Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2,3-diarylfluorenones by domino 'twofold Heck/electrocyclization/dehydrogenation' reactions of 2,3-dibromoindenone

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ARTICLE INFO

Article history:
Received 7 February 2013
Revised 28 February 2013
Accepted 4 March 2013
Available online xxxx

Keywords:
Catalysis
Palladium
Heck reaction
Domino reactions
Indenones

ABSTRACT

Domino double Heck/electrocyclization/dehydrogenation reactions of 2,3-dibromo-1*H*-inden-1-one with styrenes provide a convenient synthesis of 2,3-diarylfluorenones.

Fluorenones are an important structural scaffold found in many natural products, such as dengibsin, dengibsinin, and dendroflorin which have been isolated from Asiatic orchid *Dendrobium gibsonii* Lindley.[1] Fluorenones constitute the central core of a variety of compounds which exhibit important biomedical activity as well as optical and electronic properties. For example, they act as virus and enzyme inhibitors,[2,3] organic light emitting devices (OLED),[4] photosensitizers,[5] and liquid crystals (Fig. 1).[6,7] Because of the multifold applications of fluorenone derivatives, several synthetic methodologies have been developed which include, for example, Friedel–Crafts type cyclizations of biarylcarboxylic acids,[8] oxidations of fluorenol and fluorenes,[9,10] intramolecular Diels–Alder reactions of conjugated enynes or diarylacetylene systems,[11a,b] formal 3+3 cyclocondensations of 1,3-bis(silyloxy)-1,3-buatdienes,[11c] and remote metalation of 2-biphenylcarboxamides or 2-biphenyloxazolines.[12]

In the last decade palladium catalyzed cross-coupling reactions have been applied to the preparation of the fluorenone moiety. Examples include Pd-catalyzed cyclizations of *ortho*-iodobenzophenones,[13] the Pd-catalyzed cyclocarbonylation of *ortho*-halobiaryls,[14] the annulation of arynes to 2-haloarenecarbaldehydes,[15] sequential coupling of aryl halides, alkynes, and arynes,[16] reactions of 2-iodophenyl-(2-phenyl-benzylidene)-amines,[17] and reactions of aromatic amides with aryl halides.[18] Fluorenones have been recently prepared by Pd-catalyzed C–H activation of aryl aldoxime ethers with arenes[19] or with aryl iodides followed by oxidative Heck cyclization,[20] by sequential reaction of 2-bromobenzaldehydes with arylboronic acids,[21,22] by double CH-activation of diarylketones,[23] and by decarboxylative C–H arylation of benzoic acids under radical conditions.[24] The synthesis of arylated fluorenones has only scarcely been reported so far.[18,22–25] In recent years, we have studied the synthesis of benzoannulated heterocycles by domino double Heck electrocyclization reactions.[26,27] Herein, we wish to report the first application of this methodology to indenones. The domino double Heck electrocyclization reactions of 2,3-dibromoindenone with styrenes provides a convenient approach to 2,3-diarylfluorenones which are not readily available by other methods.

The palladium catalyzed reaction of 2,3-dibromoindenone (**1**), which was prepared according to the literature,[28] with styrene **2a** afforded fluorenone **3a** by a domino double Heck electrocyclization reaction in up to 95% yield (Scheme 1, Table 1).[29,30] The reaction had to be thoroughly optimized because the yields were, under standard conditions, very low. The best yields were obtained when $Pd(OAc)_2$ (5 mol %) in the presence of *t*-Butyl-X-Phos (10 mol %) was used as the catalyst (Table 1, entry 4, Fig. 2). The reaction was carried out in DMF at 65 °C and was completed already in 5 h. The yields dropped when other catalysts and ligands

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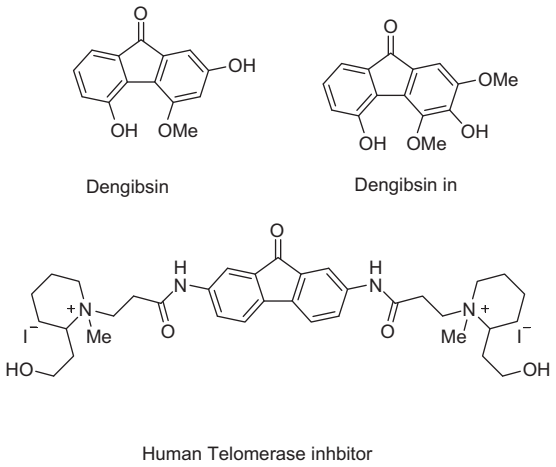
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.011



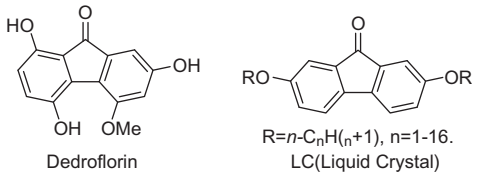
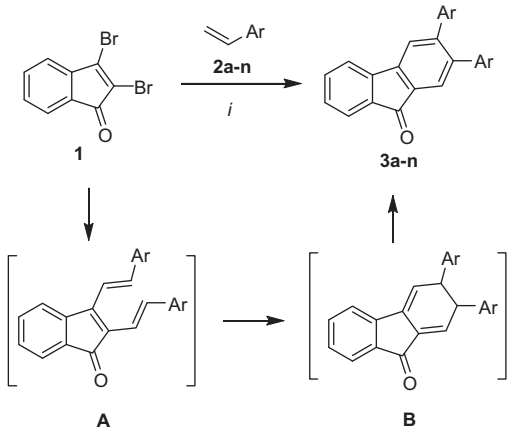


Figure 1. Important natural and synthetic fluorenones.



Scheme 1. Synthesis of **3a–n**. Reagents and condition: (a) **2a–n** (2.3 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (10 mol %), NEt_3 (8 equiv), DMF, 65 °C, 5 h.

or other solvents and higher temperatures were employed. It is interesting to note that the novel, more sterically hindered ligand *t*Butyl-X-Phos gave a considerable better yield thanparent X-Phos. It is noteworthy, that the electrocyclization proceeded already at

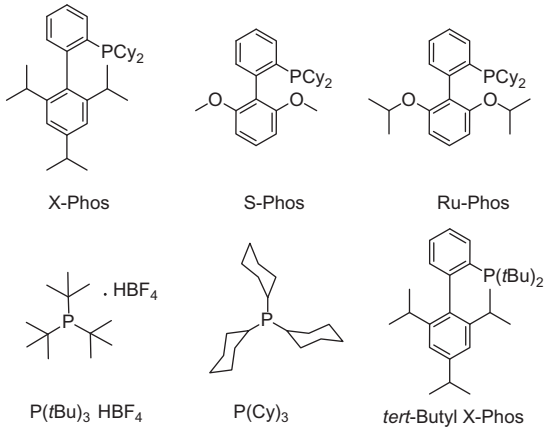


Figure 2. Structures of ligands.

Table 2
Synthesis of **3a–n**

2,3	Ar	Yield[a] (%)
a	4-(*t*BuO)C_6H_4	95
b	4-*t*BuC_6H_4	92
c	4-(MeO)C_6H_4	81
d	4-(EtO)C_6H_4	85
e	4-MeC_6H_4	77
f	3-MeC_6H_4	89
g	Ph	80
h	4-BrC_6H_4	75
j	3-BrC_6H_4	71
i	4-ClC_6H_4	70
k	3-ClC_6H_4	73
l	4-FC_6H_4	72
m	3-FC_6H_4	68
n	4-(MeCO)C_6H_4	65

[a] Isolated yields.

65 °C while other substrates, such as 2,3-dialkenylthiophenes,[26] require temperatures of up to 200 °C.

Having the optimized conditions in hand, we next focused on the preparative scope. The reaction of **1** with styrenes **2a–n** afforded fluorenones **3a–n** in 65–95% yields (Table 2). The yields of products **3a–g**, derived from styrenes containing electron donating substituents, were higher than the yields of the other products which are derived from styrenes containing electron withdrawing substituents. It is noteworthy, that brominated styrenes **2h,j** could be successfully employed without competing side reactions. This might be explained by the fact that carbon atoms C-2 and C-3 of indenone **1** are rather electron poor and more rapidly undergo the oxidative addition with the Pd catalyst than the respective carbon atom of the styrene. The acetyl substituted styrene **2n** also underwent the reaction in good yield.

Table 1
Optimization of the reaction conditions for **3a**

No.	Catalysis	Ligand	Solvent	Base	*T* (°C)	*t* (h)	Yield[a] (%)
1	$Pd(PPh_3)_4$	—	DMF	NEt_3	50	48	20
2	$Pd(PPh_3)_4$	—	Toluene	iPr_2NEt	80	24	43
3	$Pd(OAc)_2$	Ru-Phos	DMF	NEt_3	65	5	68
4	**$Pd(OAc)_2$**	***t*-Butyl-X-Phos**	**DMF**	**NEt_3**	**65**	**5**	**95**
5	$Pd(OAc)_2$	$P(Cy)_3$	DMF	NEt_3	50	48	34
6	$Pd(OAc)_2$	$P(Cy)_3$	Toluene	iPr_2NEt	80	24	52
7	$Pd(OAc)_2$	S-Phos	DMF	NEt_3	65	5	63
8	$Pd(OAc)_2$	X-Phos	Toluene	NEt_3	80	5	75
9	$Pd(OAc)_2$	$P(tBu)_3{\cdot}HBF_4$	DMF	Na_2CO_3	50	48	30

[a] Isolated yields.

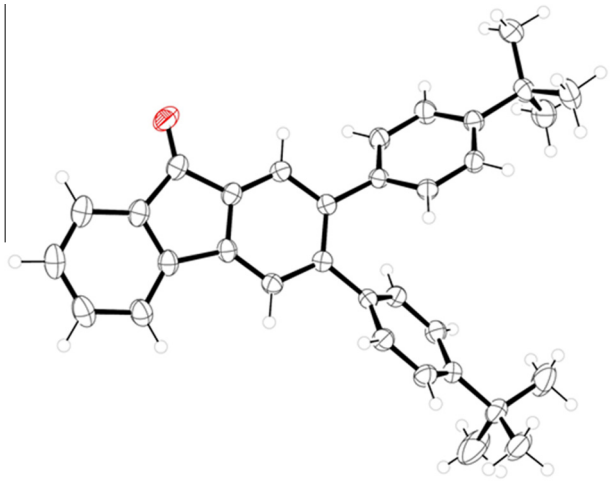


Figure 3. Ortep plot of **3b.**

The structures of all products were analyzed by spectroscopic methods. The structure of **3b** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[31]

In conclusion, we have reported a new and convenient synthesis of 2,3-diarylfluorenones by domino double Heck/electrocyclization/dehydrogenation reactions of 2,3-dibromo-1*H*-inden-1-one.

Acknowledgments

Financial support by the DAAD (scholarships for O.A.A. and A.K.), by the Ministry of Higher Education and Scientific Research Iraq (support of H.H.M.), and by the State of Mecklenburg-Vorpommern (scholarship for M.H.) is gratefully acknowledged.

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29. General procedure for the synthesis of fluorenones **3a–n.** In a pressure tube (glass bomb) a suspension of $Pd(OAc)_2$ (6 mg, 0.025 mmol) and *t*-Butyl-X-Phos [2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl] (21 mg, 0.05 mmol) in DMF (3 mL) was flushed with Ar and stirred at 20 °C to give a brownish transparent solution. To the stirred solution were added 1,2-dibromoindanone **1** (143 mg, 0.5 mmol), the styrene (2.3 equiv 1.15 mmol) and NEt_3 (8.0 equiv, 0.6 mL, 4.0 mmol). The reaction mixture was stirred at 65 °C for 5 h. The solution was cooled to 20 °C, poured into a mixture of brine and CH_2Cl_2 (25 mL each), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 20 mL), dried (Na_2SO_4), concentrated in vacuo, and passed through a column (flash silica gel, heptanes–EtOAc) to yield the product.
30. **2,3-**Bis[**4-**(*tert*-butoxy)phenyl]-**9*H*-**fluoren-**9-**one **(3a).** Compound **3a** was isolated as a yellow solid (226 mg, 95%), mp: 139–141 °C: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9H, $OC(CH_3)_3$), 1.25 (s, 9H, $OC(CH_3)_3$), 6.72–6.80 (m, 4H, ArH), 6.92 (d, 2H, *J* = 8.7 Hz, ArH), 6.97 (d, 2H, *J* = 8.5 Hz, ArH), 7.21 (td, 1H, *J* = 7.3, 1.1 Hz, ArH), 7.40 (td, 1H, *J* = 7.4, 1.0 Hz, ArH), 7.45–7.47 (m, 2H, ArH), 7.60 (br d, 1H, *J* = 7.2 Hz, ArH), 7.63 (s, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.8, 28.9 ($3CH_3$), 78.5, 78.6 (C), 120.3, 122.5 (CH), 123.6 (2CH), 124.3, 126.4, 129.0 (CH), 130.2 (2CH), 133.1 (C), 134.7 (CH), 134.8, 135.6, 135.9, 141.3, 143.1, 144.2, 146.7, 154.5, 154.9 (C), 193.4 (CO). IR (KBr): ν = 3093, 3054, 3030, 2972, 2931, 2873 (w), 1711 (s), 1681, 1674, 1668, 1651, 1645, 1633 (w), 1613, 1601 (m), 1574, 1567, 1557, 1538, 1532 (w), 1506 (m), 1478, 1471 (w), 1453 (m), 1416, 1389 (w), 1363 (m), 1308, 1298 (w), 1159 (s), 1125, 1099, 1088, 1026, 1012, 944, 922, 914 (w), 890, 854, 843 (s), 769, 728 (m), 684, 666, 646, 640, 626, 602, 599, 547, 532 (w) cm^{-1}. GC–MS (EI, 70 eV): *m/z* (%) = 476 ([M]$^+$, 4), 365 (27), 364 (100), 318 (4), 305 (6), 276 (5). HRMS (ESI–TOF/MS): calcd for $C_{33}H_{33}O_3$ [M+H]$^+$: 477.24242; found: 477.24221.
31. CCDC-929181 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.