Stereoselective Synthesis of 2-Oxyenamides

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Dedicated to Herbert Mayr on the occasion of his 75th birthday.

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Abstract: An improved route for the highly stereoselective synthesis of (Z)-2-oxyenamides is reported. The desired products can be accessed in only three steps from aminoacetaldehyde dimethyl acetal as common, readily available building block in a highly modular fashion. The improved procedure has been applied to the synthesis of various acylated and sufonylated oxyenamides. Mechanistic and theoretical studies provide a conclusive rationale for the observed stereoselectivities.

Introduction

Enamides and the corresponding encarbamates constitute a class of versatile building blocks for organic synthesis.[1] Due to the electron-withdrawing group on the nitrogen, they display an increased chemical stability compared to the parent enamines together with a diminished but still notable nucleophilic character (Figure 1). This delicate balance between reactivity and stability renders enamides excellent substrates for the synthesis of highly functionalized amines and nitrogen-containing heterocycles. Apart from their application in asymmetric hydrogenation reactions for the synthesis of chiral amines,[1a] enamides have been successfully utilized in the highly stereoselective construction of various nitrogen-containing scaffolds.[1,2]

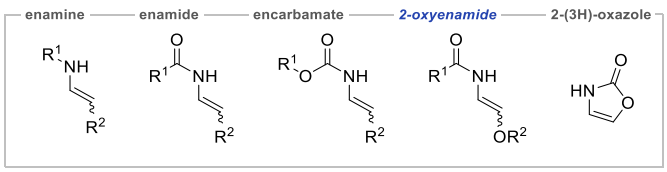


Figure 1. Enamines, Enamides, Encarbamates, 2-Oxyenamides and 2-(3*H*)-oxazolone.

Furthermore, the enamide moiety is frequently found in natural products.[3] In stark contrast, synthesis and application of 2-oxyenamides, enamide derivatives containing an additional oxygen functionality at the β-carbon, has been sparsely studied so far.[4] The 2-(3*H*)-oxazolone heterocycle, a cyclic 2-

oxyenamide mostly studied in cycloaddition reactions, is the only notable exception.[5] Interestingly, the 2-oxyenamide motif is also present in some natural products, e.g. the pacidamycins[6] and sansanmycins[7] from the uridyl peptide family or the miuraenamides, a class of cyclic polyketide-peptide hybrids.[8]

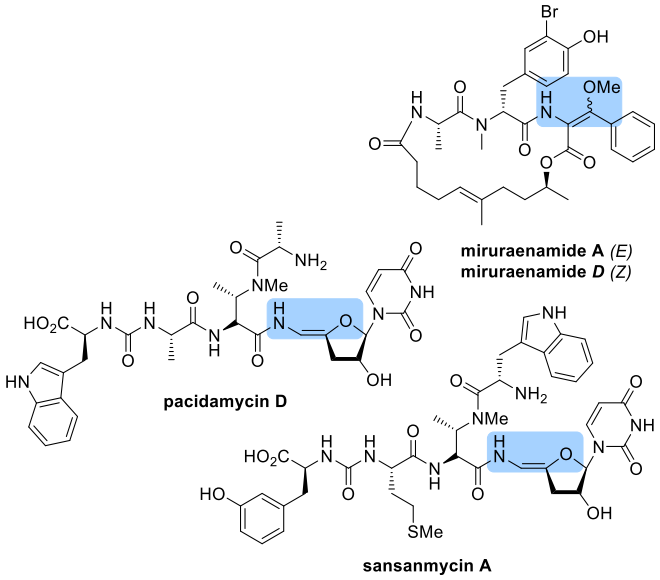
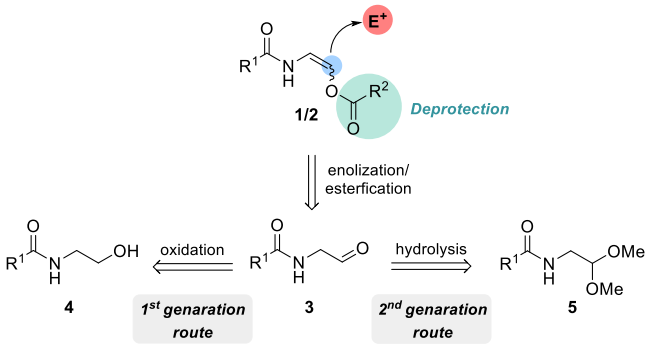


Figure 2. 2-Oxyenamide containing natural products.

We have recently described the application of (*Z*)-2-oxyenamides in the diastereoselective synthesis of 1,3-diamino-2-alcohols.[9] Our studied showed, that 2-oxyenamides display a similar reactivity pattern as their parent carbon-substituted enamides and could serve as new type of building block for the stereoselective construction of the 1,2-aminoalcohol scaffold. Key to their successful application was the development of a stereoselective preparation of the required (*Z*)-2-oxyenamides. In our preliminary communication, we reported the synthesis of five selected (*Z*)-2-oxyenamides and (*Z*)-2-oxyencarbamates bearing an acyl functionality on the oxygen atom. Herein, we disclose an improved synthetic route towards 2-oxyenamides, 2-oxyencarbamates and 2-oxyenimides with an expanded substrate scope. Furthermore, we provide mechanistic studies which help to rationalize the highly stereoselective formation of the (*Z*)-configured oxyenamides.

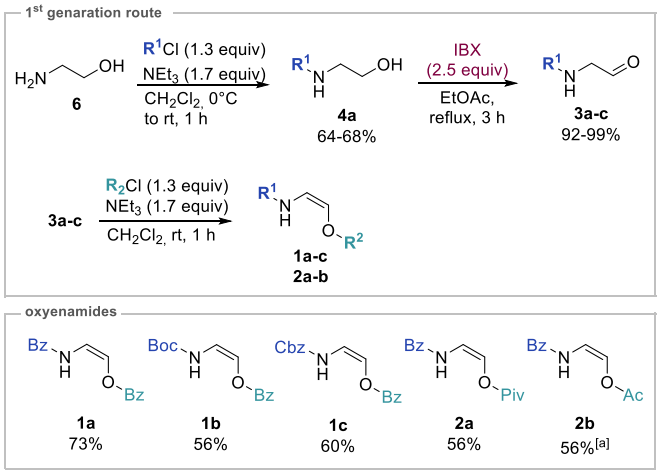
Results and Discussion

At the beginning of our studies, we selected acyl-protected 2-oxyenamides of type **1/2** as most promising substrates for our purposes (Scheme 1). At first, the electron-withdrawing acyl group on the oxygen substituent should render the embedded enol ester moiety less nucleophilic than the enamide functionality.[10] In turn, a chemoselective reaction with electrophiles should occur on the β-carbon (highlighted in blue). Furthermore, we envisioned, that 2-acyloxyenamides should be readily accessible form the corresponding protected amino aldehyde **3**. Finally, incorporation of an ester functionality should facilitate further manipulations, such as deprotection to the free alcohol.



Scheme 1. Retrosynthetic rationale towards 2-acyloxyenamides.

In our initial studies, protected 2-aminoacetaldehyde derivatives were prepared in two steps from 2-aminoethanol **6** (Scheme 2). Selective *N*-acylation afforded the *N*-protected aminoalcohols **4a-c** in 64-68% yield. Oxidation with IBX furnished the three aldehydes **3a-c** in 92-95% yield. In general, aldehydes of type **3** are not stable. We observed a more or less rapid decomposition upon storage at ambient temperature, in particular in solution. Therefore, the *N*-protected aminoacetaldehydes (3) were always synthesized on demand and directly utilized in the subsequent step. Treatment of **3** with the appropriate acid chloride and NEt_3 in CH_2Cl_2 furnished the desired 2-oxyenamides and -encarbamates **1a-c** and **2a-b** in 56-73% yield. The acetyl-protected 2-oxyenamides **2b** was synthesized from aldehyde **2a** using acetic anhydride as acylating agent in the presence of 20 mol% DMAP.[11] Interestingly, exclusive formation of the (*Z*)-isomer was observed for all products.[12]

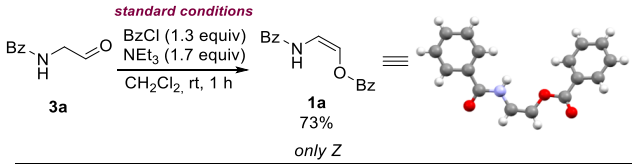


Scheme 2. 1st generation route via IBX oxidation. [a] The reaction was carried out with Ac_2O (1.3 equiv), NEt_3 (1.7 equiv) and DMAP (0.2 equiv). Bz = benzoyl; Piv = pivaloyl; Ac = acetyl; Boc = *tert*-butoxycarbonyl; Cbz = benzyloxycarbonyl.

Effects of deviations from the standard reaction conditions for the final oxyenamide formation are summarized in table 1. Replacement of DIPEA with NEt_3 afforded the desired product in comparable yield and excellent Z-selectivity (entry 2). The use of other organic bases led to either reduced yields (DBU and DBN; entry 3 and 4) or a complete shutdown of the reaction (pyridine, DMAP or DABCO, entires 5-7). Inorganic bases such as K_2CO_3 and NaOMe furnished only trace amounts of the expected product. (entries 8-9). Similar yields of the oxyenamide **1a** were obtained in THF, $CHCl_3$ or MeCN (entries 10-12). Substitution of CH_2Cl_2 with DMF or toluene led to reduced yields of 37% and 61%

(entries 13-14). Again, exclusive formation of the *Z*-isomer was observed in all cases. It has to be mentioned, that all 2-oxyenamides are moderately sensitive towards acid and some simple precautions have to be taken in order to avoid decomposition (see experimental section/supporting information for further details).

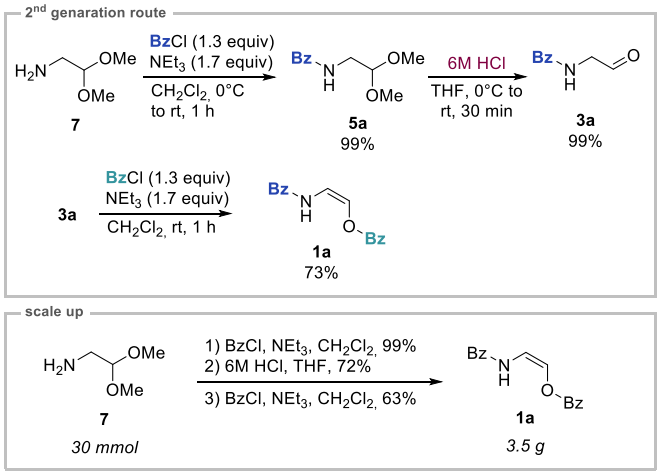
Table 1. Investigation of the reaction conditions.



Entry	Deviations from standard conditions	Yield [%][a]	*E:Z* ratio[b]
1	none	81, 73[c]	<2:98
2	DIPEA instead of NEt_3	71	<2:98
3	DBU instead of NEt_3	69	<2:98
4	DBN instead of NEt_3	38	<2:98
5	pyridine instead of NEt_3	nr	-
6	DMAP instead of NEt_3	nr	-
7	DABCO instead of NEt_3	nr	-
8	K_2CO_3 instead of NEt_3, solvent MeCN	traces	<2:98
9	NaOMe instead of NEt_3, solvent MeCN	traces	<2:98
10	THF instead of CH_2Cl_2	75	<2:98
11	$CHCl_3$ instead of CH_2Cl_2	77	<2:98
12	MeCN instead of CH_2Cl_2	80	<2:98
13	DMF instead of CH_2Cl_2	37	<2:98
14	toluene instead of CH_2Cl_2	61	<2:98

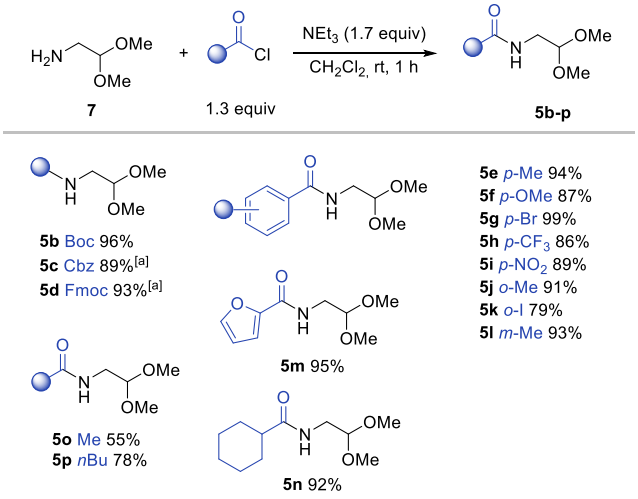
[a] Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [b] The *E:Z* ratio was determined by ^{1}H NMR of the crude product. [c] Isolated yield.

In the further course of our work, we realized, that, although proceeding with high chemoselectivity and efficiency, the limited availability and high price of IBX created a bottleneck for a more systematic exploration of the substrate scope and scale-up studies.[13] Furthermore, we encountered problems with regards to reproducibility during the scale-up of the oxidation. Therefore, we decided to explore a redox-neutral route from aminoacetaldehyde dimethyl acetal **7**, a readily available bulk chemical (Scheme 4).



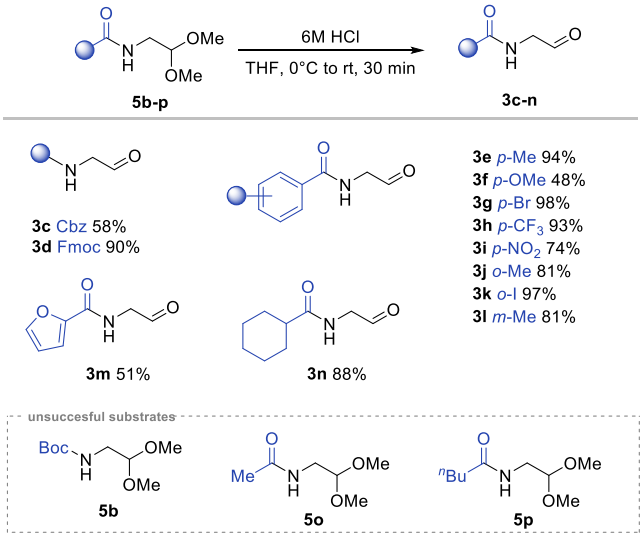
Scheme 4. 2nd generation route and scale-up.

Reaction of **7** with benzoyl chloride in the presence of NEt_3 afforded the protected aminoacetaldehyde derivative **5a** in 99% yield.[14] Cleavage of the acetal with aqueous HCL in THF[14] proceeded rapidly, furnishing the desired free aldehyde in 99% yield after a simple aqueous work-up. Direct treatment of the obtained crude aldehyde **3a** with our standard reaction conditions led to the 2-oxyenamide **1a** in identical yield and stereoselectivities. This modified procedure greatly facilitated scale-up of our oxyenamide synthesis. Using the 2nd generation approach, we routinely synthesized 3.5 g batches of 2-benzoyloxyenamide **1a** in 65-70% overall yield from cheap aminoacetaldehyde dimethyl acetal **7**. In the further course of our studies, we prepared various *N*-protected aminoacetaldehyde dimethyl acetal derivatives **5b-p** in high to excellent yields (Scheme 5). Aromatic and aliphatic residues (R^1) were incorporated with similar efficiencies. The introduction of carbamoyl-based protecting groups, proceeded in the same manner, affording the the Boc-, Cbz, or Fmoc-protected products **5b-d** in 89-96% yield.



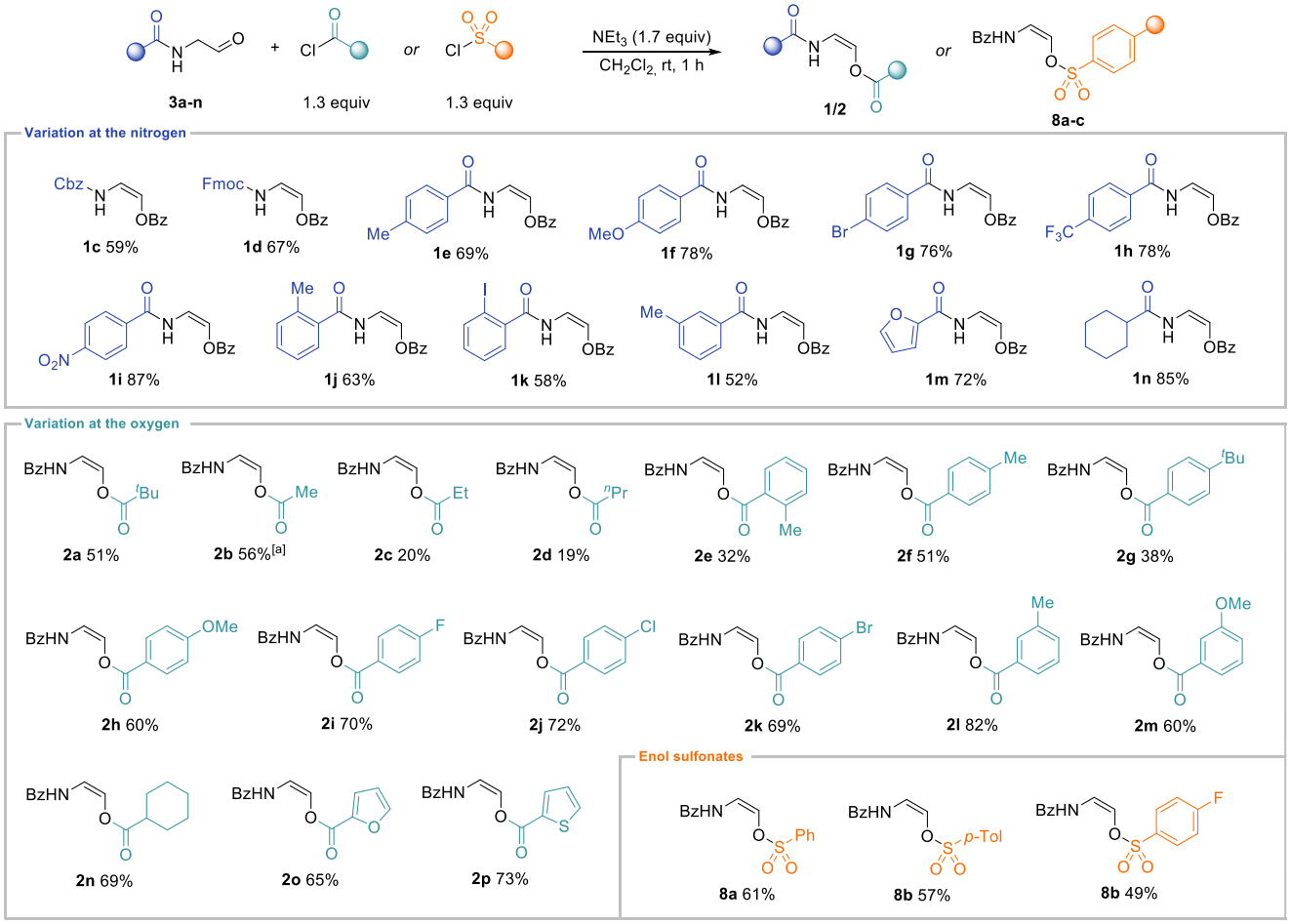
Scheme 5. Synthesis of *N*-protected protected aminoacetaldehyde dimethyl acetal derivatives **5b-p**. [a] Reaction conditions: K_2CO_3 (3.0 equiv), Et_2O/water (1:1), 0°C to rt, 16 h. Fmoc = fluorenylmethoxycarbonyl.

Next, the obtained acetals were hydrolyzed with aq. HCl in THF (Scheme 6). Efficient cleavage was observed in almost all cases and the corresponding aldehydes **3c-n** were isolated in 48-98% yield and sufficient purity after aqueous workup. Only in the case of the acid-labile Boc-protected acetal **5b** and two acetales with an aliphatic residue (**5o-p**) the formation of the desired product could not be observed.



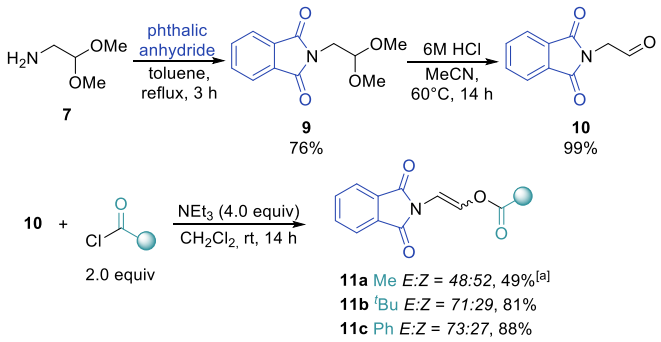
Scheme 6. Synthesis of *N*-protected protected aminoacetaldehydes **3c-n** via acetal hydrolysis.

The formed crude aldehydes were directly subjected to the next step, the base-mediated enol ester formation (Scheme 7). Reactions with different *N*-protected protected aminoacetaldehydes containing an aromatic or heteroaromatic amide functionality proceeded smoothly, affording the expected 2-oxyenamides **1c-n** 52-87% yield, always as analytically pure *Z*-isomer. Whereas, treatment of the cyclohexylamide derivative **2n** with benzoyl chloride led to the formation of the 2-oxyenamide **1n** in 85% yield, a slightly reduced yield was observed for the *meta*-toluoyl derivative **1l**. On the other hand, reactions with the carbamates **2c-d** delivered the desired Cbz- and Fmoc-protected oxyencarbamates **1c** and **1d** in 59% and 67% yield. Treatment of the aldehyde **3a** with different benzoic acid chlorides furnished the expected 2-oxyenamides **2a-p** in high yields and excellent stereoselectivities. Only in the case of a sterically hindered *ortho*-toluoyl residue (**2e**) a lower yield of 32% was observed. Acylation with acetic anhydride, pivaloyl and cyclohexanoyl chloride led to the formation of the desired products **2b**, **2a** and **2n** in a 51-69% yield. Reactions with other aliphatic acid chlorides, such as ethanoyl or *n*-propanoyl chlroide, afforded the oxyenamides **2c-d** in significantly lower yields of 19-20%. In order to extend the scope of available 2-oxyenamdies, we explored the synthesis of derivatives bearing other residues on the amine or oxygen functionality. At first, the incorporation of an electron-withdrawing sulfonyl group was studied. To our delight treatment of aminoaldehyde **3a** with arene sulfonyl chlorides under otherwise identical conditions directly afforded the enolsulfonates **8a-c** in 49-61% yield. Also in these cases, exclusive formation of the *Z*-isomer was observed.



Scheme 7. Synthesis of 2-oxyenamides **1/2** and enol sulfonates **8a-c** – substrate scope. [a] The reaction was carried out with Ac_2O (1.3 equiv), NEt_3 (1.7 equiv) and DMAP (0.2 equiv).

Next, we prepared the phthalimide-derived aminoacetaldehyde dimethyl acetal **9** in 76 % from phthalic anhydride and aminoacetaldehyde dimethyl acetal (Scheme 8). Subsequent hydrolysis of **9** with aqueous HCl led to the formation of the phthalimide-derived aminoacetaldehyde **10** in 99% yield.

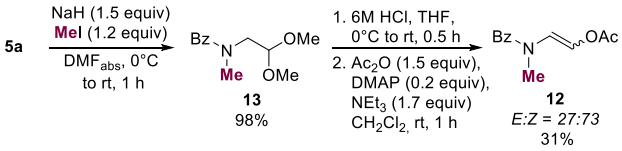


Scheme 8. Synthesis of 2-oxyenimides **10a-c**. [a] The reaction was carried out with Ac_2O (1.3 equiv), NEt_3 (1.7 equiv) and DMAP (0.2 equiv).

Treatment of **10** with benzyol chloride, pivaloyl chloride or acetic anhydride afforded the desired 2-oxyenimides **11a-c** in 49-88 % yield. Longer reaction times and 1.5-2.0 equivalents of the acylating agent were necessary to ensure complete conversion of the aldehyde **10**. Surprisingly, these

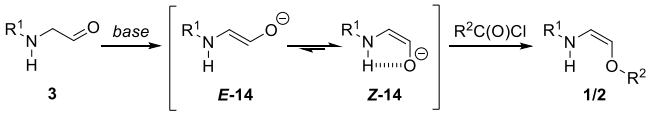
transformations afforded a mixture of the two stereoisomers **(*E*)-11** and **(*Z*)-11**. Whereas, acylation with acetic anhydride furnished a 1:1 mixture of the *E*- and the *Z*-isomer of oxyenimide **10a**, a preferential formation of the *E*-isomers was observed for the pivaloyl- and benzoyl derivatives **11b** and **11c**.

Since oxyenimides of type **11** lack a free N-H, one could envision a crucial role of intramolecular hydrogen bonding in the observed stereoselective outcome of the reaction or an additional stabilization of the *Z*-oxyenamide products. To further evaluate the role of intermolecular H-bonding, we synthesized the *N*-methylated oxyenamide **12**. At first, Bz-protected aminoacetaldehyde dimethyl acetal **6a** was treated with MeI and NaH to afforded the *N*-methyl derivative **13** in 98% yield. Hydrolysis of **13** with using our general procedure afforded the corresponding aldehyde (not shown), which proved to be very unstable. Therefore, the crude aldehyde was subjected directly to the acylation with acetic anhydride, furnishing the desired *N*-methylated oxyenamide **12** in 31% yield over two steps. Interestingly a stereoselective formation of the *Z*-isomer **(*Z*)-12** was observed in this case.



Scheme 9. Synthesis of the *N*-methylated 2-oxyenamide **12**.

Overall, the observed results for the parent oxyenamides (**1**), the oxyenimides of type **11** and the *N*-methylated oxyenamide **12** provide preliminary evidence, that the N-H group and also intramolecular hydrogen bonding might play key roles in the stereochemical outcome of the reaction. We initially assumed, that stabilization via intramolecular hydrogen bonding leads to a preferred formation of the (*Z*)-enolate (14) in equilibrium, resulting in the observed stereoselective generation of the (Z)-oxyenamides.

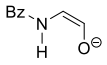
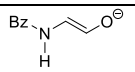
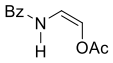
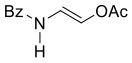
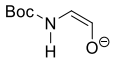
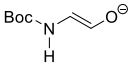
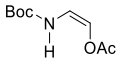
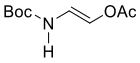
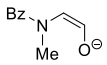
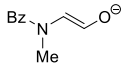
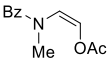
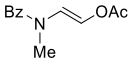
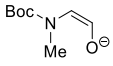
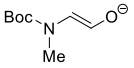
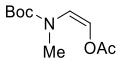
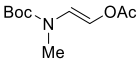
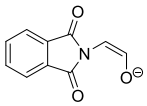
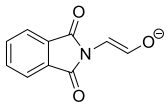
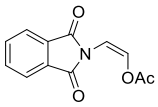
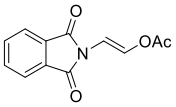


Scheme 10. Preliminary mechanistic proposal.

To get a better understanding of the observed diastereoselectivity and to gain further insights into the nature of the oxyenamides, we performed a computational analysis for selected structures at the DLPNO-CCSD(T)/Extrapolate(3/4,def2)/SMD(CH_2Cl_2)//M06-2X-D3/6-311+G(d,p)/SMD(CH_2Cl_2). In this analysis, we focused on the different stabilities of the intermediate oxyenamide anions **14** and the final acetylated oxyenamides for selected *N*-protected systems. Our calculations indicate very high endergonicities for the initial deprotonations of the parent oxyenamide by NEt_3 leading to separated ions, which is most likely caused by the unfavourable charge separation. It can be expected that ion pairs substantially reduce this energy difference, but we did not attempt to determine accurate reaction energies for this step because of the high flexibility of all cation-anion combinations. Instead, we concentrate on the relative Gibbs free energies ($\Delta\Delta G = \Delta G_Z - \Delta G_E$) for representative examples of the

anionic intermediates **14** and the final products. Those results are summarized in Table 1 and selected structures are depicted in Figure 3 (see the Supporting Information for more structures).

Table 2. Relative Gibbs Free Energies $\Delta\Delta G$ (in kJ mol^{-1}) for oxyenamide anions and acetylated oxyenamides.[a]

Entry	Structure		$\Delta\Delta G$
1	 ***Z*-14a**	 ***E*-14a**	–21
2	 ***Z*-2d**	 ***E*-2d**	–8
3	 ***Z*-14b**	 ***E*-14b**	–13
4	 ***Z*-2q**	 ***E*-2q**	–11
5	 ***Z*-14c**	 ***E*-14c**	–8
6	 ***Z*-12**	 ***E*-12**	–2
7	 ***Z*-14d**	 ***E*-14d**	–6
8	 ***Z*-2r**	 ***E*-2r**	+7
9	 ***Z*-14e**	 ***E*-14e**	-5
10	 ***Z*-11a**	 ***E*-11a**	+2

[a] DLPNO-CCSD(T)/Extrapolate(3/4,def2)/SMD(CH2Cl2)//M06-2X-D3/6-311+G(d,p)/SMD(CH_2Cl_2).

For the secondary amides **2d,q** and **14a,b** our calculations indicate a strong thermodynamic preference for the *Z*-configured structures. This finding is in good qualitative agreement with the experimental formation of almost exclusively *Z*-configured products. When the N–H group is replaced by N-Me groups (**12,2r** and **14c,d**), the energy differences are getting substantially smaller and the additional steric interaction between the methyl and acetyl groups results in a destabilization of the Z-configured isomers. Our DFT calculations further indicate that the π-systems within most acetylated oxyenamides are coplanar or slightly distorted due to steric interactions in the *Z*-form. In contrast, many anionic oxyenamides feature a perpendicular orientation of the π-systems of the amide and enolate substructures (e.g., ***E*-14b** in Figure 3). Almost all *E*-configurated oxyenamide anions as well as Z-configured tertiary oxyenamides ***Z*-14c,d** prefer this orientation, while the secondary *Z*-oxyenamides ***Z*-14a,b** feature coplanar structures.

For the experimentally studied anionic systems **14a** and **2d**, the intramolecular N–H…O hydrogen bond contributes 7.5 and 5 kJ mol^{-1} in the *Z*-isomers according to our NBO analysis,[15] while no hydrogen bond could be detected in the acetylated species **2d** and **2q**. Thus, the oxyenamide anions **14** are at least partially stabilized through this intramolecular hydrogen bond.

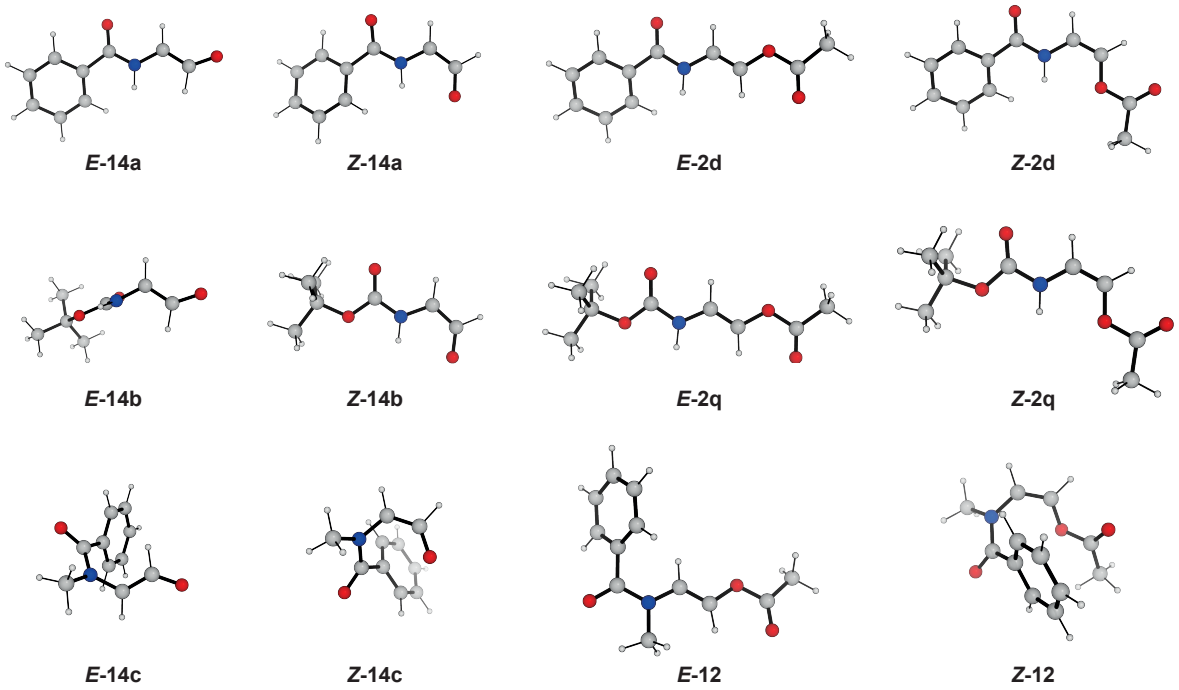


Figure 3. Calculated structures for selected oxyenamide anions **14** and their acetylated analogues **2** and **12**

Conclusion

In summary, we have developed an improved 2nd generation route for the synthesis of 2-oxyenamides. Aminoacetaldehyde dimethyl acetal, a readily available bulk, is used as common building block. Various acylated and sulfonylated oxyneamides can be accessed in in three steps in a highly modular fashion. The desired products are formed in good yields and the process is amendable to a gram-scale synthesis of oxyenamides. All oxyenamide products containing a free N-H functionality are formed exclusively as (Z)-isomer. In case of *N*-methylated or phthaloyl-based derivatives lacking an N-H-bond, a mixture of the *E*- and *Z*-isomer is obtained. For oxyenamides containing a secondary amide, DFT calculations show strong thermodynamic preference for the *Z*-configured product and even more pronounced preference for the intermediate *Z*-enolate. Calculated energy differences for compounds lacking a free N-H functionality are much smaller. Calculations also indicate a partial stabilization of the *Z*-configured enolates through intramolecular hydrogen bonding. Results from the DFT calculations are in good agreement with our experimental findings.

Experimental Section

For general experimental conditions, detailed experimental procedures, analytical data, and ^{1}H, ^{13}C and ^{19}F NMR spectra, as well as computational details see the Supporting Information. The following procedure serves as a representative example.

GP (*Synthesis of the (Z)-oxyenamides* **1/2**)

To a stirred solution of Et_3N (1.7 equiv) and the corresponding acyl chloride (1.3 equiv) in CH_2Cl_2 (2 mL/mmol) was added dropwise a solution of the aldehyde **3** (1.0 equiv) in CH_2Cl_2 (2 mL/mmol) over 5 min. The reaction mixture was stirred for 1 h at room temperature. After TLC analysis showed complete consumption of the aldehyde, saturated $NaHCO_3$ solution was added (20 mL). The organic layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. Purification by flash chromatography afforded the desired (*Z*)-oxyenamide **1/2** as analytically pure product. All oxyenamides of type **1/2** tend to decompose upon contact to any type of acid. Therefore, column chromotography was performed with 0.2 vol% NEt_3 as additive. $CDCl_3$ for NMR spectroscopy was passed through short plug of basic alumina before use.

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Keywords: enamides • DFT calculations • synthetic methods • enolate • *Z*-selective

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charge from the Cambridge Crystallographic Data Centre. Configurations of all other compounds were assigned by analogy based on ^{1}H and ^{13}C NMR spectroscopy.

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