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A Convenient Synthesis of Substituted 2-Phenylnaphthalenes From Phenylacetones

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Abstract: Treatment of phenylacetones **1** with boron tribromide gives the 1,3-dimethyl-2-phenylnaphtalenes **2** in good yields by a tandem aldol condensation-intramolecular Friedel-Crafts cyclization. In the cases of methoxyphenylacetones, a demethylation occurs leading to 1,3-dimethyl-2-hydroxyphenylnaphtols. © 1997 Published by Elsevier Science Ltd.

Investigation of new methods for the regioselective synthesis of highly substituted naphtalenes have received significant attention in recent years[1-6]. Since 1-arylnaphtalenes are attracting attention as the basic skeleton of several biologically active natural products and pharmaceuticals[7-11], these compounds have been one of the synthetic targets. As a part of our works on the synthesis of new biologically active polyhydroxylated compounds, we have examined the application of boron tribromide[12] to the demethylation-dimerization of various methoxylated C_6C_3 reagents. In the present paper, we report the dimerization of phenylacetones to give various 1,3-dimethyl-2-phenylnaphtalenes which possess the isomeric skeleton of several biologically active lignan-type natural products[13].

The self-condensation of ketones is well-documented[14] but often requires long and rather complicated procedures. The acid-catalysed aldol condensation of phenylacetone has previously been reported by Cort et al[15]. They showed the formation of 1-benzyl-3-methylnaphtalene from phenylacetone and 70% sulfuric acid under reflux. This result was not surprising since unsymmetrical aliphatic ketones undergo self-condensation by attack of the carbonyl group on the less hindered α carbon atom. 4-Methyl-1,5-diphenylpent-3-en-2-one was formed[16] and cyclized to give 1-benzyl-3-methylnaphtalene under strong acidic conditions. We thought that the regioselectivity of the aldol condensation can be modified by preparing a pre-formed enol derivative such as an enol borinate[17]. Since we also needed a Lewis acid able to cleave the methylethers, we chose boron tribromide which is probably also able to react with ketones to give enol borinates. As expected, phenylacetone **1a** gave 1,3-dimethyl-2-phenylnaphtalene **2a**[18] in high yield (see table 1).

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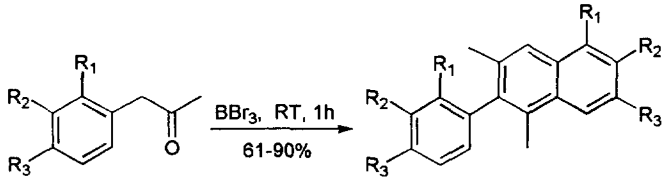


1 **2**

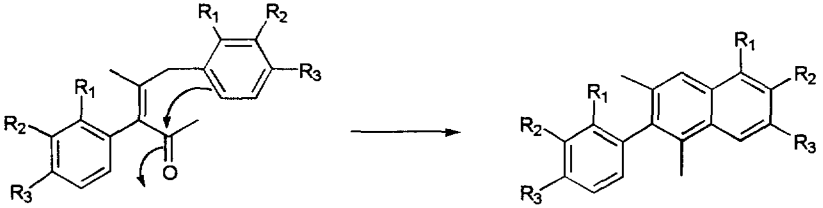
Table 1. 1,3-Dimethyl-2-phenylnaphtalenes **2**[19,20] prepared

Starting material	R_1	R_2	R_3	Product	R_1	R_2	R_3	Yield[a] in **2**
1a	H	H	H	**2a**	H	H	H	90%
1b	OCH_3	H	H	**2b**	OH	H	H	61%[b]
1c	H	OCH_3	H	**2c**	H	OH	H	81%
1d	H	H	OCH_3	**2d**	H	H	OH	83%
1e	H	OCH_3	OCH_3	**2e**	H	OH	OH	77%

a. Yield of purified compounds

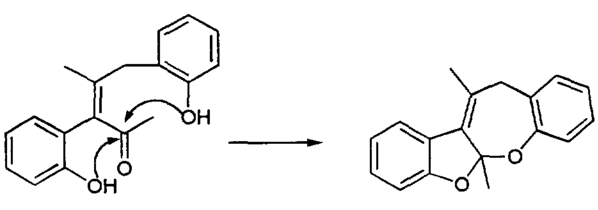
b. **2b** was obtained with 16% of **3**

Boron tribromide reacted with phenylacetone to give a boron enolate which reacted stereoselectively with another molecule of phenylacetone to give the non-isolated 4-methyl-3,5-diphenylpent-3-en-2-one.This aldol condensation product underwent an intramolecular Friedel-Crafts reaction. The ^1H nmr spectrum of the crude product indicated also the presence of 1-benzyl-3-methylnaphtalene (<5%).



2

In the cases of the methoxylated phenylacetones, the total demethylation occured but required one additionnal equivalent of BBr_3 by methoxy group. In the case of **1b**, two major products, the expected naphtol **2b** and an intramolecular acetal **3** were obtained. The intermediate α,β-unsaturated ketone gave **3** as a by-product which cannot be obtained in the other examples.



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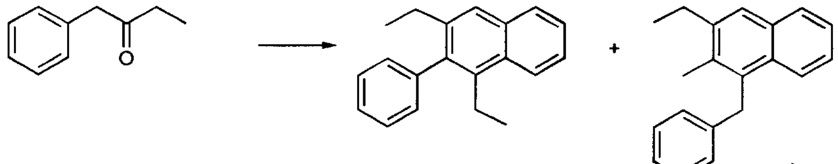
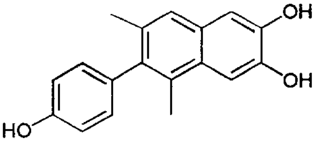
Nevertheless, the regioselectivity of the aldol condensation decreased when 1-phenylbutan-2-one **1f** was used: the ^1H nmr spectrum of the crude product showed a mixture of 1,3-diethyl-2-phenylnaphtalene (60%) **2f** and 1-benzyl-3-ethyl-2-methylnaphtalene (40%) **4**.



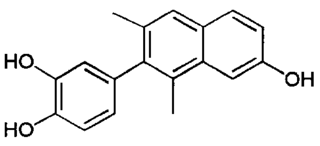
2f **4**

The intramolecular Friedel-Crafts reaction was also highly regioselective as attested by the formation of only one product from **1c** or **1e**. The structures of **2b-e** have been established from the spectroscopic data[21] and homonuclear Overhauser effect experiments. For example nOe experiments on compound **2d** gave the following results: the irradiation of the methyl group at 2.02 ppm gave a nOe of 14% of the proton at 7.47 ppm, the irradiation of the methyl group at 2.19 ppm gave a nOe of 16% of the proton at 7.17 ppm and the irradiation of the proton at 7.47 ppm gives nOe's of 7% of the methyl group at 2.02 ppm and 9% of the proton at 7.65 ppm. These results, in association with the coupling constants unambiguously proved the proposed structure.

Additionnally, the cross-condensation had been undertaken on an equimolar mixture of **1d** and **1e**. Four different naphtols were obtained. Due to the different numbers of hydroxy groups, the cross-condensation naphtols were easily separated from **2d** and **2e** by liquid chromatography. From a solution of chloroform, the major cross-condensation product crystallized. Its spectroscopic data are consistent with the structure of **2de**, product of the condensation of the enol borinate of **1d** and the ketone **1e**. This cross-condensation yielded (in pure isolated compounds) **2d** (17%), **2de** (20%), **2ed** (7%) and **2e** (5%). As expected, **2d** and **2de** were the major products since the enol borinate of **1d** is more easily formed than the enol borinate of **1e**.



2de



2ed

In conclusion, we have shown that boron tribromide can promote the dimerization of methoxylated phenylacetones leading to new 1,3-dimethyl-2-phenylnaphtols. The unsustituted phenylacetone **1a** gives 1,3-dimethyl-2-phenylnaphtalene **2a**, a compound of particular interest in the field of forensic chemistry. Further studies are presently undertaken in four different directions: (i) the synthesis of enolates in order to promote cross-condensation, (ii) the use of other Lewis acids which are able to form an enol derivative(iii) the generalisation to phenylethanals and phenylpyruvic acids and (iv) the generalisation to nitrophenylacetones since the nitro group can be easily converted to the hydroxy group.

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(19) All new compounds have ^1H and ^{13}C nmr, ms and combustion analysis data consistent with the structures shown.

(20) Experimental procedure: BBr_3 (1M in CH_2Cl_2, 10mL, 10mmol for **1a**, 15mL, 15mmol for **1b-d** or 20mL, 20mmol for **1e**) was added dropwise to a solution of phenylacetones (5mmol) in CH_2Cl_2 (20mL) at room temperature. The mixture was stirred for 1h, then water (40mL) was added dropwise.

(2a): The CH_2Cl_2 layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 (20mL). The CH_2Cl_2 layers were dried ($MgSO_4$) and the solvent evaporated to give the crude products which were purified by flash chromatography (Acetone/cyclohexane: 1/9).

(2b) and **(3)**: The CH_2Cl_2 layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 (20mL). The CH_2Cl_2 layers were dried ($MgSO_4$) and the solvent evaporated to give the crude products which were purified by flash chromatography (Acetone/cyclohexane: 1/9)

(2c): The solid was filtered and dried. The CH_2Cl_2 layer was separated and dried ($MgSO_4$). The solid was refluxed in CH_2Cl_2. The CH_2Cl_2 solution was filtered. From these CH_2Cl_2 solutions, **2c** crystallized as dark needles.

(2d) or **(2e)**: The mixture was filtered to give **2d** or **2e**. The solid was washed with water, dried and crystallized from acetone.

(21) Spectroscopic data of **2d**: ^1H (DMSO-6d): 2.02 (3H, bs), 2.19 (3H, s), 6.84 (2H, d, ^3J=8.5 Hz), 6.94 (2H, d, ^3J=8.5 Hz), 7.03 (1H, dd, ^3J=8.7 Hz, ^4J=2.2 Hz), 7.17 (1H, dd, ^4J= 2.2 Hz, ^5J=0.9 Hz), 7.47 (1H, bs), 7.65 (1H, d, ^3J=8.7 Hz), 9.40 (1H, bs), 9.60 (1H, bs) ; ^{13}C (DMSO-6d): 16.4 (q), 21.5 (q), 105.9 (d), 115.1 (d), 117.7 (d), 125.3 (d), 126.9 (s), 129.0 (d), 129.1 (s), 130.1 (d), 130.7 (s), 131.6 (s), 132.3 (s), 140.0 (s), 154.9 (s), 156.0 (s); EIMS (70 eV): 264 (100), 249 (13), 149 (18), 107 (56); m.p. = 210°C (acetone).

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