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Geometry-Selective Synthesis of *E* or *Z* *N*-Vinyl Ureas (*N*-Carbamoyl Enamines)

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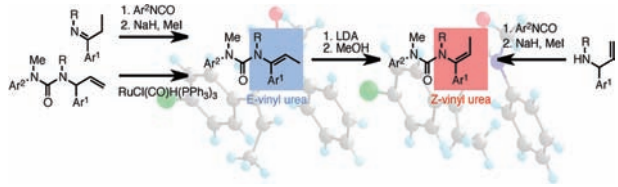
ABSTRACT



***N*-Vinyl ureas are emerging as a valuable class of compounds with both nucleophilic and electrophilic reactivity. They may be made by capturing the enamine tautomer of an imine with an isocyanate, a reaction which in general leads to the *E* isomer of the vinyl urea. Deprotonation of such a vinyl urea, or of an allyl urea, generates a dipole stabilized *Z*-allyl anion which may be protonated to return the *Z*-vinyl urea. Isomerization of an allyl urea with a Ru complex provides an alternative route to *E*-vinyl ureas.**

Chemical interest in ureas as a compound class has typically highlighted their structural and medicinal properties rather than their reactivity: ureas are generally stable to acid and base and have powerful hydrogen bonding abilities, making them key functional components of foldamers[1] and other supramolecular structures,[2] ligands or catalysts,[3] and drugs.[4] Recently, however, some new aspects of the reactivity of ureas have come to the fore, particularly with regard to amination chemistry[5] and functionalization by selective lithiation.[6,7] We have reported that *N*-aryl ureas are valuable starting materials for intramolecular arylation reactions.[8,9] In parallel with these reports, it has also become evident that ureas of certain classes undergo relatively mild solvolysis[7,9,10] to reveal amines or isocyanates, further enhancing their potential utility.

Ureas bearing *N*-alkenyl substituents **1** (i.e., *N*-vinyl ureas, or *N*-carbamoyl enamines) display useful and remarkable reactivity toward organolithiums and other strong bases. They may be deprotonated to yield urea-substituted allyllithiums,[11] or they may undergo umpolung carbolithiation by nucleophilic attack of the organolithium on the (nominally nucleophilic) β-position of the enam-

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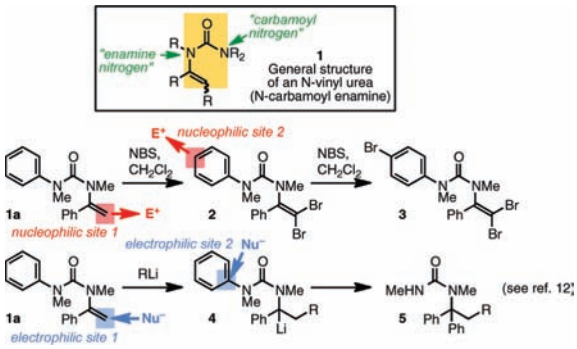
ine.[12] This polarity inversion is clearly illustrated by the comparison between the two reactions shown in Scheme 1. *Electrophilic* attack of bromine on *N*-vinyl urea **1a** gives

Scheme 1. Polarity-Promiscuous Additions to *N*-Vinyl Ureas



initially the β-bromoenamine **2** as expected, with excess bromine leading to further electrophilic substitution at the *N*-aryl ring to yield **3**. Remarkably, *nucleophilic* attack on the self-same vinyl urea **1** by an organolithium takes place at the same sites; initial carbolithiation at the β carbon of the enamine to give **4** is followed by attack of the resulting benzyllithium on the N-aryl ring of **4** to give **5** after rearrangement and protonation.[12]

The synthesis and reactivity of enamides in general has received attention in recent years,[13] but the synthetic potential of vinyl ureas is not matched by the number of methods for their synthesis. There are scattered reports of addition of imines to isocyanates to yield vinyl ureas,[14] but none of these reports address the issue of geometrical isomerism in the product. In this paper we describe our work on both general synthetic approaches to this functional class and also on methods which allow the synthesis of either geometric isomer of trisubstituted alkenes bearing urea substituents.

N-Acyl enamides can in general be formed by acylation of an imine in the presence of base.[13,14] We found that when *N*-methyl imines **7**, formed quantitatively from the corresponding acetophenones **6** (R = H), were treated with aryl isocyanates, *N*-vinyl ureas were formed in moderate to good yield (Scheme 2). The products were isolated after methylation at the carbamoyl nitrogen (see Scheme 1) to yield the 1,1-disubstituted vinyl ureas **1a**−**j** (Table 1).

The reaction between imines and isocyanates was also successful for the synthesis of 1,1,2-trisubstituted alkenyl

Scheme 2. Synthesis of Vinyl Ureas via Imines

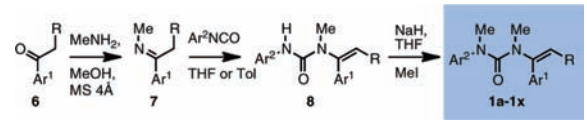


Table 1. Synthesis of *N*-Vinyl Ureas from Ketones **6** by Trapping Imines **7** with Isocyanates (Scheme 2)

1	Ar^1 =	Ar^2 =	R =	yield[a]/%	ratio[b] *E*/*Z*
1a	Ph	Ph	H	65	–
1b	Ph	*p*-$MeOC_6H_4$	H	42	–
1c	Ph	*p*-ClC_6H_4	H	32	–
1d	Ph	*o*-BrC_6H_4	H	35	–
1e	*p*-$MeOC_6H_4$	Ph	H	21	–
1f	*p*-ClC_6H_4	Ph	H	38	–
1g	*p*-FC_6H_4	Ph	H	29	–
1h	*p*-MeC_6H_4	Ph	H	35	–
1i	*m*,*p*-di$OMeC_6H_3$	Ph	H	41	–
1j	$PhCH_2$=CH_2-	Ph	H	63	–
1k	Ph	*m*-$MeOC_6H_4$	Me	40	94:6[c]
1l	Ph	*p*-$MeOC_6H_4$	Me	50	95:5
1m	Ph	*p*-FC_6H_4	Me	34	94:6
1n	Ph	*p*-ClC_6H_4	Me	20	92:8
1o	Ph	*p*-MeC_6H_4	Me	40	96:4
1p	Ph	*o*-$MeOC_6H_4$	Me	37	85:15
1q	Ph	*o*-MeC_6H_4	Me	39 (42[e])	91:9
1r	Ph	1-naphthyl	Me	35	93:7[c]
1s	*p*-$MeOC_6H_4$	Ph	Me	55	90:10[c]
1t	*p*-ClC_6H_4	Ph	Me	53	95:5[c,d]
1u	*p*-MeC_6H_4	Ph	Me	45	92:8[c]
1v	*p*-FC_6H_4	Ph	Me	46 (50[e])	95:5[c]
1w	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	Me	38 (40[e])	92:8
1x	Ph	*p*-MeC_6H_4	Ph	32	80:20

[a] Yield from ketone **6**. [b] Ratio determined by NMR. [c] *E* geometry of major isomer confirmed by NOE. [d] *E* geometry of major isomer confirmed by X-ray crystallography.[15] [e] Isolated yield of unmethylated urea **8**.

ureas **1k**−**1x** (Table 1).[16] Yields are quoted with respect to starting ketone **6** (R = Me) and, over the three steps, were moderate at best. However, no intermediate purification was required, and the reaction could be carried out on a multigram scale. In most cases, the conversion from the imine **7** to the urea **1** was carried out as a one-pot operation, but the intermediate urea **8** could also be isolated if required (Table 1 shows isolated yields for **8q**, **8v**, **8w**).

In the case of the 1,1,2-trisubstituted ureas, we found that the products were reliably formed as their *E* isomers, generally with >90:10 selectivity. The *ortho*-substituted **1p** was formed with slightly lower selectivity, presumably due to greater steric hindrance at the Ar^2 ring, and selectivity was also lower in the formation of the substituted stilbene **1x**. Selectivity was confirmed in several cases by NOE experiments and for **1t** by X-ray crystallography[15] (see Scheme 3).

It was possible to isomerize the *E* isomer of **1t** to its *Z* isomer straightforwardly simply by treatment with LDA and

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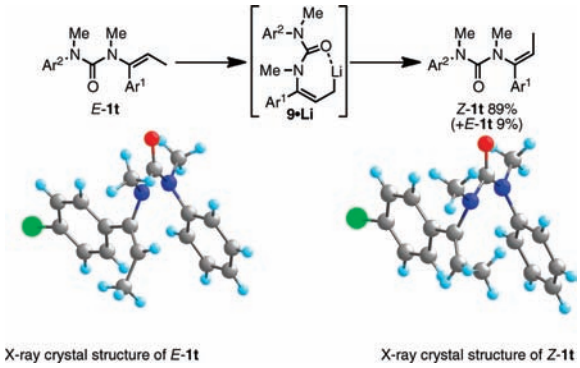
(15) X-ray crystallographic data for *E*-**1t**, *Z*-**1t**, **1y**, and **17k** have been deposited with the Cambridge Crystallographic database, deposition numbers CCDC 786909, 786910, 796730, and 796729.

(16) Tetrasubstituted products were formed only in very low yield and were highly unstable to purification.

Scheme 3. Conversion of the *N*-Vinyl Urea **1t** from *E* to *Z*

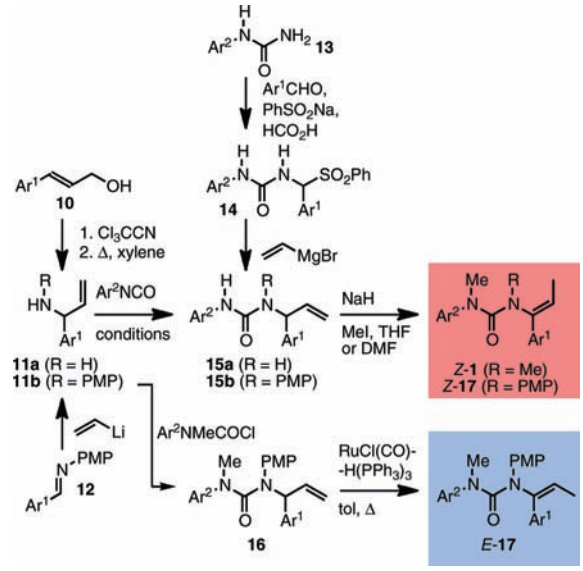


reprotonation with MeOH (Scheme 3). Both *E*- and *Z*-**1t** were characterized by X-ray crystallography.[15] LDA is known to form allyllithiums from *N*-vinyl ureas,[11] and allyllithiums substituted with donor substituents generally adopt a *Z* configuration to facilitate Li-donor interactions.[17] Provided conditions which promote orgonolithium rearrangement are avoided, the γ-reprotonation of the allyllithium occurs with retention of *Z*-geometry.[18]

Since the presumed allyl anion intermediate **9**[11,19] in this isomerization could in principle also be formed by deprotonation of an allyl (rather than a vinyl) urea, we found that a more direct route to the *Z* isomers could be realized by starting from an allylamine rather than an imine (Scheme 4). The allyl amines **11** were made either by Overman rearrangement of allyl alcohol **10**[20] (leading to primary amine **11a**) or by addition of vinyllithium to imine **12**[21] (giving PMP protected amine **11b**).[22] Addition of these amines to aryl isocyanates gave the ureas **15a** and **15b** respectively. An alternative but less versatile approach to **15a** involved vinylation of the sulfone **14**,[23] itself available from urea **13**.

Methylation of **15b** and dimethylation of **15a** both required the same conditions, sodium hydride and methyl

Scheme 4. *N*-Vinyl Ureas from Allylamines



iodide, with the best yields being obtained in DMF as opposed to THF. In both cases the *Z*-vinyl ureas were obtained (Table 2). Presumably, under the reaction conditions, an allyl anion forms at least to some extent, which is then protonated in the γ position to return the *Z* isomer of the product. It is interesting to note that the same

Table 2. Synthesis of *N*-Vinyl Ureas from Allylamines **11** by the Methods of Scheme 4

1 or **17**	via	Ar^1 =	Ar^2 =	R =	yield[a,b] /%	ratio *E*/*Z*[d]
1k	**10**, **11a**	Ph	*m*-$MeOC_6H_4$	Me	43[c]	<5:95[f]
1l	**10**, **11a**	Ph	*p*-$MeOC_6H_4$	Me	75	2:98[f]
1n	**10**, **11a**	Ph	*p*-ClC_6H_4	Me	67	<5:95[f]
1y	**10**, **11a**	Ph	*o*-FC_6H_4	Me	49	<5:95[g]
1z	**10**, **11a**	Ph	*p*-CNC_6H_4	Me	75	5:95
1aa	**13**, **14**	Ph	Ph	Me	74	<5:95
17a	**12**, **11b**	Ph	*m*-FC_6H_4	PMP	94	<5:95
17b	**12**, **11b**	Ph	2,6-diMeC_6H_3	PMP	72	<5:95
17c	**12**, **11b**	Ph	*m*-$MeOC_6H_4$	PMP	89	<5:95
17d	**12**, **11b**	Ph	*o*-MeC_6H_4	PMP	75	<5:95
17e	**12**, **11b**	Ph	*p*-ClC_6H_4	PMP	75[c]	<5:95
17f	**12**, **11b**	Ph	*p*-MeC_6H_4	PMP	85	5:95
17g	**12**, **11b**	Ph	*p*-CNC_6H_4	PMP	97	<5:95
17g	**11b**, **16**	Ph	*p*-CNC_6H_4	PMP	56	80:20
17h	**12**, **11b**	Ph	*m*-$CF_3C_6H_4$	PMP	73	5:95
17i	**12**, **11b**	Ph	Ph	PMP	75[c]	5:95
17j	**12**, **11b**	*p*-ClC_6H_4	Ph	PMP	55[c]	<5:95
17k	**12**, **11b**	*p*-ClC_6H_4	*p*-MeC_6H_4	PMP	67	6:94[g]
17l	**12**, **11b**	*p*-ClC_6H_4	*p*-CNC_6H_4	PMP	81	<5:95
17m	**12**, **11b**	*p*-CNC_6H_4	Ph	PMP	20	<5:95

[a] From **11a**, **11b**, or **16**. [b] Alkylation of **15** carried out in DMF unless otherwise stated. [c] Alkylation of **15** carried out in THF. [d] Determined by NMR. [e] Final product treated with silica to induce isomerization (see below). [f] Geometry of major isomer confirmed by comparison with *E*-**1**. [g] Geometry of major isomer confirmed by X-ray crystal structure.[15]

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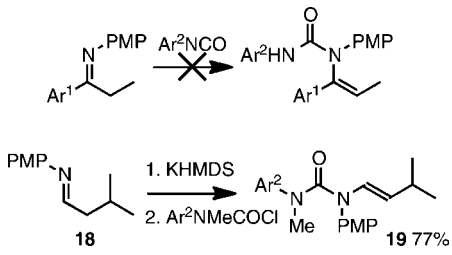
reaction conditions evidently fail to generate this allyl anion from the isomeric vinyl ureas **7** (R = Me), since methylation of this compound leads to the *E* vinyl urea (Scheme 2). This must be a kinetic effect, with α-deprotonation being faster than γ-deprotonation.[24]

The route to *Z*-**1** and *Z*-**17** shown in Scheme 4 allowed the synthesis of *N*-vinyl ureas bearing either aryl or alkyl groups on the enamine nitrogen. However, we found that the synthesis of *E*-**17** in a manner analogous to the synthesis of *E*-**1** shown in Scheme 2 was not applicable to the *N*-aryl subclass of vinyl ureas. No reaction was observed between *N*-arylimines and isocyanates (Scheme 5). We were however

Scheme 5. Synthesis of an *E*-Vinyl Urea from an Azaenolate

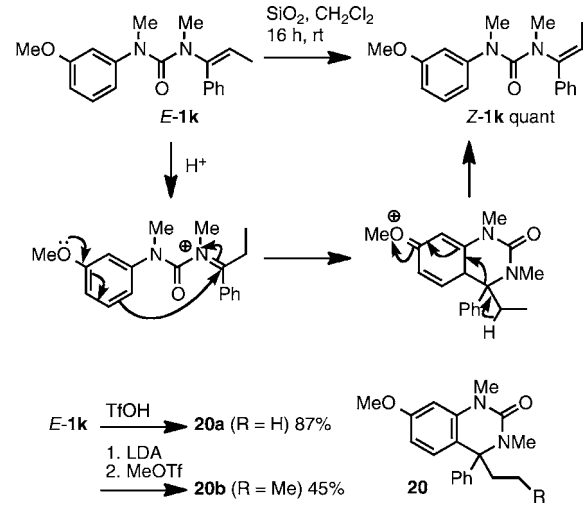


able to make such an *E N*-vinyl urea in one case by first treating the imine **18** with potassium hexamethyldisilazide to form the potassium azaenolate, which was then *N*-acylated with a carbamoyl chloride to form, directly, the *E*-vinyl urea **19** in 77% yield.

Nonetheless, the lack of nucleophilicity at nitrogen in *N*-aryl imines left us without a general route to *E*-vinyl ureas bearing an aryl substituent on the enamine nitrogen. We therefore explored alternative methods for the isomerization of the allyl ureas **9** which would avoid the *Z*-selective formation of an allyl anion. *N*-Acyl allyl amines may be isomerized to *N*-acylenamines not only with base but also with the Ru complex $RuCl(CO)H(PPh_3)_3$.[25] We therefore converted the allyl urea **11b** directly to the fully *N*-alkylated allyl urea **16**, avoiding the use of base to prevent isomerization, and treated it with $RuCl(CO)H(PPh_3)_3$ in refluxing toluene to induce migration of the double bond to the vinylic position. The product **17g** was formed with *E* selectivity complementary to that seen with the method employing base.

In most cases the *E*- and *Z*-vinyl ureas were stable to isomerization during workup and purification or on standing. However, a notable exception was presented by the urea **1k** carrying a 3-methoxyphenyl substituent, which isomerized readily on contact with silica during purification. For example, stirring *E*-**1k** in a suspension of silica in dichloromethane overnight gave *Z*-**1k** quantitatively. We presume that trapping of the acylenamine as a cyclic cation (Scheme 6) is involved in this isomerization, since this pathway is

Scheme 6. Isomerisation and Cyclization of *N*′-3-Methoxy Vinyl Ureas



uniquely favorable with a 3-methoxyphenyl urea. Evidence that a cyclic intermediate is involved came from treatment of *E*-**1k** trifluoromethanesulfonic acid: a cyclic product **20a** was formed in 89% yield by intramolecular Friedel−Crafts alkylation of the methoxy-substituted ring. A related product was formed when the allyl anion derived from *E*-**1k** was treated with methyl triflate. After neutral workup, the cyclic urea **20b** was obtained, presumably by cyclization of the first-formed vinyl urea in the triflic acid generated on workup (Scheme 6).

In conclusion, we show that simple *N*-alkyl vinyl ureas may be made from imines by N-acylation with isocyanates. Where geometrical isomerism is possible, these are formed predominantly as their *E* isomers but can be isomerized to their *Z* isomers by treatment with a strong base. Alternatively the *Z* isomers may be formed by methylation and isomerization of the corresponding allyl ureas.

This last method works equally for the synthesis of *Z*-*N*-aryl vinyl ureas, but the unreactivity of *N*-arylimines toward isocyanates means that the *E* isomers must be made by Ru-catalyzed isomerization of the corresponding allyl ureas.

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Supporting Information Available: Full experimental and characterization details for all compounds; X-ray crystallographic data for *E*- and *Z*-**1t**, **1y**, and **17k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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