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NOTE

Simple Synthesis of 2,4-Di(1-adamantyl)phenol

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2,4-Di(1-adamantyl)phenol was prepared from phenol and 1-bromoadamantane in chlorobenzene in the presence of copper(I) salts. $Cu(CH_3CN)_4PF_6$ has been found an efficient catalyst for this synthesis.

Key Words: Synthesis, 1-Bromo adamantane, 2,4-Di(1-adamantyl)phenol.

The introduction of bulky adamantyle substituents in reagents and asymmetric ligands has been advantageous for reactivity and enantioselectivity[1–4]. 2,4-Di(1-adamantyl)phenol (3) has been employed for its antiinflammatory properties and used in the treatment of several diseases like rheumatoid arthritis, psoriasis, gout, osteoarthritis and osteoporosis[5]. In this article, the simple synthesis of compound 3 by thermal reaction is reported.

Adamantyl-substituted phenols were first reported by Ong[6]. Diadamantylation of phenol (1) was reported to be a very difficult reaction. So, 2,4-di(1-adamantyl)phenol (3) was obtained in 29% yield from phenol (1) and large excess (6 equiv.) of 2 in CCl_4, in the presence of activated silica gel as catalyst[5].

The thermal reaction of phenol (1) is performed with excess of 2 in chlorobenzene. So, in the absence of catalyst, 4-(1-adamantyl)phenol (4) is obtained in high yield[7–9]. It has been observed that some Cu(I) salts could catalyze the formation of 3. The nature of the Cu(I) salt was found to be important. So, the catalytic action of CuCN or CuI on a mixture of phenol (1) and 1-bromoadamantane (2) (molar ratio: 1 : 2.4) in chlorobenzene has afforded compound 3 in 30% yield (**Scheme-1**).

Under the same reaction conditions, we have used tetrakis(acetonitrile)copper(I) hexafluorophosphate [$Cu(CH_3CN)_4PF_6$] as catalyst is used. This reaction has given a mixture of two products, 2,4-di(1-adamantyl)phenol (3) in 70% and compound 4 in 14% yields (**Scheme-1**).

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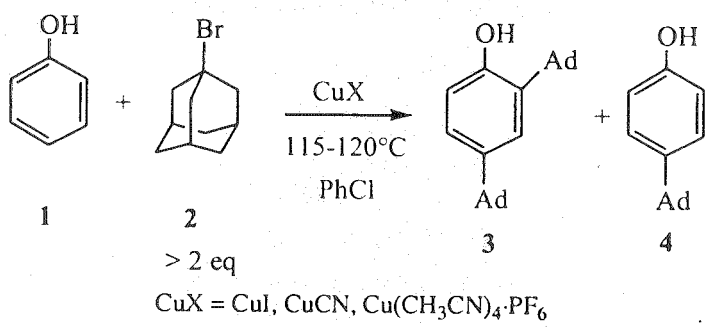

Scheme-1

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are reported in δ values relative to chloroform (δ 7.26 for proton NMR and δ 77.0 for carbon NMR). Infrared spectra were obtained on a Nicolet FTIR-205 spectrometer. All reagents and chemicals used were obtained from the Aldrich and Acros Chemical Companies.

Synthesis of compound 2,4-di(1-adamantyl)phenol (3)

In a stoppered vessel, a mixture of phenol (94.1 mg, 1 mmol), 1-bromoadamantane (516 mg, 2.4 mmol), tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.6 mg, 0.05 mmol) and chlorobenzene (4 mL) was allowed to react under nitrogen and smooth stirring at 115–120°C for 40 h. After cooling to room temperature and exhaust of HBr, the reaction mixture was filtered on a short column of silica gel with elution by petroleum ether. Green by-products, arising from the destruction of the copper catalyst, were retained by silica gel. Removal of solvents afforded a mixture of 4 (major), 3 (minor) and 2 to which was added tetrakis(acetonitrile)copper(I) hexafluorophosphate (93 mg, 0.25 mmol). and chlorobenzene (4 mL). The mixture was allowed to react under the same conditions (115–120°C) for 18 h. After cooling to room temperature, exhaust of HBr and removal of chlorobenzene under vacuum, chromatography on silica gel with elution by petroleum ether afforded 3 in 70% yield. Then elution with petroleum ether : ethyl acetate: 19 : 1 afforded 4 (14%).

Compound 3: R_f: 0.55 (with ethyl acetate : petroleum ether: 20 : 80); m.p.: 205°C; IR (KBr, cm^{-1}): 3498, 2902, 2846, 1605, 1503, 1447, 1342, 1253, 811, 595, 493; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, 1H, J = 2.4 Hz, H_3 phenol), 7.04 (dd, 1H, J = 8.2, 2.4 Hz, H_5 phenol), 6.59 (d, 1H, J = 8.2 Hz, H_6 phenol), 4.60 (s, 1H, OH), 2.14 (pseudo d, 6H, J = 3.0 Hz, 3C$\underline{H}_2$, correlates with C at 40.61 ppm), 2.08 (two broad, 6H, 6C$\underline{H}$, correlates with C at 29.09 and 29.05 ppm), 1.89 (pseudo d, 6H, J = 2.9 Hz, 3C$\underline{H}_2$, correlates with C at 43.47 ppm), 1.84–1.70 (m, 12H, 6C$\underline{H}_2$, correlates with C at 37.09 and 36.84 ppm); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.05 (Cipso, C_1), 143.47 (1C, Cipso, C_4), 135.49 (1C, Cipso, C_2), 123.49 (1C, $\underline{C}H$, C_3), 122.91 (1C, $\underline{C}H$, C_5), 116.20 (1C, $\underline{C}H$, C_6), 43.47 (3C, $\underline{C}H_2$, adamantyl), 40.60 (3C, $\underline{C}H_2$, adamantyl), 37.08 (3C, $\underline{C}H_2$, adamantyl), 36.91 (1C, Cipso, adamantyl), 36.83 (3C, $\underline{C}H_2$, adamantyl), 35.82 (1C, Cipso, adamantyl), 29.08 (3C, $\underline{C}H$, adamantyl), 29.04 (3C, $\underline{C}H$, adamantyl).

Compound 4: R_f: 0.36 (with ethyl acetate : petroleum ether: 20 : 80); m.p.:

187°C; IR (KBr, cm^{-1}): 3321, 2907, 2847, 1613, 1597, 1514, 1447, 1442, 1368, 1246, 1236, 1185, 833, 806, 576, 539; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, 2H, J = 9.8, 2.14 Hz, H_3 phenol), 6.79 (dt, 2H, J = 9.8, 2.14 Hz, H_2 phenol), 4.02 (s, 1H, OH), 2.08 (m, 3H, CH adamantyl), 1.87 (d, 6H, J = 2.7 Hz, CH_2 adamantyl), 1.81–1.70 (m, 6H, CH_2 adamantyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.17 (1C, Cipso, C_1), 143.88 (1C, Cipso, C_4), 126.00 (2C, CH, C_3, C_5), 114.81 (2C, CH, C_2, C_6), 43.37 (3C, CH_2 adamantyl), 36.77 (3C, CH_2 adamantyl), 35.54 (1C, Cipso adamantyl), 28.97 (3C, CH adamantyl).

Conclusion

In summary, adamantylphenol derivatives have been prepared under mild and simple operating conditions. A simple synthesis of 2,4-di(1-adamantyl)phenol (**3**) using mild Lewis acid is described. The tetrakis(acetonitrile)copper(I) hexafluorophosphate has been found a suitable catalyst for this reaction.

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