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Synthesis of Vinylogous Carbamates by Rhodium(II)-Catalyzed Olefination of Tertiary Formamides with a Silylated Diazoester

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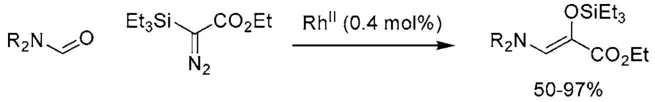
ABSTRACT



Treatment of tertiary formamides with a silylated diazoester in the presence of a rhodium(II) catalyst leads to the formation of 3-amino-2-silyloxyacrylates in good yield. No olefination is observed if a nonsilylated diazo compound is employed.

The reaction of metal carbenes derived from α-diazocarbonyl compounds with heteroatom lone pairs is a well-established method for the preparation of ylids.[1] Recently, the use of α-silylated α-diazoesters compounds has been found to be beneficial in a range of ylid-forming[2] and other metal carbene reactions;[3] better selectivity and fewer side-reactions than with the parent diazoesters are frequently observed. In this communication, we describe the use of such a silylated diazoester in an unusual and unexpected formamide olefination reaction.

As part of a program directed toward the synthesis of the sarain alkaloids, we recently synthesized bicyclic aminal **1**.[4] It was anticipated that treatment of **1** with silylated diazoacetate **2**[5] in the presence of an appropriate metal catalyst would lead to formation of an ammonium ylid **3** from the more nucleophilic of the nitrogen atoms, followed by rearrangement to a ring-expanded product **4**. Contrary to these expectations, when **1** and **2** were heated in benzene in the presence of 10 mol % rhodium(II) acetate, the major product obtained was the vinylogous carbamate **6**. This product arises from reaction of the intermediate metal carbene with the formamide oxygen to give **5** and subsequent rearrangement (Scheme 1).

The scope and limitations of this reaction were next explored. Using 1-formylpyrrolidine (**7a**, Figure 1) as a test substrate,[6] it was established that 0.4 mol % rhodium(II)

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Scheme 1. Unanticipated Generation of a Vinylogous Carbamate

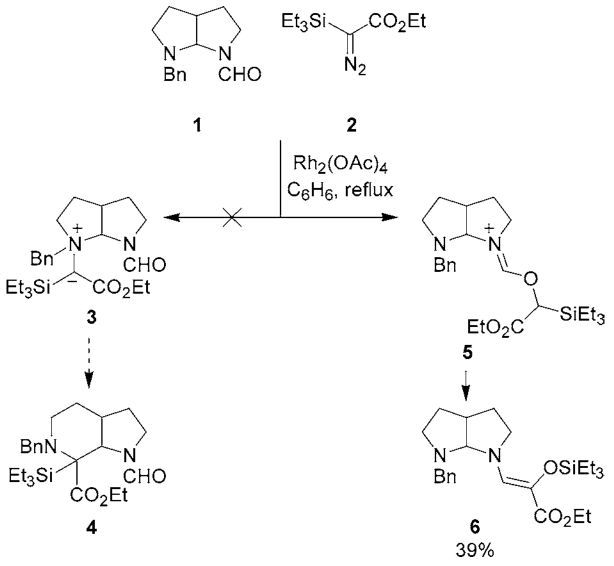
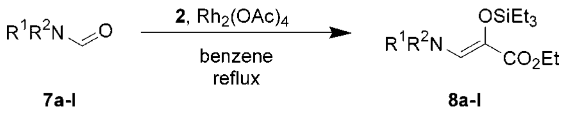


Table 1. Conversion of Formamides to Vinylogous Carbamates[a]



entry	amide	time	product	yield %
1	**7a**	90 min	**8a**	80[b]
2	**7b**	90 min	**8b**	83[c]
3	**7c**	45 min	**8c**	90
4	**7d**	90 min	**8d**	87
5	**7e**	240 h[d]	**8e**	63
6	**7f**	165 min	**8f**	82
7	**7g**	45 min	**8g**	64
8	**7h**	90 min	**8h**	90
9	**7i**	90 min	**8i**	97
10	**7j**	90 min	**8j**	85
11	**7k**	90 min	**8k**	69
12	**7l**	180 min	**8l**	50[e]

[a] Conditions: **7a**−**l** (1 mmol), **2** (1.25 mmol), Rh$_2$(OAc)$_4$ (4 μmol), benzene (6 mL), reflux. [b] Yield of 89% was obtained after 16 h. [c] Yield of 92% was obtained after 16 h. [d] Further **2** (1.25 mmol) and Rh$_2$(OAc)$_4$ (4 μmol) were added after 144 h. [e] Ratio of *Z*:*E* isomers was 3:2.

acetate was sufficient to catalyze the reaction, and the corresponding alkene **8a** could be obtained in ≥80% yield as a single geometric isomer, by chromatography on alumina (entry 1, Table 1). The (*Z*)-geometry of the double bond was established by observation of a nuclear Overhauser enhancement between the CH_2N protons of the pyrrolidine ring and the methylene protons of the triethylsilyl moiety. Control experiments established that no reaction took place in the absence of the rhodium catalyst and that if ethyl diazoacetate was used in place of the silylated analogue **2**, the starting amide was recovered unchanged.[7]

Similarly efficient reactions were observed with piperidine- and morpholine-derived formamides (entries 2−4), but when 1-formyl-4-methylpiperazine (**7e**) was employed as the substrate, the reaction proceeded very slowly (entry 5). This reduced reactivity was ascribed to competitive complexation of the rhodium catalyst by the tertiary amine of the substrate.[8] Nevertheless, a moderate yield of alkene **7e** could be obtained after an extended reaction time. 1-Formylpiperazines in which the coordinative ability of the second nitrogen was lowered by substitution with a bulky benzhydryl group (**7f**, entry 6) or by derivatization with a 3-chlorophenyl substituent (**7g**, entry 7) underwent reaction at a similar rate to compounds **7a**−**d**.

Formamides derived from acyclic secondary amines were also converted to the corresponding vinylogous carbamates in moderate to high yields under these reaction conditions (entries 8−12). In the case of formanilide **7l**, the alkene product **8l** was obtained as a mixture of geometric isomers (entry 12). For all other substrates, solely the (*Z*)-alkenes were obtained.

It is noteworthy that in all cases, the only product isolated from the reaction was the vinylogous carbamate: for the piperazine-derived formamides **7e**−**g**, no products arising from ammonium ylid formation were observed, and in the case of alkene-containing substrates **7i** and **7j**, no cyclopropane products were obtained.

The reaction described in this letter is analogous to an intramolecular reaction of some amido diazoketones that has been reported by Padwa et al.[9] Related intramolecular reactions between diazoketones and thiolactams were utilized

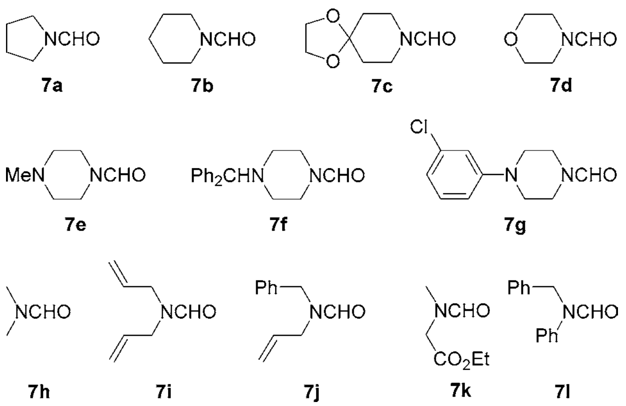


Figure 1. Tertiary formamides subjected to the olefination conditions.

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[6] Formamides were used as received from commercial sources or prepared by reaction of the corresponding secondary amines with ethyl formate; see: Moffat, J.; Newton, M. V.; Papenmeier, G. J. *J. Org. Chem.* **1962**, *27*, 4058.

[7] In this case, peaks corresponding to diethyl maleate and diethyl fumarate could be observed in the ^1H NMR spectrum of the crude reaction mixture.

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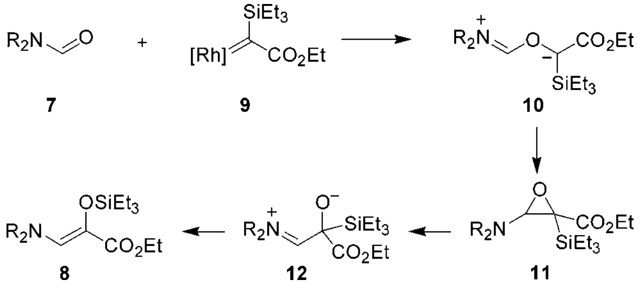
by Danishefsky et al. in syntheses of A58365A[10] and indolizomycin,[11] and one example of an intermolecular reaction between a thiolactam and ethyl diazoacetate was also reported.[10] In addition, Corey has reported the conversion of some cyclic secondary amides to imidates using ethyl diazoacetate and a rhodium catalyst.[12]

The mechanism we propose for this conversion is essentially the same as that put forward by Padwa for intramolecular reactions (Scheme 2).[9] Reaction of the diazo compound with the metal catalyst leads to a rhodium carbene species (**9**), which serves to transfer the carbene moiety to the carbonyl group of the amide, giving carbonyl ylid **10**. Cyclization of this intermediate to an epoxide **11** is followed by ring-opening to zwitterion **12**. Finally, silyl group migration from carbon to oxygen[13] gives the observed product **5**.

Scheme 2. Proposed Course of the Olefination Reaction



The importance of the triethylsilyl group to this process can be judged by the fact that attempts to carry out reactions between ethyl diazoacetate and tertiary formamides do not lead to any olefination of the amide; instead, the diazo compound is consumed unproductively in the formation of diethyl maleate and diethyl fumarate, and the amide is recovered unchanged. This "carbene dimerization" is suppressed, relative to reaction with the formamide substrate, upon silylation of the diazo compound.[14] This may be attributable to the increased steric hindrance that pertains to the silylated compound, and/or to the π-acceptor character of the silyl substituent, which renders the diazo compound less nucleophilic. The unusual chemoselectivity observed with formamides **1**, **7e**, and **7f**, in which the metal carbene reacts with a formamide oxygen rather than the ostensibly more nucleophilic tertiary amine, may also be steric in nature.

The stereoselectivity of the olefination is likely to be thermodynamically controlled; while the reaction may initially give a mixture of isomers, rapid conversion to the thermodynamically more stable (Z)-isomer is expected to occur[15] under the reaction conditions, due to the partial single-bond character of the olefin. Only with the anilide-derived product **8l**, in which the degree of electron-release from the nitrogen is lower, is this equilibration suppressed, resulting in the observed mixture of (E)- and (Z)-isomers.

In conclusion, we have discovered a new and general method for the conversion of tertiary formamides to α-silyloxy-β-dialkylaminoacrylates. We are currently investigating further transformations of these intriguing products.[16]

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Supporting Information Available: Experimental procedures; full spectroscopic details for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra for compounds **6** and **8a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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