Supplementary material:

A reaction database for small molecule pharmaceutical processes integrated with process information

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A. Reaction pathway

A.1 Pathway 1: BHC Ibuprofen synthesis

The reactive pathway is illustrated in Figure A.1:

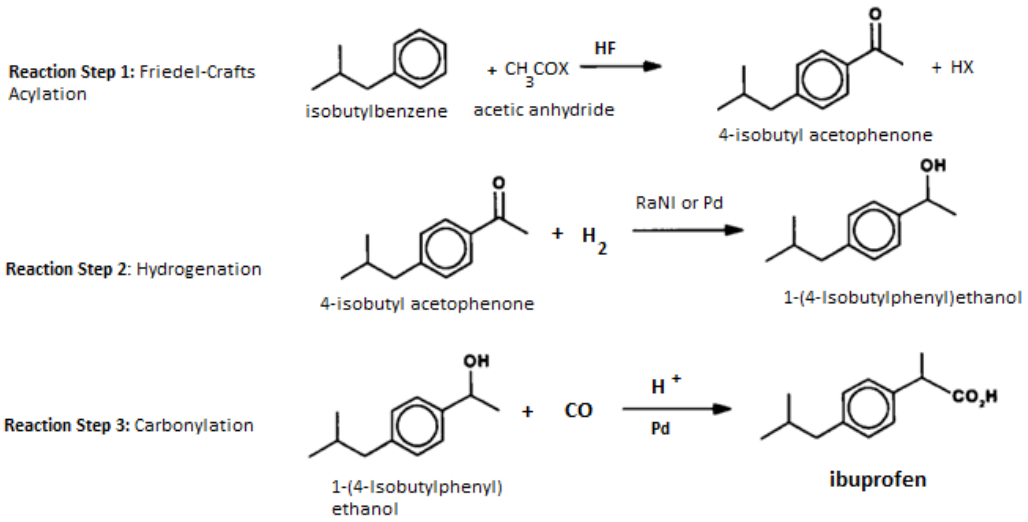

Figure A.1 BHC reaction pathway, obtained from Elango et al.

The reaction information, together with the solvent and catalyst data are given in Table A.1.

Table A.1 Reaction information as retrieved from the database

Reaction information	**Friedel Crafts (batch)**	**Friedel Crafts (flow)**	**Hydrogenation**	**Carbonylation**
Reaction	Isobutylbenze + Acetic anhydride→4 isobutylacetophenone+acetic acid	Isobutylbenze + acetylating agent (AcF+AcAc)→4 isobutylacetophenone+ H2O + HF	4 isobutylacetophenone + H2 → isobutyl phenyl ethanol	isobutyl phenyl ethanol + CO →Ibuprofen
Composition (Reactant A: Reactant B, in moles eq.)	1:2	1:2	1:1	1:1
Solvent	HF	HF	-	-
Catalyst	HF	HF	Rakey Nickel	Pd
By Products	Not reported	Not reported	Isobutyl ethyl benzene	3IPPA;IBS;HE

The reaction conditions for the reactions in BHC ibuprofen synthesis are given in Table A.2:

Table A.2 Reaction Conditions for the reactive steps

Reaction Conditions	**Friedel Crafts (batch)**	**Friedel Crafts (flow)**	**Hydrogenation**	**Carbonylation**
Temperature	80°C	60-70 °C	70 °C	130 °C
Pressure	10 atm	10 atm	6.89 atm	165atm
Time	3hr	2hr	3hr	2.6 hr
Catalyst amount	50eq. HF	50eq. HF	0.3eq. Rakey Nickel	0.007 mol% PdCl2, ligand: 0.08 mol% PPh3
Solvent amount	50eq. HF	50eq. HF	-	-

The available experimental data is given in Table A.3.

Table A.3 Available experimental data as retrieved from the database

Type of Data	**Friedel Crafts (batch)**	**Friedel Crafts (flow)**	**Hydrogenation**	**Carbonylation**
Conversion	85%	77%	>99%	99%
Selectivity(Main Product; By-products)	81%	100%	98.5%; 1.5%(by product)	96.6%; 1.0%; 0.00%; 0.8%
Reaction Yield	-	77%	-	-
Process Yield	-	90%	-	-
Experimental	Starting and end points	Starting and end points	Starting and end points	Starting and end points
Model	no	no	Yes (parameter estimation is needed)	Yes (parameter estimation is needed)

A.1 Pathway 3: Bogdan et al. Ibuprofen Synthesis

The Bogdan Ibuprofen synthesis consist of three reactive steps, the first one is a Friedel Crafts acylation of IBB with propionic acid, the second one is an aryl migration step using TMOF and finally a saponification step to produce the ibuprofen salt.

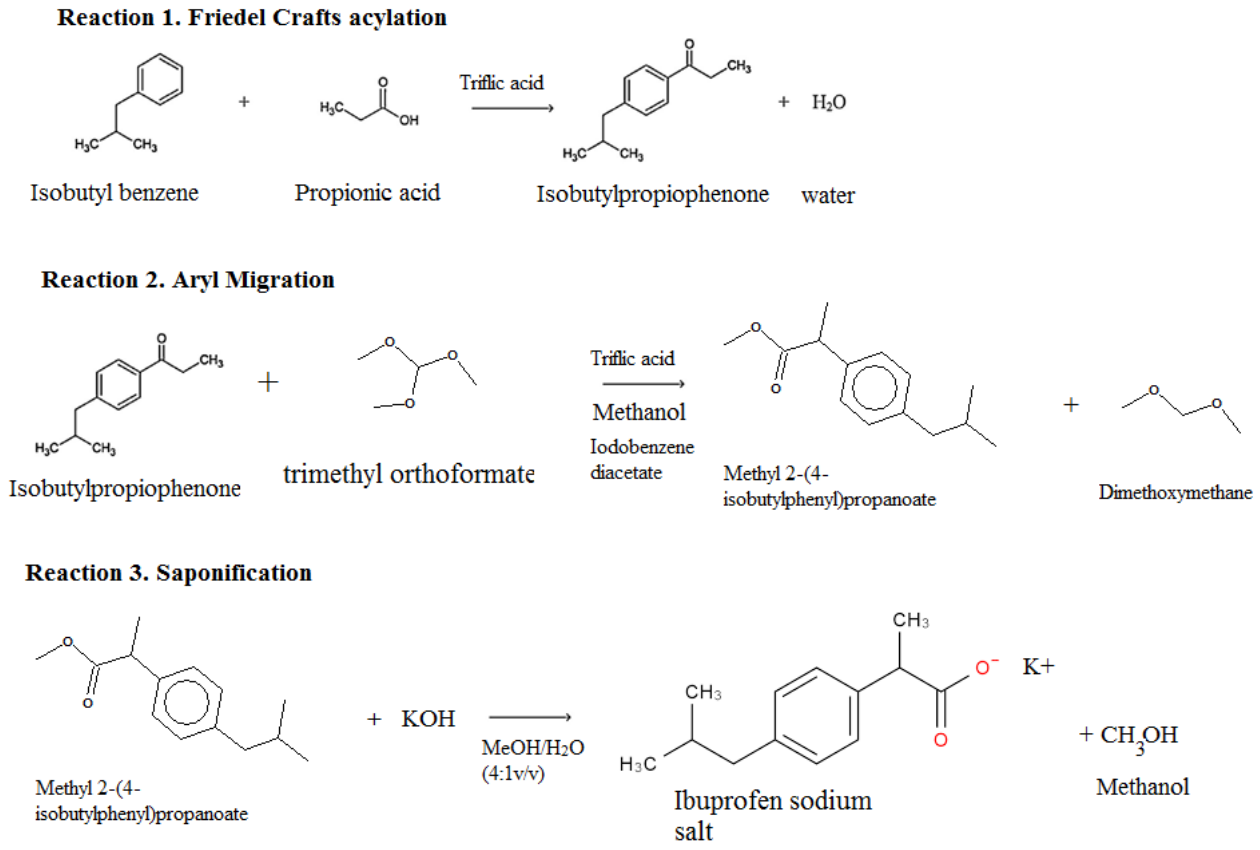

Figure A.2 Bogdan et al reaction pathway for the ibuprofen synthesis, obtained from Bogdan et al.

The reaction conditions for the reaction in Bogdan ibuprofen synthesis are listed in Table A.5.

Table A.4 Reaction information retrieved from the database

Reaction information	Friedel Crafts (flow)	Aryl Migration (flow)	Saponification (flow)
Reaction	Isobutylbenzene + Propionic acid→4'-Isobutylpropiophenone +water	4'-Isobutylpropiophenone + trimethyl orthoformate→Methyl-2-(4-isobutylphenyl)propanoate + Dimethoxymethane	Methyl-2-(4-isobutylphenyl)propanoate + KOH →Ibuprofen-K+ + methanol
Composition (Reactant A: Reactant B, in moles eq.)	1:1	1:4	1:20
Solvent	-	MeOH	MeOH/H2O
Catalyst	Triflic acid	1 eq. Iodobenzene diacetate	-
Acid/Base	5eq. Triflic acid	5eq. Triflic acid	-
By Products	-	-	-

The available experimental data is given in Table A.6.

Table A.5 Reaction Conditions for the three reactive steps

Reaction Conditions	Friedel Crafts (flow)	Aryl Migration (flow)	Saponification (flow)
Temperature	150 °C	50 °C	65 °C
Pressure	1 atm	1 atm	1 atm
Time	10 min	2 min	3 min
Catalyst amount	Triflic acid	1 eq. Iodobenzene diacetate	-
Solvent amount	-	32eq. MeOH	MeOH/H_2O (4:1v/v)

40 The available experimental data is given in Table A.7.

41 **Table A.6** Available experimental data retrieved from the database

Type of Data	Friedel Crafts (flow)	Aryl Migration (flow)	Saponification (flow)
Conversion	92%	98%	99%
Selectivity(Main Product; By-products)	-	-	-
Reaction Yield	-	-	-
Experimental	Steady state data for different tau	Steady state data for different tau	Steady state data for different tau
Model	no	no	no

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