Studies on the Synthesis of Highly Substituted Naphthol: Preparation of 6-Hydroxy-5,7-dimethoxy-2-naphthoic Acid, Isolated from *Ulmus Thomasii*

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An improvement to a known procedure, affording substituted 4-hydroxy-2-naphthoic acid derivatives from aromatic aldehydes, is described and its general applicability shown through the preparation of a natural naphthalene derivative isolated from *Ulmus thomasii*.

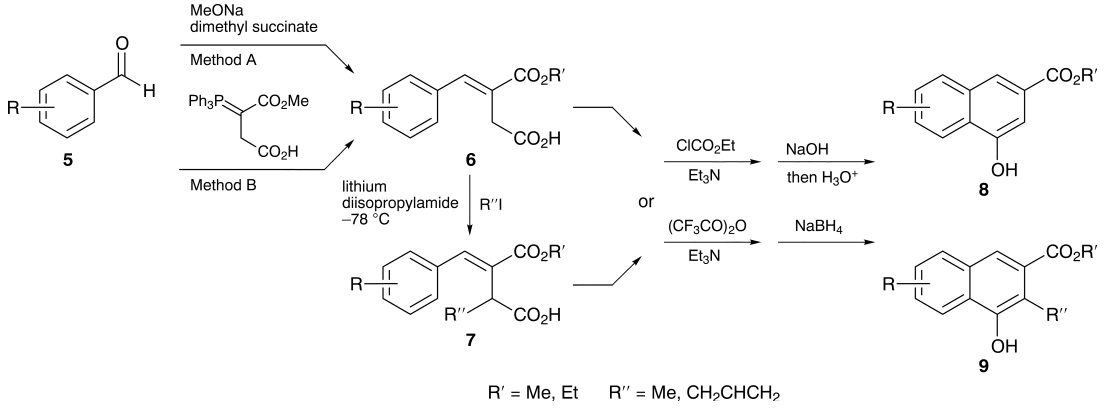
Recently,[1] we have developed a benzoannulation[2] procedure in which divinylketene[3] derivatives are easily generated at room temperature from 3-methoxycarbonyl-6-arylhexa-3,5-dienoic acid, using triethylamine/ethyl chloroformate as activating agent, to give 4-aryl-3-hydroxybenzoic esters in high yields. A further study[4] has shown that a double bond of the heteraromatic ring can function as the γ,δ-double bond of the dienoic system. Accordingly we decided to investigate the general applicability of the mixed anhydride/Et_3N method for the synthesis of the naphthol derivatives starting from 3-alkoxycarbonyl-4-arylbuten-3-oic acid.

Our procedure works under mild conditions, affording 4-hydroxy-2-naphthoic acid derivatives. In a typical experiment (Scheme 2) 3-alkoxycarbonyl-4-aryl-3-butenoic acid **6** or **7** was treated at room temperature with 2.1 equiv. of a suitable activating agent (ethyl chloroformate or trifluoroacetic anhydride) followed by the dropwise addition of an excess (3–4 equiv.) of triethylamine. The thus formed mixed anhydride is unstable in base and can be isolated only in a deficiency of triethylamine. As mentioned above, the excess of base induces the conversion of **6** or **7** into a vinylketene intermediate which cyclizes through a 1,6-electrocyclic reaction to give **8** or **9** (or its carboxyethyl–trifluoroacetyl derivative).

The overall process is very fast (about 15 min at 0–20 °C) and the mild conditions used tolerate a wide pattern of substituents on the aromatic ring. The starting mono acid–mono ester was obtained through a classical Stobbe condensation or by using triphenyl(α-carbethoxy-β-carboxyethyl)phosphonium betaine when the substituents on the aromatic ring are labile towards the strong basic conditions of the direct condensation.

The cyclization step was performed in THF solution and the crude product, which is a phenolic derivative, was isolated at the phenol-ester **8** or **9** upon rapid treatment with alcoholic NaOH (2 equiv.) followed by acidification. If trifluoroacetic anhydride is the activating agent, reductive deprotection with $NaBH_4$ is also possible and becomes the method of choice when the substituent group is labile in basic hydrolytic conditions.

The yields of products purified upon crystallization or chromatography column (Table 1) are very good (80–90%



Scheme 2

Table 1 Isolated yields for the condensation reaction of aldehydes **5a**–**f**, affording **6a**–**f**, and for the cyclization reaction of acids **6a**–**f**, **7a**–**b** to esters **8a**–**f**, **9a**–**b**

Aldehyde	R	Acid	R′	R″	Yield (%)[a]	Ester	Cycliz. method	Yield (%)
5a	H	**6a**	Et	H	85[B]	**8a**	$ClCO_2Et/Et_3N$	57
5b	2,3,4-OMe	**6b**	Me	H	69[A]	**8b**	$ClCO_2Et/Et_3N$	91
5c	3,5-OMe 4-OBz	**6c**	Me	H	59[A]	**8c**	$ClCO_2Et/Et_3N$	84
5d	*p*-Cl	**6d**	Et	H	78[B]	**8d**	$ClCO_2Et/Et_3N$	50
5d	*p*-Cl	**6d**	Et	H	78[B]	**8d**	$(CF_3CO)_2O/Et_3N$	80
5d	*p*-Cl	**7a**	Et	Me	55[B,b]	**9a**	$(CF_3CO)_2O/Et_3N$	83
5d	*p*-Cl	**7b**	Et	CH_2CHCH_2	58[B,b]	**9b**	$(CF_3CO)_2O/Et_3N$	85
5e	*p*-CN	**6e**	Et	H	71[B]	**8e**	$(CF_3CO)_2O/Et_3N$	71
5f	*p*-MeS	**6f**	Et	H	70[B]	**8f**	$ClCO_2Et/Et_3N$	61

[a]A, B are the condensation methods. [b]The yield includes both the condensation and alkylation step.

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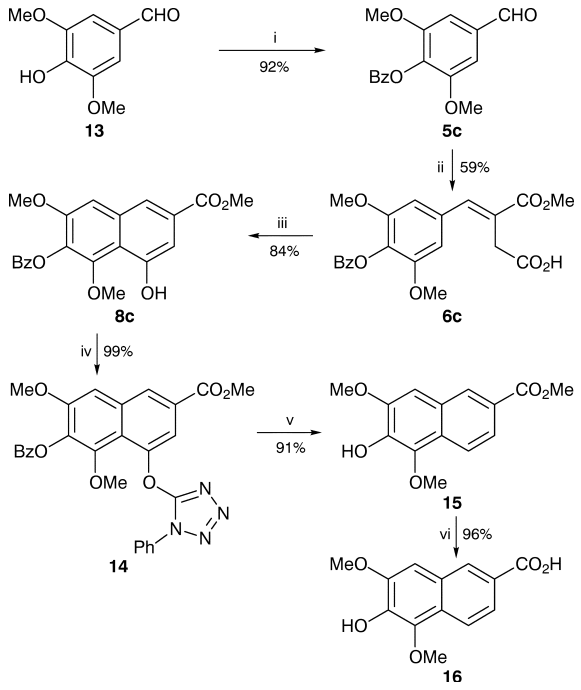


Scheme 3 *Reagents and conditions*: i, B_2Cl, DMF, Na_2CO_3; ii, dimethylsuccinate, MeONa/MeOH; iii, $ClCO_2Et/Et_3N$; iv, 5-Cl-1Ph-1H-tetrazole, Na_2CO_3, DMF; v, H_2, Pd/C; vi, NaOH, then H_3O^+

in the preparation of **8b**, **8c**) when the substituent group R activates the aromatic ring towards the electrophilic attack of the intermediate ketene.

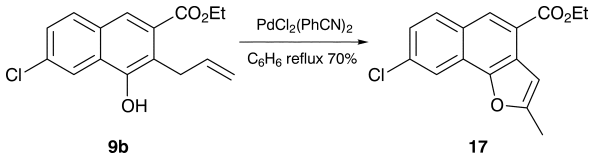
If ethyl chloroformate is used and the starting acid lacks an activating group at the *meta* position or the aromatic ring bears an electron-attracting substituent, the yields drop to 50–60% (**8a**, **8d**–**8f**) and a complementary amount of the ethyl ester of acids **6** is observed in the reaction mixture. We assume that ethanol, derived from the decomposition of mixed anhydride, reacts with the surviving ketene to give the ethyl ester. According to our scheme the same procedure, performed by using $(CF_3CO)_2O$ and by prolonging the reaction time (0.5–3 h), gives good yields of cyclized products (**8d**, **8e**, **9a**, **9b**).

Examination of the substitution pattern of the mono acids–mono esters **6**, **7** shows the flexibility of the synthetic approach: methoxy, halo, cyano allyl and methylthio groups are unaffected to give the related naphthols **8**, **9**.

Recently new, mild, regioselective syntheses of substituted naphthalenes have received significant attention, especially for the preparation of natural products. To investigate the validity of our method in this field we prepared 6-hydroxy-5,7-dimethoxy-2-naphthoic acid **16** (Scheme 3), a naphthalene derivative isolated[12] from *Ulmus thomasii*. Our procedure compares favourably with the previous preparation,[13] in which the key step was a ring closure through a classical Friedel–Crafts reaction.

Thus, starting from commercially available syringaldehyde **13**, we synthesized the mono acid–mono ester **6c** through a Stobbe condensation between the protected phenol **5c** and dimethyl succinate. The latter was cyclized using the $ClCOOEt/Et_3N$ system and the product **8c** was isolated as a phenol-ester derivative upon basis (NaOH, 2, equiv.) treatment followed by acidification (HCl 5%).

The hydroxy group at position 4 of **8c** was easily removed, *via* hydrogenolytic treatment of **14**. The phenyltetrazolyl derivative **14**, in a one-pot procedure, gives **15** in 85% overall yield. The methyl ester **15** was converted into the acid **16**, whose spectroscopic data are identical to



Scheme 4

those reported in the literature.[12] The method has preparative significance because the yield in the cyclization step is high (80% *versus* 30% for the classical procedure) and the dehydrogenation of tetralin is avoided.

Moreover, treatment of 3-alkoxycarbonyl-4-arylbut-3-enoic acids **6** with 2 equiv. of lithium diisopropylamide at −78 °C affords the related dianions which can be easily alkylated at the α-position using 1 equiv. of alkyl or allyl halide (Scheme 2). Cyclization of the resulting acid (**7**) gives 4-hydroxy-3-alkyl(allyl)-2-naphthoic acid derivatives **9** in good yields. We have used this approach to build up naphthofurans using a procedure described by Kishi *et al.*[16] The synthesis of this kind of compound is shown through the preparation of compound **17** (Scheme 4) which was obtained in good yields upon warming a solution of allylphenol **9b** in presence of a palladium salt.

Thus, these results show that the mixed anhydride benzoannulation offers the following advantages: (i) the basic catalysis promoting the cyclization step is very mild and allows one to obtain a wide pattern of substituents on the naphthalene ring; (ii) substituted benzaldehydes which are the starting materials, are easily available; (iii) alkylation of the dianion of 3-alkoxycarbonyl-4-arylbut-3-enoic acid affords a useful method for the regioselective synthesis of 4-hydroxy-3-alkyl-2-naphthoic acid derivatives.

Techniques used: ^1H NMR, IR and mass spectrometry

References: 16

Schemes: 4

Table 1: Isolated yields for the condensation reactions of aldehydes **5a**–**f** affording **6a**–**f**, and for the cyclization reaction of acids **6a**–**f** to esters **8a**–**f**, **9a**,**b**

Table 2: Isolated yields for the condensation reaction of aldehydes **10a**–**c** affording **11a**–**c**, and for the cyclization reaction of acids **11a**–**c** to give esters **12a**–**c**

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