

Electronical Supporting Information (ESI)

Towards a greener synthesis of (S)-3-aminobutanoic acid: Process development and environmental assessment

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Table with material data used for the environmental assessment with the software programmes Umberto/Sabento

Table S1. Material data

<i>Compound</i>	<i>CAS</i>	<i>R-Phrase</i>	<i>S-Phrase</i>	<i>Price^a (17.10.2009)</i>	<i>Amount (supplier)</i>	<i>Price per kg</i>	<i>Density [g/cm³]</i>
(<i>E</i>)-Ethyl but-2-enoate, 1	623-70-1	11-34	16-26-36/37/39-45	5,60 €	0,5 L (Acros)	10,60 €	0,918
Benzylamine, 2	100-46-9	21/22-34	26-36/37/39-45	10,80 €	2,5 L (Acros)	4,40 €	0,981
Methyl <i>tert</i> -butyl ether	1634-04-4	11-38	9-16-24	17,30 €	25,0 L (Acros)	0,93 €	0,74
Ethyl 3-(benzylamino)butanoate, 3	-	-	-	-	-	-	-
Ethanol	64-17-5	11	7-16	15,60 €	25,0 L (Acros)	0,80 €	0,785
Benzyl (<i>R</i>)-3-(benzylamino)butanamide, (<i>R</i>)- 4	-	-	-	-	-	-	-
Benzyl (<i>E</i>)-but-2-enamide, 7	-	-	-	-	-	-	-
CAL-B	9001-62-1	-	-	14,70 €	10 g (Sigma)	1.470,00 €	-
Sodium hydroxide	1310-73-2	35	26-37/39-45	22,80 €	25 kg (Acros)	0,91 €	-
NaOH (1M aq.)	1310-73-2	34	26-37/39-45	12,90 €	10 L (Sigma)	1,29 €	1,04
Pd(C)	-	11-36/37/38	14-22	28,50 €	50 g (Sigma)	570,00 €	-
Sodium (<i>S</i>)-3-(benzylamino)butanoate, (<i>S</i>)- 8	-	-	-	-	-	-	-
(<i>S</i>)-3-Aminobutanoic acid hydrochloride, (<i>S</i>)- 9	58610-41-6	-	-	54,90 €	1 g (Sigma)	54.900,00 €	-
Toluene	108-88-3	11-38-48/20-63-65-67	36/37-46-62	12,60 €	25,0 L (Acros)	0,58 €	0,86
Sodium chloride	7647-14-5	-	-	12,30 €	25 kg (Acros)	0,50 €	-
HCl (1M aq.)	7647-01-0	34-37	24/25	4,20 €	2,5 L (Acros)	1,70 €	1,02
Hydrogen	1333-74-0	12	9-16-33	18,70 €	56 L (Sigma)	37.400,00 €	0,09
Merck-III ion exchanger	-	-	-	61,90 €	5 kg (Merck)	12,90 €	-
2-Propanol	67-63-0	11-36-67	7-16-24/25-26	19,70 €	25 L (Acros)	0,78 €	0,78
Diethylamine	109-89-7	11-20/21/22-35	16-26-29-36/37/39-45	3,50 €	2,5 L (Acros)	1,40 €	0,71
Silica 60 (for column chromatography)	7631-86-9	36/37	12-36/37/39	131,12 €	30 kg (Acros)	4,40 €	1,356
Ammonia solution (0.25M aq.)	1336-21-6	36/37/38	26-36	135,00 €	2 L (Acros)	7,30 €	0,92
Pd(OH) ₂ 10-20% on activated charcoal	-	36/37/38	26-36	59,70 €	50 g (Sigma)	-	-
Dowex-50-WX8 ion exchanger	11119-67-8	36/37/38	26-36	20 €	500 g (Acros)	-	-
(<i>S</i>)-3-Aminobutanoic acid, (<i>S</i>)- 5	541-48-0	36/37/38	26	-	-	-	-

^a Indicated prices are lab chemicals catalogue prices which were divided by a factor of 10 (in analogy to an economic consideration in: M. Beller, A. Zapf, W. Mägerlein, *Chem. Eng. Technol.* **2001**, *24*, 575-582.).

Table with ecotoxicity data used for the environmental assessment with the software programmes Umberto/Sabento

Table 2. Ecotoxicological data

<i>Compound</i>	<i>MAK [g/m³]</i>	<i>Risk symbol</i>	<i>Acute Toxicity [mg/kg]</i>	<i>Impact</i>	<i>Cancer</i>	<i>Mutagenic</i>	<i>Teratogenic</i>	<i>WKG</i>	<i>Impact</i>	<i>Conc.[mg/l]</i>	<i>Degredation (aerob)</i>	<i>Degredation (anaerob)</i>
(<i>E</i>)-Ethyl but-2-enoate, 1	-	F, Xi	3000 (rat)	oral	-	-	-	2	-	-	-	-
Benzylamine, 2	-	C	552 (rat)	oral	-	-	-	1	Daphnia (48h)	60	-	-
Methyl <i>tert</i> -butyl ether	180	F, Xi	4000 (rat)	oral	3	-	-	1	Fish (Pimephales promelas) (96h)	672	28 days	112 days
Ethyl 3-(benzylamino)butanoate, 3	-	-	-	-	-	-	-	-	-	-	-	-
Ethanol	960	F	7060 (rat)	oral	-	-	-	-	Daphnia (48h)	9,3	26 hours	104 hours
Benzyl (<i>R</i>)-3-(benzylamino)butanamide, (<i>R</i>)- 4	-	-	-	-	-	-	-	-	-	-	-	-
Benzyl (<i>E</i>)-but-2-enamide, 7	-	-	-	-	-	-	-	-	-	-	-	-
CAL-B	-	-	-	-	-	-	-	-	-	-	-	-
Sodium hydroxide	-	C	500 (rat)	oral	-	-	-	1	Daphnia (48h)	40,38	-	-
NaOH (1M aq.)	2	C	40 (rat)	oral	-	-	-	1	-	-	-	-
Pd(C)	-	Xi	-	-	-	-	-	0	-	-	-	-
Sodium (<i>S</i>)-3-(benzylamino)butanoate, (<i>S</i>)- 8	-	-	-	-	-	-	-	-	-	-	-	-
(<i>S</i>)-3-Aminobutanoic acid hydrochloride, (<i>S</i>)- 9	-	-	-	-	-	-	-	3	-	-	-	-
Toluene	190	F, Xn	5580 (rat)	oral	3	-	-	2	Daphnia (48h)	8	4 days	8 weeks
Sodium chloride	-	-	3000 (rat)	oral	-	-	-	1	Daphnia (48h)	1661	-	-
HCl (1M aq.)	8	C	2857 (rat)	oral	-	-	-	1	-	-	-	-
Hydrogen	-	F+	-	-	-	-	-	-	-	-	-	-
Merck-III ion exchanger	-	-	-	-	-	-	-	1	-	-	-	-
2-Propanol	500	Xi, F	5045 (rat)	oral	-	-	-	1	Fish (Pimephales promelas) (96h)	9640	168 hours	672 hours
Diethylamine	15	F, C	540 (rat)	oral	-	-	-	1	Daphnia (48h)	56	-	-
Silica 60 (for column chromatography)	-	-	>5000 (rat)	oral	-	-	-	0	Daphnia (48h)	10000	-	-
Ammonia solution (0.25M aq.)	-	C	-	-	-	-	-	1	-	-	-	-
Pd(OH) ₂ 10-20% on activated charcoal	-	Xi	-	-	-	-	-	3	-	-	-	-
Dowex-50-WX8 ion exchanger	-	Xi	-	-	-	-	-	0	-	-	-	-
(<i>S</i>)-3-Aminobutanoic acid, (<i>S</i>)- 5	-	Xi	-	-	-	-	-	3	-	-	-	-

Environmental assessment of the optimized process (this work)

- Extended mass balance

Table S3. Extended mass balance^a of new process

Input	Quantity [kg]	Output	Quantity [kg]
Hydrogen	0.0708	Hydrogen	0.0569
NaOH (0.1M)	0.2531	NaOH (0.1M)	0.2531
NaOH (1M)	2.0632	NaOH (1M)	1.7341
NaOH (2M)	3.9236	NaOH (2M)	3.0506
Methyl <i>tert</i> -Butylether	1.8734	Methyl <i>tert</i> -Butylether	1.8734
CAL-B	0.1898	CAL-B	0.1898
Benzylamine, 2	5.9620	Benzylamine, 2	1.8101
Ethyl (<i>E</i>)-but-2-enoate, 1	2.8860	Ethanol (coupling product)	1.0506
NaHCO ₃	0.3645	Benzyl (<i>R</i>)-3-(benzylamino)butanamide, (<i>R</i>)- 4 (coupling product)	4.0886
HCl (used for work-up, 1M)	10.5696	Toluene (side product)	0.6594
HCl (used for reaction, 1M)	1.5949	Sodium (<i>S</i>)-3-(benzylamino)butanoate (waste, unreacted), (<i>S</i>)- 8	0.2784
Water	11.7721	Benzyl (<i>E</i>)-but-2-enamide (side product), 7	0.3037
		Inorganic salts	2.8328
		HCl (1M)	10.5696
		Water	11.7721
		(<i>S</i>)-3-Amino butanoic acid hydrochloride, (<i>S</i>)- 9	1.0
Total	41.5232	Total	41.5232

^a mass balance calculated by Umberto 5.5 for the hypothetical production of 1 kg (*S*)-3-amino butanoic acid hydrochloride, (*S*)-**9**

Environmental assessment of the original process (published in: M. Weiß, H. Gröger, *Synlett* 2009, 1251-1254)

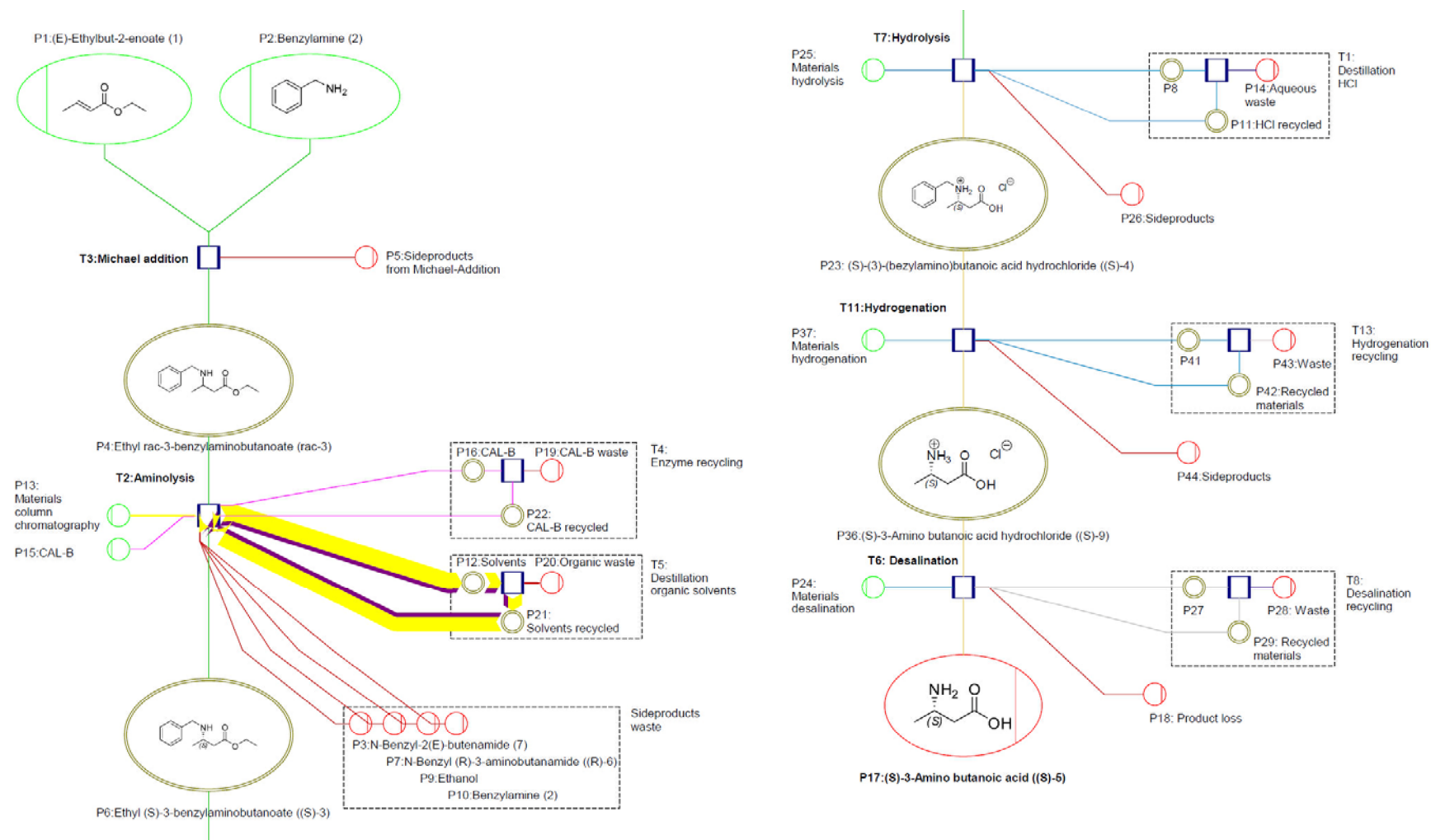
- Extended mass balance

Table S4. Mass balance^a of original process

Input	Quantity [kg]	Output	Quantity [kg]
Hydrogen	0.1124	Hydrogen	0.0903
Ethyl acetate	204.9450	Ethanol	1.6998
2-Propanol	102.4725	Ethylacetate	204.9450
Methyl <i>tert</i> -butyl ether	2.9737	2-Propanol	102.4725
CAL-B	0.3013	Methyl <i>tert</i> -butyl ether	2.9737
Ammonia (1M aq.)	3.3132	(<i>S</i>)-3-Amino butanoic acid hydrochloride, (<i>S</i>)- 9 (unreacted)	0.6365
Benzylamine, 2	9.4636	CAL-B	0.3013
Diethylamine	0.1687	Ammonia (1M aq.)	5.0200
Acetic acid	2.5100	Benzylamine	2.8732
Ethyl (<i>E</i>)-but-2-enoate, 1	4.5811	Diethylamine	0.1687
HCl (aq.)	4.6371	Acetic acid	2.5100
Water	23.9524	Benzyl (<i>R</i>)-3-(benzylamino)butanamide, (<i>R</i>)- 4 (coupling product)	6.4899
		Toluene (side product)	1.3072
		Benzyl (<i>E</i>)-but-2-enamide, 7 (side product)	0.4822
		HCl (aq.)	4.4703
		Water	21.9904
		(<i>S</i>)-3-Amino butanoic acid, (<i>S</i>)- 5	1.0
Total	359.4310	Total	359.4310

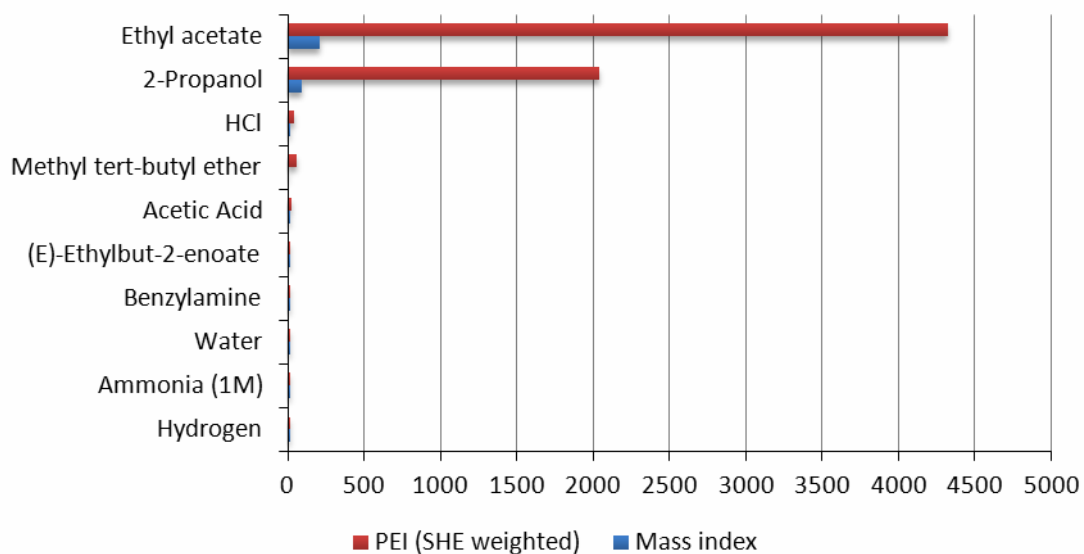
^a mass balance calculated by Umberto 5.5 for the hypothetical production of 1 kg (*S*)-3-amino butanoic acid, (*S*)-**5**; following regeneration rates are assumed for the calculation: organic solvents (90%), organic solvent mixtures (85%), water and aqueous solvents (90%), CAL-B (85%), chemical catalysts (100%), silica (300 g) for column chromatography (100%); 300 g 2-PrOH were assumed for the regeneration of silica (300 g).

- Sankey diagram of the Umberto/Sabento modelling

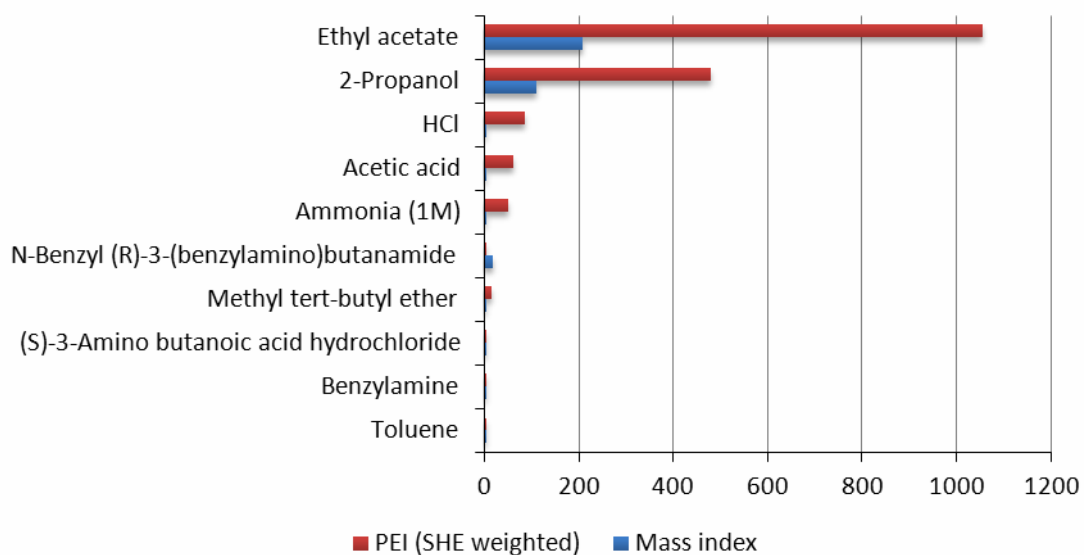


Mass flows are indicated as follows: light blue= HCl (1M aq.), dark blue= water, grey= NaOH (1M aq.), Ammonia (1M aq.), purple= auxiliary materials, yellow= organic solvents, pink= enzyme, green= (organic) material transfer, red= (organic) waste transfer.

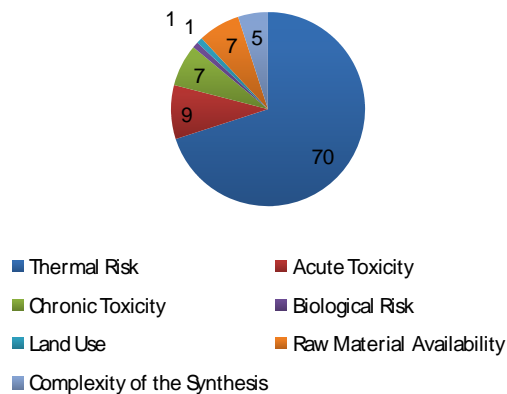
- Mass indices (in Kg) and PEI indices (in PEI/Kg) for the input materials



- Mass indices (in Kg) and PEI indices (in PEI/Kg) for the output materials



- Impact categories (input materials)



- Impact categories (output materials)

