SOLVENT SELECTION

Petr Beňovský

IMPORTANCE OF SOLVENTS

- Reaction medium (transport, combine, separate)
- Dissolution
- (In)solubility
- Kinetics
- Health
- Safety
- Environmental aspects
- Course of the reaction
- Cost (purchase, recycle, dispose)

PERSPECTIVE ON SOLVENT SELECTION

ASPECT	COMMENT
Safety	Avoid solvents that are toxic or highly flammable
Promote high-yielding reactions	Compatible with desired chemistry; Can isolate product in good yield?
Convenient (minimize processing operations)	Isolate product from reaction solvent? Operate at high concentrations?
Water miscibility	Azeotroping ability Control amount of water
Cost of bulk and recoverability	More important at end of development cycle
Environmental	Ethics, and cost of recovery and non-compliance
Long-term availability	
Acceptability for human use	
Water as solvent	But, recovery of product from aqueous layer can be costly, plus cost of disposal
Neat reactions	
Ionic liquids	

SOLVENT SELECTION GUIDES

Almost every company created specific solvent guide

SmithKline Beecham – Curzons, A.D. *et al Clean Products and Processes 1*, 82 (**1999**)

SOLVENT		Waste	Impact	Health	Safety
Alcohols	Ethylene glycol	4	9	8	10
	1-Butanol	5	7	8	8
	Diethylene glycol mono butyl ether	5	8	8	10
	Ethanol / IMS	3	7	9	6
	2-Propanol	3	10	7	7
	Methanol	3	8	4	8
	2-Methoxy ethanol	4	9	2	7
Esters	Butyl acetate	7	7	7	6
	Propyl acetate	7	6	7	6
	Isopropyl acetate	5	7	7	6
	Ethyl acetate	4	9	7	4
	Methyl acetate	2	6	5	5
Aromatics	Xylene	8	4	5	5
	Toluene	7	3	5	4

SOLVENT SELECTION GUIDES

Sanofi – Prat D. *et al Org.Process Res. Dev. 17*, 1517 (**2013**)

Solvents Guide	ETHERS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Diethyl ether	Banned	5000	OEBV2	SHB5	EHB2	Peroxides, VOC
Diisopropyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides
Dibutyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides, odor
THF	Substitution advisable	720	OEBV3 Sk	SHB4	EHB2	VOC, miscible with water, peroxides
Methyl-THF	Recommended	Not listed	OEBV2	SHB4	EHB3	Peroxides, cost
Dioxane	Substitution requested	380	OEBV3 Sk	SHB5	EHB2	Miscible with water, peroxides
Anisole	Recommended	5000	OEBV2	SHB3	EHB2	Odor
MTBE	Substitution advisable	5000	OEBV3 Sk	SHB5	EHB3	VOC
ETBE	Substitution requested	Not listed	OEBV4	SHB5	EHB3	Peroxides, lack of data
CPME	Substitution requested	Not listed	OEBV3	SHB5	EHB3	Peroxides, one supplier only
Dimethoxy ethane	Substitution requested	100	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diglyme	Substitution requested	Not listed	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diethoxymethane	Substitution requested	Not listed	OEBV4	SHB5	Not available	Reactive, considered as CMR

SOLVENT SELECTION GUIDES

- GlaxoSmithKline – Henderson, R.K. *et al Green Chemistry 13*, 854 (**2011**)

Solvent	Cas number	Melting point °C	Boiling Point °C	Waste	Environ-mental Impact	Health	Flamm-ability & Explosio	Reactivity/ Stability	Life Cycle Score	Legislation Flag
Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
t-Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
2-Methyltetrahydrofuran	96-47-9	-137	78	4	5	4	3	6	4	
Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	
Chloroform	67-66-3	-64	61	3	6	3	6	9	6	

SOLVENT CONSIDERATIONS

Watch out hydrocarbon solvents with even number of carbons (toxicity, electrostatic buildup);

Classification of solvents – ICH Harmonised Guideline Q3C – Impurities: Guideline for Residual Solvents

Class 1 – solvents to be avoided (known human carcinogens, strongly suspected human carcinogens, and/or environmental hazards, e.g. carbon tetrachloride (concentration limit 4 ppm), 1,2-dichloroethane (5 ppm), 1,1,1-trichloroethane (1500 ppm), benzene (2 ppm))

Class 2 – solvents to be limited (non-genotoxic animal carcinogens, agents of irreversible toxicity, e.g. acetonitrile (410 ppm), chlorobenzene (360 ppm), chloroform (60 ppm), *N*,*N*-dimethylformamide (880 ppm), hexane (290 ppm), methanol (3000 ppm), *N*-methylpyrrolidone (530 ppm), toluene (890 ppm))

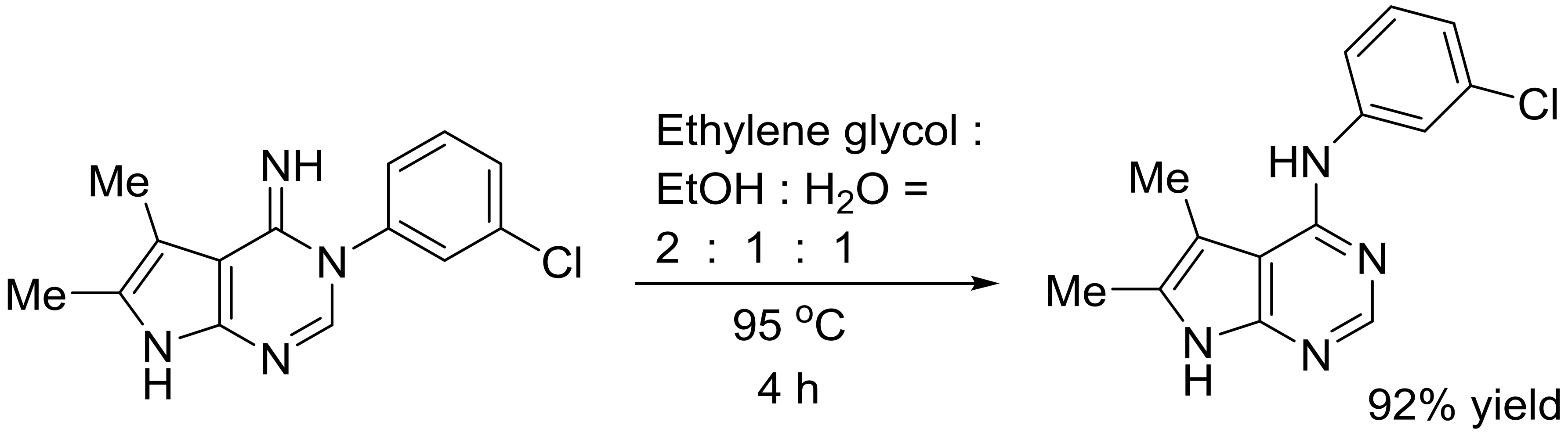
Class 3 – solvents with low toxic potential (permissible daily exposure 50 mg or more per day, e.g. acetic acid, acetone, ethyl acetate, heptane, 2-propanol, triethylamine)

Solvents for which no adequate toxicological data was found – a manufacturer is asked to supply justification for residual levels of these solvents (e.g. diisopropyl ether, petroleum ether, trifluoroacetic acid)

SOLVENT CONSIDERATIONS

The best reaction solvent is the one that crystallizes the product directly from the reaction

Novartis – the Dimroth rearrangement – temperature and solubility turned out to be the most important – the product simply precipitated from the reaction mixture



Fischer, R.W. *Org.Process Res. Dev.5*, 581 (**2001**)

SOLVENT CONSIDERATIONS

Homogeneous vs. Heterogeneous
Reactions using gases
Insolubility is sometimes advantageous (the Schotten-Baumann reaction, the Finkelstein reaction)

Menshutkin (1890)
The reaction rate of the reaction rate of triethylamine with alkyl halides providing quaternary ammonium salts strongly depends on a solvent (hexane **1**, acetone **338**, benzyl alcohol **739**)

Solvents commonly used in **academia** are not often welcomed for **industrial** applications

Safety first !

SOLVENT CONSIDERATIONS

Solvent	TWA (ppm)
Acetone	500
EtOAc	400
MeOH	200
t-BuOH	100
MTBE	50
MeCN	20
DMF	10
Pyridine	1
2-Methoxyethanol	0.1

TWA = Time-Weighted Average shift for five days for nearly for safe exposure over an 8 h shift for five days for nearly all workers

SOLVENT CONSIDERATIONS

Also, always consider physical-chemical properties like

- Flash point
- Flammability
- Boiling point
- Melting point
- Electrostatic charge accumulation
- Recycling potential
- Cost of solvent
- Environmental aspects
- Cost of disposal
- Polarity

SOLVENT CONSIDERATIONS

Solvents **rarely used** in the pharmaceutical industry

Solvent	Disadvantage	Alternative replacement
Diethylether	Flammable	MTBE
Diisopropylether	Peroxide formation	MTBE
Hexane	Electrostatic charge Neurological toxicity	Heptanes, *i*-octane
Chloroform	Mutagenicity, environmental aspects, toxicity	Dichloromethane, 2-MeTHF, toluene
Benzene	Toxicity	Toluene
Ethylene glycol	Toxicity	1,2-Propandiol
Acetonitrile	Animal teratogen, potential acetamide generation (genotoxic)	2-propanol, acetone - water

SOLVENT CONSIDERATIONS

Solvents **preferred** for process development (Pfizer)

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexanes
Ethanol	Toluene	Diisopropyl ether
2-Propanol	Methyl cyclohexane	Diethyl ether
Ethyl acetate	MTBE	Dichloroethane
i-Propyl acetate	*i*-Octane	Dichloromethane
Methanol	2-MeTHF	Chloroform
Methyl ethyl ketone	DMSO	DMF
n-Butanol	AcOH	NMP
t-Butanol	Ethylene glycol	1,4-Dioxane
		Benzene
		Carbon tetrachloride

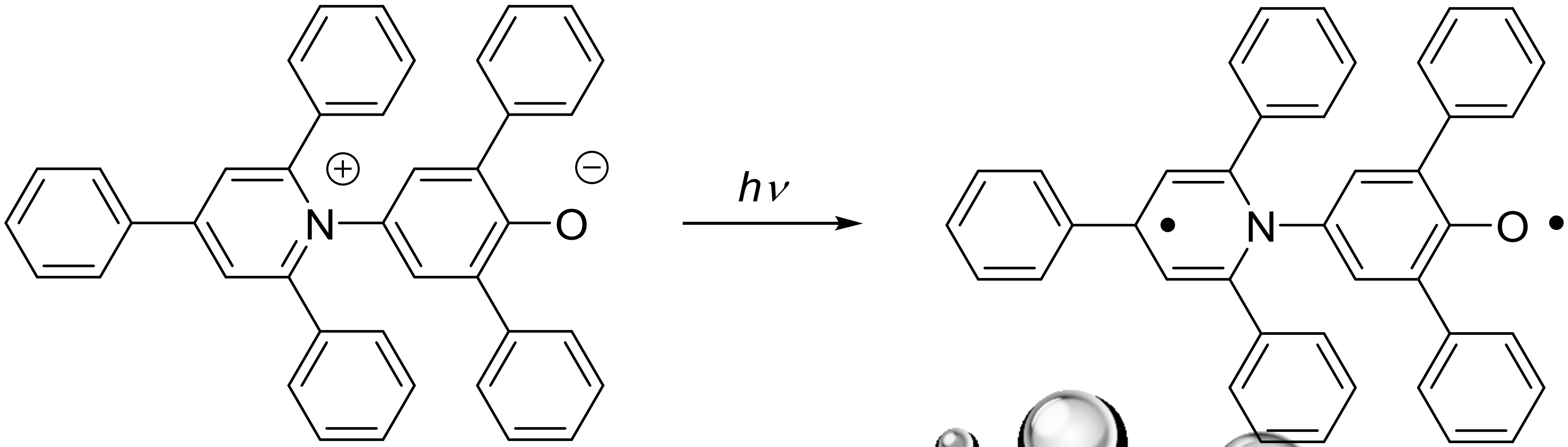
SOLVENT CONSIDERATIONS

Polarity of solvents

Reichardt, C. *Pure Appl.Chem 76*, 1903 (**2004**)

Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry,* 3 rd Ed., Wiley-VCH, **2003**

Hughes-Ingold rules ((de)stabilization of transition state)



SOLVENT CONSIDERATIONS

Polarity of solvents

E_T^N parameter – the negative solvatochromism of the $\pi \rightarrow \pi^*$ shifts of solutions of the betaine dye – more polar solvents stabilize the ground energy of the polar dye, producing thus greater shift in the position of $\pi \rightarrow \pi^*$ absorption relative to that found for solutions of the dye in tetramethylsilane.

Colors of this dye in a solvent are indikative of the polarities of the solvent and solvent combination used to dissolve it.

SOLVENT CONSIDERATIONS

Polarity of solvent

Solvent	Polarity E_T^N	Solubility in water (wt%)	Bp of water-solvent azeotrope	wt% of water removed by azeotrope	ICH solvent class
Water	1.000	-	None	None	
EtOH	0.654	∞	78 °C	4.0	3
AcOH	0.648	∞	77 °C	97	3
DMF	0.404	∞	None	None	2
Acetone	0.355	∞	None	None	3
CH_2Cl_2	0.309	1.3	38 °C	1.5	2
Toluene	0.099	0.06	84 °C	13.5	2
Et_3N	0.043	5.5	75 °C	10	3
Heptane(s)	0.012	0.0004	79 °C	12.9	3
Cyclohexane	0.006	0.006	69 °C	9	2

SOLVENT CONSIDERATIONS

Polarity of solvent mixtures

Solvent	Polarity E_T^N	Solvent mixture	Calculated E_T^N
MeOH	0.762	$EtOH:H_2O$ = 6.9:3.1	0.762
EtOH	0.654	Acetone:H_2O = 4.6:5.4	0.654
$H_2O:CH_2Cl_2$ = 0.2:99.8	0.310	H_2O:MIBK = 1.9:98.1	0.283
$H_2O:CH_2Cl_2$ = 0.2:99.8	0.310	H_2O:EtOAc = 3.3:96.7	0.253
$H_2O:CH_2Cl_2$ = 0.2:99.8	0.310	H_2O:2-MeTHF = 5.3:94.7	0.223
i-PrOAc	0.210	Heptanes:EtOAc = 0.8:9.2	0.210
MeOH:H_2O = 7:1	0.792	EtOH:H_2O = 5:3	0.783

SOLVENT CONSIDERATIONS

Tendency of solvents to form **azeotropes with water** is considered advantageous (it is not practical and economical to dry solvents using drying agents on large scale);
Be careful – dependence on pressure (**breaking the azeotrope**)

Effect of reducing distillation pressure on EtOAc – water:

Pressure (mm)	Bp (°C)	Water in azeotrope (wt%)
760	70.4	8.5
250	42.6	6.3
25	1.9	3.6

IMPURITIES IN SOLVENTS

- Absolute solvents are rather expensive, common solvents contains some amount of water, for certain operations they should be dried (azeotropic distillation, molecular sieves, use of an excess of cheap reagent);

  Denatured solvents (ethanol)

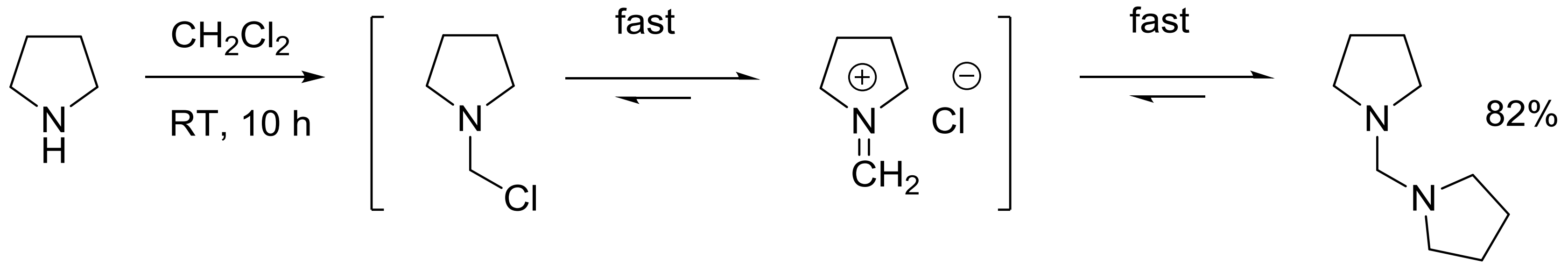
  Stabilizers (e.g. BHT in THF)

  Tendency to form (hydrogen)peroxides (diisopropyl ether, butadiene, acetaldehyde, 1,4-dioxane, styrene, acrylonitrile, 2-butanol, benzyl alcohol, THF, MIBK, 2-propyl alcohol)

IMPURITIES IN SOLVENTS

- Degradation of solvents (ethyl acetate, DMF)

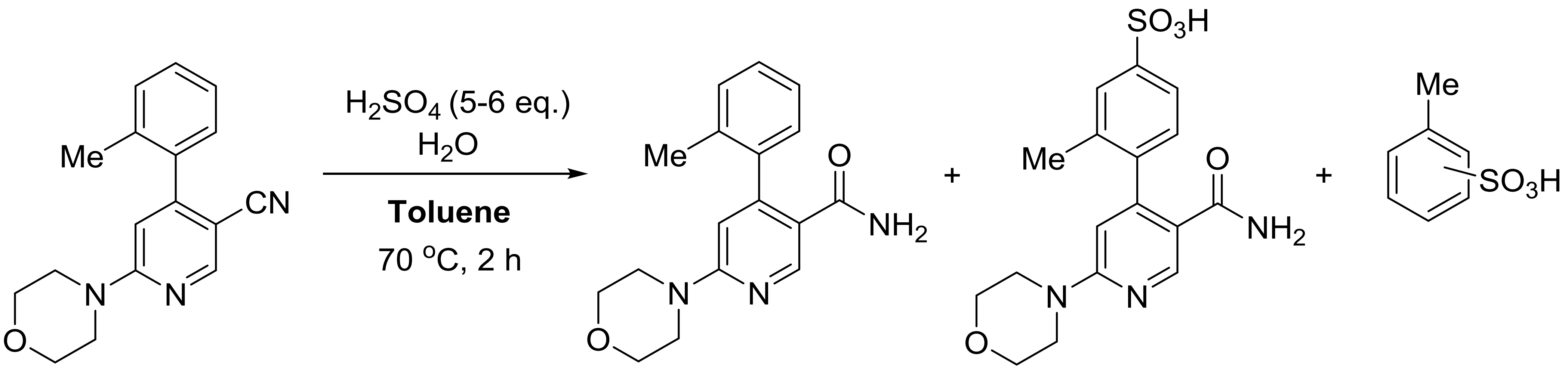
Side reactions (reesterifications, reaction with dichloromethane)



Avoid unwanted formation of esters of sulfonic acids (potentially mutagenic)

SACRIFICIAL SOLVENTS

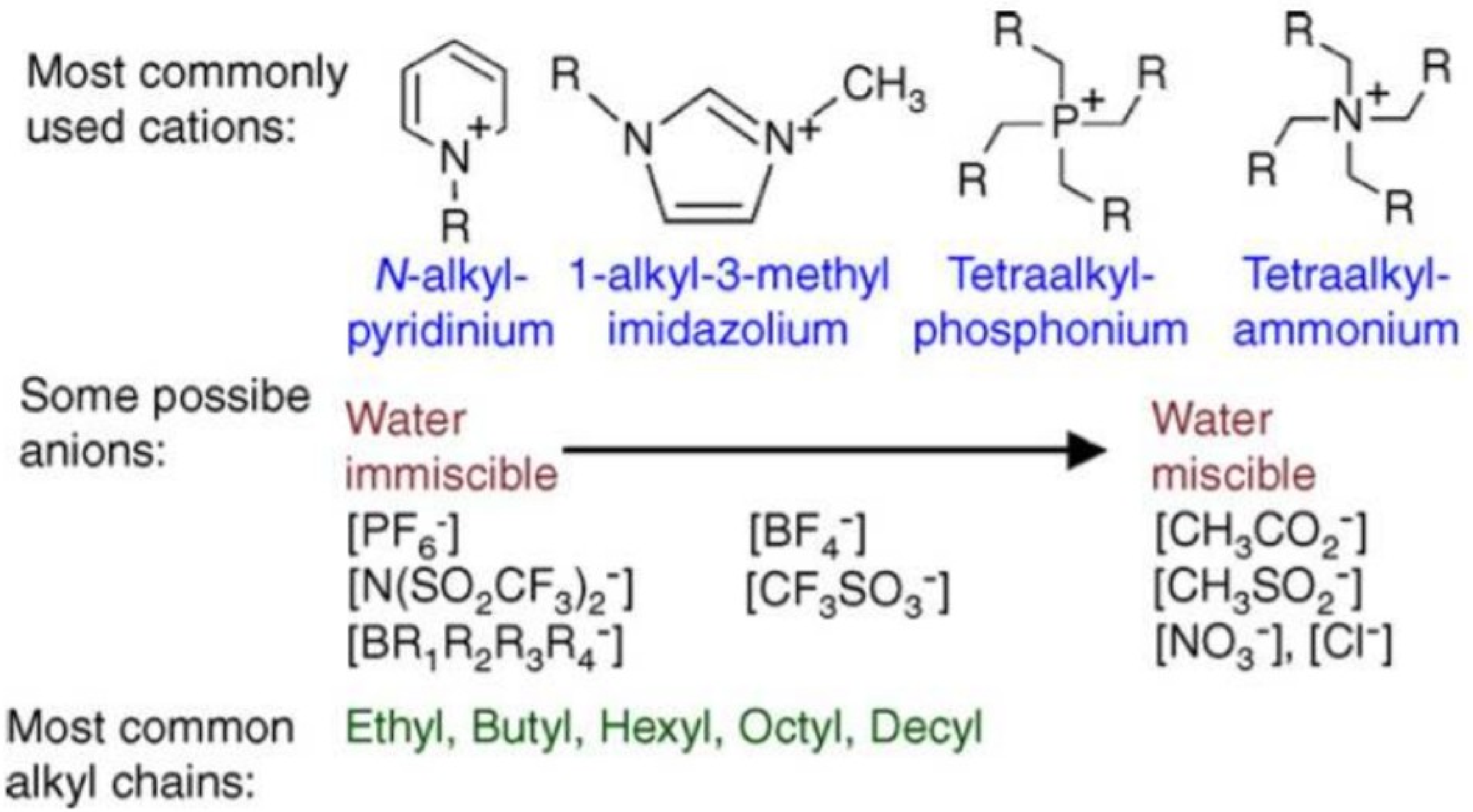
About 50 eq. of 98% H_2SO_4 at 50 ^oC for 3 h followed by an aqueous quench provided ring sulfonation in the product;
5-6 eq. of 98% H_2SO_4 in toluene at 70 ^oC for 2 h – sulfonation of the product was significantly diminished.



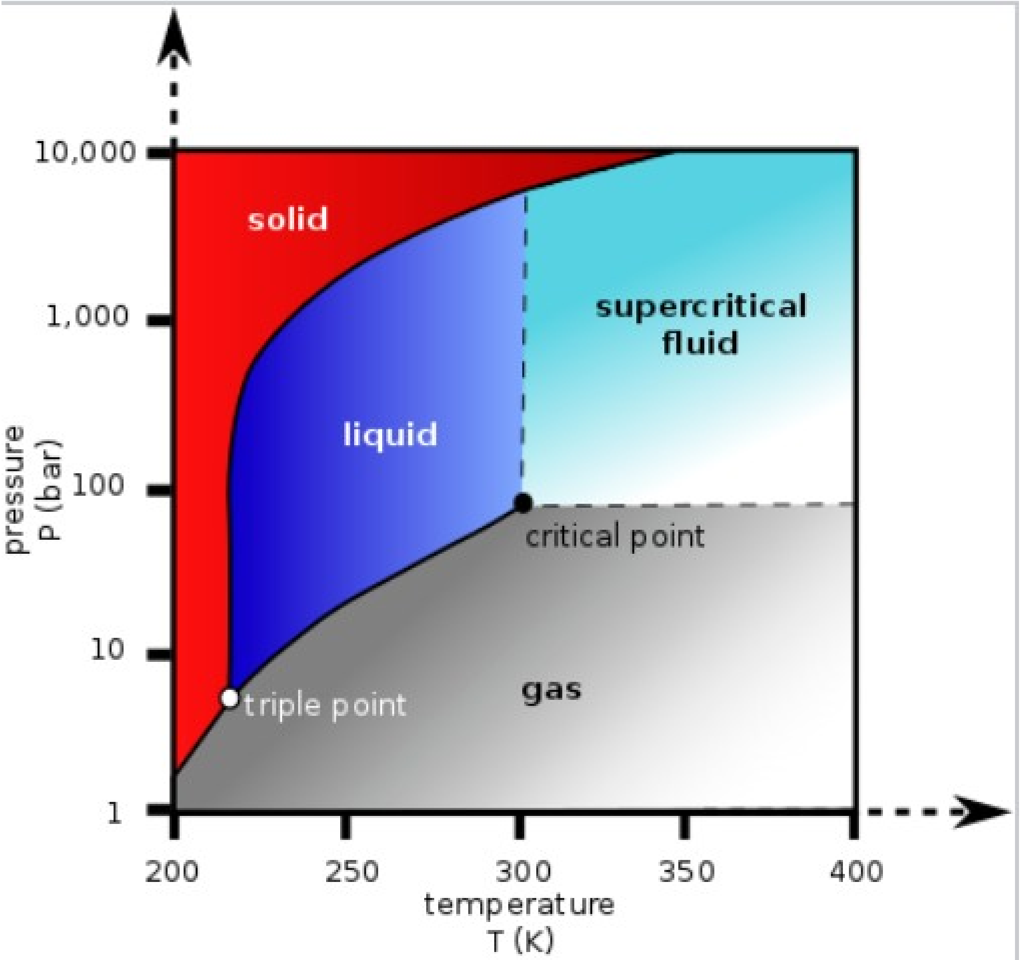
Harrington, P.J. *et al Org. Process Res. Dev. 10*, 1157 (**2006**)

IONIC LIQUIDS

- Ionic liquids are ionic compounds (salts) which are liquid below 100 °C. More commonly, ionic liquids have melting points below room temperature.



SUPERCRITICAL CARBON DIOXIDE



Peach, J.; Eastoe, J. *Beilstein J.Org.Chem. 10*, 1878 (**2014**)
Beckman, E.J. *J.Supercritical Fluids 28*, 121 (**2004**)