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Preparation of 2,7-Diaminofluorenone Derivatives by Palladium Catalyzed Amination [1]

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Summary. A convenient synthesis of *tert*-2,7-diaminofluorenonens **3a**–**3e** *via* palladium catalyzed reaction of secondary amines with 2,7-dibromofluorene and subsequent oxidation is described. In the cases were non-cyclic secondary amines are applied, the aniline derivatives **4c**–**4e** are formed as side products by a dehydrohalogenation reaction.

Keywords. Catalysis; Palladium; Palladacycle; Diamination; Aminostannane; Air oxidation.

Darstellung von 2,7-Diaminofluorenonderivativen durch palladiumkatalysierte Aminierung [1]

Zusammenfassung. Eine einfache Synthese der tertiären 2,7-Diaminofluorenone **3a**–**3e** durch palladiumkatalysierte Umsetzung von sekundären Aminen mit 2,7-Dibromfluoren und anschließende Oxidation wird beschrieben. Bei der Umsetzung mit offenkettigen sekundären Aminen werden durch eine Dehydrohalogenierungsreaktion auch die Anilinderivate **4c**–**4e** als Nebenprodukte gebildet.

Introduction

Recently, the palladium catalyzed intramolecular and intermolecular coupling of aryl halides with amines has been shown to be a mild and efficient method for the synthesis of aniline derivatives [2, 3]. This important discovery opens up a new avenue for the synthesis of many interesting organic molecules that are otherwise difficult to prepare [4]. During the course of our studies on dyestuff with an absorbance in the near infrared region, we were interested in the preparation of 2,7-diaminofluorenone derivatives [1].

In this paper we describe a two-step preparation of the ketones **3a**–**3d** *via* the diamination of 2,7-dibromofluorene (**1**) with secondary amines (**2a**–**2d**) in the presence of sodium *tert*-butoxide in toluene with $PdCl_2[P(o\text{-tolyl})_3]_2$ as catalyst and, alternatively, a direct diamination of fluorenone **5** with the aminostannane reagent **6** to **3e**.

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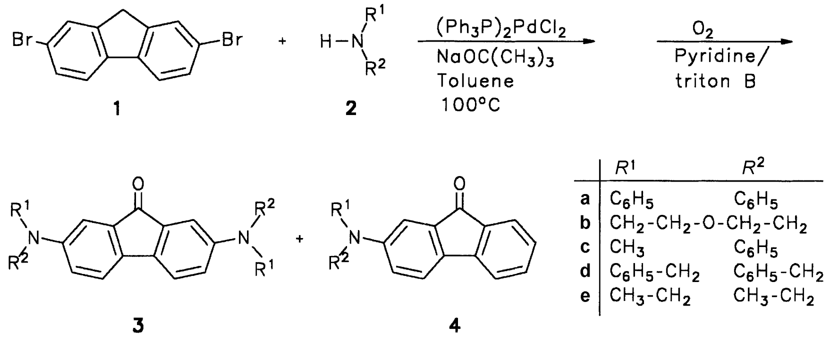
Results and Discussion

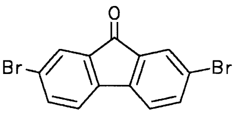
Due to the sensitivity of fluorenones toward strong bases such as sodium *tert*-butoxide [5], palladium catalyzed amination of **5** afforded the corresponding tertiary amines only in very low yields. For this reason, it was necessary first to aminate **1** and then to oxidize the product with oxygen to the corresponding fluorenone derivatives. According to this procedure, the reaction of dibromide **1** with 2.6 eq. of amine **2a** in the presence of 2.8 eq. of $NaOC(CH_3)_3$ and 2 mol% of $PdCl_2[P(o\text{-tolyl})_3]_2$ in toluene at 100°C leads in a yield of 52% to ketone **3a** after oxidation of the reaction products by oxygen in pyridine/triton B. Similarly, amination with **2b** produced ketone **3b** in 25% yield.



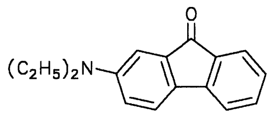
	R^1	R^2
a	C_6H_5	C_6H_5
b	$CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2$	
c	CH_3	C_6H_5
d	$C_6H_5\text{-}CH_2$	$C_6H_5\text{-}CH_2$
e	$CH_3\text{-}CH_2$	$CH_3\text{-}CH_2$

In addition to the diamination products, monoamino dehydrohalogenated fluorenone derivatives resulting from a reduction reaction were also obtained as side products in variable amounts. As an example, the amination of **1** with methylphenylamine (**2c**) afforded 60% of the diamine **3c** and 10% of the monoamine **4c**. Furthermore, the addition of **2d** lead to 36% of **3d** and 6% of **4d**.

To avoid the ring opening reaction in the amination reaction of fluorenone derivatives in the presence of a strong base, we investigated the diamination using aminostannane reagent **7**. In this case, the reaction of **5** with 3 eq. of **7** and 3 mol% of $PdCl_2[P(o\text{-tolyl})_3]_2$ afforded 42% of the diamino fluorenone derivative **3e** and 1% of **4e** after 6 h. Recently, the palladacycle **8** – which is formed by heating of $P(o\text{-tolyl})_3$ in acetic acid in the presence of $(CH_3COO)_2Pd$ – was introduced as an efficient catalyst for the *Heck* coupling of aryl bromides [6]. To test the suitability of this catalyst for the amination reaction we investigated the above reaction in the presence of 3 mol% of **8**. With this catalyst, only a weak improvement of the yield is observed. After 6 h, 58% of **3e** and 8% of **4e** were formed.



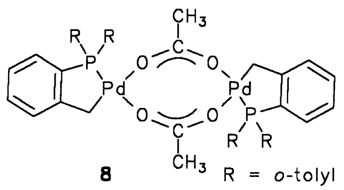
5



6

$(C_4H_9)_3Sn\text{-}N(C_2H_5)_2$

7



8 R = *o*-tolyl

Table 1. UV/Vis absorbance maxima (($\lambda_{\max}$ (lgε)) of aminofluorenones in CH_2Cl_2

3a	**3b**	**3c**	**3d**	**3e**	**4c**	**4d**	**4e**	**6**[a]
244 (4.33)				222 (4.01)	252 (4.30)	240 (3.95)	236 (4.04)	
305 (4.55)	290 (4.54)	301 (4.56)	298 (4.63)	298 (4.56)	293 (4.38)	288 (4.48)	289 (4.52)	284 (4.71)
378 (4.43)	344 (4.15)	360 (4.47)	357 (4.37)	362 (4.37)	346 (4.12)	343 (3.98)	348 (4.13)	328 (4.14)
553 (3.12)	530 (2.72)	530 (2.72)	573 (2.80)	602 (2.81)	501 (2.95)	506 (2.85)	529 (2.97)	511 (2.98)

[a] In ethanol [12]

Reports on the mechanism of Pd/P(*o*-tolyl)$_3$-catalyzed aryl amination reactions suggest that the use of P(*o*-tolyl)$_3$ favors the formation of monophosphine Pd^0 species (*L*-Pd) which are believed to be the catalytically active species [2, 3]. Oxidative addition of an aryl bromide then forms the dimeric Pd(II) intermediate [Ar-Pd(*L*)-Br]$_2$ which has been shown to result from addition of an amine to the monomeric Pd(II)-amine complex [Ar-Pd(L)(HNR^1R^2)-Br]. Elimination of HBr affords the Pd(II)-amidocomplex[Ar-Pd^{II}(L)NR^1R^2] which can undergo reductive elimination to the desired arylamines. Alternately, in cases were a β-hydrogen atom is present in this intermediate (*e.g.* addition of amines **2c** and **2d**), reversible β-hydride elimination leads to the formation of the dehydrohalogenated side products **4c** and **4d** [2a, 3d, 7].

In Table 1, the UV/Vis data of the amino fluorenones prepared are listed. As shown in this Table, **3e** ($\lambda_{\max} = 602$ nm) exhibits the most pronounced bathochromic shift in this category.

Experimental

All reported yields are isolated yields. Catalysts were prepared from palladium chloride [8] and palladium acetate [6] with tri(*o*-tolyl)phosphine. Dibromofluorene (**1**) [9] and dibromofluorenone (**5**) [10] were prepared from fluorene. Diethylaminotributylstannane (**7**) was prepared by reaction of diethylaminomagnesium bromide with tributhyltin chloride [11]. All melting points are uncorrected and were measured on a Büchi SMP-20 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 and Bruker AM-200 spectrometers in $CDCl_3$ solutions with *TMS* as internal references. IR spectra were run on a Bruker IFS 25 instrument. UV and visible spectra were measured in dichloromethane solution on a Hewlett-Packard 8452A spectrophotometer with a diode array detector. Mass spectra were taken using a Varian MAT 311 mass spectrometer. CHN analyses were obtained using a Carlo-Erba analyzer instrument (model 1104); they were found to agree satisfactorily with the calculated values.

General procedure for the palladium catalyzed amination of 2,7-dibromo-fluorene to the fluorenone derivatives **3a**, **3b**, **3c/4c**, and **3d/4d**

A mixture of 2,7-dibromofluorene (2.0 g, 6.2 mmol), secondary amine (16.0 mmol), sodium *tert*-butoxide (1.7 g, 17.3 mmol), and $PdCl_2[P(o\text{-tolyl})_3]_2$ (97 mg, 0.12 mmol) in toluene (50 ml) is heated at 100°C under argon for 6 h. After cooling to room temperature, toluene (50 ml) is added, and the reaction mixture is washed with water (3×200 ml), dried over $MgSO_4$, and the solvent is evaporated on the rotavapor. The oily product is washed with light petroleum ether (20 ml) to remove unreacted secondary amine. The resulting solid is dissolved in pyridine (30 ml); triton B (2 ml) is added, and oxygen is passed through the solution for 1 h. Pyridine is evaporated and the residue is chromatographed (silica gel; dichloromethane/light petroleum ether, 1/3) to yield the fluorenone derivatives **3a**, **3b**, **3c/4c**, and **3d/4d**.

*2,7-Bis-(N,N-diphenylamino)-fluorenone (***3a**; $C_{37}H_{26}N_2O$)

1.65 g (52%); dark violet crystals; m.p.: 219–220°C; IR (KBr): $\tilde{\nu} = 3030–3060$ (aryl-H), 1710 (C=O), 1588 (C=C), 1492, 1465, 1438, 1332, 1314, 1294, 1274, 827, 789, 749, 696, 501 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) = 244 (4.33), 305 (4.55), 378 (4.43), 553 (3.12) nm; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.0–7.4$ (m, aryl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 119.53$, 120.38, 123.50, 124.65, 128.69, 129.48, 135.93, 138.20, 147.27, 148.42, 193.23 (C=O) ppm; MS: *m/z* (r.I.) = 514 (100) [M^+], 257 (96); HRMS: found 514.2014, calcd. 514.2045.

*2,7-Dimorpholinofluorenone (***3b**; $C_{21}H_{22}N_2O_3$)

0.54 g (25%); dark violet crystals; m.p.: 274°C; IR (KBr): $\tilde{\nu} = 3050$ (aryl-H), 2850–2950 (methylene-H), 1711 (C=O), 1608 (C=C), 1587, 1477, 1445, 1282, 1266, 1238, 1120, 908, 785, 641, 523 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) = 290 (4.54), 344 (4.15), 530 (2.72) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.17$ (t, $J = 4.8$ Hz, 8H, NCH_2), 3.85 (t, $J = 4.8$ Hz, 8H, OCH_2), 6.89 (dd, $J = 8.1$ Hz, $J = 2.4$ Hz, 2H, 3-H and 6-H), 7.18 (d, $J = 2.4$ Hz, 2H, 1-H and 8-H), 7.25 (d, $J = 8.1$ Hz, 2H, 4-H and 5-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 49.29$ (NCH_2), 66.70 (OCH_2), 111.70, 120.18, 120.58, 135.78, 136.51, 151.38, 194.53 (C=O) ppm; MS: *m/z* (r.I.) = 350 (100) [M^+].

2,7-Di-(N-methyl-N-phenylamino)-fluorenone (**3c**; $C_{27}H_{22}N_2O$) *and* *2-(N-methyl-N-phenylamino)-fluorenone* (**4c**; $C_{20}H_{15}NO$)

3c: 1.45 g (60%); dark violet crystals; m.p.: 129°C; IR (KBr): $\tilde{\nu} = 3020–3060$, (aryl-H), 2945 (methyl-H), 1716 (C=O), 1592 (C=C), 1494, 1476, 1337, 1257, 1112, 834, 784, 758, 706, 695 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) = 301 (4.56), 360 (4.47), 550 (3.07) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.32$ (s, 6H, CH_3), 6.94 (dd, $J = 8.1$ Hz, $J = 2.4$ Hz, 2H, 3-H and 6-H), 7.0–7.4 (m, 14H, aryl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 40.42$ (methyl), 114.64, 120.04, 122.45, 122.87, 123.65, 129.47, 135.70, 136.68, 148.38, 149.04, 194.38 (C=O) ppm; MS: *m/z* (r.I.) = 390 (69) [M^+], 285 (38) [M^+-C_7H_7N].

4c: 0.18 g (10%); red crystals; m.p.: 94°C; IR (KBr): $\tilde{\nu} = 3020–3060$ (aryl-H), 2915 (methyl-H), 1719 (C=O), 1604 (C=C), 1590, 1493, 1458, 1339, 1133, 869, 832, 768, 734, 705 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) = 252 (4.30), 293 (4.38) 346 (4.12), 501 (2.95) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.35$ (s, 3H, CH_3), 6.93 (dd, $J = 8.2$ Hz, 1H, 3-H), 7.0–7.6 (m, 11H, aryl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 40.52$ (methyl), 113.24, 119.30, 120.99, 122.04, 123.71, 123.80, 124.21, 127.43, 129.64, 134.26, 134.79, 135.05, 135.56, 145.30, 148.12, 150.17, 194.37 (C=O) ppm; MS: *m/z* (r.I.) = 285 (100) [M^+].

2,7-Bis-(N,N-dibenzylamino)-fluorenone (**3d**; $C_{41}H_{34}N_2O$) and *2-(N,N-dibenzylamino)fluorenone* (**4d**; $C_{27}H_{21}NO$)

3d: 1.27 g (36%); blue crystals; m.p.: 220–221°C; IR (KBr): $\tilde{\nu} == 3020–3090$ (aryl-H), 2917 (methylene-H), 1705 (C=O), 1611 (C=C), 1583, 1486, 1451, 1383, 1360, 1233, 942, 805, 734 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) = 298 (4.63), 357 (4.37), 573 (2.80) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.62$ (s, 8H, *CH_2*Ph), 6.63 (dd, $J = 8.3$ Hz, $J = 2.4$ Hz, 2H, 3-H and 6-H), 7.0–7.4 (m, 24H, aryl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 54.32$ (methylene), 109.06, 117.48, 119.89, 126.69, 127.06, 128.70, 134.25, 135.85, 138.01, 148.86, 195.27 (C=O) ppm; MS: *m*/*z* (r.I.) $=570$ (96) [M^+], 479 (32) [M^+-bzl], 387 (23), 311 (19), 283 (12), 91 (100) [bzl^+].

4d: 0.14 g (6%); red crystals; m.p.: 140°C; IR (KBr): $\tilde{\nu}=3000$–3060 (aryl-H), 2901 (methylene-H), 1711 (C=O), 1600 (C=C), 1486, 1451, 1360, 1233, 942, 734 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) $=220$ (4.10), 240 (3.95), 288 (4.48), 330 (3.99), 343 (3.98), 506 (2.85) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.68$ (s, 4H, *CH*$_2$Ph), 6.71 (dd, $J=8.3$ Hz, $J=2.7$ Hz, 1H, 3-H) 7.0–7.6 (m, 16H, aryl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 54.44 (methylene), 108.61, 117.18, 118.88, 121.32, 124.10, 126.68, 126.92, 127.18, 128.77, 132.75, 134.31, 134.68, 136.03, 137.76, 145.75, 150.33, 194.48 (C=O) ppm; MS: *m*/*z* (r.I.) $=375$ (100) [M^+], 284 (38) [M^+-bzl], 91 (93) [bzl^+].

2,7-Bis-(N,N-diethylamino)fluorenone (**3e**; $C_{21}H_{26}N_2O$) and *2-(N,N-diethylamino)fluorenone* (**4e**; $C_{17}H_{17}NO$)

A solution of 2,7-dibromofluorenone (2.0 g, 5.9 mmol), (N,N-diethylamino)tributyltin (6.4 g, 17.7 mmol) and $PdCl_2[P(o\text{-tolyl})_3]_2$ (140 mg, 0.18 mmol) in toluene (50 ml) is heated at 100°C for 6 h under an argon atmosphere. The solvent is evaporated, and the residue is chromatographed (silica gel; dichloromethane/light petroleum ether, 1/1) to yield 1.28 g (67%) **3e** and 0.18 g (12%) **4e**.

3e: Dark green crystals; m.p.: 151–153°C; IR (KBr): $\tilde{\nu}=3060$ (aryl-H), 2865–2964 (alkyl-H), 1706 (C=O), 1615 (C=C) , 1579, 1494, 1467, 1443, 1392, 1372, 1362, 1294, 1261, 1195, 1187, 1068, 971, 871, 815, 787 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) $=222$ nm (4.01), 298 (4.56), 362 (4.37), 602 (2.81) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.17$ (t, $J=7.0$ Hz, 12H, CH_3), 3.35 (q, $J=7.0$ Hz, 8H, CH_2), 6.62 (dd, $J=8.2$ Hz, $J=2.5$ Hz, 2H, 3-H and 6-H), 6.94 (d, $J=2.5$ Hz, 2H, 1-H and 8-H), 7.11 (d, $J=8.2$ Hz, 2H, 4-H and 5-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=12.72$ (CH_3), 44.65 (CH_2), 108.43, 116.51, 119.80, 133.19, 135.88, 147.28, 196.15 (C=O) ppm; MS: *m*/*z* (r.I.) $=311$ (100) [M^+], 307 (64) [M^+-Me], 263 (42) [M^+-C_4H_{10}].

4e: Red crystals; m.p.: 102°C; IR (KBr): $\tilde{\nu}=3050$ (aryl-H), 2867–2969 (alkyl-H), 1704 (C=O), 1600 (C=C), 1505, 1456, 1397, 1374, 1357, 1293, 1262, 1196, 1077, 962, 819, 763, 738 cm^{-1}; UV (CH_2Cl_2): λ_{max} ($\lg\varepsilon$) $=236$ (4.04), 289 (4.52), 348 (4.13), 529 (2.97) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.21$ (t, $J=2.5$ Hz, 6H, CH_3), 3.42 (q, $J=2.5$ Hz, 4H, CH_2), 6.66 (dd, $J=8.4$ Hz, $J=2.6$ Hz, 1H, 3-H), 7.00 (d, $J=2.6$ Hz, 1H, 1-H), 7.09 (dt, $J=7.4$ Hz, $J=0.8$ Hz, 1H, 7-H), 7.28–7.31 (m, 4-H and 5-H), 7.37 (dt, $J=7.4$ Hz, $J=0.8$ Hz, 1H, 6-H), 7.54 (d, $J=7.4$ Hz, 1H, 8-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 12.68 (CH_3), 44.68 (CH_2), 107.80, 115.77, 118.71, 121.45, 124.08, 126.54, 130.93, 134.17, 134.77, 136.02, 146.18, 147.74, 195.11 (C=O) ppm; MS: *m*/*z* (r.I.) $=251$ (25) [M^+], 236 (100) [M^+-Me].

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