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P_2O_5-mediated Friedel-Crafts acylation of *activated* arenes with carboxylic acid as acylating agent

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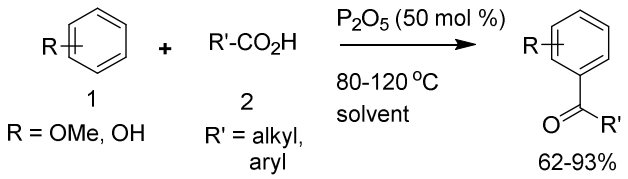
P_2O_5 has been found to be a highly efficient and environmental friendly catalyst for the liquid-phase acylation of *activated* aromatic substrates giving aromatic ketones (45-93%) in a regioselective manner. Both aromatic and aliphatic carboxylic acids can be employed as acylating source. The process is particularly demonstrated at 100 g scale in the case of anisole and acetic acid to produce 4-methoxyacetophenone.

Keywords: Friedel-Crafts acylations, phosphorus pentoxide, carboxylic acid, 4-methoxyacetophenone

Friedel–Crafts acylation (FCA) of aromatics, one of the most fundamental reactions, is used extensively, both in academia and industry, for the synthesis of aromatic ketones, the key intermediates in the production of fine and specialty chemicals, fragrances, pharmaceuticals, flavors, dyestuffs and agrochemicals[1]. Conventionally, the electrophilic acylations of aromatics with sensitive acid chlorides or anhydrides, are catalyzed by soluble Lewis acids (*e.g.* $ZnCl_2$, $AlCl_3$, $TiCl_4$) or strong protic acids (*e.g.* HF, H_2SO_4) generating substantial amount of toxic waste streams, often difficult to dispose of[2]. In recent times, the FCA of arenes with carboxylic acids as acylating agents is attracting attention as they are considered as the potential green acylating agents giving water as the only byproduct, over the traditional procedure involving acid chlorides and anhydrides[3]. In addition, carboxylic acids are stable, less toxic, environment friendly, easy handling and plenty available compounds compared to the conventional acylating agents. In this connection, several catalytic systems such as zeolites, heteropolyacids and their salts,clays, triflates of Tb, Bi, In and Ga, methanesulfonic anhydride, graphite/CH_3SO_3H and $Bi(NTf_2)_3$ have been reported to catalyze FCA using carboxylic acids as acylating agents to overcome the disadvantages associated with the conventional procedure (*e.g.* the use of toxic acid chlorides or anhydrides as acylating agents and excess amount of $AlCl_3$ as Lewis acid)[4]. Recently, P_2O_5/Al_2O_3, P_2O_5/SiO_2 or methanesulfonic anhydride has been developed as a potential reagent system for acylation of aromatcs due to its clean reaction and easy removal from reaction mixture just by simple filtration[5]. However, some of the reported methods have substrate limitation as they work only with deactivated acids. In addition, they suffer from drawbacks such as severe reactor corrosion, environmental pollution hazards, disposal of potential toxic wastes, tedious work up and difficulties in their handling. Therefore, it is desirable to develop an efficient green, useful, cleaner and environment friendly process for the regioselective FCA. Herein, we report an efficient and convenient method for the acylation of *activated* aromatic compounds with carboxylic acids as acylating source in the presence of P_2O_5 in catalytic quantities (Scheme I).

Results and Discussion

The acylation of anisole with acetic acid was selected as a model reaction to examine catalytic performance of P_2O_5. The reaction was carried out using anisole **1a** (1 mmol), AcOH **2a** (2 mmol) and P_2O_5 (20-100 mol%) at various temperatures along



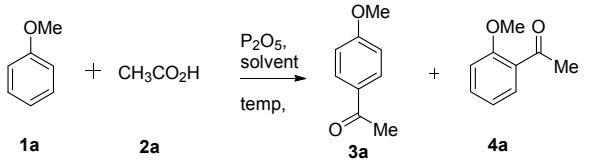
Scheme I — FCA of activated aromatics with carboxylic acids as acylating source

with various solvents. The results are summarized in Table I. When 30 mol% of P_2O_5 was employed at 40°C in dichloromethane, only 10% of 4-methoxyacetophenone (4-MAP) **3a** was obtained. In order to improve the yield, both P_2O_5 catalyst concentration and temperature were increased.

At 50°C, with 50 mol% P_2O_5, and dichloroethane (EDC) as solvent, the acylation process efficiency was significantly improved to give **3a** in 60% yield. Interestingly, on further increase of temperature (80°C), a dramatic improvement in the yield of **3a** (93%) was realized (entry 3). However, lowering the catalyst concentration at the same temperature yielded **3a** in the reduced yield (53%). Also increase of bath temperature (120°C) led to decrease in the yield of 4-MAP (62%) along with 30% of *o*-acylated product **4a** (entry 5). Use of other solvents such as cyclohexane, toluene, THF, CH_3CN or DMF was found to be less suitable for the reaction (yields up to 43% in some cases).

In order to examine the scope and limitation of P_2O_5 catalyzed FCA, reaction of various phenol and anisole derivatives with many carboxylic acids as acylating agents (Table II and Table III) was carried out. For all the cases studied, the acylated products

Table I — P_2O_5-mediated acylation of anisole: optimization studies[a]

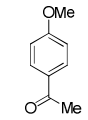
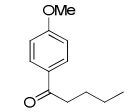
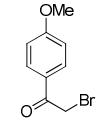
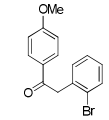
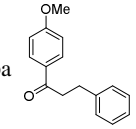
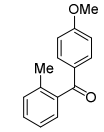
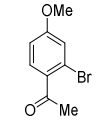
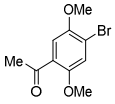
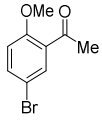
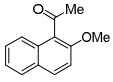


1a **2a** **3a** **4a**

S. N.	P_2O_5 (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b] **3a**	**4a**
1	30	CH_2Cl_2	40	10	10	–
2	50	EDC	50	10	60	–
3	50	EDC	80	8	93	–
4	20	EDC	80	8	53	–
5	50	EDC	120	7	62	30
6	100	EDC	80	8	60	40
7	50	cycloh-exene	85	7	49	–
8	80	THF	80	10	NR[c]	–
9	80	CH_3CN	80	10	10	–
10	80	DMF	80	12	NR	–
11	50	AcOH	120	6	43	–
12	80	AcOH	80	9	30	–
13	50	AcOH	80	9	10	–

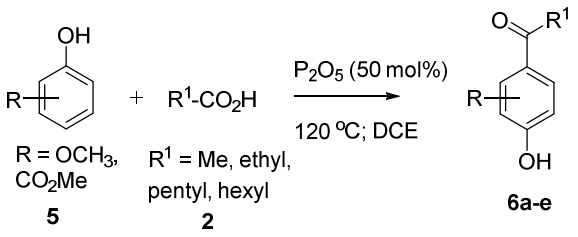
[a] Anisole (1 mmol), acetic acid (2 mmol), solvent (5 mL); [b] Isolated after column purified yields; [c]NR = no reaction.

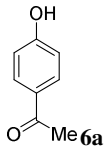
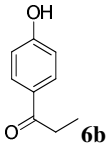
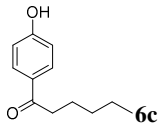
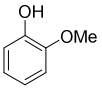
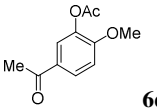
Table II — P_2O_5 mediated acylation of activated aromatics with carboxylic acids: Substrate scope [a]

S.No.	Substrate **1a-e**	Carboxylic acid **2a-f**	Product **3a-j**	Yield (%)
1	Anisole **1a**	Acetic acid **2a**	 **3a**	93
2	Anisole **1a**	Pentanoic acid **2b**	 **3b**	83
3	Anisole **1a**	Bromoacetic acid **2c**	 **3c**	60
4	Anisole **1a**	2-Bromophenylacetic acid **2d**	 **3d**	77
5	Anisole **1a**	3-Phenylpropanoic acid **2e**	 **3e**	62
6	Anisole **1a**	*o*-Toluic acid **2f**	 **3f**	56
7	3-Bromoanisole **1b**	Acetic acid **2a**	 **3g**	61
8	2-Bromo-1,4-dimethoxybenzene **1c**	Acetic acid **2a**	 **3h**	60
9	4-Bromoanisole **1d**	Acetic acid **2a**	 **3i**	60
10	2-Methoxynaphthalene **1e**	Acetic acid **2a**	 **3j**	45

[a] anisole (1 mmol), acetic acid (2 mmol), P_2O_5 (50 mol%), EDC (5 mL), 80°C, 8 h; [b] Isolated yields after column chromatography purification

Table III — P_2O_5-mediated acylation of phenol: optimization studies [a]



S.No.	Phenol	Carboxylic acid (R^1)	Product	Yield [b] (%)
1	**5a** (R=H)	CH_3 **2a**	 **6a**	70
2	**5a** (R=H)	propyl **2h**	 **6b**	77
3	**5a** (R=H)	hexyl **2i**	 **6c**	62
4	 **5b**	CH_3 **2a**	 **6d**	59

[a] Phenol (1 mmol), acetic acid (2 mmol), P_2O_5 (50 mol%), bath temp. 120°C, 12 h, 1,2-dichloroethane (5 mL); [b] Isolated yields after column chromatography purification.

3a-j were indeed obtained in reasonably high yields (45-93%) with excellent regioselectivity. For instance, when reaction of anisole with pentanoic acid **2b** was examined under the optimized condition, *p*-selective acylated product **3b** was obtained in 83% yield. Also, several carboxylic acids such as bromoacetic acid **2c**, 2-bromophenylacetic acid **2d** and 3-phenylpropanoic acid **2e** underwent the reaction with anisole **1a** to give the corresponding *p*-selective acetophenones **3c-e** in good yields (60-77%). Interestingly, the reaction of *o*-toluic acid **2f** with anisole resulted in the formation of *p*-acylated product **3f** in 56% yields, which is quite unprecedented in the literature. Also, anisoles bearing bromo groups (**3g-i**) on the aromatic nucleus underwent acylation successfully giving ketones **3g-i** in good yields (60-61%). Polyaromatic naphthalene also underwent acylation with AcOH under the same reaction conditions giving 1-acylated product **3j** in 45% yield. However, the reaction failed to undergo with less activated substrates such as benzene, toluene, halobenzenes, *etc*. which is a limitation of this process.

Table III shows the results of FCA with phenolic substrates using several carboxylic acids as acylating agents under the optimized conditions. *p*-Selective aromatic ketones **6a-e** were obtained in isolated yields ranging from 54-77%. Phenolic substrates with both electron-donating and withdrawing groups underwent the reaction successfully.

We have achieved a remarkable regioselectivity for the acylation of phenol with acetic acid by varying different reaction conditions. While doing optimization study, it was observed that when we carry out the reaction at higher temperatures with change of solvent, a remarkable reversal in regioselectivity in product formation was realized. Thus, when FCA of phenol with acetic acid as acylating source was carried out at higher temperature (160°C) in 1,2-dicholorobenzene, surprisingly, 2-hydroxyacetopheneone (**7**) was obtained exclusively in 91% yield, possibly due to the formation of phenyl acetate as the intermediate, which undergoes Fries migration to form the *o*-acylated product. This indeed was confirmed by subjecting phenyl acetate to the optimized reaction condition in the absence of acetic acid usingP_2O_5 as the catalyst and heating it to higher temperature (160°C).The results have shown the formation of *o*-hydroxyacetophenone (76%) as the major product along with *p*-hydroxyacetophenone (26%) as the minor product. In addition, the higher selectivity to *ortho* isomer can be realized possibly due to intramolecular H-bonding providing stability to the product. However, *p*-selectivity could be realized producing **6a** in 70% yield when we carry out the reaction at lower temperature (80°C, Scheme II). The mechanism of acylation is not clear although it can be reasonably assumed that the acylating source could be the corresponding acid anhydride that may be formed *in situ* on reaction of P_2O_5 with carboxylic acids.

Finally, as part of our ongoing research in the synthesis of industrially important value added products, we have undertaken the process development studies of anisole acylation towards the production of 4-metoxyacetophenone (4-MAP) in a greener way. 4-MAP is a key intermediate in the production of many pharmaceuticals, agrochemicals,

and other specialty chemicals including their use as ingredients of flavor and fragrance in soaps, detergents, cosmetics and perfumes as well as in foods, beverages and tobacco. The present methodology has been demonstrated at 100 g scale for acylation of anisole, which gave 4-MAP in 100% conversion with 98% *p*-selectivity. The process is eco-friendly and product isolation was made easier by simple distillation leaving behind phosphoric acid as the only byproduct after quenching with water (Scheme III).

Synthetic procedure for 4-MAP

A round-bottomed flask was charged with anisole (103.98 g, 961.5 mmol), glacial acetic acid (275 mL, 4807.5 mmol), P_2O_5 (272.9 g, 961.5 mmol), and EDC (330 mL). The whole mixture was stirred at 80°C for 9 h. The reaction was monitored by TLC and HPLC. On completion, the work-up of reaction mixture was done with addition of CH_2Cl_2 (500 mL) and water (150 mL) followed by organic layer separation to remove traces of phosphoric acid if any. Organic layer was removed under vacuum followed by its distillation to furnish 141.5 g of 4-methoxyacetophenone (97.99% yield).

Experimental Section

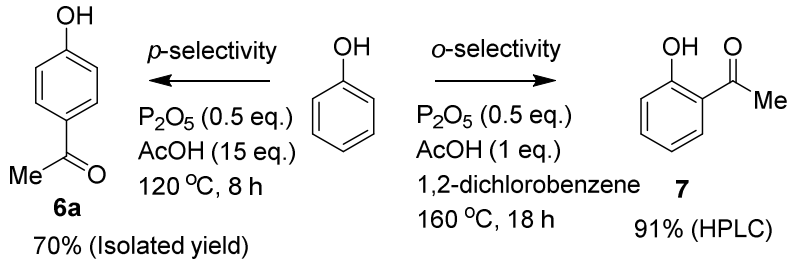
All reactions were carried out under an atmosphere of nitrogen unless otherwise noted. Solvents were purified and dried by standard procedures before use. Column chromatography was performed using silica gel (200-300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-AV (400, 500 and 200 MHz, respectively) instrument internally referenced to tetramethylsilane (TMS) or chloroform signals. The structures of known compounds were further corroborated by comparing their ^{1}H and ^{13}C NMR, and MS data with those of literature values. HR-MS were recorded on a Thermo-Finnigan LCQ Advantage Spectrometer in ESI mode with a spray voltage of 4.8 kV. All chemicals were purchased from Sigma-Aldrich and used without further purification.

Typical procedure for the synthesis of 4-methoxy acetophenone, 3a

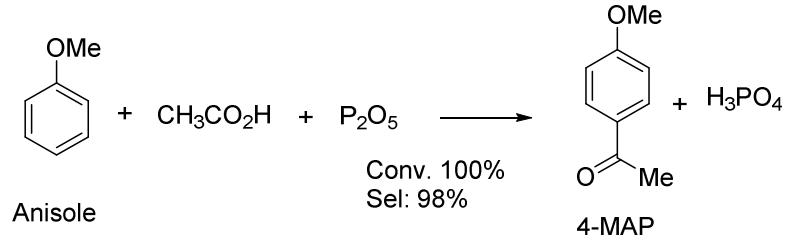
A round-bottomed flask was charged with anisole (500 mg, 4.62 mmol, 1 equiv.), glacial acetic acid (556 mg, 9.26 mmol, 2 equiv.), and P_2O_5 (328 mg, 2.314 mmol), under nitrogen atmosphere and the whole mixture stirred for 8 h at 80°C. The reaction was then monitored by TLC and after the completion of reaction; it was quenched with sodium bicarbonate solution. The work-up of reaction mixture was done CH_2Cl_2 (50 mL) and water (15 mL) to remove traces of phosphoric acid if any. Organic layer was dried over anhyd. Na_2SO_4. Solvent was removed under vacuum distillation to furnish 645 mg of 4-methoxyacetophenone.

Typical procedure for the synthesis of 4-hydroxyacetophenone, 6a

A round-bottomed flask was charged with phenol (500 mg, 5.319 mmol), glacial acetic acid (638 mg, 10.638 mmol), and P_2O_5 (372 mg, 2.659 mmol), and the



Scheme II — Regioselectivity in FCA of phenol with acetic acid over P_2O_5



Scheme III — Acylation of anisole with acetic acid over P_2O_5 at 100 g scale

whole mixture was stirred for 8 h at 120°C**.** The reaction was then monitored by TLC and after the completion of reaction, it was quenched with sodium bicarbonate solution. The usual work-up of reaction mixture was done with CH_2Cl_2 (50 mL) and water (15 mL) to remove traces of phosphoric acid if any. Organic layer was dried over anhyd. Na_2SO_4. The volatiles were removed under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1) to yield the desired product **6a** as off-white solid, 506 mg, yield 70%.

Characterization data of products

1-(4-Methoxyphenyl) ethan-1-one, 3a

Yield 93%. Colorless crystals. m.p.36-37°C[6a]. ^{1}H NMR (200 MHz, $CDCl_3$: δ 7.90 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.53 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 195.1, 162.4, 129.2, 129.4, 112.6, 95.1, 54.2, 25.1; HRMS: Calcd for: $C_9H_{10}O_2$ [M+H]+ *m/z* 151.0717. Found: 151.0716.

1-(4-Methoxyphenyl)pentan-1-one, 3b

Anisole (**1a**, 500 mg, 4.62 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel,petroleum ether/ethyl acetate = 95:5) to give **3b** as yellow liquid, 739 mg. Yield 83.13%. m.p.22-23°C [6a]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.90 (t, *J* = 7.4 Hz, 2 H), 1.70 (quint, *J* = 7.4 Hz, 2 H), 1.31 - 1.49 (m, 2 H), 0.90 - 0.98 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.01, 163.2, 130.2, 113.5, 55.3, 37.9, 26.6, 22.4, 13.8; HRMS: Calcd for: $C_{12}H_{16}O_2$ [M+H]+ *m/z* 193.1226. Found: 193.1223.

2-Bromo-1-(4-methoxyphenyl) ethan-1-one, 3c

Anisole (**1a**, 500 mg, 4.62 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **2b** as white solid, 630 mg. Yield 60%. m.p.73°C[6b]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.1 Hz, 2 H) 6.95 (d, *J* = 8.9 Hz, 2 H) 4.40 (s, 2 H) 3.88 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 189.9, 164.1, 131.3, 126.8, 114.0, 55.5, 30.7; HRMS: Calcd for: $C_9H_9BrO_2$[M+Na]+ *m/z* 250.9700. Found: 250.9677.

2-(2-Bromophenyl)-1-(4-methoxyphenyl) ethan-1-one, 3d

Anisole (**1a**, 500 mg, 4.62 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3d** as white solid, 1080 mg. Yield 77%. m.p.52°C[6c]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (m, *J* = 8.9 Hz, 2 H) 7.63 (d, *J* = 8.2 Hz, 1 H) 7.25 - 7.38 (m, 2 H) 7.12 - 7.24 (m, 1 H) 7.00 (m, *J* = 8.9 Hz, 2 H) 4.45 (s, 2 H) 3.91 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 194.9, 163.6, 135.3, 132.7, 131.6, 130.6, 129.7, 128.6, 127.5, 125.0, 113.8, 55.4, 45.4; HRMS: Calcd for: $C_{15}H_{13}BrO_2$ [M+Na]+ *m/z* 327.0000. Found: 326.9991.

1-(4-Methoxyphenyl)-3-phenylpropan-1-one, 3e

Anisole (**1a**, 500 mg, 4.62 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3e** as white solid, 689 mg. Yield 62%. m.p.96°C[6d]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.9 Hz, 2 H), 7.21 - 7.39 (m, 5 H), 6.97 (d, *J* = 8.9 Hz, 2 H), 3.91 (s, 3 H), 3.24 - 3.35 (m, 2 H), 3.05 - 3.16 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 197.8, 163.5, 141.5, 130.3, 130.0, 128.5, 126.1, 113.8, 55.5, 40.1, 30.4; HRMS: Calcd for: $C_{16}H_{16}O_2$ [M+Na]+ *m/z* 263.1002. Found: 263.1042.

(4-Methoxyphenyl)(*o*-tolyl)methanone, 3f

Anisole (**1a**, 500 mg, 4.62 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3f** as colorless liquid, 585 mg. Yield 56%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2 H), 7.24 - 7.46 (m, 4 H), 6.97 (d, *J* = 8.9 Hz, 2 H), 3.92 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 136.1, 197.3, 163.7, 139.9, 132.5, 130.8, 129.7, 127.9, 125.1, 113.7, 55.5, 19.7; HRMS: Calcd for: $C_{15}H_{14}O_2$ [M+H]+ *m/z* 227.1064. Found: 227.1065.

1-(2-Bromo-4-methoxyphenyl)ethan-1-one, 3g

3-Bromoanisole (**1b**, 500 mg, 2.67 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3g** as colorless, 372 mg. Yield 61%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (br. s., 1 H), 7.16 (br. s., 1 H) 6.88 (br. s., 1 H), 3.85 (br. s., 3 H), 2.63 (br. s., 3 H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 199.1, 161.9, 132.7, 131.6, 121.3, 119.5, 113.1, 55.7, 30.0; HRMS: Calcd for: $C_9H_9BrO_2$ [M+Na]+ *m/z* 250.9700. Found: 250.9677.

1-(3-Bromo-2,5-dimethoxyphenyl)ethan-1-one, 3h

2-Bromo-1,4-dimethoxybenzene (**1c**, 500 mg, 2.30 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3h** as white crystal, 355 mg. Yield 60%. m.p.90°C[6e]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.67 (d, *J* = 2.2 Hz, 1 H), 6.41 (d, *J* = 2.2 Hz, 1 H), 3.80 (d, *J* = 3.0 Hz, 7 H), 2.49 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 201.9, 161.2, 157.8, 125.8, 118.7, 109.0, 98.1, 55.9, 55.7, 31.7; HRMS: Calcd for: $C_{10}H_{11}BrO_3$[M+Na]+ *m/z* 282.9801. Found: 282.9759.

1-(5-Bromo-2-methoxyphenyl)ethan-1-one, 3i

4-Bromoanisole (**1d**, 500 mg, 2.67 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3i** as brown liquid, 367 mg. Yield 60%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 2.7 Hz, 1 H), 7.55 (dd, *J* = 8.8, 2.67 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 3.91 (s, 3 H), 2.61 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 198.3, 157.9, 136.1, 132.9, 129.7, 113.5, 113.1, 55.8, 31.7; HRMS: Calcd for: $C_9H_9BrO_2$ [M+H]+ *m/z* 230.9832. Found: 230.9837.

1-(6-Methoxynaphthalen-2-yl)ethan-1-one, 3j

2-Methoxynaphthalene (**1c**, 500 mg, 3.16 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **3j** as white solid. m.p.58°C, 284 mg. Yield 45%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, *J* = 9.2 Hz, 1 H), 7.83 (d, *J* = 9.4 Hz, 2 H), 7.36 - 7.57 (m, 2 H), 7.29 (d, *J* = 9.1 Hz, 1 H), 3.98 (s, 3 H), 2.70 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.9, 153.9, 131.4, 130.2, 128.7, 128.1, 127.5, 124.9, 123.9, 123.5, 112.7, 56.2, 32.6; HRMS: Calcd for: $C_{13}H_{12}O_2$[M+H]+ *m/z* 223.0726. Found: 223.0728.

1-(4-Hydroxyphenyl)ethan-1-one, 6a

Yield 70%. colorless solid. m.p.109°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 (br. s., 1 H) 2.58 (s, 3 H) 6.92 (d, *J* = 8.8 Hz, 2 H), 7.92 (d, *J* = 8.7 Hz, 2 H): ^{13}C NMR (500 MHz$CDCl_3$): δ 197.9, 160.7, 130.5, 128.8, 114.8, 29.0, 25.6; HRMS: Calcd for: $C_8H_8O_2$[M+H]+ *m/z* 137.0623. Found: 137.0626.

1-(4-Hydroxyphenyl)hexan-1-one, 6c

Phenol (**5a**, 500 mg, 5.31 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **6c** as colorless liquid, 652 mg. m.p.63°C. Yield 62%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90-7.88 (dd, *J* = 8.8 Hz, 2H), 6.90-6.88 (dd, *J* = 8.7 Hz, 2H), 2.93-2.89 (t, *J* = 4.4 Hz, 2H), 1.74-1.71 (m, 2H), 1.36-1.33 (t, *J* = 4.4 Hz, 4H), 0.92-0.88 (t, *J* = 4.4 Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 200.2, 130.9, 115.5, 96.2, 38.3, 31.7, 24.6, 22.6, 14.0; HRMS: Calcd for: $C_{12}H_{16}O_2$ [M+H]+ *m/z* 193.1221. Found: 193.1226.

5-Acetyl-2-methoxyphenyl acetate, 6d

Guiacol (**5b**, 500 mg, 4.03 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **6d** as 494 mg. m.p.66°C. Yield 59%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 - 7.93 (m, 1 H) 7.66 (d, *J* = 1.9 Hz, 1 H) 7.00 (d, *J* = 8.8 Hz, 1 H) 3.89 (s, 3 H) 2.54 (s, 3 H) 2.33 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.97, 168.8, 155.2, 139.6, 130.4, 128.1, 123.2, 111.6, 56.1, 26.3, 20.6; HRMS: Calcd for: $C_{11}H_{12}O_4$ [M+H]+ *m/z* 208.0736. Found: 208.0730.

Methyl 2-hydroxy-5-pentanoylbenzoate, 6e

Methyl salicylate (**5c**, 500 mg, 3.28 mmol) was used as the substrate under the given reaction conditions. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 95:5) to give **6e** as brown solid, 419 mg. Yield 54%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.19 (bs, 1H), 8.47-8.46 (d, 1H), 8.10-8.09 (m, 1H), 7.03-6.99 (d, 1H), 3.99 (s, 3H), 2.95-2.87 (t, 2H), 1.78-1.70 (m, 2H), 1.46-1.38 (m, 2H), 0.98-0.9 (t, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 198.2, 170.2, 165.1, 135.3, 130.9, 128.9, 117.9, 111.9, 52.6, 37.9, 26.5, 22.5, 13.9; HRMS: Calcd for: $C_{13}H_{16}O_4$[M+H]+ *m/z* 237.1126. Found: 237.1120.

Conclusion

We have developed a one-pot process for the preparation of aromatic ketones directly from cheap raw materials like activated aromatic substrates and carboxylic acids as acylating agents over phosphorous pentoxide (P_2O_5). The reaction proceeds to give *p*-selective aromatic ketones in high conversions and 99% *p*-selectivity with a simple product isolation procedure for several cases studied. Surprisingly, in the case of simple phenol, *o*-selectivity could be achieved when the reaction was conducted at high temperatures. The process is particularly

demonstrated at 100 g scale in the case of anisole and acetic acid to produce 4-methoxyacetophenone (97.99% yield). The important advantages of this method include direct use of different carboxylic acids, high regioselectivity, and availability of starting materials, easy work-up and environment friendly.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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