A Facile Synthesis of 1,8- and 1,7-Bis(chloromethyl)fluorenes

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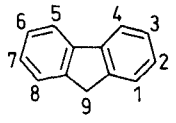
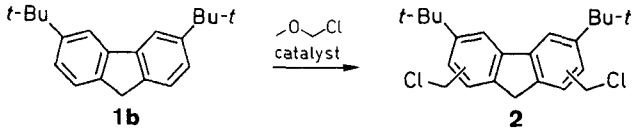
A convenient synthesis of 1,8- and 1,7-bis(chloromethyl)-3,6-di-*tert*-butylfluorenes based on a selective preparation, using the *tert*-butyl group as a positional protective group, is described.

The selective preparation of organic compounds is no doubt of importance in organic synthesis. We reported earlier on the practically selective preparation of aromatic compounds utilizing the *tert*-butyl group as the positional protective function.[2] As a part of this study we have chosen fluorene (**1a**) as a substrate. It is known[3] that the positional reactivity of fluorene (**1a**) towards an electrophilic reagent decreases in the order of 2,7- > 4,5- > 3,6- > 1,8-positions, meaning a direct introduction of electrophiles into 1- or 8-position is very difficult. In fact, long synthetic routes are necessary for the preparation of 1,8-dichlorofluorene,[4] 1,8-dimethylfluorene[5] or 1,8-fluorenedicarboxylic acid[6] starting from fluorene (**1a**) itself. Expecting the blocking of the 2,7-positions, we prepared 3,6-di-*tert*-butylfluorene (**1b**), for which nitration, chlorination and bromination were attempted.[7] However, the functional groups are introduced at the 2- or 7-position in spite of a neighboring bulky *tert*-butyl group.



1a

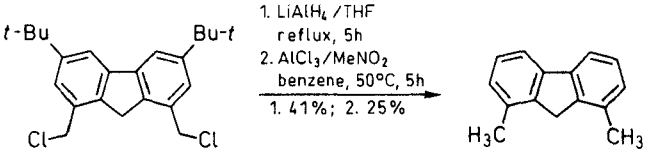


1b **2**

Catalyst	Solvent	Time (h)	Temp. (°C)	Product	Yield (%)
$ZnCl_2$	CS_2	21	50	**2a** (2,7-)	47
H_3PO_4	AcOH	18	50	**2a**	17
$TiCl_4$	CS_2	5	−5	**2b** (1,8-)	52
$TiCl_4$	CS_2	5	50	**2b**	57
$SnCl_4$	CS_2	19.5	r.t.	**2c** (1,7-)	55

Scheme 1

Here, we wish to report a positional selective chloromethylation of **1b** under Friedel–Crafts conditions (Scheme 1). Compound **1b** was prepared from diphenylmethane according to the reported method.[4] Initially, we carried out the chloromethylation of **1b** with chloromethyl methyl ether in the presence of zinc chloride as a catalyst, resulting in 2,7-substitution to give 2,7-bis(chloromethyl)fluorene (**2a**) in 47% yield. Using phosphoric acid/acetic acid as a catalyst **2a** was also obtained accompanied by a recovery of **1b**. However, surprisingly chloromethylation of **1b** using titanium(IV) chloride afforded 1,8-bis(chloromethyl)fluorene (**2b**) in 52% yield. In all cases, the rest of the product was obtained as an inseparable mixture, the ^1H NMR spectrum of which did not show clear signals of chloromethyl groups suggesting that other isomers were not formed. The reaction temperature does not seem to affect the product and the yield as shown in Scheme 1. In order to verify the formation of **2b**, it was reduced with lithium aluminum hydride followed by de-*tert*-butylation with aluminum chloride/nitromethane catalyst in benzene (Scheme 2). The melting point and ^1H NMR data of the resultant compound is consistent with those of 1,8-dimethylfluorene (**3**)[5] which is prepared from fluorene (**1a**) in seven steps.



2b **3**

Scheme 2

Interestingly, the treatment of **1b** with chloromethyl methyl ether in the presence of tin(IV) chloride as a catalyst gave a bischloromethylated fluorene in 55% yield which is different from **2a** or **2b**. The melting point is 182–185 °C which is lower than those of **2a** and **2b**. In the ^1H NMR spectrum two kinds of signals of *tert*-butyl groups appear at $\delta = 1.41$ and 1.54, which are compatible with those of **2b** and **2a**, respectively. Furthermore it shows four kinds of peaks in the aromatic region. From these results is was concluded that 1,7-bis(chloromethyl)-fluorene (**2c**) was formed. Although the activity of the Lewis acids or transition state of the reaction is presumably involved in such a selective chloromethylation, its mechanism is still not clear at the present stage. In order to obtain more information on the mechanism, chloromethylation of monochloromethylated (1- or 2-substituted) fluorene is now in progress.

All melting points are uncorrected. ^1H NMR spectra were recorded on a Nippon Denshi GSX-270 spectrometer in $CDCl_3$ with TMS as internal reference. IR spectra were measured on a Nippon Bunko JASCO IR-700. Mass spectra were obtained on a Nippon Denshi JMS-01-SG2 spectrometer at 75 eV using a direct-inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

2,7-Bis(chloromethyl)-3,6-di-*tert*-butylfluorene (2a) Using Zinc Chloride as Catalyst:

To a solution of **1b** (10 g, 36 mmol) and $ZnCl_2$ (24.5 g, 245 mmol) in CS_2 (100 mL) was added chloromethyl methyl ether (19.8 g, 245 mmol) at 50 °C. After the mixture was stirred for 21 h, it was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$) and evaporated to leave a residue, which was chromatographed using hexane/$CHCl_3$ (5 : 1) as an eluent to yield **2a** as colorless prisms; yield: 6.42 g (47%); mp 202–204 °C (hexane/$CHCl_3$).

$C_{23}H_{28}Cl_2$	calc.	C 73.56	H 7.53
(375.5)	found	73.46	7.48

IR (KBr): ν = 2964, 1623, 1477, 1404, 1360, 1259, 863, 659 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.54 (s, 18 H, 2 *t*-C_4H_9), 3.84 (s, 2 H, H-9), 4.98 (s, 4 H, 2CH_2Cl), 7.60 (s, 2 H_{arom}), 7.79 (s, 2 H_{arom}).

MS: m/z = 374 (M^+).

2,7-Bis(chloromethyl)-3,6-di-*tert*-butylfluorene(2a) Using Phosphoric Acid as Catalyst:

To a solution of **1b** (2 g, 7.2 mmol) and H_3PO_4 (16 mL) in AcOH (32 mL) was added chloromethyl methyl ether (8.1 g, 100 mmol) at 50 °C. The mixture was stirred for 18 h at 50 °C, which was then subjected to the workup procedure described above. The resultant product gave satisfactory spectroscopic data for **2a** (see above).

1,8-Bis(chloromethyl)-3,6-di-*tert*-butylfluorene (2b):

To a solution of **1b** (10 g, 36 mmol) and chloromethyl methyl ether (43.4 g, 543 mmol) in CS_2 (270 mL) was added dropwise $TiCl_4$ (13.6 g, 71.5 mmol) at − 5 °C. The mixture was stirred for 5 h at − 5 °C, poured into ice-water and extracted with CH_2Cl_2. After the extract was washed with water, dried ($MgSO_4$) and evaporated, the resultant residue was chromatographed using hexane/$CHCl_3$ (5 : 1) as an eluent to give **2b** as colorless prisms; yield: 7.03 g (52%); mp 236–239 °C (hexane/benzene).

$C_{23}H_{28}Cl_2$	calc.	C 73.56	H 7.53
(375.5)	found	73.40	7.55

IR (KBr): ν = 2960, 1480, 1401, 1365, 1254, 880, 704, 612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.41 (s, 18 H, 2 *t*-C_4H_9), 3.95 (s, 2 H, H-9), 4.76 (s, 4 H, 2CH_2Cl), 7.33 (d, J = 1.8 Hz, 2 H_{arom}), 7.77 (d, J = 1.8 Hz, 2 H_{arom}).

MS: m/z = 374 (M^+).

1,7-Bis(chloromethyl)-3,6-di-*tert*-butylfluorene (2c):

To a solution of **1b** (1.0 g, 3.6 mmol) and chloromethyl methyl ether (1.0 g, 12 mmol) in CS_2 (22 mL) was added dropwise $SnCl_4$ (2 g, 7.2 mmol) at r. t. for 20 min. After the mixture was stirred for 19.5 h, it was poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$) and evaporated to afford **2c** as colorless prisms; yield: 0.74 g (55%); mp 182–185 °C (benzene/hexane).

$C_{23}H_{28}Cl_2$	calc.	C 73.56	H7.53
(375.5)	found	73.29	7.46

IR (KBr): ν = 2964, 1480, 1365, 1254, 881, 703, 612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, *t*-C_4H_9), 1.54 (s, 9 H, *t*-C_4H_9), 3.90 (s, 2 H, H-9), 4.73 (s, 2 H, CH_2Cl), 4.98 (s, 2 H, CH_2Cl), 7.34 (d, J = 1.8 Hz, 1 H_{arom}), 7.63 (s, 1 H_{arom}), 7.76 (d, J = 1.8 Hz, 1 H_{arom}), 7.80 (s, 1 H_{arom}).

MS: m/z = 374 (M^+).

Reduction and De-*tert*-butylation of 1,8-Bis(chloromethyl)fluorene (2b) to 1,8-Dimethylfluorene (3):

To a solution of **2b** (1.0 g, 2.66 mmol) in THF (100 mL) was added $LiAlH_4$ (0.16 g, 4.22 mmol) and the mixture was refluxed for 5 h. After addition of EtOAc (50 mL), the mixture was filtered and evaporated to give the reduced product as colorless crystals; yield: 0.26 g (41%); mp 207–211 °C ($CHCl_3$/hexane). To a solution of the reduced product (0.12 g, 0.42 mmol) in benzene (17.5 mL) was added $AlCl_3$ (0.03 g, 0.22 mmol) and nitromethane (0.06 mL) at 50 °C. The mixture was stirred at 50 °C for 4 h, poured into ice-water and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$) and evaporated to give **3** as colorless prisms; yield: 0.02 g (25%); mp 154–156 °C (EtOH) (lit.[5], 154.5–155.5 °C).

^1H NMR ($CDCl_3$): δ = 2.45 (s, 6 H, 2CH_3), 3.67 (s, 2 H, H-9), 7.12 (d, 2 H, J = 7.7 Hz, H-2, 7), 7.30 (t, 2 H, J = 7.7 Hz, H-3, 6), 7.63 (d, J = 7.7 Hz, H-4, 5).

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