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Practical Synthesis of Unsymmetrical Ureas from Isopropenyl Carbamates

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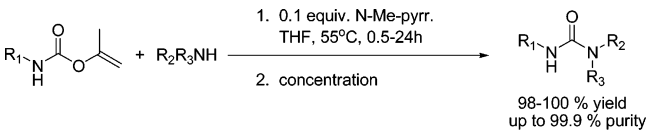

A very convenient method for the synthesis of unsymmetrical ureas is described, based on isopropenyl carbamates. The synthetic efficiency of traditional methods for urea formation, such as use of phosgene or alkyl and aryl carbamates, is limited by the formation of symmetrical urea side products or reaction reversibility. Isopropenyl carbamates react with amines cleanly and irreversibly and give unsymmetrical ureas in high yield and purity. This method is ideal for the rapid synthesis of compound libraries.

Ureas are frequently encountered subunits of synthetic targets with a wide range of applications in agrochemicals, petrochemicals, and pharmaceuticals. Used as hair dyes, additives in hydrocarbon fuels, detergents, and polymers, corrosion inhibitors, and more, ureas have also been shown to display significant biological activities as plant growth regulators.[1] Recently, potent urea-containing HIV-1 protease inhibitors[2] and p-38 MAP kinase inhibitors[3] have been disclosed. Despite the growing number of synthetic methodologies,[4−13] ureas are most commonly synthesized by reaction of an amine with phosgene[14] or carbamates.[15] Use of phosgene or phosgene surrogates[14,16] is still regarded as the traditional method for the formation of ureas, at least in industry. This approach is particularly efficient for symmetrical ureas. However, in the case of nonsymmetrical ureas, the synthetic efficiency is limited by the formation of symmetrical urea side products. Another method of choice for urea formation is the coupling of an alkyl or aryl carbamate with an amine.[15] In this case, the reaction is reversible and may not reach completion.[17] Herein we report a very convenient method for the synthesis of unsymmetrical ureas based on isopropenyl carbamates. Upon reaction with an amine, isopropenyl carbamate liberates acetone enol, which quickly tautomerizes to acetone and enables the reaction to go to completion. The method works well, is extremely clean and is ideal for the rapid synthesis of compound libraries, because simple evaporation of all volatiles yields the product in a high level of purity.

We initially compared the triphosgene and the "activated carbamate" routes to the isopropenyl carbamate reaction for the synthesis of unsymmetrical urea **1**, to gauge the efficiency of our method vs that of well-established procedures (Scheme 1).

Addition of 1-naphthylamine to isocyanate **3**, formed in situ by reaction of amine **2** with triphosgene,[16] led to

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(4) The plethora of methods to prepare ureas include reaction of an amine with carbonates,[5] *N*,*N*′-carbonyldiimidazole,[6] 1,1′-carbonylbisbenzotriazole,[7] *S*,*S*-dimethylthiocarbonate,[8] *S*-methylthiocarbamates,[9] formamides,[10] and isocyanates.[11] Ureas have also been prepared by metal-catalyzed carbonylation of amines using carbon monoxide[12] or carbon dioxide.[13]

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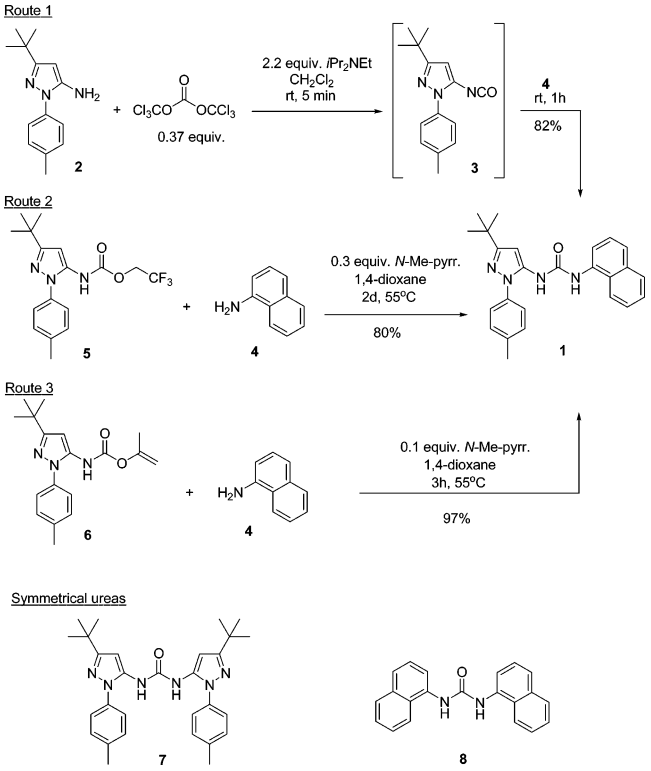
SCHEME 1. Triphosgene, Activated Carbamate, and Isopropenyl Carbamate Routes for the Formation of 1



urea **1** in 82% yield. The formation of the symmetrical ureas derived from **2** and **4** was also detected. Extensive optimization allowed for minimization of the amount of symmetrical ureas. When the mixture of amine **2** and Hünig's base was added to the solution of triphosgene and 6 equiv of Hünig's base, only 2−5% of symmetrical ureas **7** and **8** were formed. Although the method is fast and high yielding, the unavoidable formation of symmetrical ureas was its major drawback and chromatography or recrystallization was required to obtain **1** in high purity (Table 1).

When activated alkyl carbamate **5** was coupled with **4**, unsymmetrical urea **1** was obtained in 80% yield.[15d] The equilibrium was reached within 2 days at 55 °C. Kinetic studies by Aguirre and Collot showed 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 2).[17]

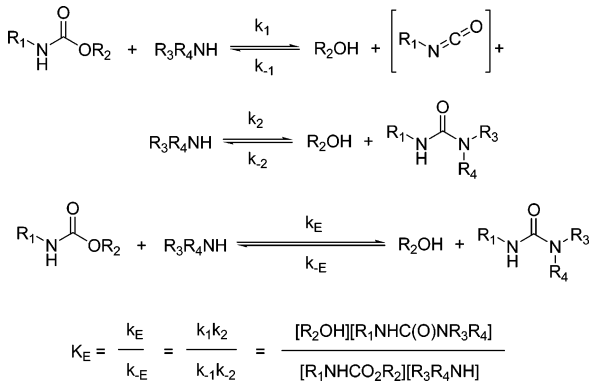
The reversibility of this reaction was confirmed by reacting **1** with trifluoroethanol in the presence of 0.3

TABLE 1. Evaluation of Triphosgene and Carbamate Routes to Urea 1

route	yield of **1**[a]	yield of **7**[a]	yield of **8**[a]	total of other impurities[b]
1	82	5	2	2
2	80	6	9	5
3	97	1	1	<1

[a] Yield determined by HPLC vs an external standard by weight %. [b] Determined by HPLC area %.

SCHEME 2. Kinetic Studies on the Reaction of Carbamates with Amines To Form Ureas



equiv of *N*-methylpyrrolidine (catalyst) in 1,4-dioxane at 55 °C, which produced carbamate **5** and 1-naphthylamine **4**. Interestingly, no free amine **2** or trifluoroethyl carbamate of **4** was observed. The equilibrium constant K_E of the reactions between the trifluoroethyl carbamate **5** and **4** in THF at 55 °C was determined to be ca. 65. This constant determined in turn that the maximum expected yield for this reaction is 89%. 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 (the pK_a of trifluoroethanol is 12.4).[17]

The obvious 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 (pK_a 10−11),[18] but also as ideal leaving groups which "self-remove" from the reaction mixture as they rapidly tautomerize to ketones and enable the urea formation to go to completion. Indeed, reaction of isopropenyl carbamate **6** with 1-naphthylamine led to **1** in less than an hour at 55 °C in 97% HPLC assay yield. Evaporation of THF, acetone, and *N*-methylpyrrolidine allowed for isolation of **1** in quantitative yield and 97% purity. The scope and limitations of our method were then explored and are summarized in Table 2.

Isopropenyl carbamates were prepared from the corresponding amines and isopropenyl chloroformate under Schotten−Baumann conditions. They were reacted with 1 equiv of amine in THF, using 0.1 equiv of *N*-methylpyrrolidine as catalyst. At reaction completion, mixtures were concentrated and the resulting crude ureas were analyzed by HPLC and NMR (Table 2).

Our study was based on the isopropenyl carbamate **6** as its structure was relevant to our developmental work.[3c] This carbamate was reacted with primary and secondary aliphatic and aromatic amines and the resulting ureas were isolated in high yield and purity. The product quality was independent of the reaction conditions: reaction of the isopropenyl carbamate **6** and amino ester

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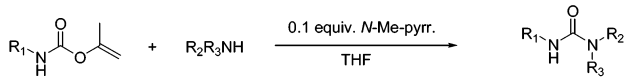
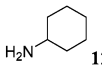
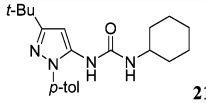
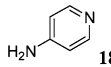
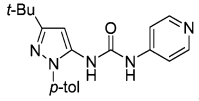
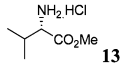
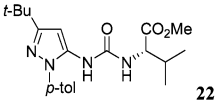
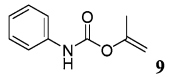
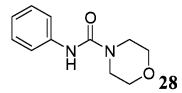
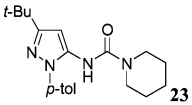
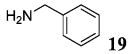
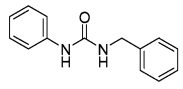
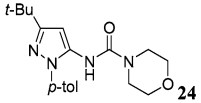
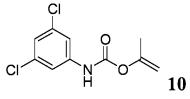
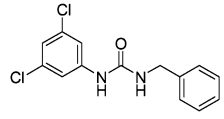
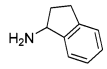
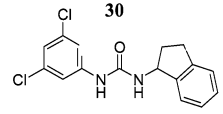
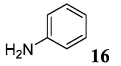
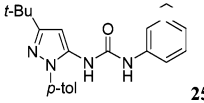
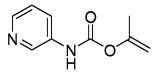
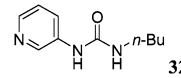
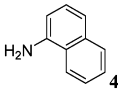
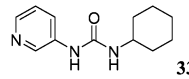
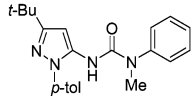
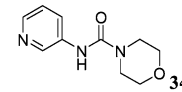
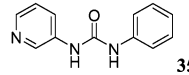
TABLE 2. Reaction of Isopropenyl Carbamates with Amines



Entry	Carbamate[a]	Amine	T (°C)	t (h)	Urea	Yield[b] (%)	Entry	Carbamate[a]	Amine	T (°C)	t (h)	Urea	Yield[b] (%)
1	**6**	 **12**	23°C	4h	 **21**	100	11	**6**	 **18**	55°C	0.5h	 **27**	99[f]
2	**6**	 **13**	23°C	22h	 **22**	95[c]	12	 **9**	**15**	55°C	72h	 **28**	99[g]
3	**6**	**13**	55°C	0.5h	**22**	95[c]	13	**9**[h]	**15**	77°C	18h	**28**	99
4	**6**	 **14**	23°C	2h	 **23**	99	14	**9**[i]	 **19**	110°C	18h	 **29**	99
5	**6**	 **15**	23°C	22h	 **24**	94	15	 **10**	**19**	55°C	21h	 **30**	100
6	**6**	**15**	55°C	0.5h	**24**	92	16	**10**	 **20**	55°C	45h	 **31**	98
7	**6**	 **16**	55°C	3h	 **25**	98	17	 **11**	*n*-BuNH$_2$	55°C	4h	 **32**	96[j]
8	**6**	 **4**	55°C	0.5h	**1**	97[d]	18	**11**	**12**	55°C	12h	 **33**	94[j]
9	**6**	 **17**	23°C	22h	 **26**	100	19	**11**	**15**	55°C	24h	 **34**	92[j]
10	**6**[e]	**17**	55°C	3h	**26**	98	20	**11**	**16**	55°C	18h	 **35**	92[j]

[a] The reaction was performed using carbamate (2.0 mmol), amine (2.0 mmol), and *N*-methylpyrrolidine (0.2 mmol) in THF (4 mL)). [b] Isolated yield, purity >98% by HPLC. [c] 1.1 equiv of *N*-methylpyrrolidine was used in this case. [d] Purity = 94% by ^{1}H NMR. [e] Reaction scale: 20 mmol. [f] Purity = 91% by ^{1}H NMR. [g] Purity = 94% by ^{1}H NMR. [h] Reaction run in EtOAc. [i] Reaction run in toluene. [j] The crude product was purified by trituration.

13 either at room temperature for 22 h or at 55 °C for 30 min gave urea **22** in 95% yield (>98% purity) in both cases (entries 2 and 3). As expected, the more nucleophilic aliphatic amines reacted more rapidly and under milder reaction conditions (e.g., entry 4 vs entries 5 and 6). In addition, reaction with more electron-rich carbamates, such as phenyl carbamic acid isopropenyl ester, required higher temperatures and longer reaction times to achieve complete urea formation (e.g. entry 14 vs entry 15). In all cases, yields and purities of crude products were superior to 92%. If required, the compounds could be purified by trituration with heptane and isolated in >92% yield (>99.5% purity) (entries 17 to 20).

In conclusion, we have demonstrated that the use of isopropenyl carbamates allows a rapid, scalable, and convenient synthesis of unsymmetrical ureas. The reaction of isopropenyl carbamates with amines irreversibly liberates acetone, which enables the reaction to go to completion. The method is easy to carry out and quite clean; it is ideal for the rapid synthesis of compound libraries as simple evaporation of all volatiles yields the product quantitatively.

Experimental Section

General Procedure. A solution of isopropenyl carbamate **6** (2 mmol) and amine **4** (2 mmol, 1 equiv) in 4 mL of THF was heated to 55 °C. *N*-Methylpyrrolidine (21 μL, 0.2 mmol, 0.1 equiv) was added. The reaction mixture was stirred at 55 °C for 30 min and cooled to room temperature. Concentration under vacuum afforded the crude product. Yield was determined by mass recovery of the crude urea. Purity was established by HPLC area %. In the case of HPLC area % purity <98%, the purity was determined by ^{1}H NMR. ^{1}H NMR purity was recorded, using dimethyl fumarate as internal standard.

Supporting Information Available: Detailed experimental procedures of carbamates **6** and **9**−**11** and of ureas **1** and **21**−**35** and ^{1}H and ^{13}C NMR spectra of ureas **1** and **21**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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