

Short Note

## Ethyl 4,4''-Difluoro-5'-hydroxy-1,1':3',1''-terphenyl-4'-carboxylate

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**Abstract:** A simple and novel route for the synthesis of new terphenyl derivative as well as oxidative aromatization of  $\alpha,\beta$ -unsaturated cyclohexenone to the corresponding phenol derivative is developed. The present work involves the condensation of ethylacetoacetate with 4,4'-difluoro chalcone followed by the aromatization using chloramine-T in acetic acid to yield the title compound (**3**). The synthesized compound (**3**) is well characterized by IR, NMR, LCMS and elemental analysis.

**Keywords:** 4,4'-difluoro chalcone; cyclohexenone derivative; aromatization; chloramine-T; terphenyl derivative

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Phenyl group and polysubstituted aromatics are key structures of great efficacy in synthetic, medicinal and natural product chemistry. In recent years, it has been reported that some terphenyls exhibit considerable biological activities like potent anticoagulant, immunosuppressant, antithrombotic, neuroprotective, specific 5-lipoxygenase inhibitory and cytotoxic activities [1]. Because of their promising biological activities and important properties, terphenyls have kindled increasing research interest. Therefore, synthesis of polysubstituted aromatics is a fascinating area in organic field [2]. Classical approaches are based on aromatic substitution, which introduces a substituent to the benzene ring. Synthetic methodologies based on this route were developed including electrophilic or nucleophilic substitutions [3,4], coupling reactions catalyzed by transition metals [5] and metallation functionalization reactions [6]. However, these approaches have some drawbacks from

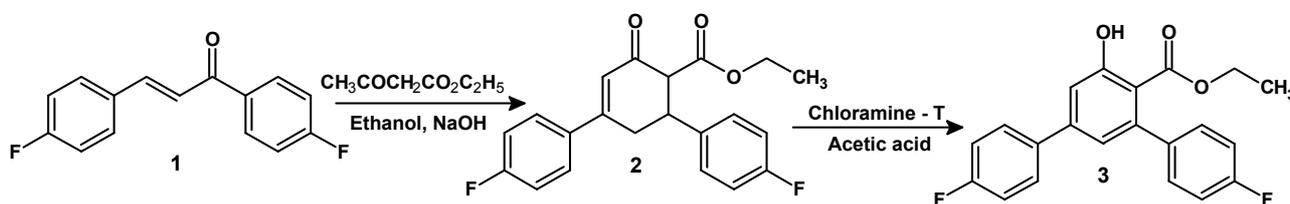
the view of atom economy or environmental concern [7]. The methods that construct the aromatic backbone from acyclic precursors have received increasing interest recently due to their short synthetic steps and selective nature [8].

Aromatization of substituted cyclohexenones to the corresponding phenol or phenyl ether derivatives is of great interest. Iodine in methanol is being used as a novel reagent for the conversion of 2-cyclohexen-1-ones into the corresponding anisole derivatives [9-13].

In view of the pharmacological importance of terphenyls and in continuation of our work on synthesis of various derivatives of 4,4'-difluoro chalcone [14-21], we have developed a simple and novel method for the synthesis of new *m*-terphenyl derivatives as well as a new method for the oxidative aromatization of substituted  $\alpha,\beta$ -unsaturated cyclohexenones to the corresponding phenol derivatives using chloramine-T with a good yield. Also this method is advantageous over the conventional method as far as work up procedure and yield is concerned.

The purity of the compound is checked by single-spot TLC, and the compound is characterized on the basis of spectral data (IR, NMR and LCMS) and elemental analysis. Spectral data of the synthesized compound **3** is in full agreement with its proposed structure. In the IR Spectrum, a broad band appeared at  $3439\text{ cm}^{-1}$  is due to phenolic OH group. The absorption bands at 3055, 2989,  $2906\text{ cm}^{-1}$  are due to aliphatic CH groups and an absorption band at  $1653\text{ cm}^{-1}$  is due to carbonyl group of the ester. In  $^1\text{H-NMR}$  spectrum, the signals of the respective protons of the title compound are verified on the basis of their chemical shifts, multiplicities, and coupling constants. A triplet at  $\delta$  0.96 and quartet at  $\delta$  4.02 ppm confirms the presence of methyl and methylene protons of the ester chain. The multiplet at  $\delta$  7.05–7.72 is due to ten aromatic protons. The singlet at  $\delta$  10.23 is due to the phenolic proton. The  $^{13}\text{C-NMR}$  spectrum shows peak at  $\delta$  167.29 for a carbonyl carbon. Due to the *para*-fluoro substituents in two phenyl rings, eight phenyl carbon signals of these two rings in  $^{13}\text{C-NMR}$  spectrum, the signals are split into doublets due to 2, 3 and 4 bond coupling with  $^{19}\text{F}$ . The mass spectrum shows the presence of a peak at  $m/z$  354 ( $\text{M}^+$ ) in accordance with the molecular formula. Elemental analysis also gives satisfactory results for the title compound.

**Scheme 1.** Synthesis of ethyl 4,4''-difluoro-5'-hydroxy-1,1':3',1''-terphenyl-4'-carboxylate.



## Experimental

Melting point was taken in open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F254 coated aluminium plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer in KBr (max in  $\text{cm}^{-1}$ ).  $^1\text{H}$  (400 MHz) NMR spectrum was recorded on a Bruker AMX 400 spectrometer, with 5 mm PABBO BB-1H TUBES and  $^{13}\text{C}$  (100 MHz) NMR spectrum was recorded for approximately 0.03 M solutions in  $\text{DMSO-d}_6$  at 100 MHz with TMS as internal standard. LCMS was obtained using Agilent 1200 series

LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmbH).

Ethyl 4,6-bis(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate (**2**) was prepared by the condensation of ethyl acetoacetate with the 4,4'-difluoro chalcone (**1**) according to the method described in our previous work [22]. In a round-bottomed flask, a mixture of  $\alpha,\beta$ -unsaturated cyclohexenone, **2** (3.56 g, 10 mmol) and chloramine-T (5.62 g, 20 mmol) in 50 mL acetic acid was refluxed with stirring for 12 h. The reaction mixture was cooled to room temperature and quenched into 200 mL ice cold water. The solid thus obtained was filtered, washed with water and recrystallized from absolute ethanol to give the title compound as a white crystalline solid (3.1 g, 88%).

Melting point: 100–101 °C.

LCMS:  $m/z = 354$  ( $M^+$ ).

IR (KBr):  $\nu_{\max}$  ( $\text{cm}^{-1}$ ), 3439 (broad, O-H phenolic), 3055, 2989, 2906 (C-H aliphatic), 1653 (C=O ester), 1606 (C=C aromatic), 1276 (C-O), 1215 (C-F).

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta/\text{ppm}$ , 0.96 (t, 3H,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 4.02–4.07 (q, 2H,  $\text{CH}_2$ ), 7.05–7.72 (m, 10H, Ar-H), 10.23 (s, 1H, OH).

$^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta/\text{ppm}$ , 13.59 ( $\text{CH}_3$ ), 60.42 (CO- $\text{CH}_2$ ), 112.94, 114.99 (d), 115.66 (d), 118.68, 119.98, 128.84 (d), 130.04 (d), 135.74 (d), 136.38 (d), 140.16, 141.52, 155.36, 160.57 (d), 163.00 (d), 167.29 (C=O).

Elemental analysis: Calculated for  $\text{C}_{21}\text{H}_{16}\text{F}_2\text{O}_3$ , C, 71.18%, H, 4.55%; Found: C, 71.14%, H, 4.54%.

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