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Achieving functional group diversity in parallel synthesis: solution-phase synthesis of a library of ureas, carbamates, thiocarbamates, and amides using carbamoylimidazolium salts

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ABSTRACT

A convenient protocol for the parallel solution-phase synthesis of a library of thiocarbamates, ureas, carbamates, and amides from carbamoylimidazolium salts has been developed. The crystalline carbamoylimidazolium salts are readily synthesized from secondary amines, CDI and iodomethane, and act as stable carbamoylation reagents. A common set of reaction conditions and a straightforward non-chromatographic liquid–liquid extraction purification protocol were developed for reactions with thiols, amines, phenols, and carboxylic acids, giving the products with high purities and yields. The resultant library incorporates diversity arising from the choice of reaction partners and the functional group linkage generated in the couplings.

Generating structural diversity is one of the major concerns in the design of small-molecule libraries.[1] Most libraries are synthesized using stepwise approaches in which the synthetic steps employed are usually, by necessity, common to all library members. For example, a library constructed through the coupling of a set of carboxylic acids and amines achieves diversity through the choice of coupling partners, rather than the amide functionality linking the two fragments, which is common to every library member. Most libraries are synthesized by one or more of such pairwise fragment couplings,[2,3] using common reaction steps, with molecular diversity arising through the choice of building blocks employed rather than the functionality linking the fragments.[4] This limitation can, in principle, be overcome by incorporating functional group diversity as a design element in the library synthesis.[5] For example, acylation reactions of amines, alcohols, thiols, and enolate derivatives would lead to a library composed of amides, esters, thioesters, and 1,3-dicarbonyl compounds (Fig. 1a). The challenge with such an approach, particularly when using semi- or fully automated syntheses, is that it is often not possible to establish a common set of reaction and purification conditions suitable for each functional group linker, by virtue of the different types of coupling chemistry employed.[6] Our goal was to establish whether such an approach could be developed in the context of carbamoylation reactions using carbamoylimidazolium salts **3**. We now report the realization of this strategy using a parallel solution-phase library synthesis of ureas, carbamates, thiocarbamates, and amides (Fig. 1b), using a common set of reaction and purification conditions.

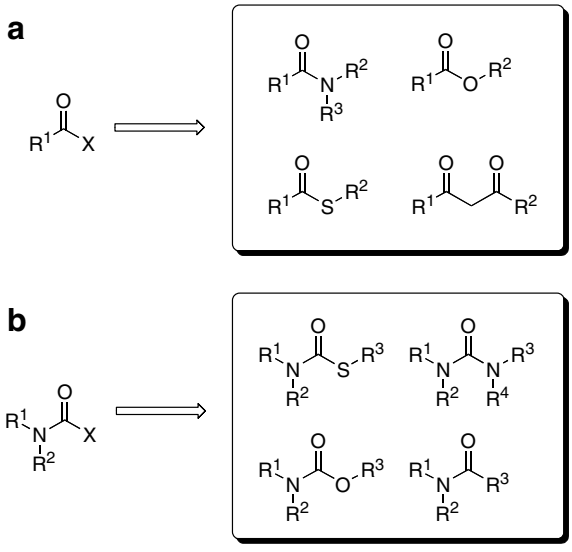

Figure 1. Libraries incorporating diversity in the linker group derived through (a) acylation or (b) carbamoylation.

Previous studies have established carbamoylimidazolium salts **3** as versatile N,N′-disubstituted carbamoyl cation equivalents[7–10] that overcome many of the drawbacks associated with carbamoyl chlorides,[11] which are the most commonly used carbamoylating

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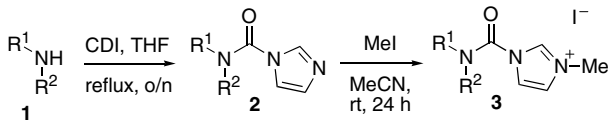
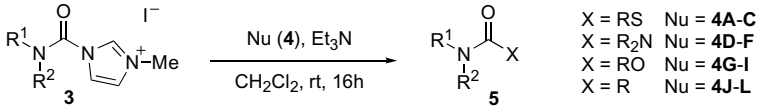


Scheme 1. Synthesis of carbamoylimidazolium salts **3**.

reagents. The salts **3** are in most cases readily synthesized, air-stable crystalline solids that can be stored for extended periods of time at room temperature.[7] Their application toward library synthesis has been limited to a parallel synthesis of a library of tetra-substituted ureas.[7c] However, they are known to react with several classes of nucleophiles, including amines, alcohols, phe-

Table 1
Parallel synthesis of a library of thioureas, ureas, carbamates, and amides from the reaction of carbamoylimidazolium salts **3** with thiols, amines, alcohols, and carboxylic acids[a]

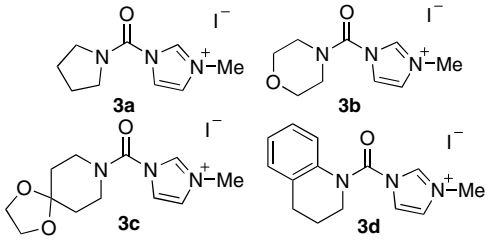


Nucleophile (**4**)	**3a**		**3b**		**3c**		**3d**	
	Yield[b]	Purity[c]	Yield[b]	Purity[c]	Yield[b]	Purity[c]	Yield[b]	Purity[c]
4A	94%	⩾95[d]	98%	94	87%	94	95%	98
4B	99%	93	94%	93	98%	96	98%	94
4C	Quant	⩾99	99%	⩾99	Quant	⩾99	Quant	95
4D	Quant	⩾95[d]	Quant	⩾95[d]	Quant	⩾95[d]	98%	99
4E	86%	⩾99	91%	⩾99	83%	96	Quant	⩾99
4F	Quant	⩾95[d]	97%	⩾95[d]	88%	⩾95[d]	Quant	95
4G	92%	98	Quant	⩾99	Quant	⩾99	99%	⩾99
4H	98%	97	Quant	99	95%	98	97%	98
4I	93%	⩾99	Quant	⩾99	Quant	⩾99	99%	97
4J	88%	⩾95%[d]	98%	⩾95[d]	Quant	⩾95[d]	87%	94
4K	99%	⩾95[d]	Quant	⩾95[d]	99%	⩾95[d]	89%	⩾99
4L	92%	⩾99	98%	⩾99	Quant	92	Quant	99

[a] **3** (1.25 equiv), **4** (1.0 equiv) and NEt_3 (1.0 equiv) were stirred for 16 h at room temp.
[b] Isolated yields following aqueous work-up.
[c] Purity determined by HPLC analysis (UV_{254}, Hewlett–Packard series 1100MSD electrospray ionization mass spectrometer).
[d] Purity determined by ^1H NMR analysis.

nols, thiols, and carboxylic acids.[7–10] To achieve the goal of the current study, a single set of reaction and purification conditions were required for the reaction of **3** with different classes of nucleophiles, using a parallel solution-phase synthesis approach. We were particularly interested in establishing a protocol that would not require the use of any type of chromatographic purification, but which would give the products in high yield and purity.

Carbamoylimidazolium salts **3a–d** were chosen as representative examples for the purpose of library synthesis, and were synthesized using the previously reported protocol (Scheme 1). Thus, refluxing the secondary amines **1** with *N*,*N*′-carbonyldiimidazole (CDI) (1.1 equiv) in THF afforded carbamoylimidazoles **2**, which were isolated in excellent yields and purity after only an aqueous work-up. Reaction of **2** with iodomethane (4.0 equiv) in acetonitrile at room temperature for 24 h gave the corresponding carbamoylimidazolium salts **3a**–**d**, which were isolated by simple evaporation in vacuo of the volatile reagents and solvents.[12] Further purification of the salts was not necessary, although salts **3a**–**d** can be recrystallized if required.



With the imidazolium salts **3a**–**d** in hand, we next set about developing a common set of reaction conditions suitable for urea, amide, carbamate, and thiocarbamate formation. A series of screening studies were run to establish the effect of solvents, base additives, reaction time, and stoichiometry.[7] Dichloromethane was found to be an optimal solvent, and the use of triethylamine as a base resulted in complete reaction conversion within 16 h at room temperature. A small excess of the imidazolium salts **3** was required to push reactions to completion.

With optimized conditions established, a solution-phase parallel synthesis of a small 48-member demonstration library of compounds was completed using the coupling of **3a**–**d** with 3 different thiols, 3 amines, 3 phenols, and 3 carboxylic acids (Table 1). The 4×12 library comprised four different types of functional group linkers; thiocarbamates from reaction with thiols, ureas from reaction with amines, carbamates from reaction with phenols, and amides from reaction with carboxylic acids. The library was synthesized using a 12-tube Radleys carousel on a 0.4 mmol scale, using a slight excess of the salts **3** (1.25 equiv) with triethylamine (1.0 equiv).[13,14] Since the by-products from the reactions as well as the unreacted starting materials are water soluble, or could be made water-soluble by an acid–base reaction, a liquid–liquid extraction procedure using a sequential acidic (1 N HCl) and basic wash (1 N NaOH) was used for product purification. The extractions were carried out using a reservoir (syringe barrel) containing a hydrophobic membrane (two 20 μm polyethylene frits) that allows only the passage of the denser organic phase (i.e., the dichloromethane layer).[15,16] After concentration in vacuo the products **5** could be obtained in excellent yields and purities. Purities were determined by ^{1}H NMR, and for those compounds possessing a good chromophore by HPLC using a UV_{254} detector. In all cases the purity as determined by NMR was $\geqslant$95%, and by HPLC was $\geqslant$92%.

In conclusion, a solution-phase parallel synthesis of a small focused library of thioureas, ureas, carbamates, and amides has been achieved through the coupling of different classes of nucleophiles with carbamoylimidazolium salts using a common set of reaction conditions and a straightforward liquid–liquid extraction purification protocol. The strategy allows for diversification of the linking functional group to be incorporated as a key element in the design of a single library, using identical coupling conditions. It is anticipated that this approach will find utility for the synthesis of other directed libraries. Further studies on the use of carbamoylimidazolium salts and related chemistry will be reported in due course.

Acknowledgments

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10. The salts **3** have also been used for solid-phase organic syntheses, see: Zheng, C.; Combs, A. P. *J. Comb. Chem.* **2002**, *4*, 38–43.
11. Carbamoyl chlorides are in most cases not commercially available or have to be prepared from amines and phosgene. Moreover, they are highly reactive, prone to hydrolysis, and unstable, making them unsuitable for long-term storage, and unattractive as combinatorial building blocks.
12. The salts **3** are much more reactive than **2** as carbamoyl transfer reagents. See Refs. 7e and 9.
13. The library synthesis was carried out in a 12-position Radleys carousel station. The imidazolium salts **3** (0.50 mmol, 1.25 equiv) were suspended in CH_2Cl_2 (4.0 mL). Nucleophile **4** (0.40 mmol, 1.0 equiv) and Et_3N (0.40 mmol, 1.0 equiv) were then added, and the reactions stirred at room temperature for 24 h. The crude reaction mixtures were diluted with CH_2Cl_2 (15 mL) and 1 N HCl (10 mL), shaken and poured into a 70 mL Bond Elute Reservoir® (Varian). The organic layer was collected in a test tube, while the aqueous layer was left in the reservoir. The organic layer was mixed with 1 N NaOH (5 mL) and poured again through the Bond Elute Reservoir®. The products **5** were obtained after concentration in vacuo and were analyzed without further purification.
14. The Radleys carousel is a 12-position reactor that is capable of running 12 reactions in parallel. The system uses glass tubes with magnetic stirring, heating/reflux, and inert atmosphere capabilities. See: Radleys Discovery Technologies, Shire Hill, Saffron Walden, Essex, CB11 3AZ, United Kingdom (http://www.radleys.com/).
15. Bond Elute Reservoir® tubes (polypropylene syringe barrel packed with hydrophobic frits) are available from Varian Sample Preparation Products, 24201 Frampton Ave., Harbor City, CA 90710, Part No.: 1213–1018.
16. The Bond Elute Reservoirs® can be used for aqueous extractions only if the organic phase (i.e., in this case dichloromethane) is denser than the aqueous phase. The frit achieves a gravity 'filtration' by allowing passage of the dichloromethane layer, but preventing passage of the less dense aqueous layer as a result of the hydrophobic frit. The Bond Elute Reservoirs® could be reused by washing using acetone/water, followed by drying.