecular condensation of *ortho*-carboxyl benzyl ketones or enol ether derivatives[12] is a key step in many isocoumarin syntheses. In the case of **5**, however, harsh conditions were required to achieve lactone formation. Since the condensation under acidic conditions may result in concomitant cleavage of the methyl ester at C-3, various mixtures of acids and methanol were applied. Finally, isocoumarin **6** was readily obtained when **5** was refluxed in a 1:1 mixture of methanol and concentrated aqueous HBr. The product **6** precipitated from the mixture in 55–68% yield. The solid was very poorly soluble and required no purification except washing and drying. We are confident that this method of converting aldehyde **3** into isocoumarin **6** is convenient for large-scale preparation. As subsequent step, isocoumarin derivative **6** was converted into the benzyl ether **7** (81% yield) previous to its use in coupling reactions.

According to our strategy, isocoumarin **7** should be inserted into rubromycin syntheses by means of palladium-catalyzed coupling reactions with appropriately functionalized naphthoquinone moieties. To prove this concept, base-labile lactone **7** was employed in first Sonogashira[13] and Heck[14] reactions. The Sonogashira couplings were carried out under standard conditions[15] in DMF (Scheme 2). Both phenylacetylene derivative **8** and 3-methoxypropyne derivative **9** were cleanly obtained in high yields (84% and 91%).



Scheme 2 *Reagents and conditions:* a) R-C≡CH, $Pd(OAc)_2$, PPh_3, CuI, Et_3N, DMF, r.t., 8 h.

Heck reactions of **7** with *tert*-butyl acrylate and 3-buten-2-one proceeded smoothly, the latter being performed under Jeffery's mild conditions.[16] The α,β-unsaturated carbonyl compounds **10** and **11**[17] were isolated in 71% and 91% yield, respectively (Scheme 3).



Scheme 3 *Reagents and conditions:* a) *tert*-Butyl acrylate, $Pd(OAc)_2$, PPh_3, LiCl, Et_3N, DMF, 85 °C, 8 h; b) 3-buten-2-one, $Pd(OAc)_2$, *n*-Bu_4NCl, $NaHCO_3$, DMF, r.t., 72 h.

In summary, we reported a robust protocol for the preparation of a 6-iodo isocoumarin building block very suitable for rubromycin syntheses. The feasibility of palladium-catalyzed couplings on the base-sensitive lactone **7** was demonstrated, paving the way for our future projects.

Acknowledgment

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References

(1) (a) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Tetrahedron Lett.* **1966**, 3525. (b) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Chem. Ber.* **1969**, *102*, 126. (c) Brockmann, H.; Zeeck, A. *Chem. Ber.* **1970**, *103*, 1709.

(2) γ-Rubromycin was isolated from *Streptomyces collinus* and showed antibiotic activity against various bacteria strains.

(3) (a) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4709; *Angew. Chem.* **2001**, *113*, 4845. (b) Siu, T.; Qin, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4713; *Angew. Chem.* **2001**, *113*, 4849.

(4) Syntheses of isocoumarin fragments: (a) Trash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29. (b) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567.

(5) Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842.

(6) For related directed *ortho*-metallations of aromatic acetals, see: (a) Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921. (b) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (c) Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653. (d) Li, C.; Lobkovsky, E.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484.

(7) **Procedure for the Carboxylation 1 → 2:** *n*-BuLi (1.86 mL, 2.50 M in hexanes, 4.65 mmol) was added at 0 °C to a solution of 1.26 g (3.88 mmol) of **1** in 25 mL of dry cyclohexane. The mixture was stirred at r.t. for 3 h, recooled to 0 °C and 1.00 mL (12.9 mmol) of methyl chloroformate were added. Stirring was continued overnight and the reaction was allowed to warm up to r.t. After quenching with 10 mL of sat. aq Na_2CO_3, the layers were separated and the aqueous layer was extracted with 3 × 10 mL of Et_2O. The combined organic layers were concentrated in vacuo and the residue was dissolved in 25 mL of THF. Then, 37% HCl (aq, 4 mL), 0.70 g (12.0 mmol) KF and 5 mL of H_2O were added and the mixture was stirred at r.t. until TLC indicated complete conversion (6–24 h). The mixture was washed with 20 mL of brine. The layers were separated and the aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Column chromatography (silica gel, EtOAc–hexane = 1:1) provided 0.47 g (58%) **2** as reddish solid. Analytical data for methyl 6-formyl-3-hydroxy-2-methoxybenzoate (**2**): mp 102–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, OMe), 3.98 (s, 3 H, CO_2Me), 6.45 (br s, 1 H, OH), 7.11, 7.55 (2 d, *J* = 8.4 Hz, 2 × 1 H, 4-H, 5-H), 9.79 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 53.0 (q, CO_2Me), 62.5 (q, OMe), 116.6, 129.9 (2 d, Ar), 127.0, 127.6, 144.4, 154.4 (4 s, Ar), 166.9 (s, CO), 189.0 (d,

CHO) ppm. IR (KBr): ν = 3150 (O-H), 3005 (=C-H), 2950–2840 (–C-H), 1740, 1660 (C=O), 1600, 1560, 1505 (C=C) cm^{-1}. MS (EI, 80 eV, 170 °C): *m/z* (%) = 210 (99) $[M]^+$, 195 (57) $[M – CH_3]^+$, 182 (46), 179 (71) $[M – OCH_3]^+$, 151 (100) $[M – CO_2CH_3]^+$, 136 (62), 121 (91), 107 (49), 92 (36), 80 (50), 65 (44), 51 (55), 39 (32). Anal. Calcd for $C_{10}H_{10}O_5$ (210.2): C, 57.14; H, 4.80. Found: C, 56.86; H, 4.54.

(8) Hajipour, A. R.; Arbabian, M.; Ruoho, A. E. *J. Org. Chem.* **2002**, *67*, 8622.

(9) The constitution of **3** was confirmed by a NOESY experiment.

(10) (a) α-Bromination of methyl methoxyacetate: Gagliardi, S.; Nadler, G.; Consolandi, E.; Parini, C.; Morvan, M.; Legave, M.-N.; Belfiore, P.; Zocchetti, A.; Clarke, G. D.; James, I.; Nambi, P.; Gowen, M.; Farina, C. *J. Med. Chem.* **1998**, *41*, 1568. (b) Arbuzov reaction leading to **4**: Guay, V.; Brassard, P. *Synthesis* **1987**, 294.

(11) Assignment of the diastereoisomers was made on the basis of NOESY experiments.

(12) (a) Adler, E.; Magnusson, R.; Berggren, B. *Acta Chem. Scand.* **1960**, *14*, 539. (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 453. (c) Also see refs. 3a,4b.

(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

(14) (a) Heck, R. F.; Nolley, J. P. Jr. *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (c) Review: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(15) For a scope of reaction conditions, see: Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**, 213.

(16) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

(17) **Procedure for Heck Reaction 7 → 11:** To a solution of 95 mg (0.20 mmol) of **7** and 0.04 mL (0.50 mmol) freshly distilled 3-buten-2-one in 3 mL of dry DMF were added 59 mg (0.21 mmol) of tetra-*n*-butylammonium chloride, 44 mg (0.52 mmol) of $NaHCO_3$ and 4 mg (0.02 mmol) of palladium(II) acetate. The mixture was stirred at r.t. and the conversion was monitored by TLC. After 72 h, the mixture was diluted with 3 mL of EtOAc and washed with 2 × 3 mL of brine. The layers were separated and the aqueous layer was reextracted with 1 × 5 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Column chromatography (silica gel, EtOAc–hexane = 1:1) provided 76 mg (91%) **11** as yellow solid. Analytical data for methyl 7-benzyloxy-8-methoxy-1-oxo-6-(3-oxo-but-1-enyl)-1*H*-isochromene-3-carboxylate (**11**): mp 169 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, 4′-H), 3.86 (s, 3 H, CO_2Me), 3.92 (s, 3 H, OMe), 5.13 (s, 2 H, CH_2), 6.77 (d, *J* = 16.6 Hz, 1 H, 2′-H), 7.33–7.46 (m, 5 H, Ph), 7.53 (s, 1 H, 4-H), 7.55 (d, *J* = 16.6 Hz, 1 H, 1′-H), 8.01 (s, 1 H, 5-H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 27.3 (q, C-4′), 52.9 (q, CO_2Me), 61.8 (q, OMe), 76.3 (t, CH_2), 112.1 (d, C-4), 117.3, 132.3, 136.37, 136.40, 142.0, 152.2, 155.2 (7 s, Ar, C-3, Ph), 122.2 (d, C-5), 128.70, 128.71, 129.0 (3 d, Ph), 131.5 (d, C-2′), 135.5 (d, C-1′), 156.2, 160.3, 198.0 (3 s, CO) ppm. IR (KBr): ν = 3090–3005 (=C-H), 2950–2850 (-C-H), 1750, 1730, 1675 (C=O), 1620, 1600, 1550, 1500 (C=C) cm^{-1}. MS (EI, 80 eV, 170 °C): *m/z* (%) = 408 (5) $[M]^+$, 366 (12) $[M – C_2H_2O]^+$, 275 (12), 91 (100) $[C_7H_7]^+$, 43 (18), 28 (21). HRMS (EI, 80 eV, 170 °C): *m/z* calcd for $C_{23}H_{20}O_7$: 408.1209. Found: 408.1224.