Supporting information for the paper

Electrosynthesis of Phenyl-2-propanone from Benzyl Bromides and Acetic Anhydride in an Unsupported Micro-Flow Cell Electrolysis Process

1. Experimental Details

1.1. Chemical Reagents

The reagents benzylbromide (Aldrich, 99%), 4-bromobenzylbromide (Aldrich, >98%), 4-methylbenzylbromide (Aldrich, 97%), 4-methoxybenzylbromide (Aldrich, >98%), 1-phenylethylbromide (Aldrich, 97%), acetic anhydride (Fisher, >97%), dichloromethane (DCM, Fisher, >99%), MgSO4 (Fisher, >99%) were used without further purification. The solvent used was *N*,*N*-dimethylformamide (DMF, Fluka, 99%, stored over molecular sieve, H_2O ≤0.01%) and was further dried over molecular sieve 3A (Lancaster, 1-2 mm beads) for 72 h prior to use.[1] All solutions were degassed with nitrogen (BOC gases, UK) before cyclic voltammetric measurements and preparative electrolysis.

1.2. Instrumentation

Cyclic voltammetric (CV) experiments were carried out with an Autolab PGSTAT30 system (Eco Chemie, The Netherland) in a conventional three electrode cell in the presence of supporting electrolyte (0.1 M *n*-Bu_4NBF_4). For conventional CV measurements, a Pt disc (diameter 0.5 mm or 3 mm) electrode was used as the working electrode. A Pt wire and silver wire (both diameter 0.1 mm) were used as the counter and the reference electrode, respectively. For microelectrode CV experiments a Pt micro-disc working electrode (diameter 25 μm) was used and a Pt wire and silver wire (both diameter 0.1 mm) were used as the counter and the reference electrode.

A Harvard PHD 2000 syringe pump was used to pump the reaction solution without addition of electrolyte through the micro reactor cell system at controlled flow rate. The cell consisted of two glass plates (3 cm length, 2 cm width, 6 mm thickness) forming the bottom and top with two holes connecting PEEK tubes (I.D. 0.24 mm) which acted as the flow inlet and outlet. Two equally sized Pt foils (4 mm width and 15 mm length, 50 μm thickness, Goodfellow Cambridge Limited, purity 99.99%) were used as working and counter electrodes and PTFE spacers (Bohlender GmbH, Germany) with thicknesses of approximately 120 μm were used to produce a rectangular flow reacting zone (3 mm width and 15 mm length) with a working area of 45 mm^2 and inter-electrode distance of 160 μm, as described recently.[2]

A scale-up experiment by parallel-connecting four equal single cells was also evaluated using acylation reactions of benzyl bromide derivatives with acetic anhydride. Each cell had an individual inlet and outlet. Flow rate was controlled by a syringe pump with four channels. Voltage for each cell was individually controlled by a potentiostat. Examination of flow indicated that each cell had an equal flow rate by measuring volume flow rate.

The electrochemical acylation reaction of a benzyl bromide derivative with acetic anhydride was carried out with controlled potential and in the absence of supporting electrolyte. During typical reaction runs, product samples were collected in a product vial for a duration of 30 minutes, weighted and a known amount of decane was added as an internal standard. Samples were treated with distilled water to remove unreacted acetic anhydride and DMF, the remaining organic material then extracted using dichloromethane, collected and dried over $MgSO_4$. The samples were analysed by GC/MS (Varian 2000) equipped with a capillary column (CP SIL 8, 30 m length, Phenomenex). The GC column temperature was held initially at 70 ^oC for 4 min, ramped at 20 ^oC/min to reach 240 ^oC which was then held for 12 min. All compounds are known and were also characterized on the basis of the agreement of their ^1H NMR data with literature data.

1.3. Characterization of Products

All compounds produced by electrosynthesis are known and have been purified and characterised on the basis of the agreement of their ^{1}H-NMR data with literature data.

Phenyl-2-propanone[3]: ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.16 (3H, s, $COCH_3$), 3.69 (2H, s, $PhCH_2$), 7.20-7.34 (5H, m, Ph). MS: *m/z* (%): 134 (25) [M^+], 119 (10) [$C_8H_7O^+$], 91 (100) [$C_7H_7^+$], 77 (5) [$C_6H_5^+$], 65 (50) [$C_5H_5^+$], 43 (95) [$C_3H_7^+$]. Retention time 8.1 min.

3-Phenyl-2-butanone[4]: ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.40 (3H, d, J 7.0 Hz, $PhCHCH_3$), 2.04 (3H, s, $COCH_3$), 3.72 (1H, q, J 7.0 Hz, PhCH), 7.20-7.30 (5H, m, Ph). MS: *m/z* (%): 148 (10) [M^+], 133 (25) [$C_9H_9O^+$], 105 (100) [$C_8H_9^+$], 91 (8) [$C_7H_7^+$], 77 (35) [$C_6H_5^+$], 43 (35) [$C_3H_7^+$]. Retention time 8.5 min.

p-Tolylacetone[3]: ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.00 (3H, s, $COCH_3$), 2.31 (3H, s, $PhCH_3$), 3.49 (2H, s, $PhCH_2$), 7.11 (4H, d, J 7.9 Hz, Ph). MS: *m/z* (%): 148 (25) [M^+], 105 (100) [$C_8H_9^+$], 91 (10) [$C_7H_7^+$], 77 (30) [$C_6H_5^+$], 43 (30) [$C_3H_7^+$]. Retention time 9.1 min.

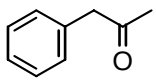
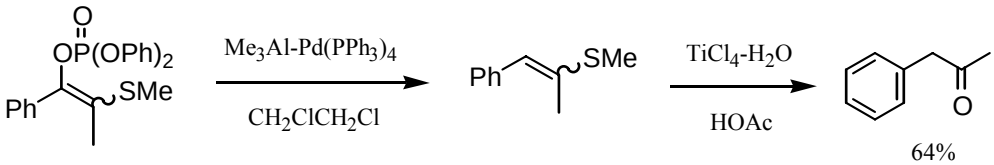
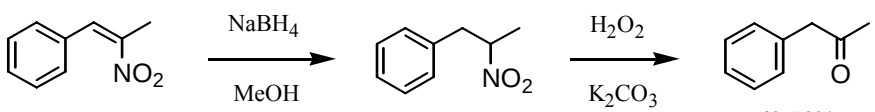
p-Methoxyphenylacetone[3]: ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.02 (3H, s, $COCH_3$), 3.49 (2H, s, $PhCH_2$), 3.79 (3H, s, $PhOCH_3$), 6.78 (2H, d, J 7.9 Hz, Ph), 7.24 (2H, d, J 7.9 Hz, Ph). MS: *m/z* (%): 164 (100) [M^+], 121 (75) [$C_8H_9O^+$], 91 (50) [$C_7H_7^+$], 77 (30) [$C_6H_5^+$], 65 (50) [$C_5H_5^+$], 43 (75) [$C_3H_7^+$]. Retention time 10.1 min.

p-Bromophenylacetone[3]: ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.10 (3H, s, $COCH_3$), 3.56 (2H, s, $PhCH_2$), 7.05 (2H, d, J 8.4 Hz, Ph), 7.44 (2H, d, J 8.4 Hz, Ph). MS: *m/z* (%): 213 (25) [M^+], 170 (30) [$C_7H_6Br^+$], 90 (35) [$C_7H_6^+$], 43 (100) [$C_3H_7^+$]. Retention time 10.5 min.

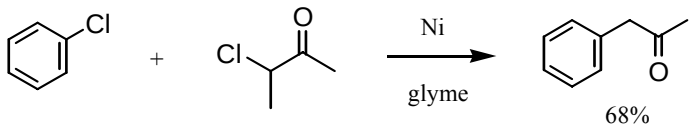
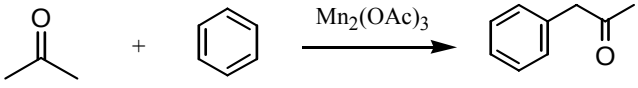
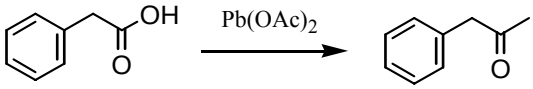
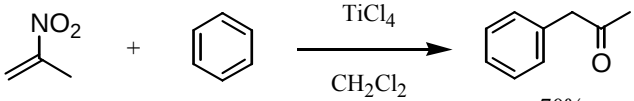
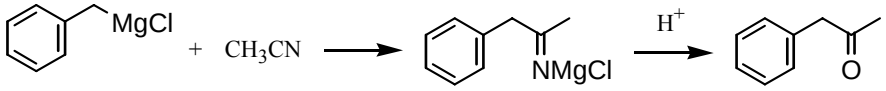
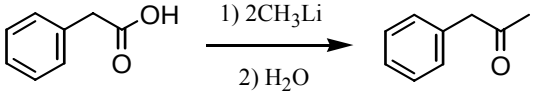
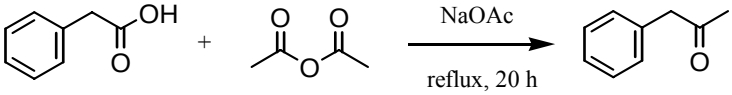
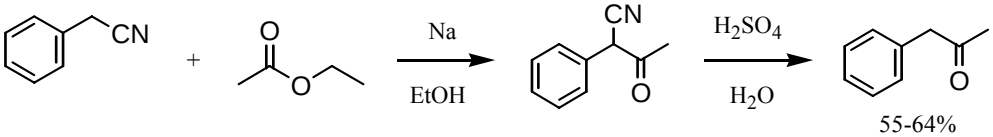
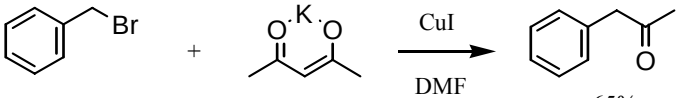
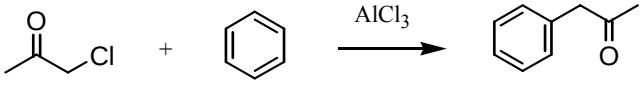
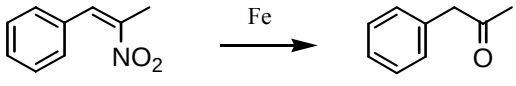
1.4. Additional Information Concerning P2P Synthesis in Literature

Phenyl-2-propanone, commonly referred to as P2P, is probably the most popular intermediate for the manufacture of amphetamine and methamphetamine, and also presumably a versatile intermediate for the synthesis of pharmaceuticals, agrochemicals and fragrances. There are considerable numbers of synthetic routes to producing this compound, due to the relatively simple structure of the compound and because of its common use. Many of the earliest routes have been more or less abandoned due to restrictions on the pre-precursors used to make it, but a number of new methods for making this compound, ranging from simple one-step to elaborate multi-step variants have been developed. Most of P2P syntheses require the presence of a catalyst such as organometallic complexes, metal acetates, metal halides, or Grignard reagent to give overall yields of up to 70 %. However, there is a general need for greener and cleaner methods for example based on atom efficient electrochemical technology. Many of the routes for making P2P described in the literature are outlined in Table 1, and for more synthetic routes see the reference.[5]

Table 1. Syntheses of P2P described in the literature

Route	Reactants and catalysts used	Reference
1	$Bu_3SnOMe + AcOCMe{=}CH_2 \longrightarrow [Bu_3SnCH_2COMe] + AcOMe$ $[Bu_3SnCH_2COMe] + ArBr \xrightarrow{Pd(PPh_3)_4}$  $+ Bu_3SnBr$ 60%	3
2	 $Me_3Al\text{-}Pd(PPh_3)_4$, CH_2ClCH_2Cl; $TiCl_4\text{-}H_2O$, HOAc 64%	5
3	 $NaBH_4$, MeOH; H_2O_2, K_2CO_3 60-70%	6

Continued **Table 1.**

Route	Reactants and catalysts used	Reference
4	 68%	7
5	 40%	8
6	 50%	9
7	 70%	10
8	 40%	11
9	 70%	12
10	 33-56%	13
11	 55-64%	14
12	 65%	15
13	 32%	16
14	 70%	17

1.5. Cyclic Voltammetry Data

1.5.1. The reduction halfwave potentials ($E_{1/2}$) obtained for benzyl bromide derivatives

Conventional cyclic voltammograms for each reactant were obtained at 0.5 mm diameter platinum disc electrode immersed in 0.1 M *n*-Bu_4NBF_4-DMF solution containing 3 mM reactant at scan rate of 1 V/s. The reduction halfwave potentials ($E_{1/2}$) obtained for each reactant are shown in Table 2.

Table 2. The reduction halfwave potentials ($E_{1/2}$) for each reactant obtained at 0.5 mm diameter platinum disc electrode immersed in 0.1 M *n*-Bu_4NBF_4-DMF solution containing 3 mM reactant at scan rate of 1 V/s

Reagent	$E_{1/2}$/V *vs.* Ag	Reagent	$E_{1/2}$/V *vs.* Ag
4-Bromobenzylbromide	-1.73	Benzyl bromide	-1.85
1-Phenylethylbromide	-1.77	4-Methoxybenzylbromide	-1.90
4-Methylbenzylbromide	-1.78	Ferrocene	0.75

In order to determine the overall number of electrons involved in the cathodic processes, CV experiments using a 25 μm diameter Pt micro-disc working electrode were performed in DMF solution containing ferrocene (added as a standard) for each reagent with 0.1 M *n*-Bu_4NBF_4. In this case, the limiting current (I_{lim}) can be expressed using equation (1).

$$I_{lim} = 4nFDCr \qquad (1)$$

In this expression, I_{lim} is the limiting current, n refers to the number of electrons transferred at the electrode, *F* is Faraday constant (96,485 C/mol), *D*, *C* and *r* refer to the diffusion coefficient, the

concentration of reactant in the solution and the radius of the micro-disc electrode. The electrochemical oxidation of ferrocene ($D = 1.0 \times 10^{-9}$ m^2s^{-1})[2] serves as a "calibration" one electron transfer process. The calibrated value of the radius can then be employed for calculation of 'n' when using the measured limiting current of reactant. The calculated 'n' value (see Table 3) clearly confirms two electron processes in all cases.

Table 3. Cyclic voltammetry data obtained in 0.1 M *n*-Bu_4BNF_4-DMF for the reduction of benzyl bromides at a scan rate of 10 mV/s at a 25 µm diameter Pt disc working electrode

Reactant	C_R[a]/molm^3	D[b]/ 10^{-9} m^2s^{-1}	I_{lim-R}[c]/ 10^{-9} A	n_{cal}[d]
Benzyl bromide	3.0	1.0[18]	26.0	1.8
4-Bromobenzylbromide	3.0	1.0[e]	27.0	1.9
1-Phenylethylbromide	3.0	1.0[e]	27.0	1.9
4-Methylbenzylbromide	3.0	1.0[e]	27.5	1.9
4-Methoxybenzylbromide	3.0	1.0[e]	26.5	1.8

[a] C_R is the concentration of the reactant. [b] D refers to the diffusion coefficient. [c] I_{lim-R} is the limiting current of the reactant. [d] The n_{cal} is the calculated number of electrons transferred at the electrode, [e] Assumed to be similar to the value for benzyl bromide.

1.5.2. CV behaviour of benzyl bromide over 3 mm diameter disc Pt, Au and glass carbon working electrode obtained with presence of varied amount of acetic anhydride

CV behaviour of benzyl bromide over 3 mm diameter Pt, Au and glass carbon disc working electrode obtained with presence of varied amount of acetic anhydride are shown in Figure 1A-C.

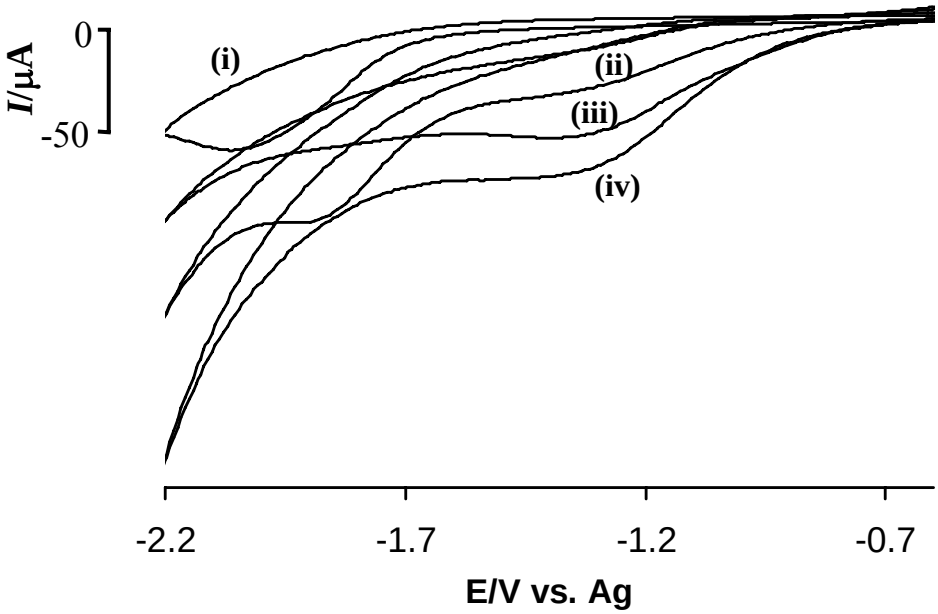


Figure 1A Cyclic voltammograms (scan rate of 100 mVs^{-1}) obtained at a 3 mm diameter Pt disc electrode immersed in 0.1 M *n*-Bu_4NBF_4-DMF for (i) 3 mM benzyl bromide, (ii) 3 mM benzyl bromide in the presence of 15 mM acetic anhydride, (iii) 3 mM benzyl bromide in the presence of 30 mM acetic anhydride, and (iv) 3 mM benzyl bromide in the presence of 60 mM acetic anhydride.

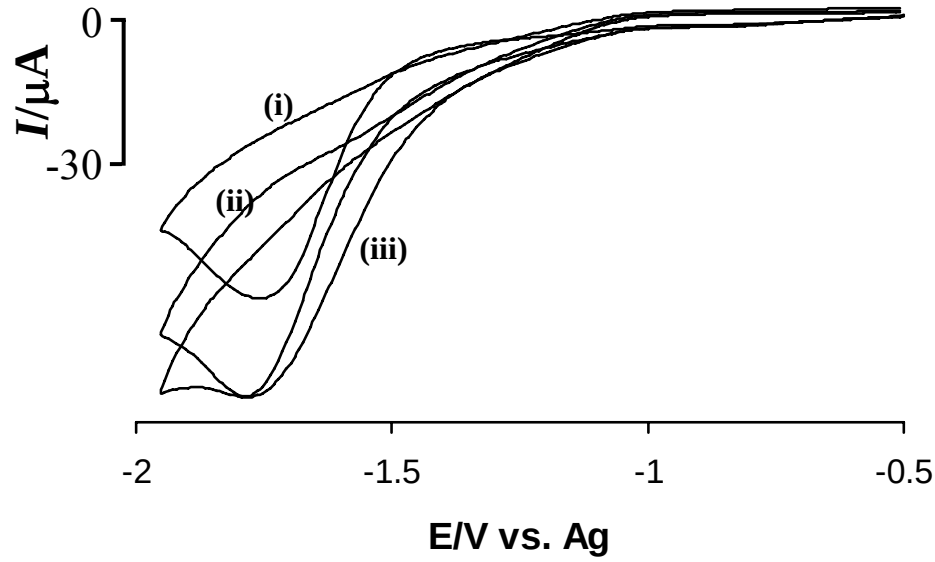


Figure 1B was cyclic voltammograms (scan rate of 100 mVs^{-1}) obtained at a 3 mm diameter Au disc electrode immersed in 0.1 M *n*-Bu_4NBF_4-DMF for (i) 3 mM benzyl bromide, (ii) 3 mM benzyl bromide in the presence of 30 mM acetic anhydride, and (iii) 3 mM benzyl bromide in the presence of 60 mM acetic anhydride.

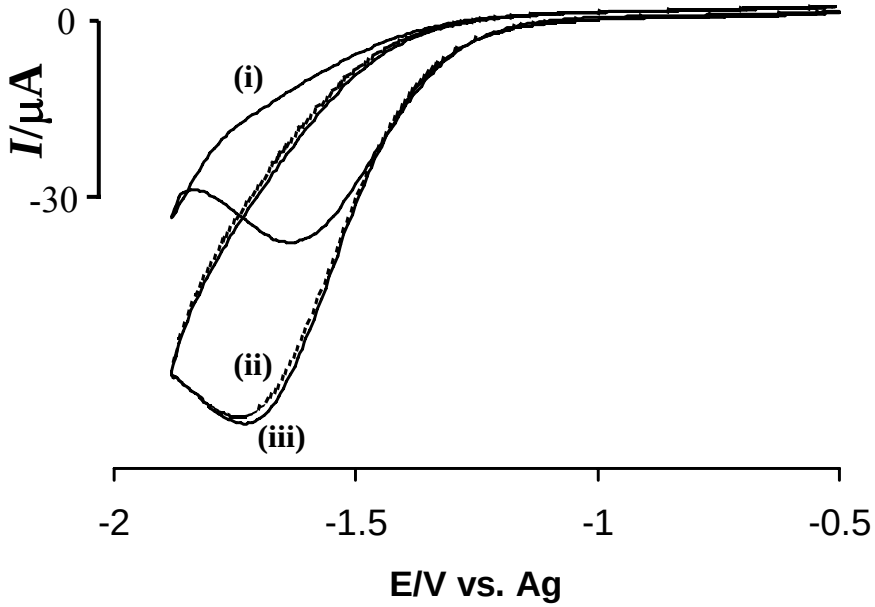


Figure 1C was cyclic voltammograms (scan rate of 100 mVs^{-1}) obtained at a 3 mm diameter GC (glass carbon) disc electrode immersed in 0.1 M *n*-Bu_4NBF_4-DMF for (i) 3 mM benzyl bromide, (ii) 3 mM benzyl bromide in the presence of 30 mM acetic anhydride, and (iii) 3 mM benzyl bromide in the presence of 60 mM acetic anhydride.

1.6. Bromine testing using 5% starch solution

0.75 g of sodium iodide was added to 1 ml of the product mixture. After sodium iodide completely dissolved, 1 ml of 5% starch solution was added to. No characteristic blue-black colour was observed. For comparison, a positive testing was also conducted in which 0.75 g of sodium iodide was added to 1 ml of 5 mM bromine (the same concentration as that to be obtained in the product mixture) in DMF solvent. After sodium iodide completely dissolved, 1 ml of 5% starch solution was added to, the characteristic blue-black colour was quickly observed because bromine oxidized the iodide to iodine which changed starch colour. A negative testing was also carried out under the

same conditions by using sodium bromide replacing bromine. No blue-black colour was observed after adding starch solution.

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