A New Route for the Preparation of Fluorene Derivatives using Friedel–Crafts Intramolecular Cyclobenzylation

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A convenient preparation of fluorene derivatives based on a novel Friedel–Crafts intramolecular cyclobenzylation, involving the action of Cl_2CHOMe and $TiCl_4$ on a variety of biphenyls (constructed such that electrophilic substitution occurs *ortho* to the biphenyl linkage), is described.

Although there are numerous reports on the synthesis of fluorenes from 2-mono- and 2,2′-di-substituted biphenyls using cyclization reactions,[3–5] there has not been any report concerning Friedel–Crafts intramolecular benzylation of 2-halomethylbiphenyls to give fluorenes. Recently we reported[6] that the chloromethylation of 4,4′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl **1b** affords the Friedel–Crafts intramolecular benzylation products, 2,7-dimethoxy-1,3,6,8-tetramethylfluorene derivatives in 20–40% yield. However, the selective preparation of substituted fluorenes using Friedel–Crafts intramolecular cyclobenzylation by the action with chloromethyl methyl ether was very difficult because of low yields as well as their separation from the reaction mixture. On the other hand, Meth-Cohn and co-workers have reported[7] that Lewis acid catalysed formylation of diarylmethanes with dichloromethyl methyl ether affords anthracenes by a direct Bradsher reaction. However, this is limited to the preparation of benzothiophene derivatives. This strategy is proposed to be employed for the preparation of fluorene derivatives. Here we report the first success in the formation of a fluorene skeleton *via* a Friedel–Crafts intramolecular benzylation during the action of Cl_2CHOMe and $TiCl_4$ on 4,4′-di-*tert*-butylbiphenyl **1a** and 4,4′-dimethoxy-3,3′5,5′-tetramethylbiphenyl **1b**, which are constructed such that electrophilic substitution occurs *ortho* to the biphenyl linkage.

A series of biphenyls **1a–d** was prepared according to previous reports.[6,9] On treatment of **1a** with Cl_2CHOMe (7 equiv.) in the presence of $TiCl_4$ at 0 °C for 5 h, the expected 2,7-di-*tert*-butyl-9-chloro-4-formylfluorene **5a** was obtained in 78% yield along with 2,7-di-*tert*-butyl-4-formylfluoren-9-one **6a** in 5% yield.

The same result was obtained in the case of compound **1b**. The reaction was again carried out under the same conditions and the expected 9-chloro-4-formyl-2,7-dimethoxy-1,3,6,8-tetramethylfluorene **5b** was obtained in 87% yield.

It was also found that treatment of 2,2′,3,3′-tetramethoxybiphenyl **1c** with $TiCl_4$ for 24 h under the same conditions as described above resulted only in a quantitative recovery of starting compound. This result indicates that two methoxy groups at the *ortho* position of compound **1c** might disturb the electrophilic substitution at both the 2- and 2′-positions of the biphenyl.

Similar treatment of 4,4′-di-*tert*-butyl-2,2′-dimethylbiphenyl **1d** with Cl_2CHOMe in the presence of $TiCl_4$ afforded 4,4′-di-*tert*-butyl-6-formyl-2,2′-dimethylbiphenyl **7** in 70% yield. The present novel intramolecular benzylation reaction is strongly affected by the methyl groups at the 2- and 2′-positions of the biphenyls which are forced to arrange in a conformation appropriate for the subsequent further intramolecular benzylation reaction.

However, from consideration of molecular models, 2,2′-dimethylbiphenyl **1d** is unlikely to form an intermediate suitable for undergoing intramolecular cyclobenzylation, because a chloromethoxymethyl group at the 6-position would be pushed away from the 6′-position of the other benzene ring in order to avoid crowding between the two methyl groups at the 2- and 2′-positions.

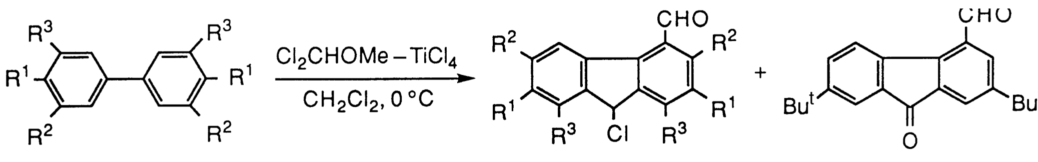
The reduction of **5a** with chlorohydroalane in diethyl ether afforded the 4-hydroxymethyl derivative **10** in 64% yield. Successive conversion of the hydroxymethyl group to a methyl group was achieved *via* the chloromethyl derivative.

Recently, we have found that Nafion-H, a perfluorinated resin sulfonic acid,[10] catalyses Friedel–Crafts benzylations of

Table 1 Formylation of substituted biphenyls **1** with Cl_2CHOMe to give fluorenes **5**

Run	Biphenyl **1**	*t*/h	Product **5** (%)[a]
1	**a**	5	**a** (78)[b]
2	**b**	5	**b** (87)
3	**c**	24	**d** (0)[c]

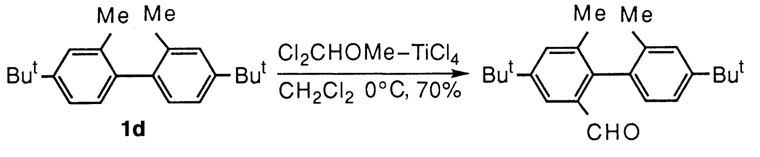
[a]Isolated yields. [b]2,7-Di-*tert*-butyl-4-formylfluoren-9-one **6a** was obtained in 5% yield. [c]Starting compound **1c** was recovered in almost quantitative yield.



1a $R^1 = Bu^t$, $R^2 = R^3 = H$
b $R^1 = OMe$, $R^2 = R^3 = Me$
c $R^1 = R^2 = OMe$, $R^3 = H$

5a $R^1 = Bu^t$, $R^2 = R^3 = H$
b $R^1 = OMe$, $R^2 = R^3 = Me$
c $R^1 = R^2 = OMe$, $R^3 = H$

6a



(3)

1d

7

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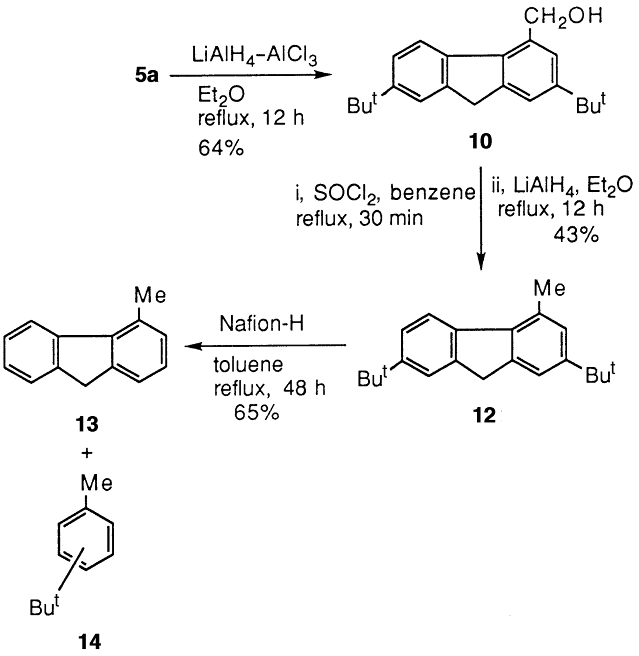

Scheme 2

benzene and substituted benzenes with benzyl alcohols under relatively mild conditions. The Nafion-H-catalysed *trans*-alkylation of **12** in toluene afforded the desired 4-methylfluorene **13** in 65% yield together with formation of *tert*-butyltoluene **14**. *Trans*-alkylation of **12** with Nafion-H catalyst gave a better yield than that achieved with $AlCl_3$–$MeNO_2$ catalyst (30%).[12]

Although 4-methylfluorene **13** has been prepared by passing 2,2′-dimethylbiphenyl over Pd–charcoal at 450 °C,[13] the preparative conditions are very severe as an experimental laboratory procedure in comparison with our method. Furthermore, Kajigaeshi *et al.*[12] have reported the construction of the fluorene skeleton using an Ullmann coupling reaction of 4,4′-di-*tert*-butyl-2,2′-diiododiphenylmethane. However, the introduction of iodine groups at the 2,2′-positions of 4,4′-di-*tert*-butyldiphenylmethane seems quite difficult and leads to low product yield and difficult product separation. Utilizing the present novel Friedel–Crafts intramolecular cyclobenzylation reaction we have developed a much more convenient procedure to convert 4,4′-di-*tert*-butylbiphenyl **1a** directly to 4-methylfluorene **13**. Consequently, the preparative route to compound **13** can be accomplished in six steps starting from biphenyl.

Techniques used: ^{1}H NMR, IR, MS, VPC analysis

References: 13

Schemes: 2

Equations: 4

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