

# Functionalized silica gels for amide coupling reactions

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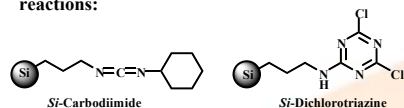
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## Amide coupling reactions

- This type of reaction is commonly used in drug discovery and development because of the bioavailability of the amide groups
- Usually used for the condensation of amines and carboxylic acids
- These reactions can be done in homogenous or heterogeneous phase
- Work-up is facilitated by using solid-supported reagents
- Silica-based reagents offer great advantages over polymers-based reagents
- SiliCycle has developed the following two functionalized silica gels for amide coupling reactions:



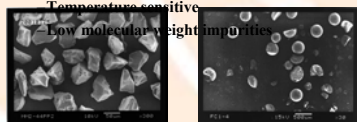
## Solid-Supported products

### Functionalized silica gels

- Solvent independent pore structure (no swelling)
- High surface area
- Reproducible loading from lot to lot
- High purity (insoluble matrix)
- Free flowing, no static charge build-up
- Stable at high temperature (>189°C, DMSO)

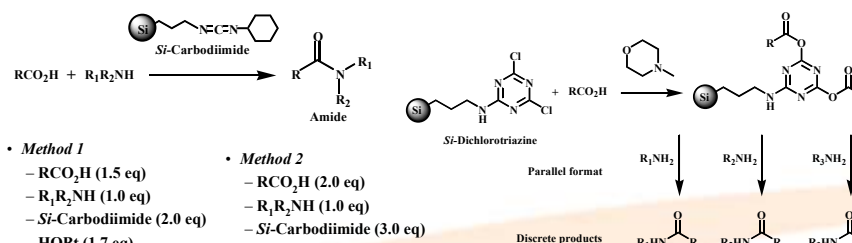
### Polymer-based products

- Cons
  - Swelling required
  - Solvent dependent
  - Static charge build-up
  - Large quantities costs
  - Temperature sensitive
  - Low molecular weight impurities



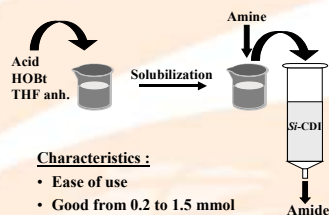
Silica in toluene 110°C 4 hours Polystyrene in toluene 110°C 1 hour

## Synthesis of amides with functionalized silica gels



- Method 1**
- RCO<sub>2</sub>H (1.5 eq)
  - R<sub>1</sub>R<sub>2</sub>NH (1.0 eq)
  - Si-Carbodiimide (2.0 eq)
  - HOBt (1.7 eq)
  - Si-Carbonate
- Method 2**
- RCO<sub>2</sub>H (2.0 eq)
  - R<sub>1</sub>R<sub>2</sub>NH (1.0 eq)
  - Si-Carbodiimide (3.0 eq)

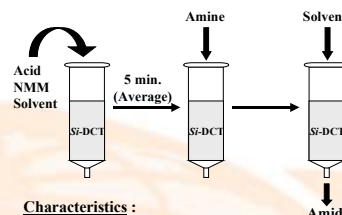
## Use of Si-CDI cartridges



### Characteristics :

- Ease of use
- Good from 0.2 to 1.5 mmol (from 0.5 g to 5 g of Si-CDI)
- Scalable
- Scavenge excess acid and HOBt with Si-Amine and Si-Carbonate

## Use of Si-DCT cartridges



### Characteristics :

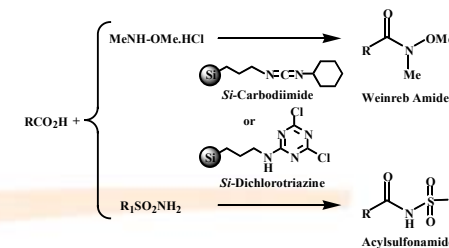
- Ease of use
- Good for 0.2 to 1.5 mmol (from 0.5 g to 5 g of Si-DCT)
- Scalable and fast

Acid	Amine	Si-CDI			Si-DCT	
		Yield % (Purity <sup>a</sup> %)			Yield % (Purity <sup>a</sup> %)	
		Method 1	Method 2	Cartridges	Bulk	Cartridges
Benzoic acid	Aniline	85.0 (99.1)	86.7 (96.4)	81.5 (97.2)	100.0 (98.9)	100.0 (98.5)
"	Benzylamine	100.0 (95.4)	80.1 (98.1)	100.0 (98.7)	100.0 (97.8)	99.6 (96.7)
"	Phenylethylamine	98.7 (97.1)	78.7 (98.3)	100.0 (98.8)	100.0 (98.4)	99.9 (96.5)
Phenoxyacetic acid	Tert-Butylamine	100.0 (97.4)	100.0 (94.0)	98.2 (94.5)	99.5 (99.0)	92.7 (95.3)
"	1,2,3,4-Tetrahydroisoquinoline	99.8 (95.0)	100.0 (92.5)	97.2 (92.4)	91.1 (92.0)	70.0 (94.0)
Boc-Phe-OH (L)	Phenylethylamine	100.0 (97.6)	100.0 (97.6)	99.2 (90.1)	99.8 (97.9)	91.1 (95.4)
Fmoc-Phe-OH (D)	"	N.A.	100.0 (>95 <sup>b</sup> )	N.A.	100.0 (>95 <sup>b</sup> )	100.0 (>95 <sup>b</sup> )
Z-Val-OH	"	100.0 (>95 <sup>b</sup> )	93.5 (>95 <sup>b</sup> )	100.0 (>95 <sup>b</sup> )	100.0 (>95 <sup>b</sup> )	98.3 (>95 <sup>b</sup> )
3-Iodobenzoic acid	Benzylamine	100.0 (98.5)	100.0 (97.1)	100.0 (94.5)	100.0 (99.0)	99.9 (98.9)
Heptanoic acid	Ethanolamine	72.2 (95.5)	84.3 (98.0)	81.3 (95.5)	78.2 (68.0)	53.2 (95.0)

<sup>a</sup>: Determined by GC-FID, <sup>b</sup>: Determined by <sup>1</sup>H NMR, Yields refer to the isolated product

For detailed procedures, visited our website at : [http://www.silicycle.com/html/english/products/product\\_line.php?cat\\_id=18](http://www.silicycle.com/html/english/products/product_line.php?cat_id=18)

## Synthesis of Weinreb amides and Acylsulfonamides



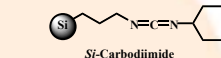
Acid	Amine	Si-CDI Yield % (Purity %)	Si-DCT Yield % (Purity %)
<i>Synthesis of Weinreb Amides</i>			
Benzoic acid	<i>N,O</i> -Dimethylhydroxylamine	98.8 (95.5)	96.4 (94.0)
<i>t</i> -Cinnamic acid	<i>N,O</i> -Dimethylhydroxylamine hydrochloride	87.3 (94.7)	81.9 (70.0)
2-Nitrobenzoic acid		99.5 (93.2)	92.4 (79.0)
<i>Synthesis of Acylsulfonamides</i>			
Benzoic acid	Benzenesulfonamide	95.5 (71.3)	98.0 (90.0)
	Methanesulfonamide	78.8 (53.1)	71.4 (82.0)

Purity determined by GC-FID, Yields refer to the isolated product

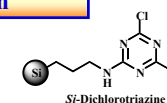
For detailed procedures, visited our website at:

[http://www.silicycle.com/html/english/products/product\\_line.php?cat\\_id=18](http://www.silicycle.com/html/english/products/product_line.php?cat_id=18)

## Conclusion



- General usage
- Robust
- One pot synthesis
- Increase yields with use of HOBt
- For general amides, esters and lactones
- HOBt easily scavenged afterwards by Si-Carbonate



- To be used with NMM
- Very fast kinetics (less than 60 min or 10 min in cartridges)
- Possible to load an acid for future use
- Amenable to parallel synthesis
- Very high yields and purities
- Use Si-Tosic Acid to remove excess NMM

### Available formats



Other formats tailored to your needs possible...

## Acknowledgements

The authors especially thank Stéphane Pelletier for compound identification and purity analysis by GC-MS and GC-FID.