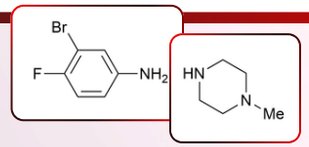
Amide Couplings in the Pharmaceutical Industry

ReactWise
AI Co-pilot for chemical process optimization

Amine

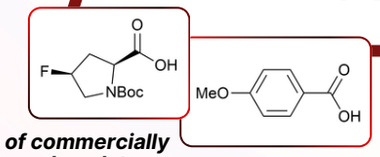
- *In the synthesis of pharmaceuticals,* ***N-heterocycles and amino acid-derived fragments*** *are common amine substrates*
- *Amide couplings can be used for* ***various other N-nucleophiles*** *as well as amines, including* ***hydroxylamines, hydrazines, carbamates and sulfonamides***



Examples of commercially available N-nucleophiles

Carboxylate

- *As with the amine,* ***amino acid-derived fragments*** *are frequently used as carboxylate coupling partners*
- ***Aryl carboxylic acids*** *are also common*
- *Carboxylates with* ***α-stereocentres may undergo racemisation*** *with strong base or activating agent*



Examples of commercially available carboxylates

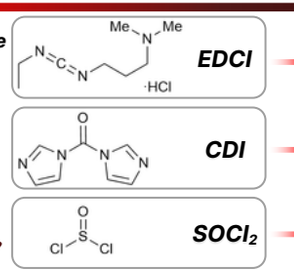
Coupling Agent

- ***Numerous (>30) coupling agents*** *have been employed on large-scale, though the* ***vast majority of couplings use one of nine coupling agents***
- ***EDCI, CDI and $SOCl_2$ are the most popular*** *coupling agents on large-scale*

Coupling Agents		
EDCI	CDI	$SOCl_2$
$(COCl)_2$	T3P	DCC
PivCl	HATU	IBCF

- *Coupling agent choice is a function of* ***cost and ease of downstream processing****, as well as reactivity*

Expensive ↓ *Cheap*



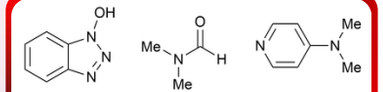
EDCI → ***Expensive but easy to use and mild***

CDI → ***Moisture sensitive, releases CO_2***

$SOCl_2$ → ***Cheap but reacts vigorously, releases HCl, requires stepwise procedure***

Additives

Most common additives used in amide couplings



HOBt ***DMF*** ***DMAP***

- ***Additives*** *are not necessary for amide couplings but lead to* ***increased reaction rates and suppressed side reactions****, which include α-stereocentre racemisation and oxazolone formation*
- *Their use* ***varies dramatically from catalytic to superstoichiometric*** *ratios (0.01 – 1.4 equivalents)*

Additive	Used with coupling agent
HOBt	EDCI, DCC, DIC
DMF	$SOCl_2$, $(COCl)_2$
DMAP	HATU, EDCI, CDI, DCC, PivCl, $(COCl)_2$

Typical Conditions

Temperature
-10 to 40 °C

Concentration
0.2 M or greater

Base Equivalents
1.5 to 3.5

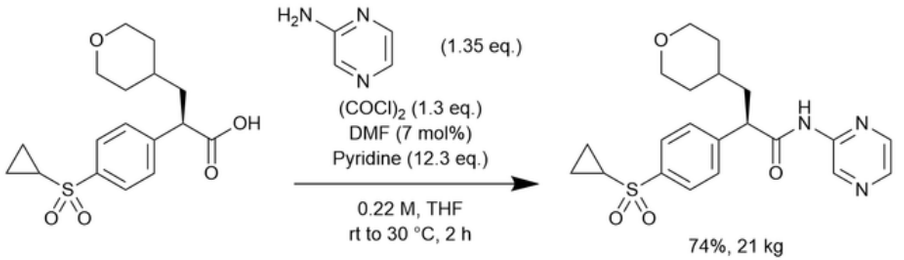
Activating agent equivalents
1 to 1.4

Amine equivalents
0.9 to 1.4

Additive equivalents
0.2

Example Large-Scale Amide Coupling (Eli Lilly, 2012)

Org. Process Res. Dev. 2012, 16, 830–835



Solvents and Bases

- ***The majority of couplings require base*** *to deprotonate carboxylic acids and* ***prevent HCl offgassing***
- ***THF and DCM*** *are the most commonly employed solvents on large scale*
- *Biphasic* ***Schotten-Baumann conditions enable the use of water*** *as a solvent (and inorganic bases) for* ***acid chloride-mediated couplings***

Organic Solvent	Base
Toluene	Na/KO^{t}Bu
2-MeTHF	Cs/K_2CO_3
Dioxane	K_3PO_4
THF	LiHMDS
^{t}BuOH	Na/KOH
DMF	DBU

Common for large-scale amidations

Other Considerations

- *Quenching amide couplings can be* ***hazardous on large scale*** *due to offgassing or exotherms*
- ***Activation is often carried out stepwise*** *prior to amine addition, though this is* ***not always necessary***
- *Ammonium salt substrates can be used if an extra equivalent of base is added*
- ***Solid-phase peptide synthesis*** *is a common synthetic method which uses amide couplings for peptide formation*

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