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Efficient synthesis of 2,5-di-*t*-butyl-4-fluorophenol☆

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Abstract

When 4-fluorophenol was refluxed with excess of *t*-butyl chloride in the presence of various catalysts, e.g. Envirocat EPZG, EPZ10, EPIC, sulfated zirconia, natural kaolinitic clay, zirconium nitrate, zinc chloride and bismuth nitrate, the product obtained was 2,5,di-*t*-butyl 4-fluorophenol in excellent yield.

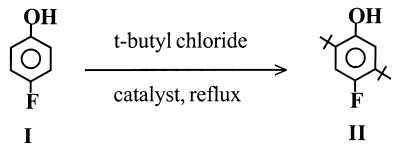
Keywords: 4-Fluorophenol; Envirocats; Natural clay; Sulfated zirconia; 2,5-di-*t*-butyl-4-flurophenol

1. Introduction

Synthesis of 2,5- and 2,6-di-*t*-butylated phenols is of great importance because of their usefulness as an antioxidants [1]. Generally *t*-butylation of phenols has been carried out using either Lewis acid [1] or Bronsted acid catalyst [2]. Recently synthesis of 2, 5-di-*t*-butyl-4-fluorophenol has been reported in very poor yield (10.2%) using 4-fluorophenol and *t*-BuCl in the presence of $AlCl_3$ as a catalyst [1]. The synthesis of 2,6-di-*t*-butyl-4-fluorophenol using expensive xenon difluoride is also described in the literature [3]. We now report a high yielding synthesis of 2,5-di-*t*-butyl-4-fluorophenol using some novel environmentally friendly catalysts.

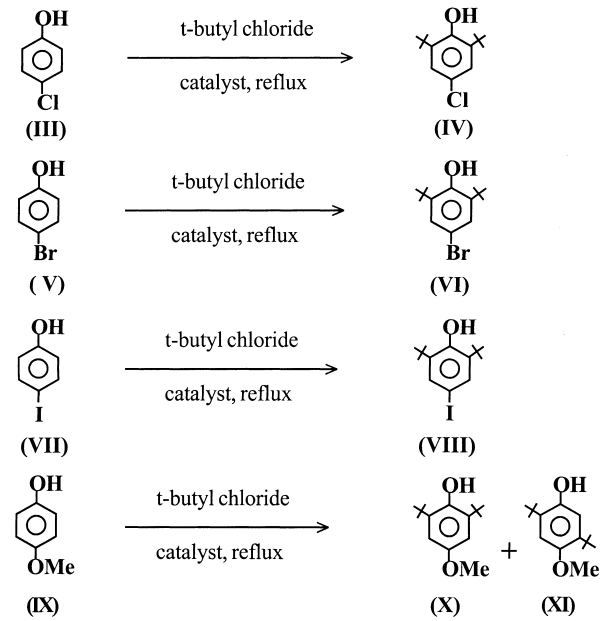
2. Results and discussion

When 4-fluorophenol was refluxed with excess of *t*-butyl chloride in the presence of heterogenous catalysts like Envirocat EPZG, EPZ10, EPIC [4–7] and sulfated zirconia [8,9] and



I II

natural kaolinitic clay [10,11], the product formed was only 2,5-di-*t*-butyl-4-fluorophenol in excellent yield (Table 1, entries 1–5) compared with reported results [3]. Use of Lewis acid catalysts like zirconium nitrate, bismuth nitrate and anhydrous zinc chloride also gave 2,5-di-*t*-butyl-4-fluorophenol in excellent yield (entries 6–8). No mono-*t*-butylated compound was observed. 2-6-Di-*t*-butyl-4-chlorophenol (IV), 2,6 di-*t*-butyl-4-bromophenol (VI) and 2,6-di-*t*-butyl-4-iodophenol (VIII) were formed when 4-chlorophenol (III), 4-bromophenol (V) and 4-iodophenol (VII) were *t*-butylated [12]. The steric hindrance of bulky 4-chloro, 4-bromo and 4-iodo substituents did not allow substitution in the 5-position.



☆This paper is dedicated to Dr. J.M. Waghmare, Vice-Chancellor, Swami Ramanand Teerth Marathwada University, on the occasion of his 65th birthday.

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Table 1
Synthesis of 2,6- and 2,5-di-*t*-butyl-4-substituted phenols

Entry	Phenol	Catalyst	Product	Reaction time (min)	Yield (%)
1	I	EPZG	II	10	95
2	I	EPZ10	II	10	94
3	I	EPIC	II	10	98
4	I	Sulphated zirconia	II	180	85
5	I	Natural clay	II	10	85
6	I	Zirconium nitrate	II	240	85
7	I	Zinc chloride	II	10	90
8	I	Bismuth nitrate	II	10	77
9	III	Natural clay	IV	10	72
10	III	EPZ10	IV	10	70
11	V	Natural clay	VI	10	64
12	V	EPZ10	VI	10	67
13	VII	Natural clay	VIII	10	60
14	VII	EPZ10	VIII	10	65
15	IX	Natural clay	X + XI (3:2)	20	63
16	IX	EPZ10	X + XI (3:2)	10	71

The reaction of 4-methoxyphenol (IX) with *t*-butyl chloride gave both the 2-6-di-*t*-butyl-4-methoxyphenol (X) and 2,5-di-*t*-butyl-4-methoxyphenol (XI) [3]. Although the methoxy group is not as strong a donor as the hydroxy group, the influence of the *t*-butyl in 2-*t*-butyl-4-methoxyphenol, the reaction intermediate, is sufficient to direct the second *t*-butyl to the 5-position.

The fluorine 2p orbital of 4-fluorophenol can overlap with the aromatic carbon better than the 3p orbital of chlorine in 4-chlorophenol, 4p orbital of bromine in 4-bromophenol or 5p orbital of iodine in 4-iodophenol. Therefore, fluorine is a more activating group than chlorine, bromine and iodine [13,14]. But the more electron withdrawing inductive effect of fluorine makes it a less activating group than hydrogen [13,14]. The orientation of the alkyl group in 4-fluorophenol is due to fluorine groups whereas the orientation of alkyl group in 4-chlorophenol, 4-bromophenol and 4-iodophenol is due to phenolic-OH groups. The alkylation of 4-fluorophenol gives exclusively 2,5-dialkylated product because of the small size of fluorine, the π-donor effect of fluorine and intermediate, 2-*t*-butyl directing effect.

3. Experimental details

^{1}H NMR spectra were obtained from a 90 MHz Varian FT-NMR instrument whereas IR spectra were recorded on a Bomem MB 104 FT-IR spectrometer. Envirocat EPZG, EPZ10, EPIC and sulfated zirconia were procured from Contract Chemicals, England and MEL Chemicals, England, respectively. Natural kaolinitic clay was obtained from the Padappakara mine of Quilon District, Kerala, India and was purified and supplied by Dr. Lalithambika, RRL, Trivandrum. EPZG, EPZ10, EPIC, sulfated zirconia and natural kaolinitic clay were used as supplied without activation/calcination. Zirconium nitrate, bismuth nitrate and anhydrous $ZnCl_2$ were of analytical grade. 4-Fluorophenol, 4-chlorophenol, 4-bromophenol, 4-iodophenol and 4-methoxyphenol were purchased from Lancaster Chemicals, England.

3.1. Preparation of 2,5-di-t-butyl-4-fluorophenol

A mixture of 4-fluorophenol (5 mmol), *t*-butyl chloride (10 ml) and catalyst (100 mg) was refluxed for specified time (table) and the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered off and washed with diethyl ether (3×10 ml). The solvent was removed under vacuum and the crude product obtained was purified by column chromatography (petroleum ether:ethylacetate = 9:1 as an eluent). Physical constant, IR, ^{1}H NMR and ^{13}C NMR values of the product II match with the reported data [3].

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