Communications to the Editor

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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 47.[1] A GENERAL, EFFICIENT, AND CONVENIENT SYNTHESIS OF DIARYLHEPTANOIDS[2]

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An efficient synthesis of physiologically interesting diarylheptanoids has been carried out through direct C-acylation using diethyl phosphorocyanidate (DEPC) followed by Grignard reactions with aldehydes.

KEYWORDS —— diarylheptanoid; C-acylation; diethyl phosphorocyanidate; β-ketonitrile; Grignard reaction; β-ketol

Linear diarylheptanoids, a group of compounds having the general structure of Ar-C_7-Ar, have been isolated from plants belonging to Zingiberaceae and Beturaceae.[3] Some diarylheptanoids have interesting physiological actions such as a choleretic action in rats and dogs,[3b] inhibition of prostaglandin biosynthesis,[3h] and contraction of the guinea pig ileum.[3f] Hikino and coworkers[4] recently found that many diarylheptanoids have antihepatotoxic effects. In order to investigate their physiological actions in more detail, it is desirable to prepare various diarylheptanoids very conveniently in large amounts. However, there is almost no report on the general synthesis of these physiologically interesting compounds.[5]

We now report a general, efficient, and convenient synthesis of diarylheptanoids. The key steps of the synthesis are the direct C-acylation using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[6] and the Grignard reaction with aldehydes, which method has been employed for the synthesis of DL-[n]-gingerols.[7]

Direct condensation of 3-arylpropionic acids **1**[8] with tert-butyl cyanoacetate was smoothly carried out with DEPC in the presence of triethylamine in dimethylformamide. Thermal treatment of the C-acylated products **2** in dimethylformamide, followed by the carbonyl protection with hot ethylene glycol afforded the nitriles **3**, which were reduced with diisobutylaluminum hydride in diethyl ether to give the aldehydes **4**. The efficiency of each step was preparatively satisfactory, as shown in Table I.

The Grignard reaction of **4** with various 2-arylethyl magnesium bromides in tetrahydrofuran afforded the protected β-ketols **5**, which were subjected to deprotection to give diarylheptanoids **6** containing DL-β-ketol skeletons, as shown in Chart 1. The overall yields of **6** from **1** were 23-48%.

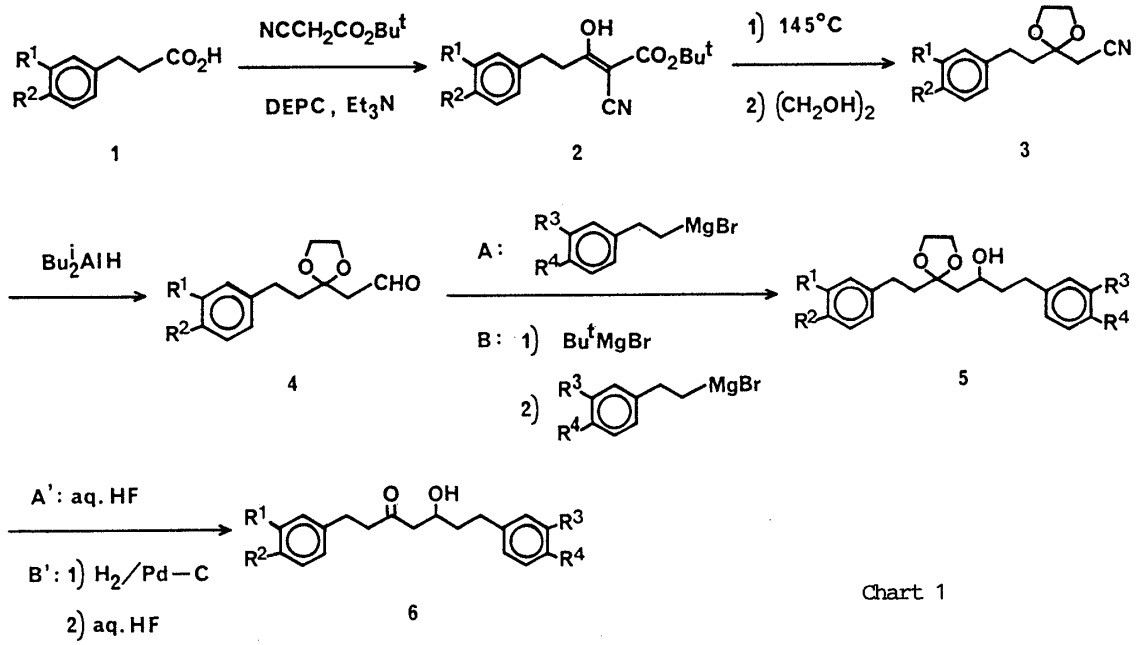


Chart 1

Table I. Preparation of Aldehydes 4

Compound	R^1	R^2	Yield (%) of 2	Yield (%) of 3	Yield (%) of 4	mp (°C) of 2	mp (°C) of 3	mp (°C) of 4
a	H	H	85	73	79	51.5-52.5	56-57	a)
b	H	HO	79	70	70	130-131	106-108	104.5-106.5
c	$PhCH_2O$	$PhCH_2O$	75	87	80	89-90	88-89.5	83-84
d	CH_3O	HO	78	94	76	88-89	114-116	80-81[b]

a) Colorless oil.
b) The aldehyde **4d** was prepared according to the literature.[7]

Table II. Preparation of Diarylheptanoids 6

Compound	R^1	R^2	R^3	R^4	Method[a]	Yield (%)	mp (°C)
5a-1	H	H	H	H	A	67	b)
5a-2	H	H	H	$PhCH_2O$	A	68	55-57
5a-3	H	H	CH_3O	$PhCH_2O$	A	61	b)
5b-1	H	HO	H	$PhCH_2O$	B	90	108-110
5b-2	H	HO	$PhCH_2O$	$PhCH_2O$	B	88	94-98
5c-1	$PhCH_2O$	$PhCH_2O$	H	$PhCH_2O$	A	82	73-75
5c-2	$PhCH_2O$	$PhCH_2O$	$PhCH_2O$	$PhCH_2O$	A	65	b)
5d-1	CH_3O	HO	H	H	B	96	b)
5d-2	CH_3O	HO	CH_3O	$PhCH_2O$	B	95	b)

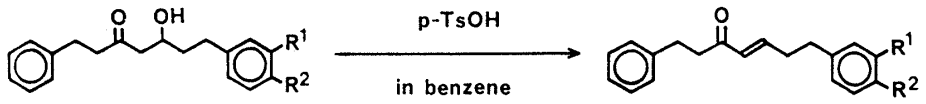
Table II.(continued)

Compound	R^1	R^2	R^3	R^4	Method[a)]	Yield (%)	mp (°C)
6a-1	H	H	H	H	A'	99	70-72
6a-2	H	H	H	HO	B'	88	59.5-61
6a-3	H	H	CH_3O	HO	B'	87	b)
6b-1	H	HO	H	HO	B'	100	119-121
6b-2	H	HO	HO	HO	B'	100	100-103
6c-1	HO	HO	H	HO	B'	97	b)
6c-2	HO	HO	HO	HO	B'	67	b)
6d-1	CH_3O	HO	H	H	A'	90	b)
6d-2	CH_3O	HO	CH_3O	HO	B'	82	80-81.5

a) See Chart 1 on the conversion of 4→5→6.

b) Colorless oil.

Some other diarylheptanoids were also prepared, as follows. The β-ketols **6a-1** and **6a-3** were dehydrated in hot benzene containing p-toluenesulfonic acid to give the α,β-unsaturated ketones **7a** and **7b** as colorless oils in 96 and 64% yields, respectively.



6a-1, $R^1=R^2=H$ 7a, $R^1=R^2=H$

6a-3, $R^1=CH_3O$, $R^2=HO$ 7b, $R^1=CH_3O$, $R^2=HO$

Treatment of the aldehyde **4a** with lithium phenylacetylide in tetrahydrofuran at -15°C for 1 h and at room temperature for 2 h afforded the hydroxy alkyne **8** (pale yellow oil), which was reduced with lithium aluminum hydride in diethyl ether to give the hydroxy alkene **9** (colorless oil) in 72%

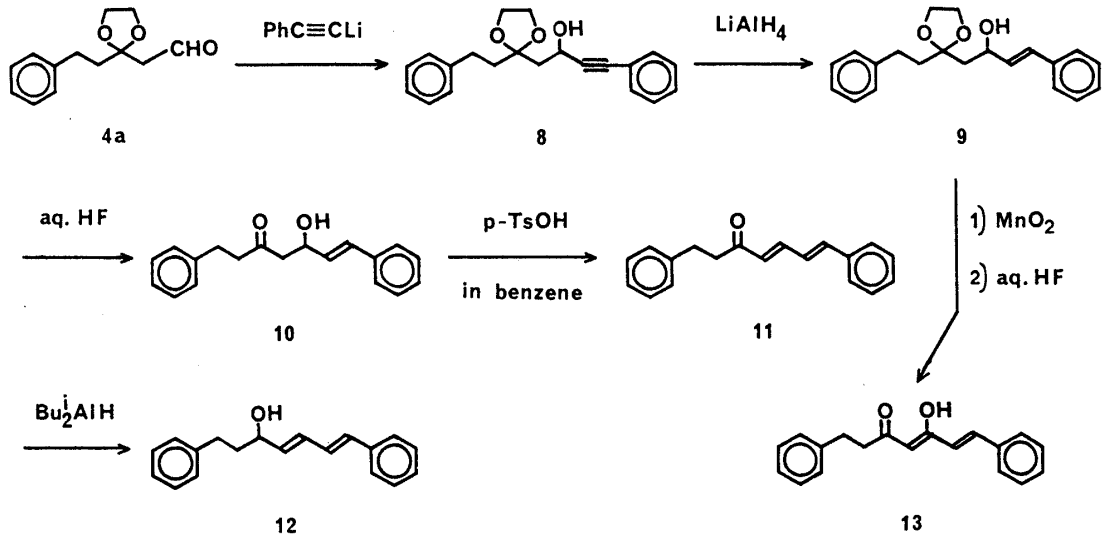


Chart 2

yield from **4a**. The β-ketol **10** (colorless oil) was obtained in 78% yield by treatment of **9** with 46% aqueous hydrogen fluoride in acetonitrile for 6 min at room temperature. Similar dehydration of **10** as above afforded the unsaturated ketone **11** (mp 64-65°C) in 64% yield, which was reduced with diisobutylaluminum hydride in diethyl ether at -30°C for 1 h to give the alcohol **12** (mp 78-80°C) in 89% yield. On the other hand, the hydroxy alkene **9** was treated successively with active manganese dioxide (81% yield) and aqueous hydrogen fluoride (72% yield) to furnish the diketone **13** (mp 74-75.5°C), as shown in Chart 2.[9]

The present method offers not only a general, efficient, convenient, and straightforward avenue to the physiologically interesting diarylheptanoids, but also a general entry to various β-ketols.

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8) 3-(3,4-Dibenzyloxyphenyl)propionic acid (**1c**, mp 120-122°C) was prepared from (3,4-dibenzyloxy)cinnamic acid by its catalytic hydrogenation over 5% palladium on alumina in dioxane. The other starting acids **1a** and **1b** are commercially available.
9) All compounds exhibited satisfactory spectral and physical properties.

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