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An Efficient New Protocol for the Formation of Unsymmetrical Tri- and Tetrasubstituted Ureas

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Abstract: A new method for producing unsymmetrical, tetrasubstituted ureas from N, N'-carbonyldiimidazole (CDI) is presented. Carbamoyl imidazolium salts are prepared from the reaction of CDI with a secondary amine, followed by alkylation with MeI. Secondary amines add with ease to imidazolium salts at room temperature to give unsymmetrical, tetrasubstituted ureas in excellent yields.

A common motif in many pharmaceutically active compounds is the presence of urea functionality. Unlike unsymmetrical di- and tri-substituted ureas, there are only a few methods for the formation of unsymmetrical tetrasubstituted ureas.[1] The most well established method involves treatment of a carbamoyl chloride (synthesized from phosgene and a secondary amine) with a secondary amine.[2] This method suffers from drawbacks: (i) toxicity of phosgene; and (ii) carbamoyl chlorides are often unstable and can be difficult to isolate with high purity. Recently, Katritzky has demonstrated the use of 1,1'-carbonylbisbenzotriazole[3] as a phosgene equivalent for the synthesis of unsymmetrical tetrasubstituted ureas.[4] In this method, a carbamoyl benzotriazole is formed as an intermediate from 1,1'-carbonylbisbenzotriazole and a secondary amine. This method also suffers from disadvantages: (i) the sodium salt of the secondary amine must be heated under reflux with the intermediate carbamoyl benzotriazoles; and (ii) 1,1'-carbonylbisbenzotriazole is not commercially available and must be synthesized from benzotriazole and phosgene.

We now report an experimentally straightforward and general protocol for the synthesis of unsymmetrical tetrasubstituted ureas **5** (Scheme 1). Our approach utilizes *cationic carbamoyl imidazolium intermediates*[5] **3**, derived from the commercially available and easily handled crystalline solid, precursor, N, N'-carbonyldiimidazole[6] (CDI). CDI has previously been utilized to synthesize N,N'-disubstituted ureas via carbamoyl imidazoles **2**.[7] Tetrasubstituted ureas, however, have not been synthesized using a CDI or carbamoyl imidazole based approach, because of the low reactivity of amines with N,N-disubstituted carbamoyl imidazoles **2**. Activation of *acylimidazoles* as the corresponding resonance-stabilized imidazolium salts, by N-alkylation of the imidazole moiety, is well known to increase their reactivity toward nucleophilic attack.[8] We reasoned that carbamoyl imidazoles **2** would be similarly activated by initial conversion to the carbamoyl imidazolium salts **3**. Subsequent addition of an amine **4** to **3** would then furnish the tetrasubstituted ureas **5** (Scheme 1).

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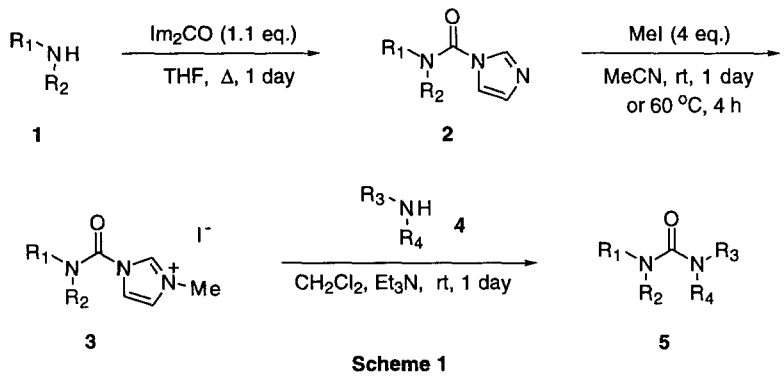
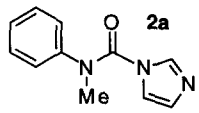
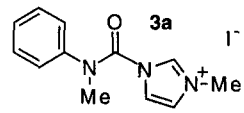
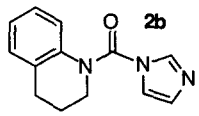
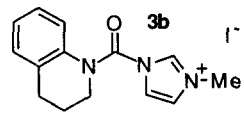
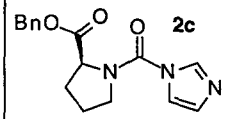
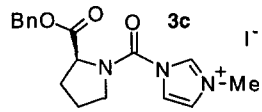


Scheme 1

N-methylaniline, tetrahydroquinoline and L-proline benzyl ester were chosen as representative starting materials **1** for the synthesis of the ureas. Stable, isolable carbamoyl imidazoles **2** were produced in high yields from these amines using CDI (Table 1).[9] N-methylaniline and tetrahydroquinoline efficiently gave **2a** and **2b** after refluxing with CDI in THF for 24 and 36 hours, respectively. Heating of L-proline benzyl ester hydrochloride with CDI afforded undesirable byproducts, but when stirred at room temperature for two days with one molar equivalent of triethylamine in CH_2Cl_2, cleanly formed the desired carbamoyl imidazole **2c** in high yield. The carbamoyl imidazoles did not require further purification for use in the subsequent steps. Stirring of **2** with MeI (4 molar equivalents) in MeCN for one day at room temperature produces the imidazolium salts **3** quantitatively (Table 1).

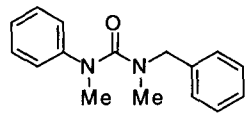
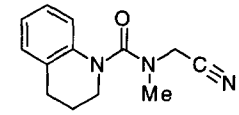
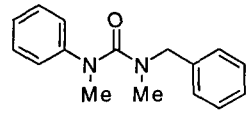
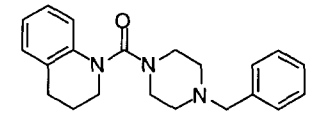
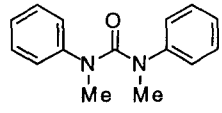
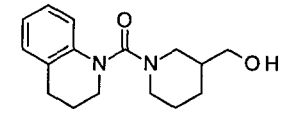
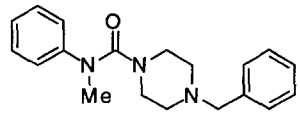
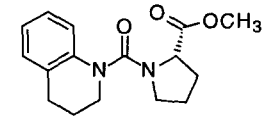
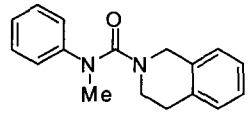
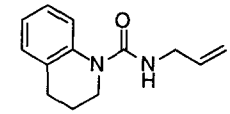
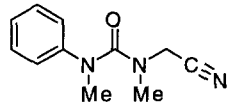
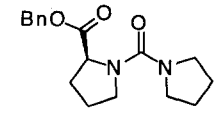
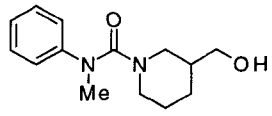
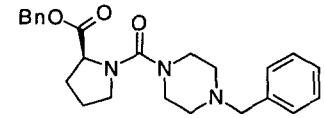
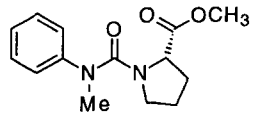
Table 1. Carbamoyl Imidazole and Imidazolium Salt Formation

Carbamoyl Imidazole	Yield of 2	Imidazolium Salt	Yield of 3
 **2a**	87%	 **3a**	>99%
 **2b**	88%	 **3b**	>99%
 **2c**	96%	 **3c**	98%

The imidazolium salts **3**, again required no additional purification for the final conversion to the ureas. Although the salts are hygroscopic, we have stored them for several weeks without detectable decomposition. Addition of secondary amines **4** to a solution of imidazolium salts **3** in dichloromethane with triethylamine at room temperature affords tetrasubstituted ureas **5** in high yields (Scheme 1 and Table 2).[10] The activation of the leaving imidazole group is necessary to form the desired ureas, since carbamoyl imidazoles **2** were found to be unreactive toward primary and secondary amines even under refluxing conditions for prolonged periods.

Addition of triethylamine (1 molar equivalent) resulted in improved yields of the ureas (Entries 1 and 2, Table 2). The activation and amine additions can also be carried out in a one-pot procedure, by removal of the solvent and excess MeI from the imidazolium salts, followed by addition of dichloromethane, triethylamine and the secondary amines **4**. In most cases, the only detectable byproduct of the reaction was N-methylimidazole, which was easily removed by washing the organic layer with dilute acid. This method is also useful for the formation of trisubstituted ureas. Thus, allylamine addition to **3b** afforded the corresponding tetrahydroquinoline derived urea (Entry 13, Table 2). The main limitation of the current protocol, is the potential for competitive attack of other functionality present in the amines **1** or carbamoyl imidazole precursors **2**, with CDI and methyl iodide respectively.

Table 2. Ureas Synthesized[a] from Imidazolium Salts 3a-c

Entry	Urea	Isolated Yield	Entry	Urea	Isolated Yield
1		80%[b,c]	9		85%
2		99%[b]	10		95%
3		88%[b]	11		96%
4		97%	12		89%
5		96%	13		84%
6		84%	14		72%
7		92%	15		81%
8		98%			

[a] Imidazolium salts 3a-c, secondary amines (or HCl salts) and triethylamine (1.0 equiv.,or 2.0 equiv. for HCl salts) in dichloromethane were stirred at room temperature overnight. [b]Reaction stirred for 4 hours. [c]Reaction conducted in the absence of triethylamine.

In conclusion, we have established an efficient new protocol for the formation of unsymmetrical, tetrasubstituted ureas. High yields of ureas are obtained under mild conditions, often without the need for chromatographic purification. Commercially available CDI is used, eliminating the necessity of using phosgene, traditionally associated with tetrasubstituted urea synthesis. Further studies on the utility of imidazolium salts **3**, and polymer-supported variants of this methodology are currently underway in our laboratory.

Acknowledgments:

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References and Notes:

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9. Staab, H. A.; Benz, W. *Liebigs Ann. Chem.* **1961**, *648*, 72-82.
10. The preparation of *3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl-phenyl-amide* (Table 2, entry 5) is representative: To a suspension of CDI (9.73 g, 60 mmol) in THF (100ml) was added N-methylaniline (5.96 ml, 55 mmol). The mixture was refluxed for 24 h before cooling to room temperature. Removal of solvent under vacuum gave a viscous orange oil which was dissolved in CH_2Cl_2 (100 ml), and washed twice with 100 ml portions of water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield a light yellow solid (9.62 g, 87%). The carbamoyl imidazole **2a** obtained was judged to be pure by ^1H and ^{13}C NMR and was used in the next step without further purification. IR (KBr disc) ν 3126, 3056, 2949, 1702, 1592, 1492, 1417, 1385, 1294, 1206, 1118, 1072, 1044, 841, 751, 736, 703, 656 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.38-7.29 (3H, m), 7.11-7.07 (2H, m), 6.81-6.76 (2H, m), 3.45 (3H, s); ^{13}C NMR. (50 MHz, $CDCl_3$) δ 149.26, 142.03, 136.80, 129.34, 127.88, 127.11, 125.10, 117.67, 39.16. To a solution of **2a** (1.60 g, 8.0 mmol) in acetonitrile (15 ml) was added methyl iodide (2.0 ml, 32.0 mmol). The mixture was stirred at room temperature for 24 h. Solvent was removed *in vacuo* to yield **3a** as a light yellow solid (2.71 g, 99%), which was used in the next step without further purification. IR (thin film) ν 3076, 1732, 1594, 1537, 1494, 1372, 1271, 1152, 1047, 1025, 983, 920, 854, 744, 702, 617 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.71 (1H, s), 7.55 (1H, br s), 7.37-7.31 (5H, m), 7.01 (1H, br s), 4.02 (3H, s), 3.45 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.01, 139.67, 137.22, 129.76, 128.32, 125.74, 122.79, 120.22, 40.33, 37.13; HRMS (FAB) m/e calcd (M^+-127) 242.1293, found 242.1296. To a solution of **3a** (343 mg, 1.0 mmol) in CH_2Cl_2 (6 ml) was added 1,2,3,4-tetrahydroisoquinoline (0.133g, 1.0 mmol) and triethylamine (0.14 ml, 1.0 mmol). The mixture was stirred at room temperature for 24h, then washed twice with 1.0 M HCl (5 ml), the organic layer dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield urea (Table 2, entry 5) as a straw-coloured oil (256 mg, 96%). The product ureas can be purified by column chromatography, but are usually greater than 98% purity (NMR). IR (thin film) ν 3491, 3061, 3024, 2928, 2840, 1650, 1595, 1429, 1299, 1254, 1162, 1076, 932, 759, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37-7.26 (3H, m), 7.16-6.94 (6H, m), 4.33 (2H, s), 3.44 (2H, t, J=6.0 Hz), 3.26 (3H, s), 2.59 (2H, t, J=6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.99, 146.62, 134.47, 133.46, 129.32, 128.37, 126.11, 126.04, 125.84, 124.40, 123.84, 47.59, 43.54, 39.47, 28.18; HRMS (EI) m/e calcd (M^+) 266.1419, found 266.1427.