

A Practical Variant of the Claisen–Eschenmoser Rearrangement: Synthesis of Unsaturated Morpholine Amides

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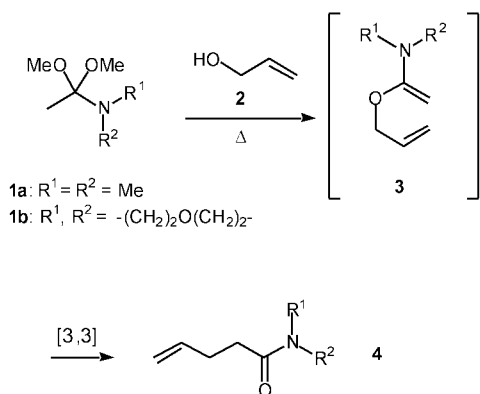
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Abstract: A Claisen–Eschenmoser type rearrangement giving rise to unsaturated morpholine-, piperidine- and pyrrolidine amides is described.

Key words: Claisen–Eschenmoser rearrangement, morpholine amides, ketene *N,N*-acetal, guanacastepene, ring closing metathesis

The Claisen–Eschenmoser rearrangement is arguably the most powerful method for the synthesis of γ,δ -unsaturated carbonyl compounds (Scheme 1).¹ It involves the reaction of an amide acetal, typically *N,N*-dimethylacetamide dimethyl acetal (DMADMA, **1a**, $R^1 = R^2 = \text{Me}$), with an allylic alcohol **2** to produce a mixed ketene acetal **3**. This intermediate then undergoes [3,3]-sigmatropic rearrangement at relatively low temperatures to afford the amide **4**. To date, the reaction has remained confined mostly to the preparation of *N,N*-dimethylamides. Relatively little attention has been given to other substituents at the nitrogen, primarily due to the somewhat tedious preparation of the corresponding amide acetals **1** ($R^1, R^2 = \text{Me}$). Typically, these reagents are made by treatment of an acetamide with an alkylating agent, followed by addition of an alkoxide.²

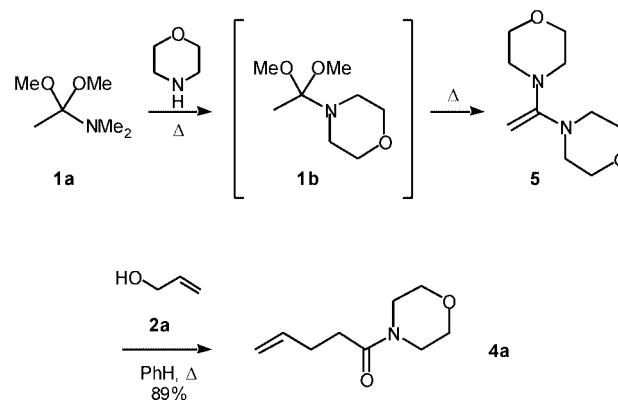


Scheme 1

In the context of a natural product total synthesis (*vide infra*), we sought to prepare γ,δ -unsaturated morpholine amides directly from allylic alcohols through a Claisen–Eschenmoser rearrangement using amide acetal **1b** [$R^1, R^2 = -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$] as the reagent. Morpholine amides

have recently emerged as viable alternatives to Weinreb amides in the synthesis of ketones.³ Although **1b** is a known compound,⁴ no procedure for its preparation has been reported in the literature. Unfortunately, all attempts to prepare **1b** from *N*-acetyl morpholine by *O*-alkylation and subsequent addition of NaOMe were met with limited success.

We now report that simple condensation of DMADMA (**1a**) with morpholine gives access to **1b** and related reagents. This uncatalyzed exchange is driven by the volatility of dimethyl amine and methanol.⁵ Heating of **1a** with excess morpholine under a stream of nitrogen initially results in a complex mixture consisting predominantly of **1b** and the known ketene *N,N*-acetal **5** (Scheme 2).⁶ Upon further heating, this mixture converts fully into **5**. Dilution with a solvent (benzene or xylenes), followed by addition of allyl alcohol (**2a**) and further heating afforded the rearranged product **4a** in 89% yield. Conveniently, the preparation of the reagent **5** and the subsequent rearrangement can be performed as a one-pot procedure.



Scheme 2

The application of these conditions to other allylic alcohols **2b–m** is summarized in Table.⁷ The reactions usually required high temperatures or sealed tube conditions. Molecules featuring quaternary centers could be prepared in good yields (entries 7 and 8). Dienols (entries 5 and 6) and secondary alcohols (entries 9 and 10) also performed well. Rearrangement of **2j** and **2k** resulted in the exclusive formation of the *E*-isomers **4j** and **4k**, respectively. Cycloalkenols, however, gave poor yields (entries 11 and 12).

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Table Synthesis of Morpholine Amides.

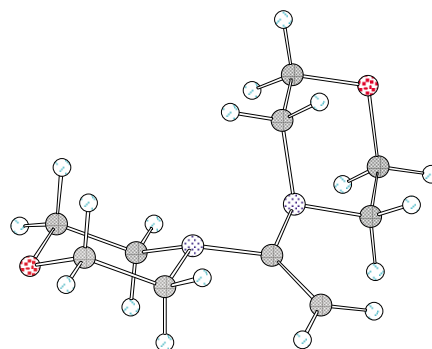
Entry	Allylic alcohol	Product	Method/yield ^a
1	2a 	4a 	(A, 89%)
2	2b 	4b 	(B, 76%)
3	2c 	4c 	(A, 77%)
4	2d 	4d 	(B, 96%)
5	2e 	4e 	(B, 75%)
6	2f 	4f 	(B, 74%)
7	2g 	4g 	(A, 73%)
8	2h 	4h 	(B, 81%)
9	2j 	4j 	(B, 84%)
10	2k 	4k 	(A, 90%)
11	2l 	4l 	(A, 36%)
12	2m 	4m 	(A, 16%)

^a Method A: **5**, PhH, sealed tube, 160 °C; Method B: **5**, xylenes, reflux

Mechanistically, the reaction proceeds presumably via rapid addition of the allylic alcohol to **5**, followed by thermal elimination of morpholine. It requires significantly

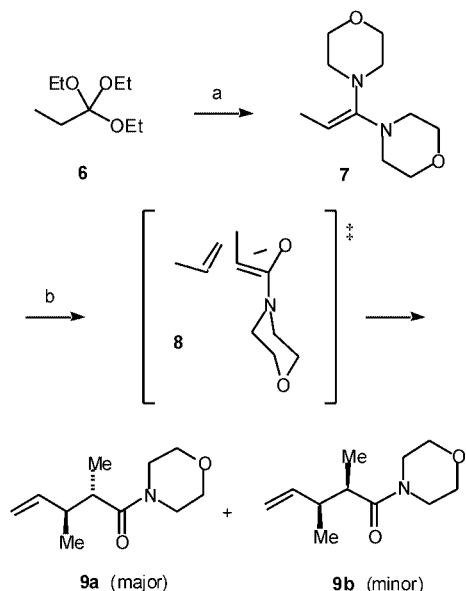
higher temperatures than the original Claisen–Eschenmoser procedure due to the slower elimination of morpholine instead of methanol. Interestingly, although ketene *N,O*-acetals are known to participate in Claisen–Eschenmoser rearrangements,⁸ ketene *N,N*-acetals like the commercially available compound **5** have not been investigated in this context.

The crystal structure of **5** is shown in Figure 1.⁹ It is one of two known X-ray crystal structures of 1,1-diamino substituted ethylenes.¹⁰ The molecule adopts a C_2 -symmetric conformation in the solid state with the C_2 -axis along the double bond. To avoid steric conflicts, the morpholine rings are twisted about 60° with respect to the alkene axis.

**Figure 1** Crystal structure of ketene *N,N*-acetal **5**.

In an attempt to make our procedure more economical, we also investigated the reaction of orthoesters with amines as a route to the ketene aminal **5** and similar compounds, e.g. **7** (Scheme 3). The preparation of dimorpholino ketene *N,N*-acetals from triethyl orthoacetate or triethyl orthopropionate (**6**) and morpholine has been previously described.^{6b,c} Reagent **7**, which was also prepared in situ and used without purification, allowed us to investigate relative diastereoselectivities. Heating of **7** with crotyl alcohol (mixture of diastereomers; *E:Z* = 18:1) resulted in a 5.1:1-mixture of diastereomeric amides **9a** and **9b**. The preference for the *anti*-diastereomer **9a** can be explained in terms of a chair-shaped transition state. Mixed ketene *N,O*-acetals are known to be formed mostly as *Z*-isomers under Claisen–Eschenmoser conditions. In combination with a *E*-allylic alcohol, this affords predominantly *anti* diastereomers, provided the reaction proceeds through transition state **8**.¹¹ The stereochemical outcome of this reaction contrasts recent results by MacMillan who observed very high *syn*-diastereoselectivities for *E*-isomers in the course of ketene–Claisen rearrangements of *N*-allyl morpholines.¹²

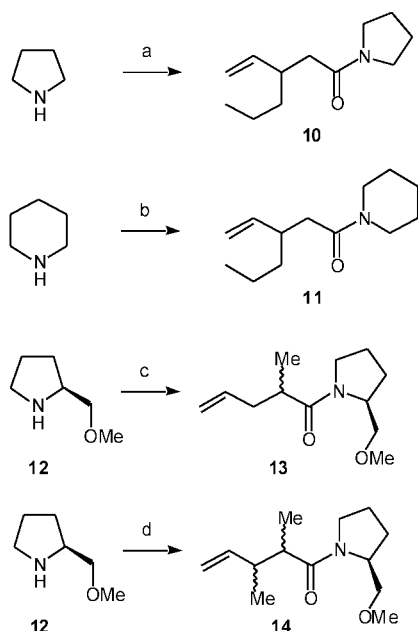
The extension of our method to other amines is shown in Scheme 4. Pyrrolidine and piperidine reacted cleanly to yield the corresponding amides **10** and **11**. It can be presumed that intermediates analogous to **5** and **7** are involved in these reactions. Chiral amines such as **12** were also explored. Heating of enantiomerically pure **12** with trimethyl orthopropionate and catalytic amounts of toluene sulfonyl chloride, followed by further heating with al-



Scheme 3 Reagents and conditions: (a) Morpholine, cat. TsCl, 160 °C. (b) Crotyl alcohol (*E*:*Z* = 18:1), PhH, sealed tube, 160 °C (84%; **9a**:**9b** = 5.1:1).

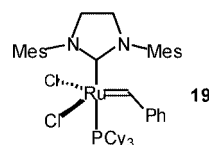
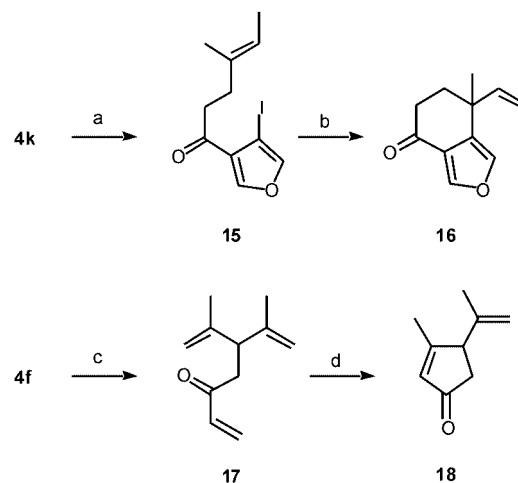
yl alcohol (**2a**) or crotyl alcohol (**2b**) afforded amides **13** and **14**, respectively, as mixtures of diastereomers. In accordance with similar reports in the literature, however, the diastereoselectivities observed were rather low.¹³

Morpholine amides **4f** and **4k** were used in a program directed towards the total synthesis of (+)-guanacastepene, a novel diterpene with potent antibiotic properties.¹⁴ Reaction of **4k** with 3-iodo-4-lithiofuran¹⁵ afforded a low



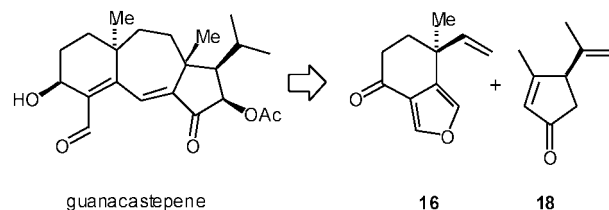
Scheme 4 Reagents and conditions: (a) **1a**, Δ \rightarrow *Z*-2-hexenol, Δ (82%). (b) **1a**, Δ \rightarrow *Z*-2-hexenol, Δ (86%). (c) **6**, cat. TsCl, Δ \rightarrow allyl alcohol, Δ (82%; 1.8:1 mixt. of diastereomers). (d) **6**, cat. TsCl, Δ \rightarrow (*E*:*Z* = 18:1), Δ (75%; 7:4:1:1 mixture of diastereomers).

yield of furyl ketone **15**,¹⁶ which underwent intramolecular Heck-cyclization to furano cyclohexanone **16**. Conversely, coupling of **4f** with vinyl magnesium bromide proceeded smoothly to furnish vinyl ketone **17** in good yield. Exposure of this substrate to Grubbs' *N*-heterocyclic carbene catalyst **19**¹⁷ resulted in clean ring closing metathesis to afford the volatile cyclopentenone **18**.



Scheme 5 Reagents and conditions: (a) 3-Iodo-4-lithiofuran, Et₂O (37%). (b) Pd₂dba₃, (*o*-tol)₃P, Cs₂CO₃, MeCN, H₂O (74%). (c) Vinyl-MgBr (82%). (d) **19** (2.5%), CH₂Cl₂ (50%).

Together, **16** and **18** represent the skeletal carbons of (+)-guanacastepene. Our retrosynthetic analysis is outlined in Scheme 6. Efforts to render the intramolecular Heck reaction and the ring closing metathesis asymmetric and join the two fragments are well underway in our laboratories and will be reported in due course.¹⁸



Scheme 6

In summary, we have developed a practical variant of the Claisen–Eschenmoser rearrangement that gives access to a variety of functionalized amides in high yields. Our simple one-pot procedure can be applied to a range of relatively unhindered allylic alcohols. Importantly, the reaction obviates the preparation of costly starting materials or the isolation of sensitive amide acetals and avoids toxic alkylating agents such as Meerwein-salts or dimeth-

yl sulfate. Future work will be directed at the synthesis of Weinreb amides using the corresponding *N,N*-ketene acetals and at the improvement of the stereoselectivities obtained to date.

Acknowledgement

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- (6) (a) Boehme, H.; Soldan, F. *Chem. Ber.* **1961**, *94*, 3109. (b) Baganz, H.; Domaschke, L. *Chem. Ber.* **1962**, *95*, 2095. (c) Adding to the usefulness of our procedure, **5** is commercially available (TCI America).
- (7) Representative Procedure, Morpholine Amide **4f**: A round-bottomed flask was charged with 8 mL morpholine (80 mmol) and dimethylacetamide dimethyl acetal (3.8 mL, 30 mmol) and the mixture was slowly heated to 190 °C over 5 hours under a steady stream of N₂. After cooling to room temperature, xylenes (10 mL) and 2,4-dimethyl-penta-2,4-dien-1-ol (1.32 g, 11.7 mmol) were added and the reaction mixture was refluxed until the allylic alcohol was consumed (14 hours) as determined by TLC (30% hexanes in ethylacetate, v/v). The solvent was partially removed using a rotary evaporator. The residue was purified by column chromatography (hexanes → ethyl acetate:hexanes = 1:1) to afford the pure product as a colorless oil (1.95 g, 8.74 mmol, 74.3%). ¹H NMR (500 MHz, CDCl₃) δ 4.84 (s, 2 H), 4.73 (s, 2 H), 3.63 (m, 6 H), 3.47 (m, 2 H), 3.21 (t, *J* = 9 Hz, 1 H), 2.54 (d, *J* = 9 Hz, 2 H), 1.66 (s, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 170.3, 145.5, 111.2, 66.9, 66.7, 49.9, 46.1, 42.0, 34.6, 20.8. IR (neat) 3077, 2966, 2855, 1650, 1643, 1432, 1271, 1234, 1115, 1034 cm⁻¹. MS (EI) *m/z* 223(23), 129(42), 114(42), 109(17), 95(100). HRMS (EI) *m/z* calcd for C₁₃H₂₁NO₂: 223.1572, found: 223.1570.
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