



A new practical method for regioselective nucleophilic aromatic alkylation of *ortho*- or *para*-methoxy-substituted aromatic esters with Grignard reagents

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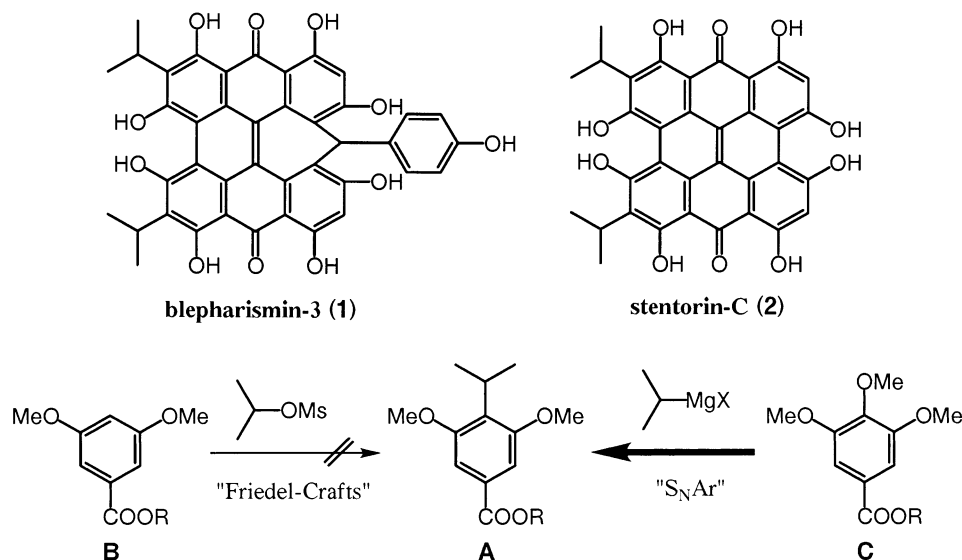
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Abstract—A new practical method for the regioselective nucleophilic aromatic alkylation of *o*- or *p*-methoxy-substituted aromatic carboxylic acids via their triethylcarbinyl ester derivatives by conducting the reactions with alkyl/aryl Grignard reagents in toluene has been developed. © 2001 Elsevier Science Ltd. All rights reserved.

Since the discovery of blepharismins, which exhibit an interesting photodynamic behavior in the unicellular organism *Blepharisma*,¹ we have been attempting to determine their mode of action.² Structurally, blepharismins are closely related to the naturally occurring polycyclic quinones such as hypericin and stentorin, and these

compounds are now being given considerable attention by scientists in several fields due to their characteristic biological activities, including anti-retroviral activity.³ However, the limited quantities of both blepharismins and their related quinone pigments available from natural sources prompted us to try to synthesize these compounds.



Scheme 1.

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As target molecules we chose blepharismine-3 (**1**) and stentorin-C (**2**),⁴ since these compounds both possess a highly symmetrical structure and an isopropyl group on the chromophore as a common structural unit. In pursuing this project, we required a facile method to obtain *p*-isopropylbenzoic acid derivative **A** as a starting substrate. Since our initial attempts based on the Friedel–Crafts-type alkylation of 3,5-dimethoxybenzoic acid derivatives, i.e. route **B**→**A**, did not give enough of the product,⁵ we adopted a completely different strategy using nucleophilic aromatic substitution (S_NAr) toward methoxy-substituted aryl esters, i.e. route **C**→**A** (Scheme 1). In this paper, we describe the realization of this idea by introducing a new protective group for carboxylic acid.

Although there have been reports of methods to carry out this type of transformation using aryloxazolines⁶ or 2,6-dialkylphenyl arylcarboxylates⁷ to dictate the S_NAr reaction course, these methods have some disadvantages in relation to the general applicability, simplicity, convenience for handling or easiness for deprotection. Therefore, there is still need to explore more efficient and concise methodologies. We found that even *t*-butyl ester **3a** could react sufficiently with *i*-PrMgCl in Et₂O at the *para*-position to give the desired product **4a** in 51% yield accompanied by significant amounts of by-products **5** and **6** (Table 1, Run 1).⁸ The reaction was quite sensitive to the solvent used, and in toluene at –78°C the yield of **4a** was increased to 77%, albeit the reaction was fairly slow (Run 3). In our extensive efforts to examine the reaction conditions, we found that the use of more-hindered triethylcarbinyl ester **3b**⁹ was reasonably convenient for facilitating the *para*-methoxy substitution in view of its effectiveness and ready accessibility. Thus, upon treatment of **3b** with 3.8 equiv. of *i*-PrMgCl at 0°C for 7 h, **4b** was obtained in 78% yield (Run 5).

The general utility of this procedure was further demonstrated by using several combinations of aryl esters and Grignard reagents (Table 2). Although cyclohexylmagnesium bromide reacted quite smoothly with **3b** to afford the adduct **10** in 90% yield (Run 1), PhMgBr and *n*-BuMgBr furnished the products **11** and **12** in 57 and 65% yields, respectively.¹⁰ Interestingly, whereas 2,6-dimethoxy compound **7** gave the mono-*ortho*-alkylated compound **13** as the major product, 2,4,6-trimethoxy homolog **8** gave mainly the 2,6-dialkylated product **16**. In the latter case, no *para*-substitution was observed. This method is particularly useful for achieving regioselective alkylation of 1-methoxy-2-naphthoic acid derivative **9** to produce sterically congested molecules **17–19** in high yields (Runs 6–8).¹¹

In conclusion, we have developed a practical and useful synthetic method for the highly regioselective alkylation of *o*- or *p*-methoxy-substituted aromatic carboxylic acid derivatives by taking advantage of triethylcarbinyl ester protection for carboxylic acid and of nucleophilic aromatic substitution at the *o*- or *p*-methoxy position using Grignard reagents. Further studies to apply this method to the total synthesis of blepharismins and stentorin are now in progress.

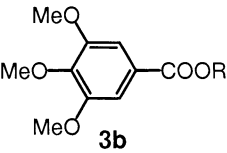
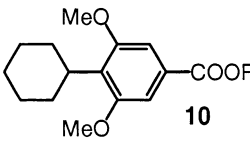
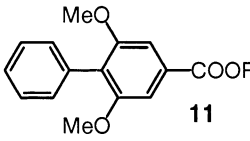
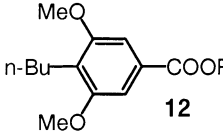
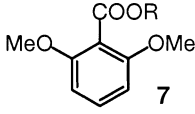
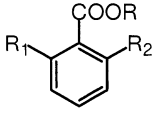
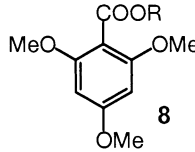
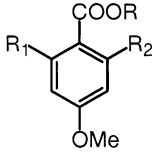
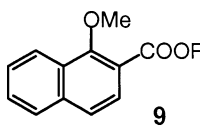
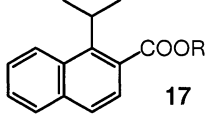
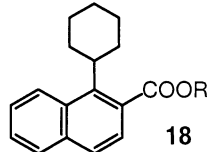
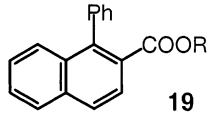
Typical experimental procedure for the preparation of **4**: To a solution of ester **3b** (155 mg, 0.50 mmol) in toluene (2 ml) at 0°C was added dropwise *i*-PrMgCl (0.98 M in Et₂O; 1.94 ml, 1.9 mmol) under Ar, and the mixture was stirred for 7 h at 0°C. After quenching by adding water, the mixture was extracted with AcOEt. The extracts were washed with brine, dried (Na₂SO₄), and concentrated. The crude product was purified by preparative TLC (hexane/acetone=4:1) to give **4** (126 mg, 78%; *R*_f 0.63) as a pale yellow oil. Unreacted **3b** (5 mg, 3%; *R*_f 0.41), tertiary alcohols **5** (17 mg, 12%; *R*_f 0.46) and **6** (9 mg, 6%; *R*_f 0.27) were isolated from the later fractions.

Table 1. Reaction of **3** with *i*-PrMgCl under various conditions

Run	3	Equiv. of <i>i</i> -PrMgCl	Solvent	Conditions	Yield (%) ^a			
					3	4	5	6
1	3a	1.5	Et ₂ O	0°C–rt, 11 h	0	51	27	12
2	3a	3.0	CH ₂ Cl ₂	–78°C, 4 days	26	61	2	3
3	3a	3.0	Toluene	–78°C, 5 days	11	77	5	6
4	3b	2.0	Toluene	0°C, 23 h	8	68	9	9
5	3b	3.8	Toluene	0°C, 7 h	3	78	12	6

^a Isolated yield.

Table 2. Regioselective nucleophilic aromatic alkylation of aryl esters with Grignard reagents^a

Run	Substrate (R = C(Et) ₃)	Grignard Reagent (equiv.)	Product(s) (R = C(Et) ₃)	Yield, % ^b
		Temp (°C), Time (h)		
1		c-C ₆ H ₁₁ MgBr (3.8) rt, 4		90
2	3b	PhMgBr (3.8) rt, 4		57 ^c
3	3b	n-BuMgBr (3.8) rt, 2		65 ^d
4		i-PrMgCl (2.5) rt, 4	 13 ; R ₁ = i-Pr, R ₂ = OMe 14 ; R ₁ = R ₂ = i-Pr	59 ^e 13
5		i-PrMgCl (2.0) rt, 3.5	 15 ; R ₁ = i-Pr, R ₂ = OMe 16 ; R ₁ = R ₂ = i-Pr	36 ^f 53
6		i-PrMgCl (2.0) 0, 1.5		89
7	9	c-C ₆ H ₁₁ MgBr (2.0) 0, 2.5		94
8	9	PhMgBr (2.0) 0, 2.5		98

^a All reactions were performed in toluene as the solvent. ^b Isolated yield. ^c Unidentified complex by-products were formed. ^d 15% of 3,4,6-(MeO)₃C₆H₂C(*n*-Bu)₂OH was also formed. ^e 16% of the free carboxylic acid (**13**, R=H) was also isolated. ^f 5% of the free carboxylic acid (**15**, R=H) was also isolated.

Acknowledgements

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8. To suppress ester carbonyl alkylation, the use of Cu(I) salts caused a significant decrease in reactivity of the reagents.
9. All triethylcarbinyl esters were prepared in almost quantitative yields by reacting acyl halides with 1.2 equiv. of a lithium salt of triethylcarbinol in THF overnight at room temperature. Deprotection of this functional group was achieved quantitatively by exposure to 5 equiv. of CF₃COOH in CH₂Cl₂. The reaction was generally completed within 4 h at rt.
10. At present, we have no clear explanation for these differences in the reactivity of Grignard reagents.
11. It is well known that the naphthalene ring is highly susceptible to nucleophilic aromatic alkylation by organolithium or Grignard reagents. See, for example: (a) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955–4968; (b) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3018–3026 and references cited therein.