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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6903–6905

Synthesis of fluorenones based on a '[3+3] cyclization/Suzuki cross-coupling/Friedel–Crafts acylation' strategy

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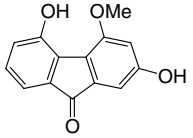
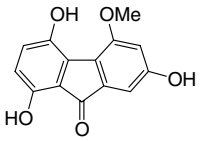
Received 30 May 2006; revised 5 July 2006; accepted 6 July 2006
Available online 4 August 2006

Abstract—Functionalized fluorenones were prepared by sequential '[3+3] cyclization–Suzuki cross-coupling/Friedel–Crafts acylation' reactions.

Fluorenones are of pharmacological relevance and occur in a number of natural products, such as dengibsin, dengibsinin, or dendroflorin.[1] Fluorenones have been prepared, for example, by intramolecular Friedel–Crafts acylations of biaryls.[2] Snieckus and co-workers reported the synthesis of fluorenones based on remote aromatic metalation.[3] Some years ago, Chan and co-workers reported[4] the synthesis of arenes by [3+3] cyclization of 1,3-bis-silyl enol ethers[5] with 3-(silyloxy)alk-2-en-1-ones. We have recently reported the application of this methodology to the synthesis of dibenzo[*b*,*d*]pyran-6-ones[6] and a variety of functionalized arenes.[7] Some years ago, the synthesis of fluorenones using a Suzuki coupling/intramolecular Friedel–Crafts acylation sequence has been reported.[8] Herein, we report an efficient synthetic approach to fluorenones based on a '[3+3]cyclization/Suzuki cross-coupling/Friedel–Crafts acylation' strategy.

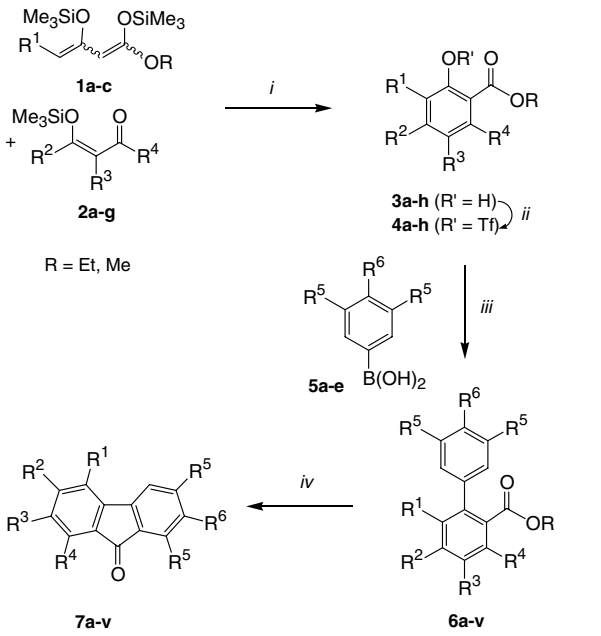


Dengibsin



Dendroflorin

The $TiCl_4$ mediated [3+3] cyclization of 1,3-bis-silyl enol ether **1a** with 4-silyloxy-3-methylpent-3-en-2-one (**2a**) afforded the salicylate **3a**, which was transformed into triflate **4a**.[7] The Suzuki reaction of the latter with boronic acids **5a–c** afforded the biaryls **6a–c**.[6,9] Treatment of the latter with concentrated sulfuric acid afforded the fluorenones **7a–c** in high yields (Scheme 1, Table 1).[10] Fluorenones **7d–f** were prepared based on cyclization



Scheme 1. Synthesis of fluorenones **7a–v**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) Tf_2O, pyridine, −78→20 °C; (iii) $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.6 equiv), dioxane, reflux, 4–20 h; (iv) H_2SO_4, 1 h.

Keywords: Cross-coupling reactions; Cyclizations; Fluorenones; Palladium; Silyl enol ethers.
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doi:10.1016/j.tetlet.2006.07.025

Table 1. Products and yields

3, 4	6, 7	R^1	R^2	R^3	R^4	R^5	R^6	% (3)[a]	% (4)[a]	% (6)[a]	% (7)[a]
a	**a**	H	Me	Me	Me	H	OMe	51[b]	96[b]	79	85
	b	H	Me	Me	Me	H	H			87	92
	c	H	Me	Me	Me	H	Me			87	90
b	**d**	H	Ph	H	Me	H	OMe	52[b]	90[b]	84	—
	e	H	Ph	H	Me	H	H			79	91
	f	H	Ph	H	Me	H	Me			75	80
c	**g**	H	Me	H	Me	H	OMe	38[b]	97[b]	95	90
	h	H	Me	H	Me	H	H			91	85
	i	H	Me	H	Me	H	Me			44	91
d	**j**	H	Me	$-(CH_2)_4-$		H	OMe	32[b]	97[b]	58	61
	k	H	Me	$-(CH_2)_4-$		H	H			89	91
	l	H	Me	$-(CH_2)_4-$		H	Me			83	89
e	**m**	H	Me	Et	Me	H	OMe	45[b]	89[b]	71	92
	n	H	Me	Et	Me	H	H			46	91
	o	H	Me	Et	Me	H	Me			75	89
f	**p**	H	Et	H	Et	H	H	44	89	88	92
	q	H	Et	H	Et	H	Me			76	93
	r	H	Et	H	Et	H	OMe			86	80
	s	H	Et	H	Et	OMe	OMe			59	91
g	**t**	Et	Me	Me	Me	H	OMe	13	94	44	92
h	**u**	H	Me	Cl	Me	H	OMe	62[b]	98	82	90
	v	H	Me	Cl	Me	H	Cl			90	89

[a] Yields of isolated products.
[b] Known compounds, see Refs. 6 and 7.

of **1a**,**b** with 1-phenyl-1-(silyloxy)but-1-en-3-one (**2b**). Fluorenones **7g**–**i** are available based on cyclization of **1a**,**b** with 4-(silyloxy)pent-3-en-2-one (**2c**). The tetracyclic fluorenones **7j**–**l** were prepared from 2-acetyl-1-(silyloxy)cyclohex-1-ene (**2d**). Fluorenones **7m**–**o** were obtained based on cyclization of **1a**,**b** with 4-silyloxy-3-ethylpent-3-en-2-one (**2e**). Fluorenones **7p**–**s** are available based on cyclization of **1a**,**b** with 5-(silyloxy)hept-4-en-3-one (**2f**). The cyclization of **2a** with 1,3-bis-silyl enol ether **1c**, prepared from ethyl 3-oxohexanoate, afforded the salicylate **3g** which was transformed into the fluorenone **7t**. The chlorinated fluorenones **7u**,**v** were prepared based on cyclization of **1a**,**b** with 4-silyloxy-3-(chloro)pent-3-en-2-one (**2g**).[7f]

In conclusion, a variety of functionalized fluorenones were prepared based on a '[3+3] cyclization/Suzuki coupling/Friedel–Crafts acylation' strategy.

Acknowledgements

We are grateful to Dr. D. Michalik, for detailed NMR studies. Financial support by the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt) is gratefully acknowledged.

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9. *General procedure for the synthesis of biaryls* **6**: A dioxane solution of the boronic acid, potassium phosphate, $Pd(PPh_3)_4$ and of the triflate **4** was stirred at 110 °C for 4–20 h. After cooling to ambient temperature, a saturated aqueous solution of NH_4Cl was added. The organic and the aqueous layer were separated and the latter was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography. Synthesis of **6a**: Starting with 4-methoxyphenylboronic acid (140 mg, 0.91 mmol), potassium phosphate (240 mg, 1.12 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), **5a** (230 mg, 0.70 mmol) and dioxane (1.8 mL), **6a** was isolated by chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a colorless oil (158 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.23$ (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.91 (m, 2H, CH), 7.02 (s, 1H, CH), 7.29 (m, 2H, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 15.4$, 17.3, 20.7 (CH_3), 51.7, 55.2 (OCH_3), 113.6, 128.8, 129.3 (CH), 131.7, 133.1, 133.5, 134.2, 136.5, 137.7, 158.8 (C), 171.1 (C=O). IR (neat, cm^{-1}): $\tilde{\nu} = 3031$ (w), 2997 (m), 2948 (m), 2865 (w), 2837 (m), 1725 (br s), 1610 (m), 1578 (w), 1516 (s), 1462 (s), 1435 (s), 1394 (m), 1321 (w), 1290 (s), 1260 (s), 1248 (s), 1180 (s), 1164 (s), 1129 (m), 1080 (w), 1043 (s). MS (EI, 70 eV): *m/z* (%) = 285 (18), 284 (M^+, 100), 253 (69), 252 (26), 238 (27). HRMS (EI): calcd for $C_{18}H_{20}O_3$ (M^+): 284.14070, found: 284.13999.
10. *General procedure for the synthesis of fluorenones* **7**: Compound **6** was dissolved in concentrated H_2SO_4. After stirring for 1 h, the solution was poured into ice water and extracted (3×) with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to give **7** as a yellow solid. Synthesis of **7a**: Starting with **6a** (96 mg, 0.34 mmol) in H_2SO_4 (4 mL), **7a** was isolated as a yellow solid (73 mg, 85%), mp = 135–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.91 (dd, 1H, $^3J = 8.2$ Hz, $^4J = 2.5$ Hz, CH), 7.03 (s, 1H, CH), 7.12 (d, 1H, $^4J = 2.5$ Hz, CH), 7.29 (d, 1H, $^3J = 8.2$ Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.8$, 14.6, 15.4 (CH_3), 55.7 (OCH_3), 108.9, 119.1, 119.7, 120.4 (CH), 129.3, 135.9, 136.3, 136.6, 138.7, 142.7, 143.2, 160.5 (C), 195.2 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu} = 3437$ (br, m), 2952 (w), 2937 (w), 2833 (w), 1696 (s), 1601 (s), 1482 (m), 1462 (s), 1433 (s), 1372 (w), 1289 (s), 1259 (m), 1222 (s), 1200 (w), 1192 (w), 1069 (w), 1031 (w). MS (EI, 70 eV): *m/z* (%) = 253 (18), 252 (M^+, 100), 237 (67), 165 (48). HRMS (EI): calcd for $C_{17}H_{16}O_2$ (M^+): 252.1145, found: 252.1143. Anal. Calcd for $C_{17}H_{16}O_2$ (252.31): C, 80.93; H, 6.39. Found: C, 80.90; H, 6.51.