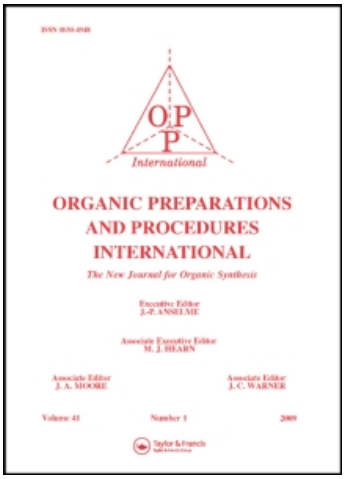

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UNSYMMETRICAL UREAS. SYNTHETIC METHODOLOGIES AND APPLICATION IN DRUG DESIGN

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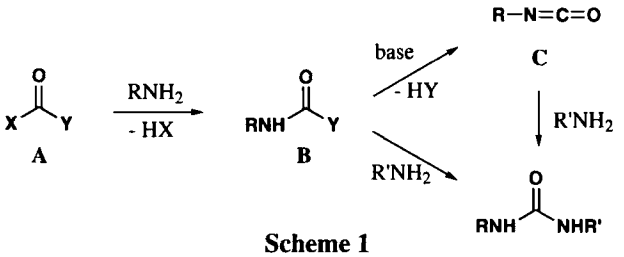
INTRODUCTION

Recent focus on ureas stems from their wide range of application in petrochemicals, agrochemicals, and pharmaceuticals.[1] Used as dyes for cellulose fibres, antioxidants in gasoline or as plant growth regulators, pesticides and herbicides, the unsymmetrical urea functional group is also encountered in several biologically active synthetic targets. In particular, potent urea-containing HIV-1 protease inhibitors[2] and p38 kinase inhibitors[3] have recently been disclosed.

Despite the growing number of synthetic methodologies, ureas are most commonly synthesized by reaction of an amine with phosgene or carbamates. Use of phosgene or phosgene surrogates is still regarded as the traditional method for the formation of ureas, at least in the industry. This approach is particularly efficient for symmetrical ureas. In the case of nonsymmetrical ureas, the synthetic efficiency is limited by the formation of symmetrical urea side products. In the last few years, however, toxic and unstable reagents such as phosgene and isolated isocyanates have been increasingly substituted for cleaner and inherently safer alternatives.[4] These include the use of carbonates or carbonyl imidazole as reagents or taking advantage of the reactivity of carbamates with amines to produce ureas.

Most methods for the synthesis of *N,N'*-unsymmetrical substituted ureas involve the reaction of an amine RNH_2 with a reagent of formula **A**. Intermediate **B** can produce an isocyanate **C**, which can then be reacted with an amine $R'NH_2$ to give the desired unsymmetrical urea. Alternatively, intermediate **B** can be reacted with amine $R'NH_2$ to lead directly to the same unsymmetrical urea. Reagents of formula **A** include phosgene, triphosgene, carbonyl imidazole, carbonyl benzotriazole, carbonates and chloroformates (*Scheme 1*).



Scheme 1

To best explain the importance of unsymmetrical ureas, the first part of this review focuses on the design and selection of drug candidates that incorporate the unsymmetrical urea functionality. Following this short introduction of medicinal chemistry for process chemists, from structural design to lead selection, the different methods developed and reagents employed for the synthesis of unsymmetrical ureas are presented and discussed.

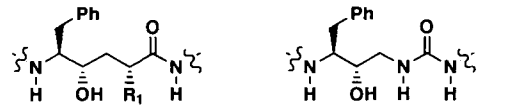
I. UNSYMMETRICAL UREA FUNCTIONALITY IN DRUG DESIGN

The urea functional group has been introduced in several potent HIV-1 protease inhibitors[2] as replacement for the hydroxylethylene isostere with particular improvement in potency. Later, this functionality was incorporated in p-38 MAP kinase inhibitors[3] as well as in 5-HT reuptake inhibitors[5] and tentative aspartic peptidase inhibitors.[6]

The biologically active ureas described in this section were generally obtained by reaction of an isocyanate with an amine. Oftentimes, the synthesis of the isocyanate was not described; and in most other cases the classical method with phosgene (X = Y = Cl in *Scheme 1*) was employed. Selected examples of syntheses of these inhibitors are fully described in the second section of the present review.

1. HIV-1 Protease Inhibitors

The RNA genome of the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), encodes an essential aspartic protease (PR).[7] Inhibition of this HIV-PR results in the production of non-infectious virions.[8] Consequently, this protease represents an attractive target for the development of a therapeutic agent for the treatment of AIDS. A variety of isosteres have been incorporated at the cleavage site of potent inhibitors of this protease. Among those, the urea isostere was originally introduced as a modification of the hydroxylethylene isostere, wherein the P1' chiral α-carbon centre is replaced with a trigonal nitrogen (*Fig. 1*).[2a]



Hydroxyethylene Isostere Hydroxyethylurea Isostere

Fig. 1

The initial targets chosen to determine the utility of this isostere led to several conclusions and one lead (*Table 1*). A marked preference for the *R*-alcohol stereochemistry was noted and a 7-fold increase in potency was obtained by replacing the Cbz group at R_3 by a Qua group (Cbz = benzyloxycarbonyl; Qua = quinoline-2-carboxamide). Systematic variations of R_1 gave minor potency changes, whereas variation of R_2 resulted in significant activity enhancements. The first lead in this series (or most effective compound) was designated **SC_52151**.[2a]

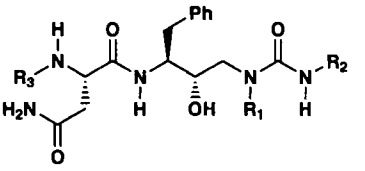


Table 1.

Cmpd	R_1	R_2	R_3	IC_{50} (nM) *R*-alcohol	IC_{50} (nM) *S*-alcohol
1	*i*-Bu	*i*-Pr	Cbz	260	----
2	*i*-Bu	*t*-Bu	Cbz	35	54,000
SC_52151	*i*-Bu	*t*-Bu	Qua	6	10,000

Cbz = benzyloxycarbonyl; Qua = quinoline-2-carboxamide

IC50 : Inhibitory Concentration 50, concentration of drug required to inhibit the biological endpoint of interest by 50%

Later high-resolution X-ray structure of the complexes of HIV-1PR with peptidomimetic inhibitors revealed the presence of a structural water molecule which hydrogen-bonded to both mobile flaps of the enzyme and the two carbonyls of the transition-state mimic of the inhibitors.[9] Cyclic urea inhibitors were designed, in which the urea oxygen displaced this structural water molecule by incorporation into the inhibitor structure (*Fig. 2*). This cyclic urea

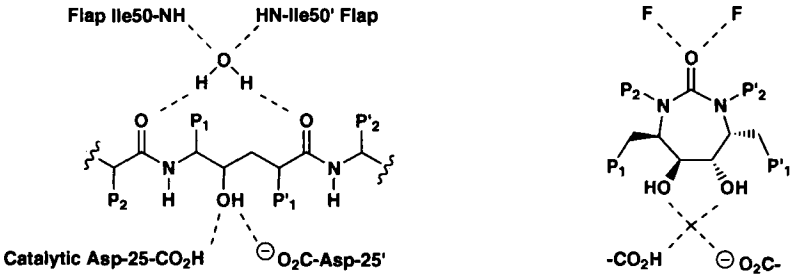
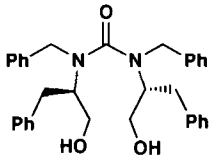


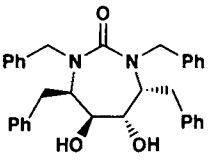
Fig. 2

scaffold, based on a series of C_2-symmetric diols, also took advantage of the principle of preorganization[10] which states that "the more highly hosts and guests are organized for binding and low solvation prior to their complexation, the more stable will be their complexes". Cyclic urea **4** has an inhibition constant (K_i) of 2.5 nM, whereas urea **3** has a K_i of 6,700 nM. This corresponds to a 4.8 kcal/mol gain in binding energy for **4** versus **3**. As expected, the preorganized inhibitor gave a higher affinity for HIV-PR than its flexible counterpart, since no conformational entropic penalty need be paid during binding, the penalty having been prepaid during the synthesis of the preorganized structure (*Fig. 3*).[2b]



3

K_i = 6700 nM
DDG = 0 kcal/mol



4

K_i = 2.5 nM
DDG = -4.8 kcal/mol

Fig. 3

Non-symmetric cyclic ureas were prepared to examine the effect of non-symmetric P2/P2' side-chains on the inhibition constant (K_i). In general, the K_i of nonsymmetric cyclic ureas such as **6** fell within the range of the K_i constituted by the two corresponding parent symmetric cyclic ureas (*e. g.* **4** and **5** for **6**, *Table 2*). This extensive structure-based optimization of the side-chains resulted in **DMP323**, which was studied in Phase I clinical trials but found to suffer from

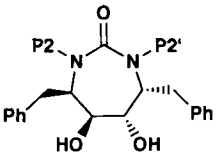
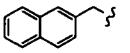
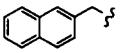
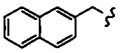
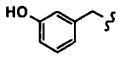
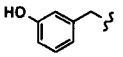
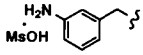
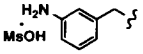
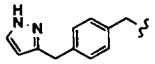
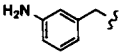
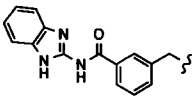
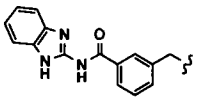
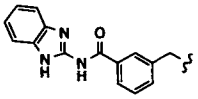
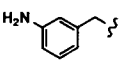
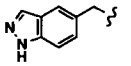


Table 2.

Cmpd	P2	P2'	K_i (nM)	IC_{90} (μM)	C_{max} (μM) bioavailability rat @ 10 mg/kg	ref
4	Bn	Bn	2.5	0.83	1.3	2b
5			0.31	3.9	0.38	2b
6		Bn	2.3	7.5	----	2b
DMP323			0.34	0.057	0.78	2b
DMP450			0.28	0.13	2.25	2b
7			0.035	0.027	----	2c
SD146			0.024	0.005	----	13
SD145			0.037	0.017	----	11
SE063			0.003	0.011	----	11

K_i: inhibition constant
IC90: Inhibitory Concentration 90, concentration of drug required to inhibit the biological endpoint of interest by 90%
C_{max}: maximum concentration of drug in the blood

variable pharmacokinetics in man. **DMP450**, the second clinical candidate had excellent water solubility (> 130 mg/mL compared to 6 μg/mL for DMP323) and exhibited high oral bioavailability in humans with a maximum concentration in the blood (C_{max}) of 6.5 μM when dosed at 750 mg as a neat powder.[2b]

In continuing efforts, DuPont Merck laboratories synthesized a second generation of cyclic inhibitors. These compounds possessed improved potencies and among those, nonsymmetric cyclic ureas had in general better oral bioavailability than the symmetric cyclic ureas (*Table 2*). In particular, compound **7** exhibited the lowest IC_{90} of 27 nM. In addition, the dog oral bioavailability of **7** was determined at 0.85 μM in C_{max} at a dose of 2.5 mg/kg, which was considered satisfactory for such a low dose.[2c]

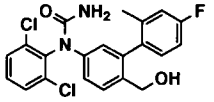
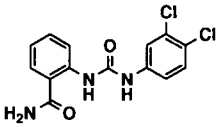
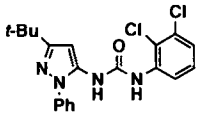
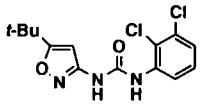
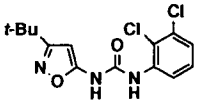
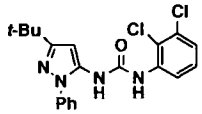
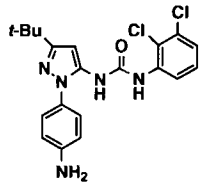
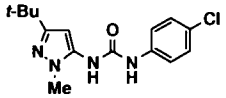
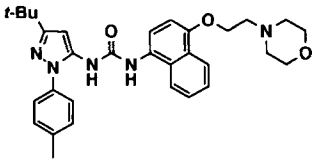
Symmetrical cyclic urea amide **SD146** displayed a remarkable resistance profile, which was believed to stem from its ability to occupy all six enzyme subsites and form 14 H bonds (*versus* 11 for nonsymmetrical **SD145**) and extensive Van der Waals contacts.[11] However, the poor bioavailability of this compound as a result of negligible water and lipid solubility precluded further development. Modifications on the P1/P1' residues were carried out in an attempt to improve upon the pharmacokinetic profile while retaining both the potency and the resistance profile, but failed to provide a new lead compound due to high clearance rate (> 5 L/h/kg).[12] Nonsymmetrical urea **SE063** was identified as a potent HIV-PR inhibitor with good oral bioavailability but only modest resistance profile against mutant strains of the virus.[13] Further SAR studies were conducted and substitution of the 3-arylindazole was not found to significantly improve the resistance profile.[2f]

2. p38 MAP Kinase Inhibitors

The mitogen-activated protein (MAP) kinase p38, also known as cytokine suppressive anti-inflammatory drug binding protein (CSBP), has been implicated in cytokine signalling, and its inhibitors are potentially useful for the treatment of arthritis and osteoporosis.[3a] Aryl and bis-aryl ureas **8** and **9** have been reported by Vertex as inhibitors of p38 kinase.[14] Pyrazole **10** was later identified in a combinatorial chemistry effort at Bayer as a reversible p38 inhibitor with a p38 α2 IC_{50} of 53 nM and a SW 1353 IC_{50} of 820 nM.

Structure-activity relationship study around screening hit **10** led to compounds **11** and **12**. These two isomers were found to be active in the same magnitude range.[3a] Optimization of this small-molecule inhibitors of p38 for cellular potency led to the discovery of **13** (p38 α2 IC_{50} of 11 nM and 13 nM respectively). 3-Aminophenylpyrazolyl urea **14** was eventually selected for further pharmacological characterization because of its superior aqueous solubility[3b] (*Table 3*).

Table 3. Selected p38 MAP Kinase Inhibitors

Cmpd	Structure	p38 α2 IC_{50} (nM)	SW 1353 IC_{50} (nM)	ref
8		2	----	14
9		100	----	14
10		53	820	3a
11		58	----	3a
12		36	----	3a
13		30	70	3b
14		13	42	3b
15		----	----	15b
BIRB 796		----	----	3c

IC50: Inhibitory Concentration 50, concentration of drug required to inhibit the biological endpoint of interest (here: p38 α2 and SW 1353) by 50%

The medicinal chemistry group at Boehringer Ingelheim obtained a cocrystal of structure **15** with recombinant p38. The unique binding mode of **15** prompted them to undertake a systematic evaluation of its pharmacophore.[15] An extensive structure-activity relationship for this class of

compound was conducted. The SAR study consisted of systematic modification of the 2 and 5-positions of the pyrazole nucleus, evaluation of the urea linkage and substitution of the right-hand side aryl moiety. This eventually led to the discovery of clinical candidate **BIRB 796**.[3c] It is particularly interesting to note that replacement of either N-H moiety of the urea linkage by a methylene or *N*-Me group resulted in a significant loss of activity. Thiourea analogue **21** also displayed a decreased binding affinity (K_d) for human p38 MAP kinase (*Table 4*).[3c] These observations underscore the importance of the urea moiety, which allows for binding with p38 through extensive hydrogen bonding and, possibly, establishing correct geometric relationships of the other components of the inhibitor.

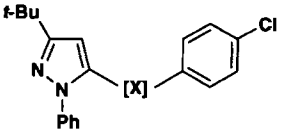
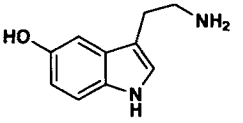


Table 4.

Cmpd	[X]	K_d (nM)
16	NHC(O)NH	8
17	$NHC(O)CH_2$	> 900
18	$CH_2C(O)NH$	1,500
19	$NHC(O)NCH_3$	7,500
20	$(CH_3)NC(O)NH$	> 1,000
21	NHC(S)NH	530

3. 5-HT Reuptake Inhibitors

In 2000, a series of unsymmetrical ureas were evaluated as selective serotonin (5-HT, **22**, *Fig. 4*) re-uptake inhibitors (SSRI) with $5\text{-}HT_{1B/1D}$ antagonistic activities.[5] Serotonin is a biogenic amine neurotransmitter with diverse physiological actions in the central and peripheral nervous systems. Disturbances in the central serotonin system have been associated with the pathogenesis of depression.

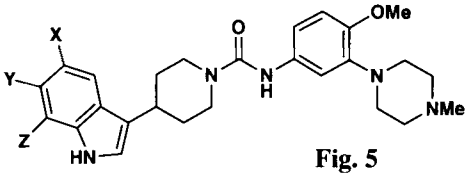


22

Fig. 4

Although SSRIs are effective in the treatment of depression, clinical improvement is obtained only after several weeks. One hypothesis to explain this effect is that the terminal $5\text{-}HT_{1B/1D}$ autoreceptors modulate the 5-HT release. These autoreceptors are inhibitory such that agonists decrease extracellular 5-HT and this results in a decreased 5-HT release. However,

blockade of terminal 5-HT_{1B} and 5-HT_{1D} receptors by selective antagonists would prevent the initial decrease in 5-HT release. Coadministration of a SSRI and a 5-$HT_{1B/1D}$ antagonist should in theory immediately increase serotonergic neurotransmission. Instead of coadministration of two separate molecules to improve the delayed onset of therapeutic action, the Merck KGaA group decided to develop a series of novel urea compounds with mixed pharmacological profiles showing both 5-HT reuptake inhibition and 5-$HT_{1B/1D}$ receptor antagonism within a single molecule. Among the new compounds presented, the ureas **23**, **24** and **25** appeared to be most promising (*Fig. 5*).[5]

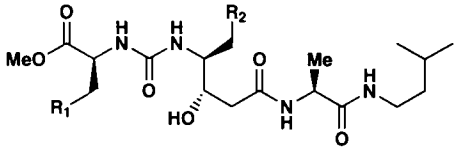


23 X = F, Y = Z = H
24 Y = F, X = Z = H
25 Z = F, X = Y = H

Fig. 5

4. Aspartic Peptidase Inhibitors

The use of mechanism-based and substrate-based design techniques led to a new class of aspartic peptidase inhibitors. The computer-generated unsymmetrical urea structures were subsequently synthesized and their enzyme inhibition potency studied. Potent pepsin inhibitors, such as **26** and **27**, were thus obtained and their binding mode was established. In fact, two X-ray crystal structures of enzyme-bound inhibitors **26** and **27** revealed a new binding mode, which was consistent with the computer prediction (*Fig. 6*).[6] This study further exemplifies the crucial importance of the urea moiety for tight-binding inhibition.



26 R_1 = Cy, R_2 = Ph Ki = 16 nM
27 R_1 = Ph, R_2 = *i*Pr Ki = 0.3 nM

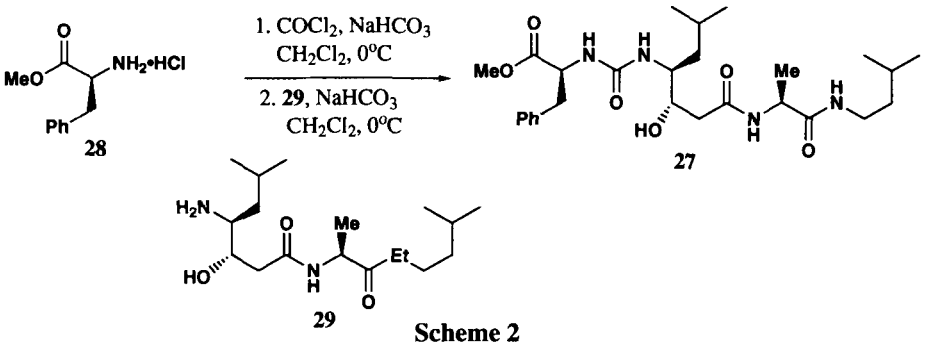
Fig. 6

II. SYNTHESES OF UNSYMMETRICAL UREAS

1. Isocyanate Intermediates and Use of Phosgene

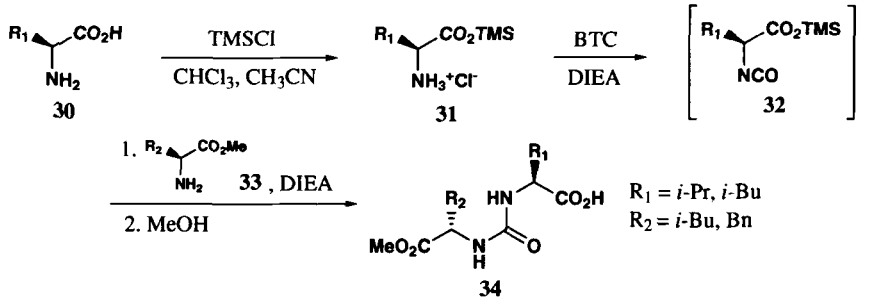
The earliest and most classical method for the preparation of ureas involves the reaction of amines with phosgene reagent. This method is particularly powerful for the production of symmetrical ureas but has also been applied to the synthesis of unsymmetrical ureas. The isocyanate intermediates are usually, but not always, prepared by reaction of an amine with phosgene in the presence of a base.[16] Subsequent reaction with a different amine gives *N,N'*-disubstituted or *N,N,N'*-trisubstituted unsymmetrical ureas. This synthetic route has largely been used by medicinal chemists as the most direct method to prepare their library of ureas in search of a lead compound (*Scheme 1*).[2a,3]

For example, unsymmetrical peptidyl urea **27**, an inhibitor of aspartic peptidases, was synthesized by reaction of **28** with phosgene followed by addition of amine **29** (*Scheme 2*).[6] Although the yield reported for the synthesis of **27** is good (91%), this particular route was inefficient in terms of use of phosgene. Indeed, an excess of 4.5 equivalents was necessary to carry out the transformation. Use of a stoichiometric amount (0.4 equiv.) of *bis*(trichloromethyl)carbonate (BTC, or triphosgene) with diisopropylethylamine (DIEA) as a base for the synthesis of other inhibitors in the series has also been reported and products were obtained in moderate to good yields (64-83%). However, in both cases, an excess of the second coupling partner was used (1.1 equiv.).[6]



Scheme 2

BTC is a stable crystalline solid and safe replacement for phosgene. It was successfully utilized for the sequential synthesis of unsymmetrical ureas, without isolation or purification of the isocyanate intermediates.[17] In a typical reaction, a mixture of an amine and DIEA as base in dichloromethane was added slowly to a solution of triphosgene in dichloromethane at room temperature. The slow reverse addition, strict stoichiometry and anhydrous conditions ensured a minimal formation of symmetrical urea from **42**. At the end of the addition, a mixture of a second amine and DIEA in dichloromethane was added slowly to the above solution to give the unsymmetrical urea in good isolated yield (85-91%) (*Scheme 3*). The reaction was found to be general: under those reaction conditions, functionalities such as unprotected alcohols were well tolerated, and no racemization was observed.[17] This methodology has been successfully applied to the

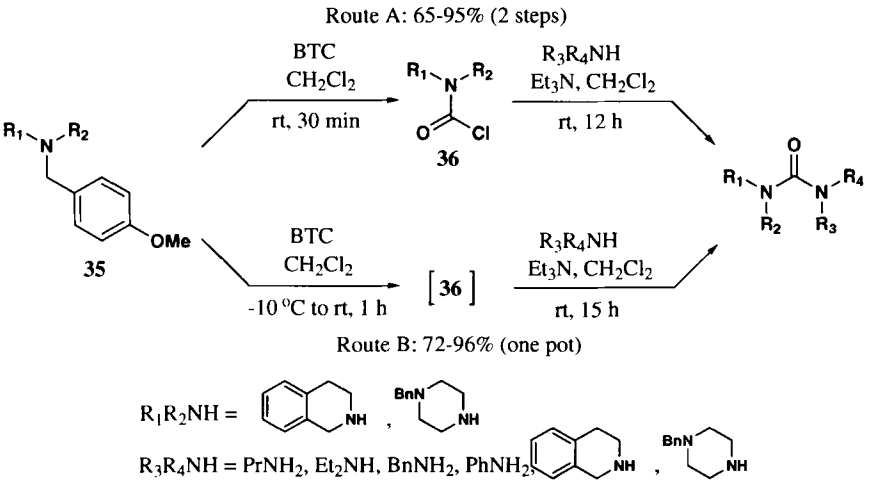


Scheme 3

synthesis of a variety of *N,N'*-disubstituted unsymmetrical ureas,[18] such as Boehringer Ingelheim's p38 inhibitor candidate **BIRB 796**.[3c]

In a particularly notable application, half acid/half ester urea dipeptides were obtained directly from α-amino acids. In this one-pot procedure, the TMS group was used as a transient carboxylic acid protecting group (*Scheme 3*). Reaction of **31** with BTC followed by addition of amino ester **33** and TMS deprotection under mild conditions led to the desired unsymmetrical ureas in moderate to good yields (45-85%).[19]

Dealkylation of benzyl-substituted tertiary amines (**35**) by reaction with a stoichiometric amount of phosgene or BTC has been reported as an efficient method to access carbamoyl chlorides (**36**). Subsequent addition of primary or secondary amines produced trisubstituted or tetrasubstituted unsymmetrical ureas in excellent yield and without any contamination by symmetrical ureas.[20] This methodology could be carried out in two steps or in one pot in similar yields, and was particularly valuable in the cases where the carbamoyl chloride intermediate is unstable (for example, the carbamoyl chloride of *N*-benzylpiperazine).[20] Reaction of BTC with tertiary amines bearing electron-rich benzyl groups afforded the best results. In particular, the *p*-methoxybenzyl group was found most effective and practical. In this study, it was also noted that the *p*-methoxybenzyl group is a known protecting group[21] for secondary amines and can conceivably be considered as an advantageous direct relay group for the synthesis of carbamoyl chlorides and therefore of unsymmetrical ureas (*Scheme 4*).[20]



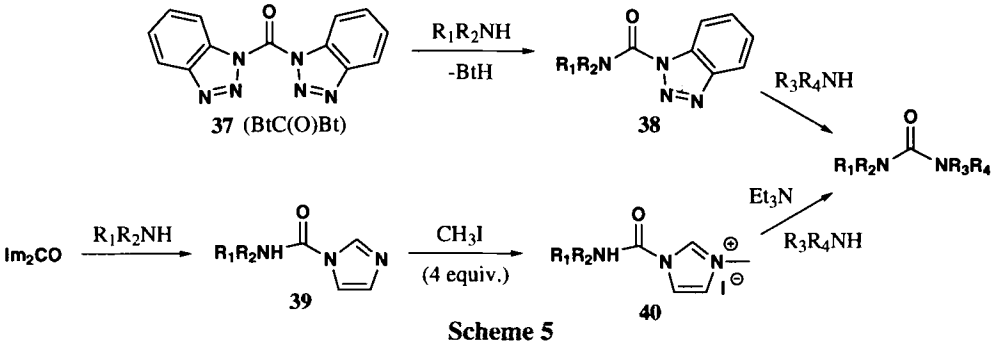
Scheme 4

The use of phosgene has several drawbacks beyond the obvious problems of high volatility and toxicity. Due to their reactivity the use of phosgene or BTC for the synthesis of unsymmetrical ureas results in the production of, oftentimes unseparable, symmetrical ureas as side products.[22] Furthermore, phosgene has been shown to react with ureas to give various degradation products.[23] This, in part, explains the search for alternative reagents and the need for new methodologies for the synthesis of unsymmetrical ureas.

2. Carbonyl Imidazole Intermediates

N,N'-Carbonyldiimidazole (CDI) is a well known and extensively utilized phosgene substitute for the synthesis of ureas.[2b] CDI is a commercially available crystalline solid which is easily handled. Unlike phosgene and BTC, the use of CDI does not generate chlorine or chlorinated byproducts and is therefore considered as a less toxic and less hazardous route to biologically active disubstituted[2e] and trisubstituted[5] unsymmetrical ureas.

1,1'-Carbonylbisbenzotriazole was the first phosgene substitute to have been reported as a safe, mild and versatile reagent for the synthesis of unsymmetrical ureas.[24] Reaction of 1,1'-carbonylbisbenzotriazole **37** with a secondary amine produced a carbamoyl benzotriazole intermediate **38**. The reaction conditions and the yields of **38** obtained were found highly dependent on the steric hindrance created by the substituents of the secondary amine. The reaction proceeded in good yields at room temperature in THF for cyclic and aliphatic amines (50-76%) whereas reflux of THF was necessary with aromatic amines (23-40%).[24] Intermediate **38** was then reacted with another secondary amine in refluxing THF for 1 to 3 days. A variety of *N,N,N',N'*-tetrasubstituted unsymmetrical ureas were prepared with this methodology (aromatic, aliphatic, bicyclic) in moderate to good yield (25-82%) (*Scheme 5*).[24] Unfortunately, 1,1'-carbonylbisbenzotriazole is not as accessible a reagent for large-scale processes as CDI.

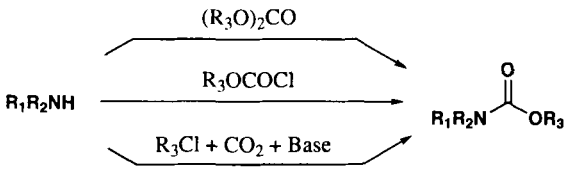


Scheme 5

Later, CDI itself was used successfully for the preparation of unsymmetrical tetrasubstituted ureas.[25] Carbamoyl imidazoles **39**, which displayed low reactivity with amines, were activated by *N*-alkylation of the imidazole moiety with MeI to give resonance-stabilized imidazolium salts. Cationic carbamoyl imidazolium intermediates **40** reacted readily with secondary amines at room temperature to produce unsymmetrical ureas in high yields (72-99%) (*Scheme 5*).[25]

3. Carbamate Intermediates

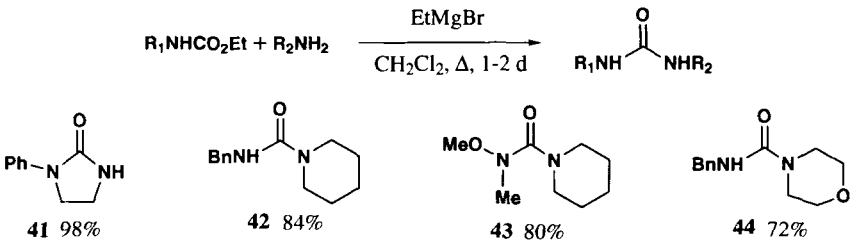
Another classical method involves the aminolysis of a carbamate. Carbamates can be synthesized either from carbonates or chloroformates (*Scheme 6*).[22,26-41] These intermediates are usually easy to isolate and purify. Depending on the nature of the departing alkoxide, reaction of carbamates with amines afford ureas in moderate to excellent yield.[22,42]



Scheme 6

Carbamates can be prepared rapidly from electron-poor diaryl carbonates and 1 equiv. of amine at room temperature in moderate to good yield. Preparation from chloroformates is generally fast and high yielding. Reaction of an amine with 1.1 equiv. of a chloroformate in the presence of a base (HCl scavenger) at 0°C to room temperature leads to the desired carbamate in less than an hour.[22,26-28] Carbamates were also synthesized by reaction of amines with carbon dioxide as phosgene replacement. In the presence of sterically hindered bases such as guanidines, amines were reported to react with CO_2 to form carbamate anion intermediates, which led to the desired carbamates by reaction with alkyl chlorides.[29]

An early method reported for the synthesis of unsymmetrical ureas involved the displacement of the ethoxy group of an ethyl carbamate by the magnesium salt of an amine generated *in situ* by treatment with ethyl magnesium bromide (*Scheme 7*). Using this methodology, tertiary carbamates were shown to undergo the substitution reaction smoothly to give ureas **43** and **44** in good yield. Mechanistically, the magnesium amide likely acted as a Lewis acid to activate the carbamate toward substitution and preclude the formation of isocyanate intermediate.[42b]



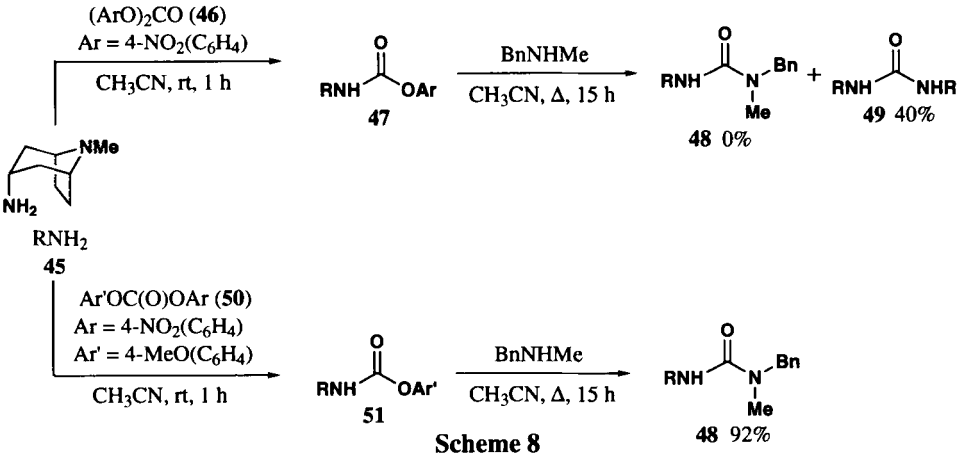
41 98% **42** 84% **43** 80% **44** 72%

Scheme 7

Aminolysis of *bis*(4-nitrophenyl)carbonate was also reported as an early method for the preparation of unsymmetrical *N,N'*-disubstituted ureas. Reaction of *bis*(4-nitrophenyl)carbonate with 1 equiv. aliphatic amines in CH_2Cl_2 at room temperature for 1 to 2 hours gave 4-nitrophenyl carbamates. In the case of aniline, the reaction was much slower and required several days to achieve completion. Subsequent reaction of the isolated carbamates with a second aliphatic amine in CH_2Cl_2 at room temperature for 4 hours led to the desired ureas in good to excellent yields (50-96%).[30]

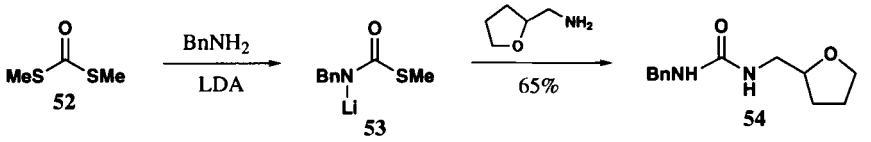
However, this method was not found suitable to incorporate aminotropane **45** in unsymmetrical ureas. In this case, large amounts of symmetrical ureas **49** formed (at the end of the reaction with 1 equiv. of **45**, the only products in the pot were 60% **46** and 40% **49** determined

by NMR). It was reasoned that intermediate **51** was more reactive to the nucleophile (*i. e.* **45**) than the carbonate. To avoid this problem, a series of unsymmetrical diaryl carbonates were synthesized. In particular, 4-methoxyphenyl-4-nitrophenyl carbonate was found effective in the formation of **48** in 92% yield (*Scheme 8*). Extension of this one-pot procedure to other primary amines was equally straightforward. The slow and inefficient reaction of the produced carbamates with *N*-methylbenzylamine was circumvented by addition of DBU.[31]



Scheme 8

S,S-Dimethyldithiocarbonate (DMDTC) was reported as a mild and a safe-handling phosgene substitute for the synthesis of ureas.[32-34] DMDTC was prepared from methanol, carbon disulfide and the non-volatile, albeit carcinogenic, dimethyl sulfate.[32,33] Reaction of DMDTC with benzylamine in the presence of LDA gave the lithium salt of *N*-benzyl-*S*-methylthiocarbonate in quantitative yield. Salt **53** was found to be relatively stable to nucleophilic substitution at room temperature, therefore preventing the formation of symmetrical dibenzyl urea. Treatment with aqueous HCl followed by reaction with aliphatic amines led to unsymmetrical ureas in moderate yields (40-68%) (*Scheme 9*).[34] *S*-Methylthiocarbonates could also be synthesized by reaction of primary amines or amino esters with CS_2, followed by methylation using MeI and subsequent hydrolysis in the presence of $ZnCl_2$. Treatment with 2 equivalents of a primary or secondary amine led to unsymmetrical ureas in modest to good yield (60-89%).[42c]



Scheme 9

Carbamates can either be isolated by basic work-up and stored for a long period of time without degradation,[30,35] or be used *in situ* for the preparation of the target urea by addition of an amine and Et_3N as base.[36] Although 4-nitrophenyl carbamates were found extremely valuable intermediates, the generation and removal of the highly colored 4-nitrophenol byproduct remain

often an issue. As a consequence, phenyl carbamates are usually preferred by process groups and were shown efficient as *in situ*-generated or isolated intermediates for the large scale preparation of unsymmetrical ureas.[26-28] In DMSO, phenyl carbamates were found to react with amines at room temperature and generated ureas in a rapid and high yielding fashion. The phenol byproduct was removed by basic wash (1 M NaOH). Several representative examples are shown in *Table 5*. The reaction was found compatible with a number of functional groups and no epimerization of chiral nonracemic substrates was observed. For example urea **55** was obtained from prolinol and the corresponding phenyl carbamate in 87% yield after only 15 minutes. Use of hindered primary or secondary amines did not affect the rate of conversion and gave *N,N,N'*-trisubstituted ureas in high yield. The scope of the reaction was extended to cover amines in aqueous solution such as NH_4OH and urea **59** was isolated in 74% yield. Aromatic amines like aniline required higher temperature and urea **60** was obtained at 85 °C for 1 hour in 87% yield.[28] In contrast to the alternative approaches using strong bases for carbamate deprotonation,[37] compounds, **57**, **58** and **59** were prepared under mild and neutral conditions in high yield and were found to be enantiomerically pure.[28]

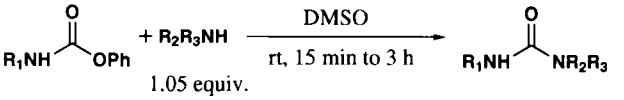
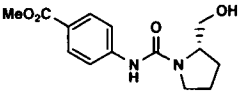
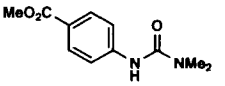
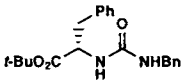
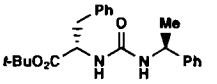
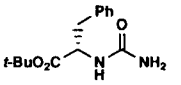
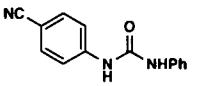
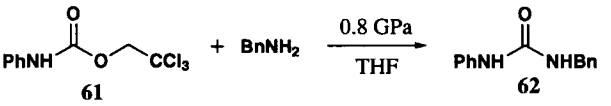


Table 5.

Cmpd	R_1NH NR_2R_3	Reaction conditions	Yield (%)
55		rt, 15 min	87
56	 ($R_2R_3NH = Me_2NH{\bullet}HCl$)	rt, 30 min	80
57		rt, 1 h	84
58		rt, 2.5 h	92
59	 ($R_2R_3NH = NH_4OH$)	rt, 2.5 h	74
60		85°C, 1 h	87

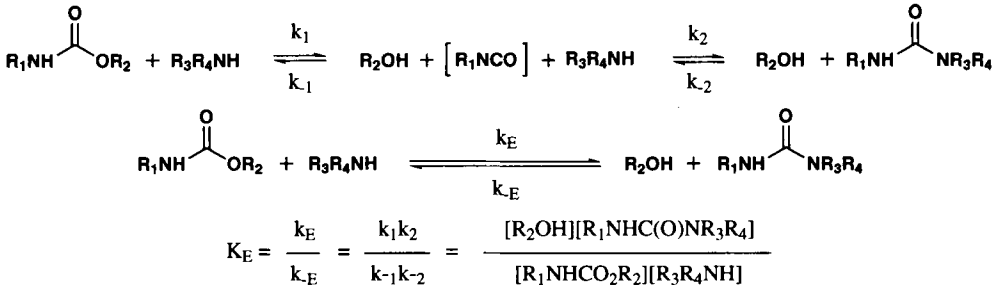
Processes involving the aminolysis of alkyl carbamates have been described. They very often require high temperature reaction conditions, and only modest yields are obtained.[38-40,42b] The DMAP-catalyzed reaction of alkyl and arylamines with $(Boc)_2O$ (81-99% yield),[38] and the deprotonation with strong bases (*t*-BuLi, NaH) of *N*-Boc protected primary anilines and amines and sequential condensation with amines (10-90% yield),[37] were also reported as methods for the preparation of unsymmetrical ureas. Condensation of 2,2,2-trichloroethyl carbamates (Troc-carbamates) and primary and secondary amines (1.2 equiv.) was also achieved under high pressure (0.8 GPa) and temperature (75-100°C) for long periods of time (30-72 h) and led to di- and trisubstituted ureas in moderate to quantitative yields (41-100%) (*Scheme 10*).[41]



75°C, 30 h, 1 atm	trace product
75°C, 30 h, 1 atm, 0.1 equiv. Et_3N	55%
80°C, 30 h, 0.8 GPa	97%

Scheme 10

Extensive kinetic studies have been conducted by Aguirre and Collot.[42a] They have shown that, in the presence of a basic amine, carbamates dissociate into isocyanate and alcohol. The isocyanate then reacts with the amine nucleophile to form a urea. Both carbamate dissociation and urea formation were shown to be equilibria. This translates into an equilibrium between carbamate, amine and urea, alcohol (*Scheme 11*). Also, the equilibrium constant was shown to be highly dependent on the acidity of the alcohol produced: more acidic alcohols shift the equilibrium toward urea formation. Hence, ureas from aryl carbamates are obtained more rapidly and in higher yields than ureas derived from alkyl carbamates.

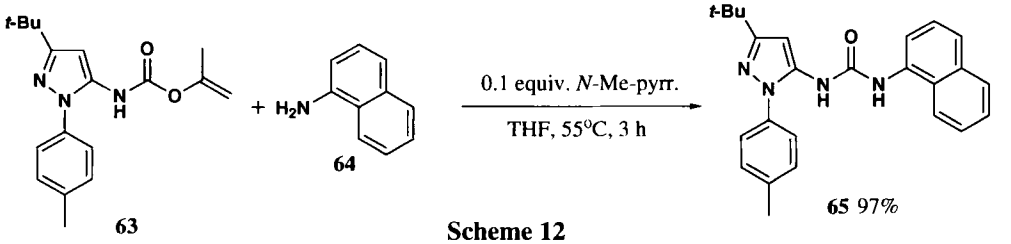


Scheme 11

Table 6. pKa of Selected Alcohols

ROH	pK_{ROH}
4-nitrophenol	7.14
phenol	9.98
2,2,2-trichloroethanol	12.2
2,2,2-trifluoroethanol	12.4
ethanol	16
t-butanol	17
enol	10-11

The solution to the reversibility of the reaction would be to remove the alcohol produced from the reaction mixture. Distillation of the alcohol or reaction with strong bases are clearly unattractive solutions, particularly when dealing with sensitive ureas. Enols can be seen not only as acidic alcohols (*Table 6*), but also as ideal leaving groups which "self-remove" from the reaction mixture as they rapidly tautomerize to ketones and enable the urea carbamate **63** with 1-naphthylamine led to **65** in less than an hour at 55 °C in 97% yield (HPLC assay). Evaporation of THF, acetone and *N*-methylpyrrolidine allowed for isolation of **65** in quantitative yield and 97% purity (*Scheme 12*).[22]



Scheme 12

4. Metal-Catalysis and Use of Carbon Monoxide and Carbon Dioxide Gases

The first possible preparation of unsymmetrical ureas by reaction of carbon monoxide and mixtures of amines involved the use of sulfur.[43] On the basis of experimental evidence a mechanism was proposed: initial formation of carbonyl sulfide from CO and S (equation 1, *Fig. 7*), condensation of carbonyl sulfide with an amine to yield an ammonium thiolcarbamate (equations 2 and 3, *Fig. 7*), decomposition of the ammonium thiolcarbamate to isocyanate and ammonium bisulfide (equation 3, *Fig. 7*), and subsequent condensation of the isocyanate with an amine to give a urea (equations 4 and 5, *Fig. 7*).[43]

The isocyanate can be produced only from a primary amine. As all the steps of the reaction mechanism are reversible (equations 4 and 5 in particular), a mixture of amines yield a mixture of symmetrical and unsymmetrical ureas. The proportion of the two ureas is determined by the relative rate of reactions 4 and 5. This method was particularly effective for the synthesis

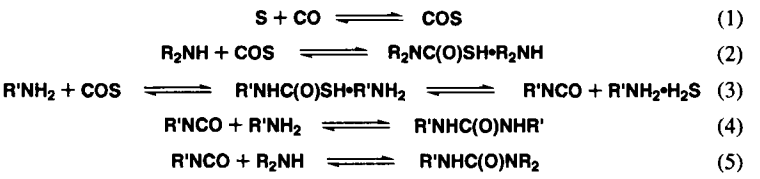
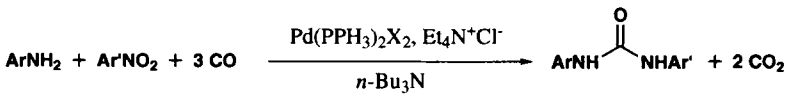


Fig. 7

of 1,1-dialkyl-3-arylureas. For example, 1,1-dimethyl-3-phenylurea, 1,1-dimethyl-3-(2-naphthyl)urea, and 1,1-dimethyl-3-(4-dimethylaminophenyl)urea were isolated in 79%, 92% and 93% yield respectively. Lower yields were obtained for trialkylureas because of the similarity of the basicity of the two aliphatic amines. Understandably, the synthesis of monosubstituted and disubstituted ureas was not selective. In the first case, an organoisocyanate RNCO and cyanic acid HNCO are possible intermediates. For disubtituted ureas, two different organoisocyanates RNCO and R'NCO can be formed and consequently result in mixtures of three products (1 unsymmetrical urea and 2 symmetrical ureas).[43]

A decade after this work, the use of selenium as catalyst for the reaction of ammonia or aliphatic amine with CO was described.[44] *n*-Butylamine was dissolved in THF, amorphous selenium was added, and CO was blown into the suspension. After complete dissolution of selenium, a *N*-*n*-butylselenocarbamate salt could be isolated. This intermediate was reacted with piperidine in THF at 20°C and air oxidation gave 98% yield of the expected unsymmetrical urea.[44] The limitation of this method is the high sensitivity of most selenocarbamates to oxidation and their difficult isolation. Their use *in situ* for the synthesis of unsymmetrical ureas was not reported and remains an open challenge.

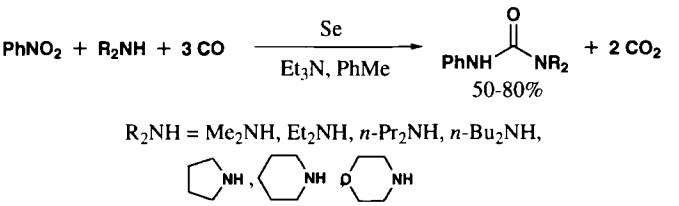
In 1975, Heck reported the reaction of aromatic nitro compounds and CO with aromatic primary amines in the presence of palladium (II) salts, organic phosphines, a basic tertiary amine and tetrabutylammonium chloride at 90°C at atmospheric pressure to form *N,N'*-diarylureas in moderate to good yield (*Scheme 13*). Unfortunately, mixtures of unsymmetrical urea, symmetrical urea, and amine from the reduction of the nitro compound were obtained, with the unsymmetrical urea product predominating.[45] It was later found, for the synthesis of phenyl ureas, that supplying amines continuously or stepwise during the period of reaction increased the yield of unsymmetrical ureas.[46]



Ar, Ar' = Ph, 4-Me-C_6H_4, 4-CO_2Me-C_6H_4, 4-Cl-C_6H_4

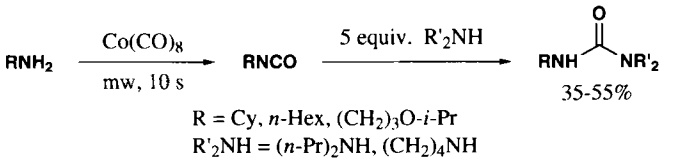
Scheme 13

This reductive carbonylation of nitrobenzene with amines was revisited using selenium as catalyst to give unsymmetrical phenyl ureas, a known class of agrochemicals and pharmaceuticals.[47] Reaction of nitrobenzene with 1 equiv. of an aliphatic cyclic or non-cyclic secondary amine in the presence of 5 mol% of selenium and 1 equiv. of triethylamine in toluene and 3 MPa CO gave unsymmetrical phenyl ureas as a single product in moderate to good yield (50-80%). However, hindered secondary amines (*e. g.* *i*-Pr_2NH or *i*-Bu_2NH) gave poor yields (0-20%). Use of primary amines as co-reagents resulted in poor selectivity as both unsymmetrical and symmetrical ureas were obtained (*Scheme 14*).[47,48] The oxidative carbonylation of amines using palladium (II) catalyst[49] was also reported for the synthesis of ureas but the selectivity and yields of unsymmetrical ureas were poor.[50]



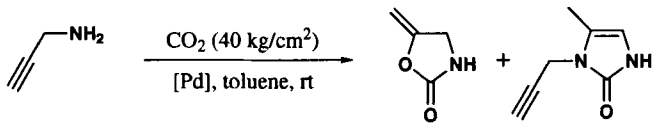
Scheme 14

A recent publication disclosed dicobalt octacarbonyl-mediated generation of ureas using high-density microwave irradiation. This direct and CO-free protocol allowed for the preparation of symmetrical ureas from primary amines in good yields (up to 86%) and unsymmetrical ureas from aliphatic amines in modest yield (35-55%). When two different primary amines were used, a mixture of products was consistently formed. In order to bypass this problem a primary amine was used in combination with an excess of a secondary amine to give trisubstituted unsymmetrical ureas (*Scheme 15*).[51]



Scheme 15

Palladium-catalyzed reaction of propargylamine with carbon dioxide has also been reported but was not found selective for the formation of ureas. A mixture of oxazolidinone **66** and imidazolidinone **67** was obtained (*Table 7*). Improved reactions conditions led to **66** as the sole product in high yield (85%). Nevertheless, **66** could in turn be reacted with aliphatic primary or secondary amines to give unsymmetrical **68** or **69** in good to high yields (*Scheme 16*).[52]

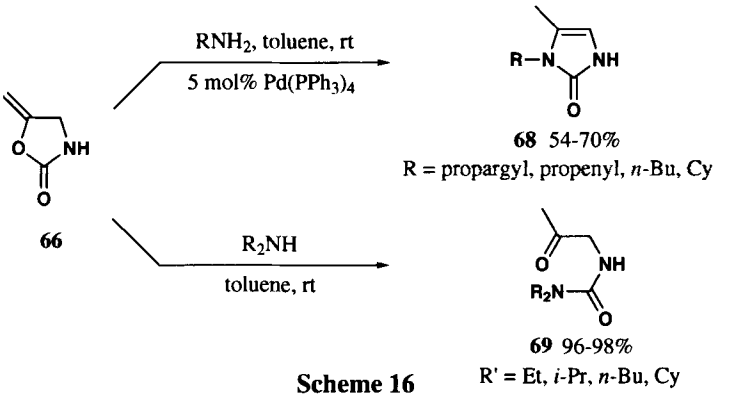


66 67

Table 7.

Catalyst	Reaction time	**66** (% yield)	**67** (% yield)
$Pd(PPh_3)_4$	24 h	35	8
$Pd(PPh_3)_4$	60 h	8	32
$Pd_2(dba)_3$	24 h	36	8
$Pd(OAc)_2$	24 h	85	0

The ruthenium-catalyzed reaction of *N*-aryl substituted formamides and aminoarenes afforded various symmetrical diarylureas in good yield (76-93%). However, attempts to extend this reaction to unsymmetrical ureas were not successful. In the best example, reaction of formanilide with *p*-tolylamine led to a mixture of *N,N'*-diphenyl urea (19%) *N*-phenyl-*N'*-*p*-tolyl urea (38%) and *N,N'*-di-*p*-tolyl urea (21%).[53]



Scheme 16

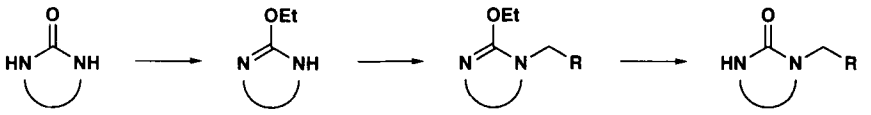
It seems clear that methodologies using CO, CO_2 or transition metals are useful for the synthesis of symmetrical ureas but have found so far limited application for the preparation of unsymmetrical ureas (except for unhindered trisubstituted phenyl ureas),[47] for a large part due to little understanding of reaction mechanisms.

5. Miscellaneous

The literature reveals a number of additional routes for the synthesis of unsymmetrical ureas, of general to very specific applications.[54-63] Methods based on supported reagents represent a specific field of application and will not be discussed herein.[64]

In a first example, the synthesis of steroidal pyrimidines has been reported by condensation of chalcones with urea[54] in good yields (74-78%). Unsymmetrical cyclic ureas, potential

drug candidates against HIV infection, were obtained in one pot by desymmetrization of urea fragments *via* formation and *N*-protection of cyclic isoureas (*Scheme 17*).[55]

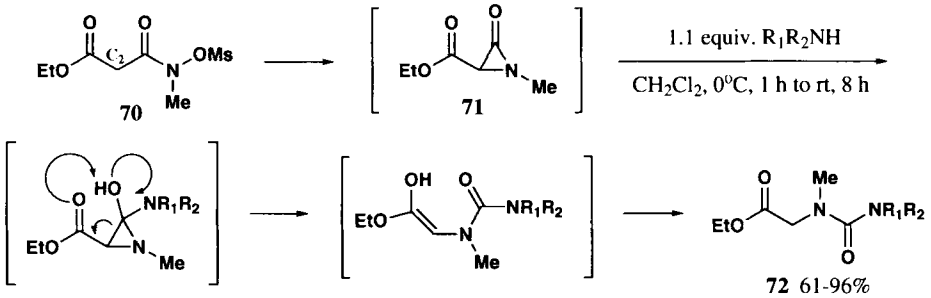


Scheme 17

Another early report described the oxidation of 4-phenylsemicarbazide hydrochloride with 2 equiv. of iodine and 6 equiv. of benzylamine or 6 equiv. of cyclohexylamine (an alternative used 1 equiv. amine and 5 equiv. of Et_3N) to give 1-benzyl-3-phenyl urea and 1-cyclohexyl-3-phenyl urea in 90 and 89% yield respectively. Despite the good results, use of toxic iodine is clearly unattractive.[56]

Unsymmetrical phenyl ureas were easily accessed by reaction of *N,N'*-diphenylurea with aliphatic amines.[57,58] The Et_3N-catalyzed reaction of diphenylurea and primary amines in DMF was reported to give the expected product in good yields (77-92%). However, the reaction of sterically hindered secondary amines did not proceed well.[57] This issue was solved with increased pressure in sealed autoclave. In this case, *N,N'*-diphenylurea was reacted with primary and secondary amines in toluene to give phenyl ureas in moderate to good yield (35-93%). In addition, no catalyst was required.[58]

In the course of a study on the origins of regioselectivity in the reaction of α-lactams with nucleophiles, a series of unsymmetrical urea peptide mimetics were formed in high yield with complete regiochemical control.[59] Malonyl hydroxamate **70** was reacted with a series of primary and secondary aliphatic and heterocyclic amines. In every case, the urea derivative **72** was the only product. It was claimed that the carbethoxy group in **70** would acidify the α-proton and facilitate the ring closure to α-lactam **71**. In addition, the electron-withdrawing effect of the same group was seen to influence the regiochemistry markedly, since only acyl attack on α-lactam **71** was observed. Ring opening to the enol followed by tautomerization led to **72** in good to excellent yield (61-96%) (*Scheme 18*).[59]

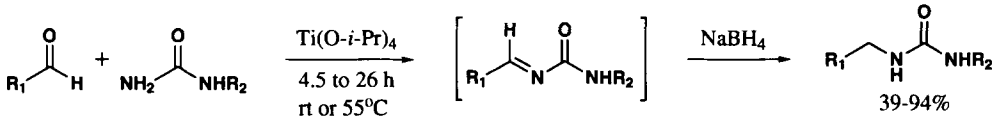


R_1R_2NH = aliphatic and heterocyclic 1° and 2° amines

Scheme 18

Unfortunately, the carbonylethoxy group at C-2 and the *N*-methyl group remain prerequisites to the success of this methodology and therefore limit the scope of application to α-carbonylethoxy-*N*-methyl unsymmetrical ureas. This methodology was further examined for 2-substituted-*N*-alkylmalonyl hydroxymates. It was found that the substituent at C-2 did not materially change the chemistry of the α-lactam intermediates produced from them, and they were converted using 5 equiv. of amine to unsymmetrical ureas in high yields (74-93%).[60]

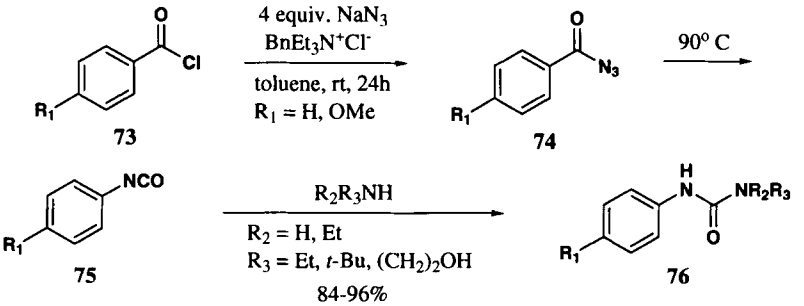
Unsymmetrical disubstituted ureas could also be obtained in high yield by a titanium (IV) isopropoxide/sodium borohydride mediated reductive amidation of aromatic aldehydes with monosubstituted ureas. In a proposed mechanism, titanium (IV) isopropoxide acts as a Lewis acid catalyst and as a water scavenger in THF, producing imines, which are subsequently reduced by sodium borohydride. Titanium (IV) isopropoxide was found compatible with a variety of functional groups such as lactams, acetonides, acetals and silyl ethers (*Scheme 19*). Nevertheless this method is limited by the reactivity of the aldehyde: aldehydes with a α-hydrogen did not undergo selective reductive amidation.[61]



R_1 = Ph, 2-Br-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-MeO-C_6H_4
R_2 = Me, Bn

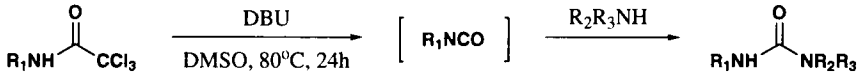
Scheme 19

Two unusual methods were recently reported for the synthesis of isocyanates, which were subsequently reacted with amines to produce unsymmetrical ureas.[62,63] In the first method, aromatic acid chloride **73** was reacted with sodium azide in toluene and in the presence of benzyltriethylammonium chloride as phase-transfer catalyst (PTC). Filtration of the solids and heating of **74** led to isocyanate **75** which was reacted directly with an amine to give *N,N,N'*-trisubstituted urea **76**, including derivatives containing hydroxyl, amine, amide, and carboxyl functional groups in excellent yield (84-96%) (*Scheme 20*).[62]



Scheme 20

Another unusual method obtained isocyanates by β-elimination of haloform from stable and readily available *N*-monosubstituted trihaloacetamides. These isocyanates were then reacted *in situ* with amines to give unsymmetrical ureas (*Scheme 21*). Trihaloacetamides were prepared by reaction of the appropriate amines with commercially available trihaloacetyl chlorides in good



R_1 = 3,4-Cl_2-C_6H_3, R_2 = Me, R_3 = *n*-Bu — **Neburon**
R_1 = Ph, R_2 = H, R_3 = 2-Me-Cy — **Siduron**

Scheme 21

yield as crystalline solids with long shelf life. The rate of reaction of these compounds with base exhibited a strong dependence on the nature of the trihaloethyl group: while tribromoacetamides underwent elimination of bromoform in DMSO at room temperature using DBU, elimination of chloroform from trichloroacetamides required heating at 80°C for several hours and trifluoroacetamides did not react even at 120°C for 2 days. Notable examples of unsymmetrical ureas synthesized using this "one-pot" methodology include well-known herbicides *Neburon* and *Siduron* (*Fig. 8*).[63]

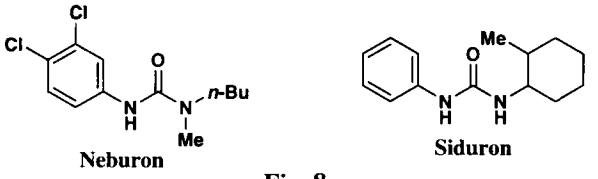


Fig. 8

III. CONCLUSION

The literature reviewed here demonstrates the importance of the urea functionality in drug design. Examples of urea-containing 5-HT reuptake inhibitors, HIV-1 protease inhibitors or p38 MAP kinase inhibitors nicely illustrate the utility and versatility of unsymmetrical ureas. As a consequence, great effort has been dedicated to the development of methodologies for the synthesis of unsymmetrical ureas, an area which will continue to be a topic of growing interest for medicinal and process chemists. For the latter especially, while the most applicable methods on an industrial scale remain the use of phosgene, CDI, carbonates or phenyl carbamates, interest in the field persists and the search for the development of practical, cost-effective and environmentally-friendly methodologies continues.

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