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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 44.¹⁾
A NEW GENERAL EFFICIENT SYNTHESIS OF DL-[n]-GINGEROLS AND RELATIVES
THROUGH DIRECT C-ACYLATION USING DIETHYL PHOSPHOROCYANIDATE (DEPC)²⁾

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DL-[n]-Gingerols (**1**) and their relatives, which have various interesting physiological actions, have been conveniently and efficiently prepared from ferulic acid (**2**) through direct C-acylation using diethyl phosphorocyanidate (DEPC) in the presence of triethylamine.

KEYWORDS — [n]-gingerol; C-acylation; diethyl phosphorocyanidate; β -ketonitrile; Grignard reaction; β -ketol

[n]-Gingerols (**1**) are known as pungent principles of ginger, in which (*S*)-[6]-gingerol ((*S*)-**1**, $n=6$) is the major member of the series.³⁾ Recently, (*S*)-[6]-gingerol and its relatives have been revealed to have various interesting physiological actions such as inhibitory action on prostaglandin biosynthesis,⁴⁾ cardiogenic action,⁵⁾ and suppressive action on the central nervous system.⁶⁾ Reported syntheses⁷⁾ of [6]-gingerol and its relatives, except one,^{7e)} have employed cross aldol condensations as a key step (fission a in **1**), but their efficiency and convenience are generally moderate.

Chart 1

We now report a new general efficient synthesis of DL-[n]-gingerols and their relatives. Salient features of this construction include (1) Grignard reactions with an aldehyde (fission b in 1), shown in Chart 1, and (2) direct C-acylation of an active methylene compound with a carboxylic acid using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) in the presence of triethylamine.⁸⁾

Catalytic hydrogenation of commercially available ferulic acid (2) over 5% palladium on carbon in methanol quantitatively afforded 3-(4-hydroxy-3-methoxyphenyl)propionic acid (3),⁹⁾ mp 90.5-91.5°C. Condensation of tert-butyl cyanoacetate with 3 was conveniently carried out in dimethylformamide by the use of DEPC and triethylamine,⁸⁾ giving the C-acylated product 4 in 78% yield as the enolic form: mp 88-89°C; IR (Nujol): 3410 (phenolic OH), 2220 (CN), 1650 $(CO_2Bu^t)cm^{-1}$; NMR ($CDCl_3$) δ : 1.53 (9H, s, Bu^t), 2.88 (4H, s, CH_2CH_2), 3.85 (3H, s, CH_3O), 5.57 (1H, broad s, phenolic OH, exchangeable with D_2O), 6.43-6.92 (3H, m, aromatic H), 13.93 (1H, broad s, enolic OH, exchangeable with D_2O). Thermal treatment of 4 in dimethylformamide at 145°C for 10 min gave the β -ketonitrile 5 in 97% yield: mp 69.5-71°C; IR (Nujol): 2240 (CN), 1730 $(C=O)cm^{-1}$. The ketonic function of 5 was protected as the ethylene acetal by treatment with ethylene glycol in refluxing benzene containing p-toluenesulfonic acid using a Dean-Stark water separator, giving the acetal 6, mp 114-116°C, in 97% yield. Alternatively, direct conversion of 4 to 6 was achieved in 89% yield by similar treatment of 4 with ethylene glycol. Reduction of 6 with diisobutylaluminum hydride in diethyl ether at -20°C for 1 h afforded the aldehyde 7 in 76% yield: mp 80-81°C, IR (KBr): 1720 $(C=O)cm^{-1}$; NMR ($CDCl_3$) δ : 9.70 (1H, t, $J=3Hz$, CHO).

Chart 2

Grignard coupling of the aldehyde 7 with various alkyl magnesium bromides was conducted in tetrahydrofuran at -15°C for 1 h and then at room temperature for 2 h, giving the protected β -ketols 8 in good yields, as summarized in Table I. Treatment of 8 with 46% aqueous hydrogen fluoride in acetonitrile at room temperature for 0.5 h afforded DL-[n]-gingerols (1) in excellent yields. The overall yield of DL-[6]-gingerol (1, n=6) from readily available ferulic acid (2) is 47% which is the highest overall yield ever achieved.⁷⁾

Table I. Preparation of DL-[n]-Gingerols (1)

n	Yield (%) of 8 ^{a)}	Yield (%) of 1	mp (°C) of 1
2	86 ^{b)}	96	67-68.5
4	83	93	72-73
6	89	95	40-41
8	85	94	32-34
10	91	78	44-45
12	73	76	53-54.5
14	85	84	64-65
16	83	96	71-72

a) All of **8** are colorless oils.

b) Methyl magnesium chloride was used.

[1]-Gingerol [5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)pentan-3-one], mp 79.5-81°C, was prepared from the aldehyde **7** by sodium borohydride reduction (84% yield), followed by treatment with hydrogen fluoride (68% yield).

A few derivatives of [6]- and [12]-gingerols were also prepared, shown in Chart 3. The β -ketonitrile **5** was converted to its O-silylated derivative **9** with N,O-bis(trimethylsilyl)acetamide. Treatment of **9** with tert-butyl magnesium chloride, followed by pentyl magnesium bromide in refluxing benzene for 1 h afforded the enaminoketone **10a**, which was hydrolyzed with 1 N sulfuric

Chart 3

acid in ethanol under reflux for 5 min to give [6]-gingerdione (**11a**), a pale yellow oil,⁴⁾ IR (film): 3430, 1700, 1610 cm^{-1} , in 55% overall yield from **5**. [12]-Gingerdione (**11b**), mp 44–45°C, IR (film): 3410, 1700, 1610 cm^{-1} , was also similarly obtained in 53% yield by the use of undecanoyl magnesium bromide. Dehydrogenation of **11a** and **11b** with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in dioxane afforded respectively [6]-dehydrogingerdione (**12a**), mp 83.5–84.5°C (lit.^{4,7c)} 83.5–84.5°C), IR (KBr): 3300, 1625, 1595 cm^{-1} , and [12]-dehydrogingerdione (**12b**), mp 70–71°C, IR (KBr): 3410, 1630, 1580 cm^{-1} .

The overall process for the preparation of [n]-gingerols and their relatives is simple, convenient, straightforward, economical, and suitable for large scale preparation. Furthermore, the method described here will have a generality as the preparative method for various β -ketols and congeners.

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