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Tandem β-Alkylation−α-Arylation of Amines by Carbolithiation and Rearrangement of *N*-Carbamoyl Enamines (Vinyl Ureas)

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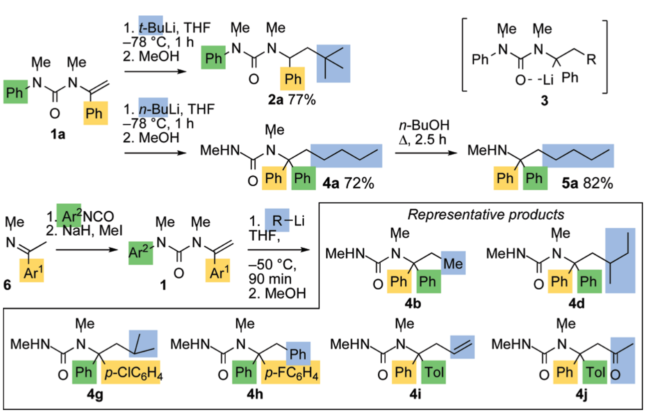
The construction of tertiary alkylamines[1] is a synthetic challenge exacerbated by the poor electrophilicity of imines.[1e] Umpolung[2] approaches to the problem involving electrophilic attack on a nitrogen-stabilized carbanion[3] are a solution, and the use of nitroalkenes allows tandem addition of substituents β and α to a nitrogen function.[4] In this paper, we report our discovery that *N*-carbamoyl enamines (*N*-alkenyl ureas) likewise exhibit umpolung reactivity, undergoing addition of organolithiums to their otherwise nucleophilic β-carbons. The addition can be coupled with N → C aryl transfer within the lithiated urea intermediate,[5,6] allowing two new C−C bonds to the α and β carbons of the alkene to be formed in a single pot.

Alkenyl urea **1a** was treated with *t*-BuLi in THF for 1 h at −78 °C. After the reaction was quenched with methanol, a single addition product **2a** was obtained in 77% yield (Scheme 1); evidently, regioselective carbolithiation of **1** occurs readily under these conditions, presumably yielding initially a proposed benzylic organolithium **3** (R = *t*-Bu). Repeating the reaction with less hindered organolithiums revealed further unconventional reactivity. With *n*-butyllithium, the rearranged product **4a** was obtained from **1** by N → C migration of the *N*-phenyl ring of **3**.[5] The product **4a** was straightforwardly converted to the tertiary alkyl amine **5a** by heating in *n*-BuOH for 2.5 h,[7] indicating that this "alkylarylation" of enamine **1a** could constitute a useful new method for the construction of multiply branched alkylamines.

Scheme 1. Umpolung Carbolithiation of Vinyl Ureas



Other *N*-vinyl ureas **1b**−**g** were made by *N*-carbamoylation of imines **6** and alkylation of the resulting ureas (Scheme 1). Table 1 shows the results of treating these *N*-vinyl ureas **1** with a range of organolithiums RLi in THF at −50 °C for 90 min.[8] In each case, carbolithiation followed by *N*-aryl migration resulted in tandem addition of two carbon substituents, R and Ar^2, across the electron-rich enamine double bond. Yields were good to excellent, and a range including methyl-, *n*- and *sec*-alkyl-, alkenyl-, and aryllithiums could be successfully added to the ureas.[9] Migration of a phenyl ring was generally faster and cleaner[8] than migrations of other (generally electron-rich) substituted aryl groups, and where a product could be made in two ways by exchanging Ar^1 and Ar^2, the alternative with the more electron-rich Ar^1 group was preferable. Unsaturated products **4i** and **4j** containing alkene or carbonyl functions were available by addition of vinyllithium or ethoxyvinyllithium.

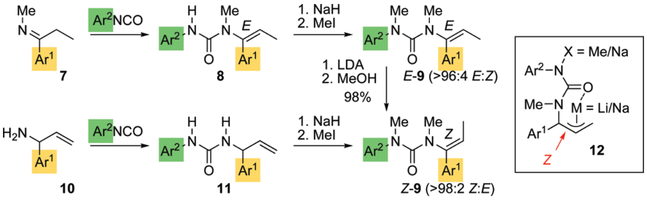
Table 1. Organolithium Additions to Vinyl Ureas **1**

entry	s.m.	Ar^1	Ar^2	R	**4**, yield (%)
1	**1a**	Ph	Ph	Bu	**4a**, 72[a]
2	**1a**	Ph	Ph	Me	**4b**, 78[b]
3	**1a**	Ph	Ph	*i*-Pr	**4c**, 74
4	**1a**	Ph	Ph	*s*-Bu	**4d**, 74
5	**1a**	Ph	Ph	Ph	**4e**, 77[c]
6	**1b**	Ph	*p*-MeOC$_6$H$_4$	*i*-Pr	**4f**, 75
7	**1c**	Ph	*p*-ClC$_6$H$_4$	*i*-Pr	**4g**, 72
8	**1d**	*p*-MeOC$_6$H$_4$	Ph	*i*-Pr	**4f**, 77
9	**1e**	*p*-ClC$_6$H$_4$	Ph	*i*-Pr	**4g**, 86
10	**1f**	*p*-FC$_6$H$_4$	Ph	Ph	**4h**, 78
11	**1g**	*p*-Tol	Ph	$-CH_2{=}CH_2$	**4i**, 75
12	**1g**	*p*-Tol	Ph	$-CH(OEt){=}CH_2$	**4j**, 96[d]

[a] Deprotected to yield amine **5a** (82%). [b] Deprotected to yield amine **5b** (76%). [c] Deprotected to yield amine **5e** (74%). [d] Mixture of **4j** and a pyrimidinedione (see the Supporting Information).

Treating the propiophenimines **7** with aryl isocyanates gave vinyl ureas **8** with >96:4 *E*/*Z* selectivity (Scheme 2).[10] Methylation returned the alkenyl ureas **9** also as >96% *E* isomer. The *Z* isomers of **9** were available by a parallel route from allylamines **10**,[11] which gave allylic ureas **11** upon treatment with aryl isocyanates. Methylation of **11** was accompanied by double-bond migration to give the ureas **9** with 98:2 *Z*/*E* selectivity.[12] (*Z*)-**9** can alternatively be made directly from (*E*)-**9** by formation of a (*Z*)-allyl anion represented as **12** (M = Li; X = Me): treatment of (*E*)-**9a** with LDA followed by methanol led to some decomposition but gave (*Z*)-**9a** with 98:2 *Z*/*E* selectivity.[13]

Scheme 2. Synthesis of (*E*)- and (*Z*)-Alkenyl Ureas



In THF at −40 °C, alkyllithiums RLi underwent clean addition to (*E*)-alkenyl ureas **9a**−**d** (which have Ar^2 = Ph) and gave carbolithiation−rearrangement products **13a**−**e** as single diastereoisomers (Table 2, entries 1−5). Ureas **13a**−**e** were readily converted to single diastereoisomers of the amines **14** in refluxing *n*-butanol (Scheme 3).[7] The relative configuration of amine **14a** was confirmed by an X-ray crystal structure[14] of its hydrochloride salt **14a**·HCl (Scheme 3), which showed that **13** and hence **14** are formed by syn addition of R and Ar^2. As expected, transposition of Ar^1 and Ar^2 within the starting material led to an inversion of

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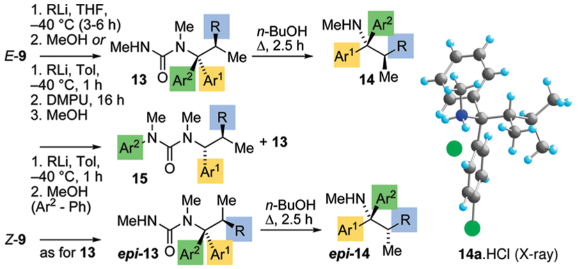
Table 2. Organolithium Additions to Vinyl Ureas **9**

entry	s.m.	X in Ar^1 = C_6H_4X	Y in Ar^2 = C_6H_4Y	R	**13** or **15**, yield (%)	**14**, yield (%)
1	(*E*)-**9a**	*p*-Cl	H	*i*-Pr^a	**13a**, 81	**14a**, 66
2	(*E*)-**9a**	*p*-Cl	H	*n*-Bu^a	**13b**, 70	**14b**, 73
3	(*E*)-**9b**	*p*-F	H	*i*-Pr^a	**13c**, 69	**14c**, 75
4	(*E*)-**9c**	*p*-Me	H	*i*-Pr^a	**13d**, 60	**14d**, 70
5	(*E*)-**9d**	*p*-MeO	H	*i*-Pr^a	**13e**, 76	**14e**, 70
6	(*E*)-**9e**	H	*p*-MeO	*i*-Pr^b	*epi*-**13e**, 60	*epi*-**14e**, 70
7	(*E*)-**9f**	H	*m*-MeO	*i*-Pr^b	**13f**, 60	**14f**, 69
8	(*E*)-**9f**	H	*m*-MeO	*n*-Bu^b	**13g**, 65	–
9	(*Z*)-**9a**	*p*-Cl	H	*i*-Pr^b	*epi*-**13a**, 75	*epi*-**14a**, 67
10	(*Z*)-**9e**	Ph	*p*-MeO	*i*-Pr^b	**13e**, 54	**14e**, 70
11	(*E*)-**9e**	Ph	*p*-MeO	*i*-Pr^c	**15a**, 85	
12	(*E*)-**9e**	Ph	*p*-MeO	*n*-Bu^d	**15b**, 85	
13	(*Z*)-**9e**	Ph	*p*-MeO	*i*-Pr^a	*epi*-**15a**, 44	
14	(*E*)-**9f**	Ph	*m*-MeO	*i*-Pr^c	**15c**, 83	
15	(*E*)-**9f**	Ph	*m*-MeO	*n*-Bu^d	**15d**, 85	
16	(*E*)-**9f**	Ph	*m*-MeO	*t*-Bu^a	**15e**, 60	

[a] THF, −40 °C, 3−6 h. [b] (1) Tol, −40 °C, 1 h; (2) DMPU, −40 to +25 °C, 16 h. [c] Tol, −40 °C, 1−2 h. [d] Et_2O, −40 °C, 90 min.

Scheme 3. Stereospecific Reactions of (*E*)- and (*Z*)-Alkenyl Ureas



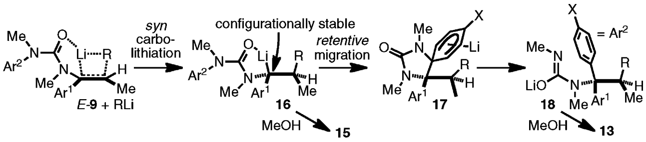
the relative configuration of the product (entries 5 and 6): the products from (*E*)-**9d** and (*E*)-**9e** are epimeric. The migrations of the more electron-rich rings of **9e** and **9f** were slower, and the best yields of **13f** and **13g** were obtained by carrying out the carbolithiation at −40 °C in toluene and adding DMPU to enforce rearrangement after the carbolithiation was complete (entries 6−8).[5a,15] Epimeric products were also formed when *E* starting materials were replaced with their *Z* isomers (entries 9 and 10). Thus, addition of *i*-PrLi to the *Z* isomer of **9e** yielded **13e**, which is epimeric with *epi*-**13e** derived from (*E*)-**9e** and identical to that produced from the "ring-transposed" (*E*)-**9d**.

Carbolithiation and rearrangement of **9** is slower than that of **1**. With **9e** and **9f**, the electron-rich aryl rings failed to migrate in the absence of DMPU,[15] and it was possible to isolate products **15** resulting from carbolithiation without rearrangement, even in THF (entries 11−16). Epimeric products were produced from (*E*)- and (*Z*)-**9f**.

Evidently, both the carbolithiation and aryl migration steps are stereospecific,[16] since either inverting the double-bond geometry in the starting material or exchanging the substituents Ar^1 and Ar^2 changes the configuration of the products. The crystal structure of **14a** indicates that the addition−migration process is mechanistically suprafacial. We propose that the reactions proceed by umpolung carbolithiation[17,18] of **9** (Scheme 4) to give a substituted benzyllithium **16** that is configurationally stable[19] on the time scale of the reaction. With electron-rich Ar^2, **16** may be trapped as **15** by retentive protonation.[17c,18a] In general, however, benzyllithium **16** undergoes retentive[5a,20] N → C aryl migration by attack of the organolithium center on the *N*-aryl ring Ar^2 (**17**), transferring Ar^2 to the position α to N and yielding lithiourea **18** and hence **13** upon protonation.

This new reaction allows the "1,2-alkylarylation" of a urea-substituted alkene and provides a valuable method for the construction of heavily substituted amines from four components: a ketone, an amine, an isocyanate, and an organolithium.

Scheme 4. Proposed Mechanism



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Supporting Information Available: Full experimental procedures, characterization data for all compounds, and crystallographic data for **14a**·HCl (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For deprotection of ureas by neutral solvolysis, see: (a) ref 5b; (b) Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 8721.

(8) At −78 °C, yields were generally lower, and at least 2 h was required for completion, except in the case of a migrating Ph group, which proceeded within 2 h at −78 °C.

(9) Furyllithium and alkynyllithiums failed to add to **1**. Phenyllithium and vinyllithium, which added cleanly to **1**, failed to add to **9**.

(10) A review of enamides: Carbery, D. *Org. Biomol. Chem.* **2008**, *6*, 3455.

(11) Allylamines **10** were made by Overman rearrangement of the cinnamyl alcohols (see the Supporting Information).

(12) We ascribe both the double-bond isomerization and the *Z* selectivity to deprotonation α to nitrogen by NaH to yield allyl anions represented as **12** (M = X = Na), which prefer a *Z* configuration. See: (a) Price, C. C.; Snyder, W. R. *Tetrahedron Lett.* **1962**, *3*, 69. (b) Beak, P.; Lee, B. *J. Org. Chem.* **1989**, *54*, 458. (c) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665. Presumably, γ-deprotonation to give the same dianion from **8** is slower.

(13) The alkene geometry was confirmed in each case by NOE studies and, for (*E*)- and (*Z*)-**9a**, by X-ray crystallography.

(14) The X-ray crystallographic data has been deposited with the Cambridge Crystallographic Data Centre under deposition number 762201.

(15) The coordinating cosolvent DMPU typically accelerates nucleophilic attack of organolithiums on aromatic rings. See: Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5060, and references therein.

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