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Diastereoselective Synthesis of Novel Aza-diketopiperazines via a Domino Cyclohydrocarbonylation/Addition Process

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Herein, we report an unprecedented, short and diastereoselective synthesis of newly reported aza-diketopiperazine (aza-DKP) scaffolds starting from amino-acids. The strategy is based on a Rh(I)-catalyzed hydroformylative cyclohydrocarbonylation of allyl-substituted aza-DKP, followed by a diastereoselective functionalization of the platform. This methodology allows the synthesis of novel bicyclic and tricyclic aza-DKP scaffolds incorporating six- or seven-membered rings, with potential applications in medicinal chemistry.

The diketopiperazine (DKP) moiety found in several natural products has been extensively studied in medicinal chemistry. However, the corresponding aza-DKP platform remains underexplored. This class of heterocycles can be viewed as a constrained dipeptidomimetic DKP analogue (Figure 1). As reported for aza-peptides, the replacement of one C$\alpha$-stereogenic center by a planar nitrogen atom could have a profound impact on both the chemical and biological properties of DKP and could offer new potential for drug discovery and chemical biology.

Recently, we have described a convenient access to original 2,4,5-trisubstituted-1,2,4-triazine-3,6-diones, both in solution and on solid-phase. In the present work, we report a diversity-oriented, efficient and stereoselective synthesis of novel bicyclic and tricyclic scaffolds derived from aza-DKP. To access such structures, we have explored a strategy based on cyclohydrocarbonylation (CHC) of allyl aza-DKP 4, followed by an acid-catalyzed diastereoselective nucleophilic addition on the resulting enamide 5 (Scheme 1). This strategy involves for the first time the catalytic hydroformylation of newly reported 1,2,4-triazine-3,6-dione system. The scope, limitations and diastereoselectivity of the approach have been carefully studied, resulting in the preparation of enantiomerically pure scaffolds with potential applications in medicinal chemistry.

Scheme 1 Strategy towards novel N-heterocyclic aza-DKP scaffolds.

To investigate the applicability of the CHC reaction on aza-DKP systems, we initially prepared a set of allyl-substituted precursors 4a-g and 4k,l according to our previously described procedure. The amino acids were converted into amino esters which were alkylated by reductive amination. The resulting secondary amines 2a-g and 2k,l as well as the proline derivatives 2h-j and 2m were reacted with bis(trichloromethyl)carbonate (BTC) and allyl or homoallyl t-butyl carbazate 1a or 1b, obtained in one step from commercially available t-butyl carbazate (see supporting information for detailed procedure). The crude semicarbazides 3a-m were then treated in TFA/water (95:5) for 1 h, resulting in the consecutive semi-carbazide deprotection and cyclization. This led to allyl derivatives 4a-m, in 27% to 77% yields from amines 2a-j, the lower yields...
being obtained with the most sterically hindered \( R^1 \) and \( R^2 \) substituents (Table 1, entries 3 and 4). Noteworthy, the preparation of aza-DKP \( 4i \) and \( 4m \) (from L-hydroxyproline) required hydroxy protection prior to semicarbazide cyclization (Table 1, entries 9 and 12). With compounds \( 4a-m \) in hand, we explored the CHC using syngas (\( H_2/CO \)) in the presence of a Rh(I) catalyst. BiPhePhos was selected as metal chelating agent to ensure formation of linear rather than branched aldehydes. All reactions were performed under acid catalysis (pyridinium p-toluenesulfonate: PPTS or camphorsulfonic acid: CSA) to promote cyclization, if any, into enamide \( 5 \) in the same reactor.

In our first attempt, we were pleased to obtain cyclized compound \( 5a \) in an excellent 82% yield from allyl compound \( 4a \), thus validating the CHC as a convenient and high yielding method for bicyclic aza-DKP synthesis (Table 1, entry 1).

Next, the scope and limitations of the reaction were evaluated on allylic aza-DKP \( 4b-m \). In all cases, the expected cyclized compounds \( 5 \) were isolated in yields ranging from 43 to 81% (Table 1), thus demonstrating the efficiency of the method, regardless of the nature of \( R^1 \) and \( R^2 \) (Table 1, entries 3-5) or of the configuration of the starting amino-acid (Table 1, entry 2). Noteworthy, CHC still occurred in reasonable yields with compounds \( 4f \) and \( 4g \) encompassing nucleophiles groups at \( R^3 \), which could possibly compete as ligand for the metal (Table 1, entries 6 and 7).

Interestingly, CHC also gave access to tricyclic L-proline-based aza-DKP \( 5h, 5i \) and \( 5j \) in good 69%, 73% and 62% yields, respectively (Table 1, entries 8, 9 and 10). This scaffold is particularly appealing for medicinal chemistry as the corresponding DKP is embedded in the core of several natural product classes used in targeted cancer therapy.

These promising results for the synthesis of six-membered rings prompted us to evaluate CHC as an entry to aza-DKP fused to seven-membered ring. Thus, with homoallylic derivative \( 4k \), the CHC reaction proceeded smoothly and \( 5k \) was obtained in moderate yield (34%). Then, we switched from PPTS to the more acidic CSA, which drives the reaction to completion and dramatically improves the yield (72%). This optimized procedure was also applied to the synthesis of tricyclic L-hydroxyproline-based aza-DPK \( 5m \) obtained in 61% yield.

With all these novel structures in hand, we decided to investigate the functionalization of the diaza-cyclohexene and diaza-cycloheptene rings in order to extend the molecular diversity of these novel scaffolds. A first experiment was carried out by subjecting compound \( 5a \) to a CSA acid-catalyzed addition of MeOH which led to hemiaminal \( 6a \) with a high 86% yield and a good diastereoisomeric ratio (dr) of 93:7 (Table 2, entry 1). The major isomer was readily isolated by preparative HPLC and was shown to be the C9-C2 trans-isomer by X-ray diffraction analysis (Figure 2). This result combined with the axial position of the methoxy group indicate that the nucleophilic attack of the acyl iminium intermediate is likely under stereoelectronic control. The out-of-plane substituents associated with the presence of...
stereocenters make the aza-DKP scaffold a promising platform to increase receptor/ligand interactions and to develop potentially active and selective compounds.10

The diastereoselective addition reaction was then extended to various enamides. As shown in Table 2, the expected compound was obtained whatever the absolute configuration at Cα (Table 2, entry 2). The steric hindrance at R2 was found to impact the selectivity (Table 2, entry 4). In contrast, when a hindered group was introduced at R1, only one diastereomer was detected by 1H NMR or HPLC analysis of the crude reaction mixtures.

The X-ray structures of compounds 6a and 6j.

Finally, to further enlarge the molecular diversity of novel aza-DKP platforms and access to diversity-oriented chemical libraries, we envisaged the incorporation at C9 of functional groups able to react with commercially available building blocks. Hence, trans-isomer 6a was reacted either with TMSN3 or with TMSCN, both in presence of BF3·OEt2 (Scheme 3).15 Thus, azide 7 was obtained in good yield (88%) and dr (>95:5). Nitrile 9 was also isolated in excellent yield (92%) but with a lower dr (68:32). Again, for both compounds, the major isomer was shown to be the C9-C2 trans-isomer (X-ray structure analysis, Supporting Information).

Besides, hydrolysis of the major isomer under acidic conditions led to carboxylic acid 10, able to react with amino...
building-blocks. Azide 7 was reduced with H$_2$/Pd in presence of di-tert-butyl dicarbonate to provide βBoc-protected compound 8 (86%). To further extend the chemical diversity of aza-diketopiperazines, compound 7 could also be engaged in Cu(I)-catalyzed azide-alkyne cycloaddition reactions.

Conclusions

Starting from the amino-acid pool, we have developed a diastereoselective approach for the preparation of a diverse range of N-heterocyclic scaffolds derived from aza-DKP. Indeed, this rapid and flexible method enables the efficient conversion of N-allyl substituted aza-DKP into newly reported bicyclic or tricyclic scaffolds containing six- or seven-membered rings by a domino CHC/addition sequence. A subsequent substitution at C-9 of the aza-DKP allows the diastereoselective incorporation of cyano and azido groups readily amenable respectively to amino or carboxylic functions which paves the way to the preparation of diversity-oriented libraries.

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Notes and references

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures and analytical data for all the compounds. Crystal structures for 5a, 5i, 5k, 6a, 7, trans-isomer of 9 and cis-isomers of 6i and 6j. See DOI: 10.1039/e000000x/