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Facile one-pot preparation of 2-arylpropionic and arylacetic acids from cyanohydrins by treatment with aqueous HI

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ABSTRACT

A novel one-pot two-step procedure has been developed to synthesize highly substituted 2-arylpropionic and arylacetic acids, by treatment with aqueous HI, from cyanohydrins. The hydrogenolytic reduction of α-hydroxy-2-arylpropionic acids was the key step of the process and the optimization of the reaction conditions led to identify aqueous HI as an appropriate and selective reagent for the reductive deoxygenation of cyanohydrins. The synthetic route described a general and efficient strategy for the preparation of large libraries of phenylacetic and phenylpropionic acids derivatives.

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1. Introduction

The CXC chemokine CXCL8 plays a major role in the activation and recruitment of polymorphonuclear cells (PMNs) during the early phase of the inflammatory response.[1] CXCL8 activates PMNs by binding two membrane receptor subtypes, CXCR1 and CXCR2, that belong to the family of seven transmembrane-G-protein coupled receptors. CXCL8 has been proposed to exert a physiopathological role in several human acute and chronic inflammatory diseases including post-ischaemia reperfusion damage, psoriasis and chronic obstructive pulmonary disease.[2] A novel class of small molecular weight CXCL8 inhibitors acting as CXCR1 allosteric modulators was firstly identified in our laboratories and, among these, reparixin (**A**)[3] was selected for clinical investigation. Structure–Activity Relationships in this series of phenylpropionic derivatives were widely investigated leading to the identification of the second generation candidate, meraxin (**B**)[4] with clearly optimized pharmacokinetic properties, Figure 1.

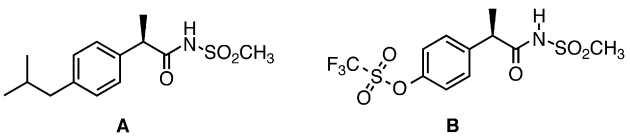
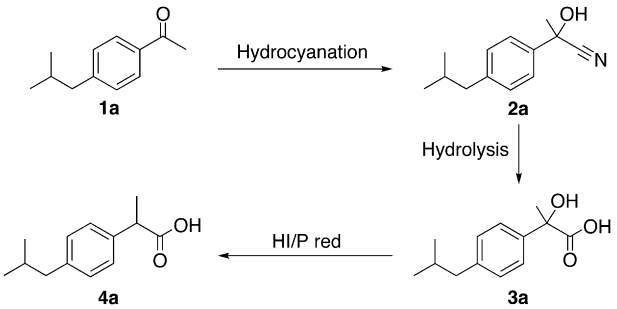


Figure 1. Reparixin (**A**) and meraxin (**B**).

Along this program, a large number of different phenylpropionic acids were synthesized following suited synthetic strategies. A variety of procedures are reported in the literature for the preparation of several phenylpropionic acids ranging from the alkylation of phenyl acetate intermediates to the Willgerodt rearrangement of propiophenones.[5a] However, only a limited amount of work has been made so far to identify a general method for the preparation of wide chemical libraries.[5b]

The synthesis of phenylpropionic acid ibuprofen (**4a**) (Scheme 1), starting from 4-*iso*-butylacetophenone (**1a**) was firstly described by Nicholson and Adams.[6] The key step of the synthesis is the hydrogenolysis of 2-hydroxy-2-(4-*iso*-butylphenyl)-propionic acid (**3a**) by the HI/P_{red} reducing couple. Compound **3a** was obtained in high yields by converting **1a** to the cyanohydrin intermediate **2a** and subsequent acidic hydrolysis. Despite the overall good yields of the process and the large availability of the starting materials, the potential of this synthetic route as a general pathway to the preparation of phenylpropionic acids was not further exploited.



Scheme 1. Synthesis of ibuprofen.

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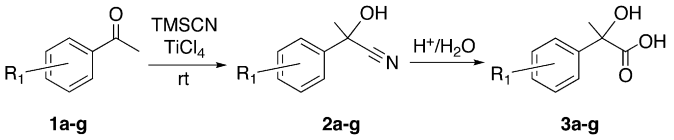
2. Results and discussion

With the aim of exploring the general applicability of this strategy, a representative selection of differently substituted acetophenones (**1a**–**g**) (Scheme 2) were converted to the corresponding cyanohydrins (**2a**–**g**) by reaction with Me_3SiCN in presence of catalytic $TiCl_4$.[7] As predictable, the reaction proceeded in high yields at room temperature with a moderate influence of the substituents on the aromatic ring.



Scheme 2. Synthesis of α-hydroxy-2-arylpropionic acids via cyanohydrins.

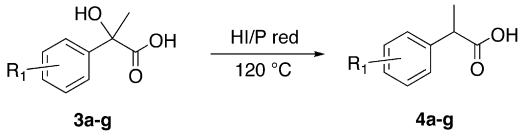
Different reaction conditions (Table 1, entry 1) for the hydrolysis of the cyano group were evaluated in parallel starting from the representative substrate 2-hydroxy-2-(4-*iso*-butylphenyl)propanenitrile (**2a**). The obtained results (Table 1, entry 1, **3a**) clearly indicated HCl 37%/dioxane as the most efficient method that was applied to the whole set leading to the desired α-hydroxy-2-arylpropionic acids in good yields (Table 1, entries 2–7, **3b**–**g**). The overall yield was poorly affected by the concurrent reversal reaction to the ketone starting material that was favoured by EDG substituents on the aromatic ring (Table 1, entries 5 and 6, **3e**,**f**).

Table 1
Catalytic hydrocyanation of acetophenone derivatives and hydrolysis to α-hydroxy-2-arylpropionic acid

Entry	Substituent (R_1)	Time (h)	Ketone (**1**)	Cyanohydrin (**2**) yield[a]	α-Hydroxy-2-aryl propionic acid (**3**), yield[a]
1	4-*iso*-Butyl	16	**1a**	**2a**, 98%	**3a**, —,[b] 10%,[c] 90%[d]
2	H	12	**1b**	**2b**, 92%	**3b**, 80%[d]
3	4-Me	16	**1c**	**2c**, 90%	**3c**, 90%[d]
4	4-CF_3SO_3	12	**1d**	**2d**, 98%	**3d**, 95%[d]
5	4-Cl	16	**1e**	**2e**, 86%	**3e**, 70%[d,e]
6	3-OMe	18	**1f**	**2f**, 68%	**3f**, 60%[d,e]
7	4-CF_3CONH	12	**1g**	**2g**, 95%	**3g**, —,[d] (80%[f])

[a] Isolated yield.
[b] H_2SO_4 aqueous /dioxane.
[c] $Hg(OAc)_2$/AcOH.
[d] HCl 37%/dioxane, reflux.
[e] Ketone was the only by-product.
[f] Trifluoroacetamide group was removed.

In the subsequent phase of this work, the obtained α-hydroxy-acids were treated with aqueous hydriodic acid in the presence of catalytic P_{red} at 120 °C according to the described procedure (Scheme 3).[6]



Scheme 3. HI/P_{red} reduction method.

In agreement with the published results, the reduction of **3a** proceeded in high yields (Table 2, entry 1) and comparable yields were obtained starting from the unsubstituted 2-hydroxy-phenylpropionic acid (entry 2, **3b**), as well as from the 4-methyl substituted analogue (entry 3, **3c**). By contrast, poor yields of the expected arylpropionic acids were achieved by reacting triflate **3d** (Table 2, entry 4) in the above conditions and no significant improvement was obtained by extending the reaction time or increasing/decreasing the reaction temperature. LC–MS analysis of the reaction products revealed that the formation of a complex mixture of organo-phosphorous compounds accounts for the observed low yields.

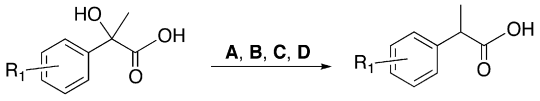
Table 2
Reduction of the α-hydroxy-2-arylpropionic acids by HI/P_{red}

Entry	Substituent (R_1)	α-Hydroxy-2-arylpropionic acid (**3**)	Time (h)	2-Arylpropionic acid (**4**), yield[a]
1	4-*iso*-Butyl	**3a**	24	**4a**, 90%
2	H	**3b**	20	**4b**, 89%
3	4-Me	**3c**	24	**4c**, 91%
4	4-CF_3SO_3	**3d**	48	**4d**, 30%
5	4-Cl	**3e**	24	**4e**, 10%
6	3-OMe	**3f**	24	**4f**, 15%
7	4-NH_2	**3g**	16	**4g**, —

[a] Isolated yield.

Unfortunately, a similar behaviour was observed with other substituted α-hydroxy-2-phenylpropionic acids **3e**, **3f** and **3g** (Table 2, entries 5–7), thus pointing out the poor chemoselectivity of the reaction that strongly limits the usefulness in the preparation of large compounds libraries.

Nevertheless, the good yields of the first two steps of the process, encouraged us to explore alternative methods for the hydrogenolytic removal of the hydroxyl group (Scheme 4).



Scheme 4. Reduction methods.

Reduction with H_2, Pd/C is a suitable method for the hydrogenolysis of benzylic alcohols and the reaction proceeded in good yields starting from the alkyl-substituted derivatives and the unsubstituted α-hydroxy-2-phenylpropionic acid (Table 3, entries 1 and 2, method A). However, the lability of several R_1 substituents in the reaction conditions (Table 3, entries 3 and 4, method A) limits the general applicability of this procedure hampering its use in parallel synthesis. As shown in Table 3 (entries 1–3, method B), a general tendency to degradation without formation of the desired product was observed when α-hydroxy-2-arylpropionic acid was treated with Fe^{2+}/HCl. The $NaBH_4$/TFA reagent was reported[8] to be used for the deoxygenation of monobenzylic alcohols but, in the proposed conditions, substrates of Table 3 showed a marked tendency to decarboxylate leading to the corresponding benzylic trifluoroacetate as the principal reaction product (entries 1–3, method C).

Also Me_3SiCl in the presence of catalytic NaI in CH_3CN was previously used for the hydrogenolytic removal of benzylic alcohols.[9a,b] However, the substrates showed in Table 3 were found poorly reactive in the above conditions and modest yields of the desired products were obtained only if starting from the two electron-rich substrates (Table 3, entries 1 and 5, method D). The intermediate cyanohydrins were also evaluated as alternative substrates for the reduction by Me_3SiCl/NaI but, unfortunately, in these conditions, EDG substituted substrates showed a marked tendency to revert to the starting acetophenones whereas cyanohydrins substituted with EWGs exhibited very poor reactivity with minimal formation of reaction products (data not shown).

Table 3
Reductive removal of hydroxy-benzylic group in different reaction conditions

Entry	R_1	Reduction method	Subs→prod	Time (h)	Products yield[a]
1	4-*iso*-Butyl	A	**3a→4a**	1	95%
		B		12	—
		C		48	Traces[c]
		D		48	20%
2	H	A	**3b→4b**	1	93%
		B		12	—
		C		48	Traces
		D		48	15%
3	4-CF_3SO_3	A	**3d→4d**	1	—, (96%[b])
		B		12	—
		C		48	Traces[c]
		D		48	—
4	4-Cl	A	**3e→4e**	1	—, (98%[b])
5	3-OMe	D	**3f→4f**	48	7%

A=H_2, Pd/C, B=Fe/HCl, C=TFA/$NaBH_4$, D=TMSCl/NaI/MeCN.
[a] Isolated yields of desired product.
[b] R_1=triflate and chlorine groups were completely removed.
[c] The most abundant by-product was the 1-phenylethyl trifluoroacetate derivative.

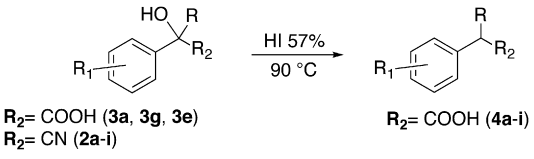
Along this work, the unexpected finding that the reduction of 2-hydroxy-2-(4-*iso*-butylphenyl)propanoic acid (**3a**) by HI proceeded in high yields in the absence of the P_{red} catalyst (Table 4, entry 1) prompted us to further explore the potential of this reducing agent (Scheme 5). Several other α-hydroxy-2-arylpropionic acids were

Table 4
Reduction of α-hydroxy-2-arylpropionic acids and cyanohydrins derivatives by HI 57% aqueous solution

Entry	R[a]/R_1	Substrates	Time (h)	2-Arylpropionic acid (**4**), yield[b]
1	R_1=4-*iso*-Butyl	**3a**	18	**4a**, 92%
2	R_1=4-CF_3SO_3	**3d**	24	**4d**, 96%
3	R_1=4-Cl	**3e**	18	**4e**, 89%
4	R_1=4-*iso*-butyl	**2a**	24	**4a**, 90%
5	R_1=H	**2b**	24	**4b**, 88%
6	R_1=4-Me	**2c**	20	**4c**, 91%
7	R_1=4-CF_3SO_3	**2d**	24	**4d**, 96%
8	R_1=4-Cl	**2e**	12	**4e**, 90%
9	R_1=3-OMe	**2f**	36	**4f**, —, (95%[c])
10	R_1=4-CF_3CONH	**2g**	24	**4g**, —, (78%[d])
11	R_1=4-NO_2	**2h**	18	**4g,** —, (70%[e])
12	R=R_1=H	**2i**	8	**4i**, 95%

[a] R=Me, entries 1–11, R=H, entry 12.
[b] Isolated yield.
[c] Methoxy group was removed.
[d] Trifluoroacetamide group was removed.
[e] Nitro group was reduced to amino group.

treated in these conditions showing a general good reactivity and the final phenylpropionic acids derivatives were recovered in good to excellent yields by a simple work-up and without need of further purification (Table 4, entries 1–3).



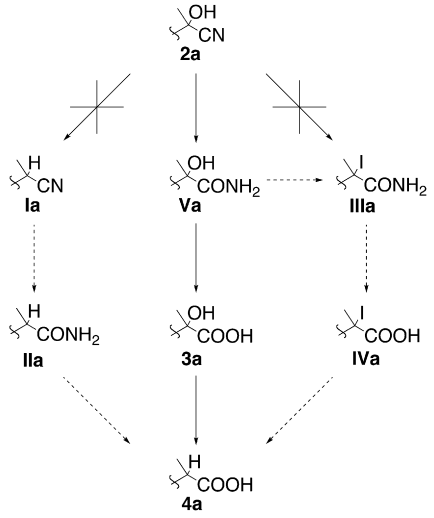
Scheme 5. HI 57% reduction method.

The above results were unexpected based on the available information on the mechanisms of the HI/P_{red} mediated alcohols reduction. Despite the synthetic utility of the reaction (hydrogenation, deoxygenation of alcohols, ketones, ketoacids and quinones, cleavage of phenol ethers and reductive cleavage of lactones),[10–12] the mechanistic aspects were not thoroughly investigated and the role of the P_{red} catalyst still remains unclear. Literature reports agree in considering P_{red} critical for the outcome of the reaction that, in the absence of, leads to very poor yields of the reduction products with predominant formation of iodinated derivatives.[13–15] Few studies have so far addressed the mechanism of this reaction and the commonly accepted pathway hypothesizes the protonation of hydroxyl group (via oxonium ion) evolving, through a carbocationic intermediate by loss of water, to the corresponding iodide that is subsequently reduced by in situ generated H_2.[9,16,17] Hydriodic acid dissociates by a reversible reaction at high temperature (120 °C) to I_2 and H_2, which is the effective reducing reagent and P_{red} plays a key role by consuming the formed I_2 affording hypophosphorous acid thus allowing the equilibrium to shift in favour of the generation of hydrogen.[13–15,18,19]

The results in Table 4 show that the unusual good reactivity of α-hydroxy-2-arylpropionic acids is strictly dependent on the specific chemical features of these substrates.

Treatment of benzylic alcohols in the HI aqueous medium led to the formation of the corresponding benzyliodides with minimal presence of the reduction products. By contrast, reacting under the same conditions the non-benzylic isomer, 2-hydroxy-3-phenylpropanoic acid, neither the deoxygenated nor the iodinated products were detected. This result is in agreement with the nucleophilic substitution pathway that is clearly disfavoured by the EWG effect of the carboxylic group.

To further investigate the specific features of the reaction, cyanohydrin (**2a**) was reacted in HI aqueous 57% and the reaction



Scheme 6. Reduction pathways of cyanohydrin **2a** into **4a** and its potential intermediates by HI 57% aqueous solution.

course was followed by LC–MS analysis (Scheme 6). In fact, neither the formation of the deoxygenated species **Ia** and **IIa** or of the corresponding iodinated derivatives **IIIa** and **IVa** was observed. Among the possible pathways described in Scheme 6, only the route through the observed **Va** and **3a** was found to account for the formation of **4a**.

The absence of iodinated compounds of 2-hydroxy-2-(4-*iso*-butylphenyl)propanenitrile (**2a**) can be associated with the presence of the electron withdrawing CN, $CONH_2$ and COOH groups that reduce the stability of the carbocation intermediate expected to be involved in the reaction pathway. In this respect, the high and specific reactivity of the carboxylic acids to the deoxygenation suggests

a change in the reaction mechanism. Considering the key role of the carboxylic function, a possible interpretation of the obtained results is that the bidentate moiety of the α-hydroxyacid could favour the formation of an intramolecular intermediate complex. The interaction between the acidic function and the iodine atom may reduce the nucleophilic properties of the halogen atom favouring, in presence of a second HI molecule, an internal disproportion with direct insertion of the hydrogen atom at the benzylic position and concomitant water elimination. Further experiments, using different radical scavengers suggest that the HI mediated reduction of 2-hydroxy-phenylalcanoic acids proceed via a radical pathway that does not occur in the presence of the P_{red} catalyst.[20]

Based on the promising results of the reactions in Table 4, we tested the possibility of setting a general process for the direct one-pot two-step conversion of the intermediate cyanohydrins to the final phenylpropionic acids. The obtained yields range from good to excellent and the final products were isolated highly pure after a simple work-up procedure. The reaction showed a good chemoselectivity over different functional groups (Table 4, entries 4–8). Reducible or acid-sensitive methoxy and trifluroacetamide groups (Table 4, entries 9 and 10) or nitro (Table 4, entry 11) are clearly labile in the reaction conditions requiring specific protection/deprotection strategies. It is interesting to observe that also mandelic acids undergo the HI_{aq} reduction to give the corresponding phenylacetic acid in a very high yield (Table 4, entry 12).

3. Conclusion

The hydrogenolytic reduction of α-hydroxy-2-arylpropionic acids is the key step of the process and the optimization of the reaction conditions led to identify aqueous HI as an appropriate and selective reagent for the reductive deoxygenation of these substrates. The high yields and conversion of the process also demonstrate that the reversal formation of cyanohydrins to acetophenones is minimal in HI aqueous medium as compared to all the other conditions previously tested and typically used in the literature.

The obtained results make the described synthetic route as a general and efficient strategy for the preparation of large libraries of phenylacetic and phenylpropionic acids starting from widely available commercial materials.

Specific chemical features of the substrate account for the unusual reactivity and selectivity of the reagent and additional studies are undergoing in order to better explore the potential usefulness of this efficient method for further synthetic applications.

4. Experimental section

4.1. General

The starting compounds **1b**, **1c**, **1e** and **1f** were purchased from commercial suppliers and used without further purification. Dry tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone; dry dichloromethane was distilled from P_2O_5. In all other cases commercially available reagent-grade solvents were employed without purification. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions: 0.25 mm thickness plates precoated with silica gel 60 F_{254}, were used. Silica gel 60 (230–400 mesh) was employed for column flash chromatography. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer: Chemical shifts (δ) for ^{1}H NMR are given in parts per million relative to $(CH_3)_4Si$ (TMS) as an internal standard. Infrared (IR) Spectra were recorded on a Perkin Elmer Spectrum One FTIR with ATR and wavelengths (ν) are reported in cm^{-1}. Elemental analysis was within ±0.4% of the theoretical values calculated for C, H and N and is reported only with symbols. Mass spectra were performed on a GC–MS apparatus (analytical column RTX-5MS) and on an LC–MS system with photodiode-array detector, using 100×2 mm column (C18, 5 μ) with linear gradient 10–90% (v/v) methanol/water with 0.035% TFA with flow rate 0.2 mL/min.

4.2. 1-(4-*iso*-Butylphenyl)ethanone (1a)[21]

To a solution of *iso*-butylbenzene (1.0 g, 7.46 mmol) in dry CH_2Cl_2 (15 mL) acetyl chloride (0.529 mL, 7.46 mmol) was added dropwise, the mixture was cooled to 0–5 °C and $AlCl_3$ (0.99 g, 7.46 mmol) was added portionwise. The resulting mixture was heated to reflux for 5 h. After cooling to room temperature, the mixture was poured into a 1 N HCl/ice solution (20 mL) and stirred for 15 min. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with water (15 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give **1a** as a colourless oil (1.23 g, 93% yield). ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2H, J=7.0 Hz), 7.20 (d, 2H, J=7.0 Hz), 2.60 (s, 3H), 2.50 (d, 2H, J=7.0 Hz), 1.90 (m, 1H), 0.93 (d, 6H, J=7.0 Hz). EIMS m/z 176 (M^+).

4.3. 4-Acetylphenyl trifluoromethanesulfonate (1d)[22]

A solution of 1-(4-hydroxyphenyl)ethanone (1.0 g, 7.35 mmol) in CH_2Cl_2 (0.1 M) was cooled at −15 °C. *i*-Pr_2NEt (1.51 mL, 8.82 mmol) was slowly added and the resulting mixture was stirred for 10 min. Next, trifluoromethanesulfonic anhydride (1.36 mL, 8.09 mmol) was added dropwise and stirring was continued for 2 h. After this time the reaction mixture was warmed to room temperature and washed with a saturated solution of NH_4Cl (2×30 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to afford **1d** as a brown oil (1.55 g, 84%). ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 2H, J=9 Hz), 7.55 (d, 2H, J=9 Hz), 2.65 (s, 3H). EIMS m/z 268 (M^+).

4.4. *N*-(4-Acetylphenyl)-2,2,2-trifluoroacetamide (1g)

To a solution of 1-(4-aminophenyl)ethanone (500 mg, 3.7 mmol) in dry CH_2Cl_2 (40 mL), trifluoroacetic anhydride (0.51 mL, 3.7 mmol) and Et_3N (0.617 mL, 4.5 mmol) were added and the solution was stirred at room temperature for 12 h. After this time the mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer washed with a 10% NaH_2PO_4 buffer (pH 4) (2×15 mL) and water (2×10 mL). After solvent evaporation, the crude compound was purified by flash chromatography (*n*-hexane/EtOAc 85:15) affording product **1g** as a light yellow oil (682 mg, 80%). ^{1}H NMR ($CDCl_3$) δ 8.15 (br s, 1H), 8.10 (d, 2H, J=9 Hz), 7.80 (d, 2H, J=9 Hz), 2.60 (s, 3H). EIMS m/z 231 (M^+). Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 51.91; H, 3.54; N, 6.10.

4.5. General procedure (A) for synthesis of cyanohydrins (Table 1)

To a solution of ketone (1.0 mmol) in CH_2Cl_2 (2.0 mL), TMSCN (1.2 equiv) was added dropwise. Next, $TiCl_4$ (0.2 equiv) was added and the resulting mixture was stirred at room temperature for the time given in Table 1. After the reaction went to completion the solvent was removed under vacuum and the crude mixture was dissolved in (5 mL) of a 1:1 (v/v) solution of acetonitrile and 3 M HCl solution and stirred at room temperature for 1 h. After this time the mixture was concentrated under reduced pressure, diluted with water (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the corresponding cyanohydrin in the yields as listed in Table 1.

*4.5.1. 2-Hydroxy-2-(4-iso-butylphenyl)propanenitrile (**2a**)*

Following the general procedure A and starting from **1a** (1.23 g, 6.94 mmol), **2a** was obtained as a light yellow oil (1.38 g, 98% yield). ^{1}H NMR ($CDCl_3$) δ 7.25–7.15 (m, 4H), 2.49 (d, 2H, J=7.0 Hz), 1.90 (m, 1H), 1.80 (s, 3H), 0.93 (d, 6H, J=7.0 Hz). EIMS m/z 203 (M^+). IR (neat, cm^{-1}) ν: 3400, 2980, 2260, 1410. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.85; H, 8.50; N, 6.93.

*4.5.2. 2-Hydroxy-2-phenylpropanenitrile (**2b**)*[23]

Following the general procedure A and starting from commercially available 1-phenylethanone (1.20 g, 10 mmol), **2b** was obtained as a beige solid (1.35 g, 92%). ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J=7.0 Hz), 7.45 (m, 3H), 2.85 (br s, 1H), 1.91 (s, 3H). EIMS m/z 147 (M^+).

*4.5.3. 2-Hydroxy-2-(4-methylphenyl)propanenitrile (**2c**)*

Following the general procedure A and starting from commercially available 1-(4-methylphenyl)ethanone (1 g, 7.5 mmol), **2c** was obtained as a yellow oil (1.1 g, 90%). ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 4H), 2.40 (s, 3H), 1.90 (s, 3H). EIMS m/z 161 (M^+). IR (neat, cm^{-1}) ν: 3390, 2980, 2250, 1411. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 6.52; N, 8.71.

*4.5.4. 2-Hydroxy-2-(4-{[(trifluoromethyl)sulfonyl]oxy} phenyl)propanenitrile (**2d**)*

Following the general procedure A and starting from **1d** (1.65 g, 6.10 mmol), **2d** was obtained as a light brown oil (1.76 g, 98%). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H, J=9 Hz), 7.25 (d, 2H, J=9 Hz), 2.83 (br s, 1H), 1.90 (s, 3H). EIMS m/z 295 (M^+), 252 (100). IR (neat, cm^{-1}) ν: 3360, 2980, 2240, 1180. Anal. Calcd for $C_{10}H_8F_3NO_4S$: C, 40.68; H, 2.73; N, 4.74. Found: C, 40.80; H, 2.71; N, 4.68.

*4.5.5. 2-Hydroxy-2-(4-chlorophenyl)-propanenitrile (**2e**)*

Following the general procedure A and starting from commercially available 1-(4-chlorophenyl)ethanone (**1e**) (1.50 g, 9.72 mmol), **2e** was obtained as a beige solid after purification by flash chromatography (*n*-hexane/EtOAc 85:15) (1.52 g, 86%). ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2H, J=9 Hz), 7.42 (d, 2H, J=9 Hz), 1.90 (s, 3H). EIMS m/z 181/183 ([$^{35/37}$Cl] M^+). IR (neat, cm^{-1}) ν: 3400, 2980, 2245, 1410. Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.72; H, 4.50; N, 7.81.

*4.5.6. 2-Hydroxy-2-(3-methoxyphenyl)propanenitrile (**2f**)*

Following the general procedure A and starting from commercially available 1-(3-methoxyphenyl)ethanone (**1f**) (1.0 g, 6.66 mmol), **2f** was obtained as a light yellow oil after purification of the crude product by flash chromatography (*n*-hexane/EtOAc 85:15) (801 mg, 68%). ^{1}H NMR ($CDCl_3$) δ 7.25–7.15 (m, 3H), 6.80 (s, 1H), 3.80 (s, 3H), 1.90 (s, 3H). EIMS m/z 177 (M^+). IR (neat, cm^{-1}) ν: 3390, 2950, 2270, 1250. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.80; H, 6.34; N, 7.83.

*4.5.7. N-[4-(1-Cyano-1-hydroxyethyl)phenyl]-2,2,2-trifluoroacetamide (**2g**)*

Following the general procedure A and starting from (**1g**) (682 mg, 2.95 mmol), **2g** was obtained as a colourless oil (723 mg, 95%) and used without further purification. ^{1}H NMR (CD_3OD) δ 11.40 (br s, 1H), 7.80 (d, 2H, J=9 Hz), 7.60 (d, 2H, J=9 Hz), 6.72 (br s, 1H), 1.86 (s, 3H). EIMS m/z 258 (M^+). IR (neat, cm^{-1}) ν: 3420, 2960, 2251, 1670. Anal. Calcd for $C_{11}H_9F_3N_2O_2$: C, 51.17; H, 3.51; N, 10.85. Found: C, 51.07; H, 3.59; N, 10.95.

4.6. General procedure (B) for preparation of α-hydroxy-2-arylpropionic acids, (Table 1)

To a solution of cyanohydrin (1.0 g) in 1,4-dioxane (10 mL), HCl 37% (5 mL) was added and the solution was heated to reflux for 12–24 h. After completion, the solution was concentrated under vacuum, the crude mixture was diluted with water (10 mL) and extracted with EtOAc (3×5 mL), the desired product was extracted with $NaHCO_3$ saturated solution (10 mL), then was gently acidified to pH=2 and extracted with EtOAc (3×5 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the corresponding α-hydroxy-2-arylpropionic acids.

*4.6.1. 2-Hydroxy-2-(4-iso-butylphenyl)propanoic acid (**3a**)*[6]

Following the general procedure B and starting from **2a** (300 mg, 1.49 mmol), **3a** was obtained as a light yellow oil (295 mg, 90%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 2H, J=7 Hz), 7.09 (d, 2H, J=7 Hz), 2.49 (d, 2H, J=7.0 Hz), 1.85 (m, 1H), 1.60 (s, 3H) 0.86 (d, 6H, J=7 Hz). ESI-MS: 221 $(M-H)^-$.

*4.6.2. 2-Hydroxy-2-phenylpropanoic acid (**3b**)*[24]

Following the general procedure B and starting from **2b** (200 mg, 1.36 mmol), **3b** was obtained as a beige solid (180 mg, 80%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.44 (m, 3H), 1.72 (s, 3H). ESI-MS: 165 $(M-H)^-$.

*4.6.3. 2-Hydroxy-2-(4-methylphenyl)propanoic acid (**3c**)*[24]

Following the general procedure B and starting from **2c** (250 mg, 1.5 mmol), **3c** was obtained as a light yellow oil (247 mg, 90%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.25–7.16 (m, 4H), 2.40 (s, 3H), 1.85 (s, 3H). ESI-MS: 179 $(M-H)^-$.

*4.6.4. 2-Hydroxy-2-(4-{[(trifluoromethyl)sulfonyl]oxy} phenyl)propanoic acid (**3d**)*

Following the general procedure B and starting from **2d** (500 mg, 1.69 mmol), **3d** was obtained as a light brown solid (498 mg, 95%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, J=9 Hz), 7.22 (d, 2H, J=9 Hz), 4.70 (br s, 2H), 1.73 (s, 3H). ESI-MS: 313 $(M-H)^-$. IR (neat, cm^{-1}) ν: 3400, 2960, 1710, 1130. Anal. Calcd for $C_{10}H_9F_3O_6S$: C, 38.22; H, 2.89. Found: C, 38.28; H, 2.79.

*4.6.5. 2-Hydroxy-2-(4-chlorophenyl)propanoic acid (**3e**)*[25]

Following the general procedure B and starting from **2e** (300 mg, 1.65 mmol), **3e** was obtained as a beige solid (232 mg, 70%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, J=9 Hz), 7.40 (d, 2H, J=9 Hz), 4.76 (br s, 2H), 1.80 (s, 3H). ESI-MS: 200/202 ([$^{35/37}$Cl] $M-H)^-$.

*4.6.6. 2-Hydroxy-2-(3-methoxyphenyl)propanoic acid (**3f**)*[24]

Following the general procedure B and starting from **2f** (300 mg, 1.65 mmol), **3f** was obtained as a white solid (130 mg, 60%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.25–7.15 (m, 3H), 6.80 (s, 1H), 3.80 (s, 3H), 1.65 (s, 3H). ESI-MS: 195 $(M-H)^-$.

*4.6.7. 2-Hydroxy-2-(4-aminophenyl)propanoic acid hydrochloride (**3g**)*

Following the general procedure B and starting from **2g** (180 mg, 0.74 mmol), **3g** was obtained as a light yellow solid (105 mg, 80%) and used without further purification. Extraction of **3g** was performed at pH=6.0/6.5. ^{1}H NMR (D_2O) δ 7.80 (d, 2H, J=9 Hz), 7.65 (d, 2H, J=9 Hz), 1.79 (s, 3H). ESI-MS: 180 $(M-H)^+$, 182 $(M+H)^-$. IR (neat, cm^{-1}) ν: 3370, 3020, 2930, 1705. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.68; H, 6.14; N, 7.78.

4.7. General procedure (C) for preparation of 2-arylpropionic acid by hydroiodic acid/red phosphorous (Table 2)

Cyanohydrin or α-hydroxyacid derivatives (1.0 mmol) were suspended in 57% aqueous hydroiodic acid (2.0 mL) red

phosphorous (1.5 mmol) was added and the mixture was heated to 120 °C. The progress of the reaction was monitored by LC–MS or TLC. After disappearance of the starting material, the reaction mixture was cooled to room temperature, and $Na_2S_2O_3$ saturated solution (5 mL) was added. The resulting aqueous phase was extracted with EtOAc (3×5 mL). To the combined organic layers, saturated solution of $NaHCO_3$ (10 mL) was added and desired product was extracted. The aqueous phase was gently acidified to pH=2 and extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to give the corresponding 2-arylpropionic acid.

4.8. General procedure (D) for preparation 2-arylpropionic and arylacetic acid by hydroiodic acid 57% aqueous solution (Table 4)

Cyanohydrin or α-hydroxyacid derivatives (1.0 mmol) were suspended in 57% aqueous hydriodic acid (2.0 mL), the mixture was heated at 90 °C and the reaction was monitored by LC–MS or TLC. After disappearance of the starting material, the reaction mixture was cooled to room temperature, and $Na_2S_2O_3$ saturated solution (5 mL) was added. The resulting aqueous phase was extracted with EtOAc (3×5 mL). To the combined organic layers, saturated solution of $NaHCO_3$ (10 mL) was added and desired product was extracted. The aqueous phase was gently acidified to pH=2 and extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to give the corresponding 2-arylpropionic acid.

4.8.1. 2-(4-iso-Butylphenyl)propanoic acid (**4a**)[3,4,6]

Following the general procedure D and starting from **3a** (200 mg, 0.90 mmol), **4a** was obtained as a white solid (171 mg, 92%) and used without further purification. Mp 47–50 °C. ^{1}H NMR (DMSO-d_6) δ 7.35–7.20 (m, 4H), 3.70 (q, 1H, J=7.0 Hz), 2.55 (d, 2H, J=7.0 Hz), 1.80 (m, 1H), 1.45 (d, 3H, J=7.0 Hz), 0.85 (d, 6H, J=7.0 Hz). ESI-MS: 205 $(M-H)^-$.

4.8.2. 2-(4-{[(Trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (**4d**)[3,4]

Following the general procedure D and starting from **3d** (160 mg, 0.54 mmol), **4d** was obtained as a white solid (155 mg, 96%). Mp 53–54 °C. ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2H, J=7 Hz), 7.35 (d, 2H, J=7 Hz), 3.95 (q, 1H, J=7.0 Hz), 1.55 (d, 3H, J=7.0 Hz). ESI-MS: 297 $(M-H)^-$. Anal. Calcd for $C_{10}H_9F_3O_5S$: C, 40.27; H, 3.04; S 10.75. Found: C, 40.88, H, 3.10, S 10.7.

4.8.3. 2-(4-Chlorophenyl)propanoic acid (**4e**)[3,4]

Following the general procedure D and starting from **3e** (150 mg, 0.75 mmol), **4e** was obtained as a white solid (129 mg, 89%). Mp 57–62 °C. ^{1}H NMR ($CDCl_3$) δ 7.35–7.20(m, 4H), 3.70 (q, 1H, J=7.0 Hz), 1.50 (d, 3H, J=7.0 Hz). ESI-MS: 183/185 ($[^{35/37}Cl]$ $M-H)^-$.

4.8.4. 2-(4-iso-Butylphenyl)propanoic acid (**4a**)[3,4]

Following the general procedure D and starting from **2a** (200 mg, 0.98 mmol), **4a** was obtained as a white solid (182 mg, 90%).

4.8.5. 2-Phenylpropanoic acid (**4b**)[3,4]

Following the general procedure D and starting from **2b** (200 mg, 1.2 mmol), **4b** was obtained as a colourless oil (157 mg, 88%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.40–7.20 (m, 5H), 3.8 (q, 1H, J=7.0 Hz), 1.50 (d, 3H, J=7.0 Hz). ESI-MS: 149 $(M-H)^-$.

4.8.6. 2-(4-Methylphenyl)propanoic acid (**4c**)[3,4]

Following the general procedure D and starting from **2c** (200 mg, 1.2 mmol), **4c** was obtained as a white solid (180 mg, 91%). Mp 37–41 °C. ^{1}H NMR ($CDCl_3$) δ 7.25–7.10 (m, 4H), 3.7 (q, 1H, J=7.0 Hz), 2.35 (s, 3H), 1.50 (d, 3H, J=7.0 Hz). ESI-MS: 164 $(M-H)^-$.

4.8.7. 2-(4-{[(Trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (**4d**)[3,4]

Following the general procedure D and starting from **2d** (160 mg, 0.54 mmol), **4d** was obtained as a white solid (155 mg, 96%) and used without further purification.

4.8.8. 2-(4-Chlorophenyl)propanoic acid (**4e**)[3,4]

Following the general procedure D and starting from **2e** (180 mg, 1.0 mmol), **4e** was obtained as a white solid after purification by flash chromatography ($CHCl_3$/MeOH/AcOH 85:15:0.2) (165 mg, 90%).

4.8.9. 2-(3-Hydroxyphenyl)propanoic acid (**4f**)[3,4]

Following the general procedure D and starting from **2f** (150 mg, 0.83 mmol), **4f** was obtained as a glassy solid (130 mg, 95%) and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 1H), 6.70–6.90 (m, 3H), 3.70 (q, 1H, J=7.0 Hz), 1.40 (d, 3H, J=7.0 Hz). ESI-MS: 165 $(M-H)^-$.

4.8.10. 2-(4-Aminophenyl)propanoic acid hydrochloride (**4g**)[3,4]

Following the general procedure D and starting from **2g** (150 mg, 0.58 mmol), **4g** was obtained as a light brown solid for precipitation of its hydrochloride salt after treatment of the organic phase with HCl (1 M) (90 mg, 78%). ^{1}H NMR (D_2O) δ 7.62 (d, 2H, J=7.0 Hz), 7.48 (d, 2H, J=7.0 Hz), 3.98 (q, 1H, J=7.0 Hz), 1.50 (d, 3H, J=7.0 Hz). ESI-MS: 164 $(M-H)^+$, 166 $(M+H)^-$.

Compound **4g** was also prepared starting from 2-(4-nitrophenyl)-2-hydroxypropanenitrile (**2h**) (190 mg, 1.0 mmol) and following the general procedure D to obtain 2-(4-aminophenyl)propanoic acid hydrochloride (**4g**) (140 mg, 70%).

4.8.11. Phenylacetic acid (**4i**)

Following the general procedure and starting from **2i** (133 mg, 1.0 mmol), **4i** was obtained as a colourless oil (130 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 10.75 (br s, 1H), 7.40–7.20 (m, 5H), 3.56 (s, 2H). LC–MS: 135 $(M-H)^-$.

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