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A Enamide-Based Diastereoselective Synthesis of Isoindolo[2,1-*a*]quinolin-11(5*H*)-ones with Three Contiguous Stereogenic Centers

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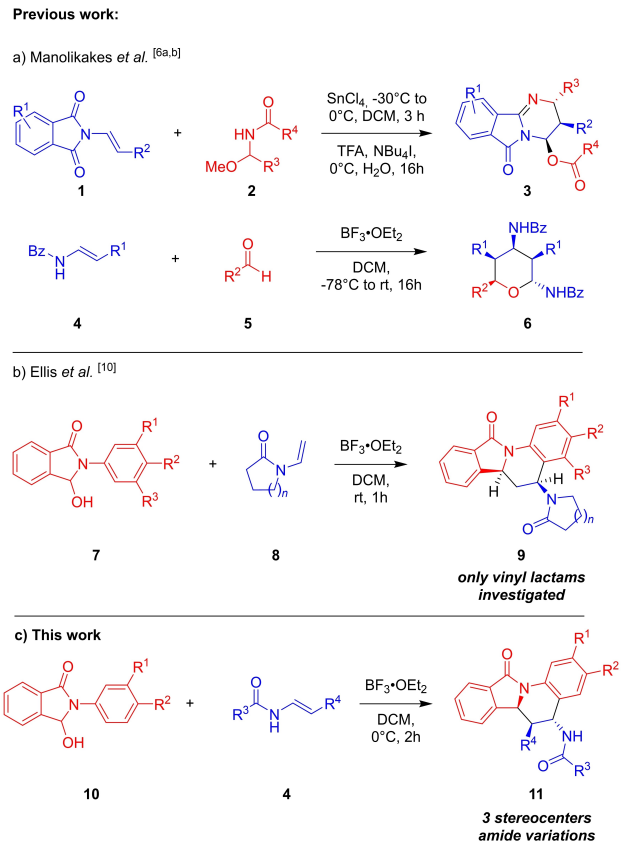
A stereoselective synthesis of isoindolo[2,1-*a*]quinolin-11(5*H*)-ones containing three contiguous stereogenic centers is described. This Lewis-acid mediated reaction of enamides with *N*-aryl-acylimines affords the desired fused heterocyclic isoindolinones in high yields and diastereoselectivities. Scope and limitations of this method are discussed. The stereochemical outcome of this transformation indicates a stepwise reaction pathway.

Introduction

Nitrogen heterocycles are ubiquitous structural motifs in natural products and active pharmaceutical ingredients.[1] Therefore, the development of novel methods for the efficient construction of nitrogen-containing heterocycles remains a highly active field of research.[2] In this context, the synthetic accessibility of so far uncommon fused heterocycles, leading to expanded scaffold diversity, is of great interest.[3] In the last 20 years, aliphatic heterocycles have gained increasing popularity.[4] Their defined three-dimensional structures offer intriguing opportunities to improve the pharmacokinetic profile of potential drug candidates.[5] Hence, there is an growing demand for novel approaches towards the synthesis of three-dimensional heterocyclic scaffolds.

In the last years we have described several methods for the rapid assembly of aliphatic heterocycles containing multiple stereogenic centers utilizing enamides as common building block (Scheme 1a).[6] Enamides and enecarbamates are highly versatile building blocks in organic synthesis.[7] Their intricate reactivity has been utilized for the construction of various heterocycles, in particular in cycloaddition reactions.[6] Among these, the Povarov synthesis of tetrahydroisoquinolines,[8] an inverse electron demand aza-Diels-Alder reaction between *N*-arylimines and enamides as electron-rich dienophiles, has been studied extensively.[7,9] An interesting example of such a reaction is the aza-Diels-Alder reaction between *N*-acyliminium cations, derived from *N*-aryl-3-hydroxyisoindolinones **7**, with tertiary enamides **8**, affording dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-ones **9** (Scheme 1b).[10] This method leads to an intriguing fused heterocyclic scaffold with two stereocenters in good yields and high stereoselectivities. However, only reactions with vinyl lactams **8** were investigated so far. We envisioned, that this process should be also amendable to secondary enamides **4** bearing an additional substituent at the beta-position. Thereby, it would enable the synthesis of dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one scaffold **11** with up to three contiguous stereocenters and different amide residues (Scheme 1c).



Scheme 1. Cyclization reactions using enamides and enecarbamates as building blocks.

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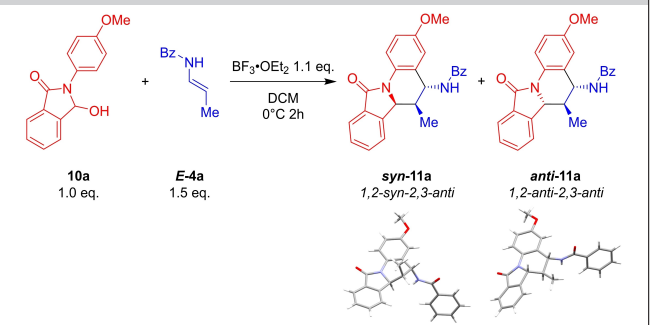
Herein, we report a novel BF_3-mediated reaction of secondary enamides and enecarbamates with *N*-aryl-3-hydroxyisoindolinones for the stereoselective synthesis of dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-ones with three adjacent stereogenic centers (Scheme 1b).

Results and Discussion

We commenced our studies by investigating the reaction between *N*-aryl-3-hydroxyisoindolinone **10a** and (*E*)-enamide ***E*-4a** (Table 1). To our delight treatment of both starting materials with $BF_3 \cdot OEt_2$ as Lewis acid in CH_2Cl_2 afforded the desired product **11**. Best yields were obtained with 1.1 equivalents $BF_3 \cdot OEt_2$ at 0 °C and a slow addition of the enamide ***E*-4a** to a mixture of the acyliminium precursor **10a** and $BF_3 \cdot OEt_2$ (entry 1). Using this optimized procedure, the fused heterocycle **11** could be isolated in 88% overall yield and a diastereomeric ratio of 77:23. Only the two shown diastereomers ***syn*-11a** (1,2-*syn*-2,3-*anti*) and **anti-11a** (1,2-*anti*-2,3-*syn*) could be detected in the crude reaction mixture.[11] Performing the reaction at ambient temperature resulted in a decreased yield (entry 2). Lower reaction temperatures (e.g. −50 °C) led to a slower reaction rate, necessitating a higher loading of $BF_3 \cdot OEt_2$, and decreased yields (entry 3). Slow addition of **4a** to the reaction mixture avoids competing decomposition of the enamide. Yet, direct addition of $BF_3 \cdot OEt_2$ to a mixture of both starting materials furnished the desired product **11** in acceptable yield (entry 4). Reduction of the amount of $BF_3 \cdot OEt_2$ led to decreased yields (entry 5). Reactions in other solvents, such as $CHCl_3$, toluene or THF did not furnish the desired product. Decomposition of the starting materials was observed in these solvents (entry 6). Only in acetonitrile formation of the product took place, albeit in a lower yield of 46% (entry 7). Efforts to replace $BF_3 \cdot OEt_2$ with catalytic amounts of different Lewis acids, such as $Bi(OTf)_3$, $Cu(OTf)_2$ or $Fe(OTf)_3$, were not successful. Only small amounts of the desired product (<10%) could be detected after prolonged reaction times (entry 8).

Table 1. Optimization of the formation of the dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one **11**.



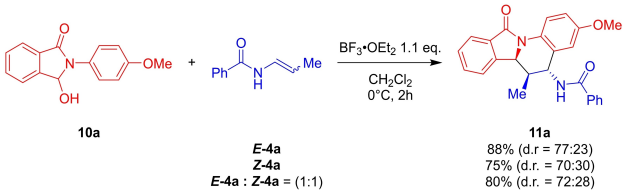
10a 1.0 eq. | ***E*-4a** 1.5 eq. | ***syn*-11a** *1,2-syn-2,3-anti* | ***anti*-11a** *1,2-anti-2,3-anti*

entry	Deviations from optimized conditions[a]	yield[b] (%)	d.r.[c]
1	none	88	77:23
2	$BF_3 \cdot OEt_2$ 1.5 equiv.; 23 °C; 3 h	67	75:25
3	$BF_3 \cdot OEt_2$ 1.5 equiv.; −50 °C; 16 h	65	76:24
4	4a added before L.A.	80	72:28
5	$BF_3 \cdot OEt_2$ 0.5 equiv.	62	77:26
6	Solvents $CHCl_3$, toluene or THF	traces or decomposition	n.d.
7	Solvent MeCN	46	74:26
8	L.A. $Bi(OTf)_3$, $Cu(OTf)_3$ or $Fe(OTf)_3$ 0.1 equiv.; RT; 16 h	traces	n.d.

[a] **10a** activated with L.A. for 5 min, ***E*-4a** added over 30 min; [b] overall isolated yield of both diastereomers after column chromatography; [c] d.r. determined by ^{1}H-NMR of crude mixture; n.d. = not determined. Bz = benzoyl.

Next, we studied the influence of the enamide configuration on the outcome of the reaction. Interestingly, reaction of both the (*E*)- and the (*Z*)-enamide **4a** afforded dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one **11a** in comparable yields and diastereoselectivities (Scheme 2). Indeed, even a 1:1 mixture of ***E*-4a** and ***Z*-4a** furnished the desired product **11a** in 80% yield and a diastereomeric ratio of 72:28. These results indicate a stepwise reaction pathway. Furthermore, these observations greatly facilitated our further research efforts. Our preferred method for the preparation of the starting enamides, a nickel-catalyzed isomerization of the corresponding allylamides,[12] usually delivers a mixture of the (*E*)- and (*Z*)-isomer. Instead of separating the two isomers of the corresponding enamide **4** by column chromatography, the formed E/Z-mixture could be used directly in all subsequent studies.[13]

With the optimized conditions established, we investigated the reaction of various enamides with *N*-aryl-3-hydroxyisoindolinone **10a** (Scheme 3). Various benzamide-derived enamides **4b–e** and the alkylamide derivative **4f** afforded the desired products **11b–f** in 75–96% yield and good diastereoselectivities. Whereas the reaction of the ethyl-substituted enamide **4h** furnished the expected dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one **11h** in 96% yield and a d.r. of 77:23, no product formation was observed in the case of vinyl enamide **4m**. On the other hand, reaction of a phenyl-substituted enamide **4i** proceeded in high yield and excellent diastereoselectivity. In the case of the sterically more demanding dimethylated enamide **4j** the desired product **11j** was obtained in 92% yield, albeit as almost equimolar mixture of two diastereomers. No reaction was observed with the bulkier enamide **4n**. This method is not limited to enamides. Reactions with the structurally related enimide **4g** and the enecarbamates **4k** and **4l** led to the formation of the expected products **11g**, **11k** and **11l**. Whereas the phthaloyl-derivative **11g** and the Boc-protected product **11l** were formed in comparable yields and diastereoselectivites, the reaction with Cbz-protected enecarbamate **4k** furnished



10a | ***E*-4a** / ***Z*-4a** / ***E*-4a** : ***Z*-4a** = (1:1) | **11a** 88% (d.r = 77:23) 75% (d.r. = 70:30) 80% (d.r. = 72:28)

Scheme 2. Influence of the enamide configuration. Yields refer to overall isolated yield of both diastereomers after column chromatography; d.r. in parentheses determined by 1H-NMR of crude mixture; Bz = benzoyl.

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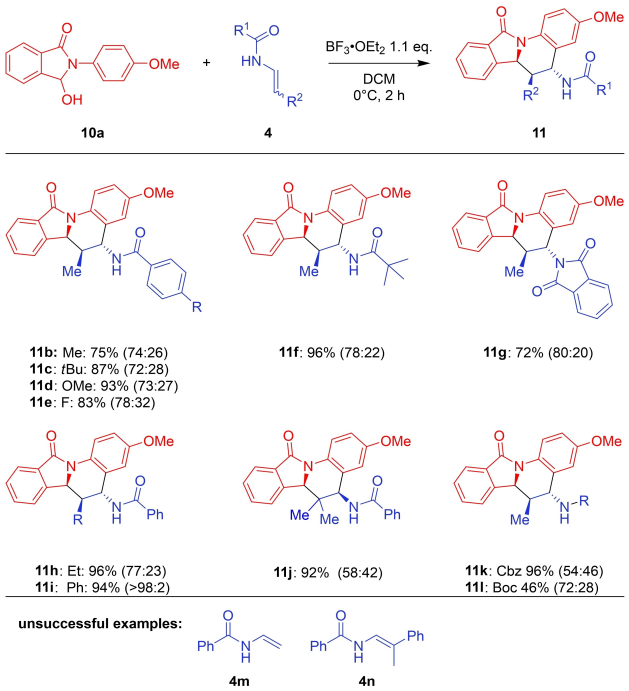
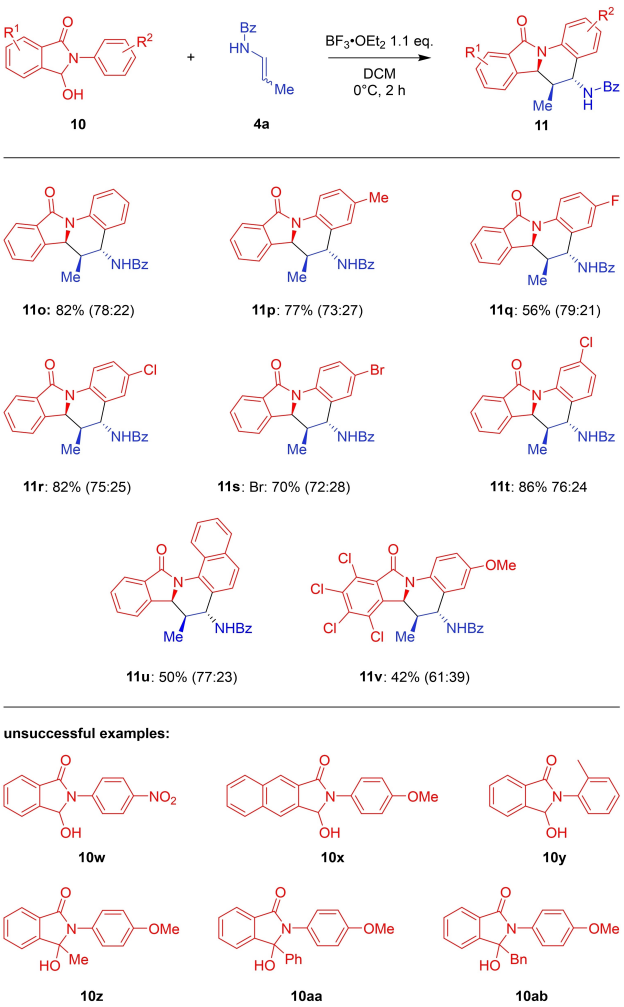
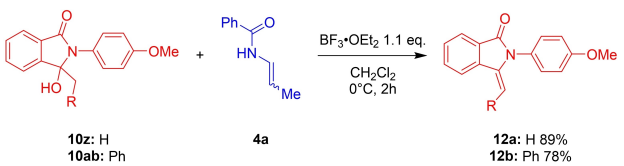


Scheme 3. Variation of the Enamide; Yields refer to overall isolated yield of both diastereomers after column chromatography; d.r. in parentheses determined by 1H-NMR of crude mixture; Cbz = benzyloxy carbonyl.



Scheme 4. Variation of the *N*-aryl-3-hydroxyisoindolinones; Yields refer to overall isolated yield of both diastereomers after column chromatography; d.r. in parentheses determined by 1H-NMR of crude mixture; Bz = benzoyl; Bn = benzyl.



Scheme 5. Acid-mediated elimination to cyclic enamides **12**.

product **11k** as a 1:1 mixture of the *syn*- and *anti*-diastereomers.

Next, we investigated reactions with different *N*-acyliminium precursors **10** (Scheme 4). Various *N*-aryl-3-hydroxyisoindolinones bearing electron-withdrawing or donating substituents (R^2) in para-position on the aryl moiety performed satisfactorily under the standard reaction conditions. The desired dihydroisoindolo[2,1-a]quinolin-11(5*H*)-ones **11o–s** could be isolated in 56–82% yield and good diastereoselectivities. Reactions with *N*-aryl-3-hydroxyisoindolinone **10t** bearing a Cl-substituent in meta position led to a regioselective formation of product **11t** in comparable yields and stereoselectivities. On the other hand, reaction of the perchlorinated starting material **10v** afforded the fused heterocycle **11v** in only 42% yield with a decreased stereoselectivity. The low yield can be attributed to the poor solubility of the *N*-acyliminium precursor **10v**, which leads to a competing decomposition of the enamide. Similar observations were made with the acylimine precursors **10w** and **10x**, which both proved to be insoluble in DCM, even in the presence of BF_3. Reactions with *N*-aryl-3-hydroxyisoindolinones bearing an ortho-substituent on the aryl residue, such as **10y**, did not afford any desired product. In addition, *N*-aryl-3-hydroxyisoindolinone derivatives **10z–ab** containing an additional carbon substituent (R^3) at the acyliminium carbon did not undergo the desired reaction.

For acylimine precursors **10z** and **10ab** a competing acid-mediated elimination to the corresponding 3-methyleneisoindolin-1-ones **12a** and **12b** was observed in the presence or absence of enamide **4a** (Scheme 5). This type of acid-mediated elimination has been described recently by Topolovcan and Gredičak.[14]

The obtained results, in particular the same stereochemical outcome for the (*E*)- and (*Z*)-enamide, indicate a stepwise reaction mechanism. A tentative mechanistic proposal for a model reaction between enamide **4a** and 3-hydroxyisoindolinone **10o** is outlined in Scheme 6. Treatment of 3-hydroxyisoindolinone **10o** with BF_3 leads to a highly electrophilic acyliminium species **15**. Addition of enamide **4a** to the acyliminium ion **15** occurs via an open transition state with an antiperiplanar

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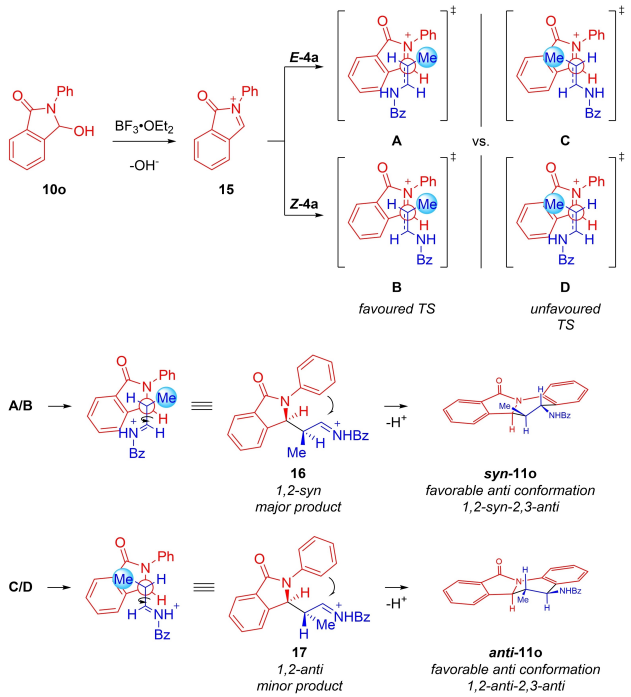

Scheme 6. Preliminary, stepwise reaction mechanism.

arrangement of the acylimine- and enamide-π-systems.[15] For the (*E*)-enamide transition state **A** is favored over transition state **B**, most probably due to steric repulsion between the methyl group and the isindolone core. In a similar manner, the addition of the (*Z*)-enamide proceeds preferably trough transition state **C**. Therefore, a diastereoselective formation of the 1,2-*syn*-intermediate **16** occurs in both cases. Intramolecular aza-Friedel-Crafts-type reaction of the newly formed acylimine species **16** leads to the fused heterocyclic product ***syn*-11 o**. The intramolecular addition proceeds with a high degree of stereoselectivity, affording a favorable 2,3-*anti* arrangement of the methyl and the amide substituent. Addition of the enamide **4** to iminium species **15** trough the less favored transition states **C** or **D** affords the 1,2-*anti* intermediate **17**. Subsequent cyclization of this reactive acyliminium species proceeds again with a high level of stereoselectivity, affording the minor diastereomer ***anti*-11 o**.

Conclusion

In summary, we have developed a diastereoselective synthesis of isoindolo[2,1-a]quinolin-11(5*H*)-ones. This novel method enables the efficient construction of intriguing fused heterocyclic scaffolds with three contiguous stereogenic centers in good to high yields. The reaction proceeds via a stepwise reaction mechanism through an open transition state, resulting in a similar stereochemical outcome irrespectively of the enamide configuration. Efforts to extend the scope of this transformation towards other fused heterocyclic scaffolds and investigations of an enantioselective version are currently being pursued in our laboratory.

Experimental Section

For general experimental conditions, detailed experimental procedures, analytical data, and 1H, 13 C and 19F NMR spectra, see the Supporting Information. The following procedure serves as a representative example. General Procedure: Synthesis of Dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-ones. A Schlenk tube, equipped with a septum and a magnetic stirrer, is charged with *N*-acyliminiumion-precursor **10** (0.50 mmol, 1.00 equiv.) and dichloromethane (2.50 mL). The solution is cooled to 0 °C and $BF_3 \cdot OEt_2$ (0.55 mmol, 1.10 equiv., 70 μL) is added. Over the course of 30 min enamide **4** (0.75 mmol, 1.50 equiv.) in dichloromethane (2.5 mL) is added dropwise. The reaction is stirred for 2 h at 0 °C. After TLC showed complete consumption of the *N*-acyliminiumion-precursor, the reaction is stopped by the addition of saturated aqueous $NaHCO_3$ (5 mL). The organic layer is separated, and the aqueous phase is extracted with dichloromethane (3x 10 mL). The combined organic layers are dried over Na_2SO_4, filtered off and the solvent is evaporated under reduced pressure. The crude product is purified and the two diastereomers separated by column chromatography (*n*-hexane:$CHCl_3$ + 3 % acetone = 8 : 2 → 2 : 8).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acyliminium ion · diastereoselectivity · enamide · nitrogen heterocycles · synthetic methods

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