A Practical and Efficient Method for the Construction of the Biphenyl Framework; Nucleophilic Aromatic Substitution on 2-Methoxybenzoates with Aryl Grignard Reagents

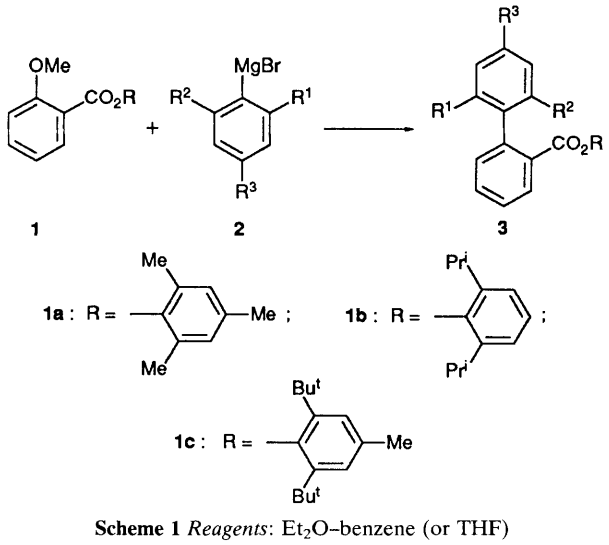
Tetsutaro Hattori, Takatsugu Suzuki and Sotaro Miyano*

Department of Biochemistry and Engineering, Faculty of Engineering, Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980, Japan

Treatment of 2-methoxybenzoic esters derived from 2,6-dialkylphenols with aryl Grignard reagents afforded 1,1′-biphenyl-2-carboxylates in excellent yields.

The biphenyl framework constitutes one of the structural features in a number of biologically active natural products, and the formation of aryl–aryl bonds has been an important problem in organic synthesis.[1] Among a variety of methods for effecting this construction, the versatility of the Meyers reaction is well documented.[2,3] In this transformation, the carboxylic function of 2-methoxybenzoic acids is converted into an oxazoline for activation of the 2-methoxy group for nucleophilic aromatic substitution (S_NAr) with aryl Grignard reagents as well as for protection of the carboxy group from the nucleophilic attack by the aryl carbanion species. Herein, we report an improved variant of the Meyers reaction where the oxazoline functionality can be replaced by readily available 2,6-dialkyl-substituted carbophenoxy substituents (Scheme 1).[4]

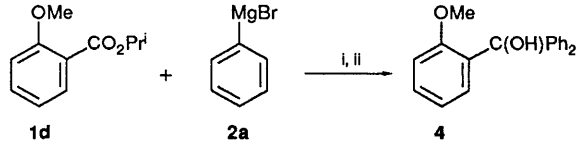
In previous papers, we have reported facile synthesis of 1,1′-binaphthyl-2-carboxylates *via* an S_NAr reaction on alkyl 1-methoxy-2-naphthoates with 1-naphthyl Grignard reagents.[5] This methodology cannot simply be applied to the construction of biphenyl system: treatment of isopropyl 2-methoxybenzoate **1d** with phenyl magnesium bromide **2a** (2 equiv.) in diethyl ether–benzene at ambient temperature for 3 h resulted in the formation of triaryl carbinol **4** (isolated yield, 75%) with no detectable amount of the S_NAr product (Scheme 2).†



Scheme 1 *Reagents*: Et_2O–benzene (or THF)

However, it was found that the carbonyl addition could be reduced by the use of esters derived from 2,6-dialkylphenols to give the biphenyl esters **3** (see Table 1). Thus, the reaction of mesityl 2-methoxybenzoate **1a** with phenyl magnesium bromide **2a** gave the biphenylcarboxylate **3a** in 56% yield accompanied by the formation of the carbinol **4** (25%) (run 1). Table 1 shows that the phenyl Grignard reagents not bearing a 2-methoxy substituent react successfully with 2,6-diisopropylphenyl ester **1b** to give biphenyl esters in synthetically useful yields. It should be noted that these diisopropylphenyl esters can be easily hydrolysed to liberate biphenyl acids by treatment with an alkali hydroxide in refluxing aqueous alcohol.‡

On the other hand, for the phenyl Grignard reagents bearing the 2-methoxy group (**2b** and **2d**), the 2,6-di-*tert*-butylphenyl moiety was required to suppress the carbonyl addition (see runs 4 and 9). It seems that the coordination of the methoxy oxygen to the magnesium centre reduces the apparent bulk of these phenyl carbanion species. It has been



Scheme 2 *Reagents and conditions*: i, Et_2O–benzene, room temp., 3 h; ii, H_3O^+ (yield 75%)

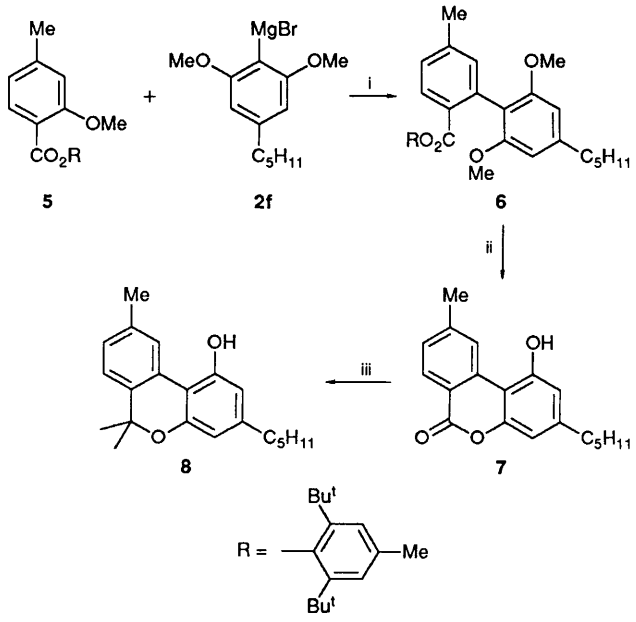
† All new compounds were substantiated by spectral data and elemental analyses. Yields are for the isolated pure products.

‡ For example, hydrolysis of **3g** was completed in 1 h by heating at reflux in 10% solution of KOH in 95% EtOH.

Table 1 Reaction of 2-methoxybenzoates **1** with aryl Grignard reagents **2** for the construction of biphenyl framework[a]

Run	1	2	R^1	R^2	R^3	Solvent	T(t/h)	3	Yield (%)
1	**a**	**a**	H	H	H	A	r.t.(6)	**a**	56
2	**b**					A	r.t.(12)	**b**	71
3	**c**					A	r.t.(20) refl(1)	**c**	96
4	**b**	**b**	MeO	H	H	A	r.t.(1)	**d**	0[b]
5	**c**					A	r.t.(1)	**e**	98
6	**a**	**c**	Me	H	H	A	r.t.(20)	**f**	70
7	**b**					A	r.t.(20)	**g**	85
8	**c**					A	r.t.(20) refl(1)	**h**	96
9	**b**	**d**	MeO	MeO	H	B	r.t.(6) refl(12)	**i**	0[b]
10	**c**					B	refl(48)	**j**	74
11	**a**	**e**	Me	Me	Me	A	refl(12)	**k**	68
12	**b**					A	refl(12)	**l**	80
13	**c**					A	refl(36)	**m**	0[c]

[a] *Reaction conditions*: **1**, 2.0 mmol; **2**/**1** = 2; r.t. = ambient temperature; refl = heated at reflux. Yields were based on isolated pure products. Solvent: A, Et_2O (7 ml)–benzene (14 ml); B, THF (15 ml). [b] Attack to the ester carbonyl. [c] No reaction except Lewis-acid-catalysed demethylation of **1c**.



Scheme 3 *Reagents and conditions*: i, THF–benzene, reflux, 24 h; ii, 57% aq. HI–Ac_2O, reflux, 2 h; iii, ref. 6

known that removal of 2,6-di-*tert*-butylphenoxy residue from the relevant ester is highly difficult in general and requires sophisticated manipulations.[6] This does not devalue the present procedure, because the phenoxy protecting group can be removed from the biphenyl esters having the 2′-methoxy substituent by acidic treatment *via* demethylative lactonisation (Scheme 3).

Cannabinol (1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran) **8** is a constituent of *Cannabis sativa L*, the synthesis of which has been the subject of interest.[7] A formal synthesis of cannabinol demonstrates the synthetic utility of the biphenyl coupling *via* the S_NAr process (Scheme 3). 2-Methoxy-4-methylbenzoate **5** was treated with 2 equiv. of 2,6-dimethoxy-4-pentylphenyl Grignard reagent **2f** in tetrahydrofuran (THF)–benzene at reflux for 24 h. After the usual work-up, column chromatography on silica gel (hexane–dichloromethane) gave the biphenyl ester **6** in 90% yield, m.p. 164–165 °C. Demethylative lactonisation of **6** by treatment with 57% aqueous hydrogen iodide in acetic anhydride at reflux for 2 h gave the lactone **7** in excellent yield (91%), m.p. 191–192 °C. Conversion of **7** into cannabinol **8** by reaction with methyl magnesium iodide followed by acidification has been described in the literature.[8]

Further work is now underway to synthesise naturally occurring, biologically interesting biphenyls by using the ester-activated S_NAr reaction.

Received, 10th June 1991; Com. 1/02765D

References

1 Review: M. Sainsbury, *Tetrahedron*, 1980, **36**, 3327.
2 Review: M. Reuman and A. I. Meyers, *Tetrahedron*, 1985, **41**, 837.
3 A. M. Warshawsky and A. I. Meyers, *J. Am. Chem. Soc.*, 1990, **112**, 8090.
4 For the preparation of sterically congested esters, see *e.g.*, R. C. Parish and L. M. Stock, *J. Org. Chem.*, 1965, **30**, 927; A. Hassner, L. R. Krepski and V. Alexanian, *Tetrahedron*, 1978, **34**, 2069.
5 H. Hotta, T. Suzuki and S. Miyano, *Chem. Lett.*, 1990, 143; T. Suzuki, H. Hotta, T. Hattori and S. Miyano, *Chem. Lett.*, 1990, 807.
6 See for example, C. H. Heathcock, M. C. Pirrung, S. H. Montgomery and J. Lampe, *Tetrahedron*, 1981, **23**, 4087.
7 J. Novák and C. A. Salemink, *Tetrahedron Lett.*, 1982, **23**, 253.
8 R. Adams, B. R. Baker and R. B. Wearn, *J. Am. Chem. Soc.*, 1940, **62**, 2204.