Organocatalytic Activation of Diethyl Glutaconate for the Diastereo- and Enantioselective Assembly of NH-Free 2,3,4-Trisubstituted Pyrrolidines
Adrien Quintard, Jean Rodriguez

To cite this version:
Adrien Quintard, Jean Rodriguez. Organocatalytic Activation of Diethyl Glutaconate for the Diastereo- and Enantioselective Assembly of NH-Free 2,3,4-Trisubstituted Pyrrolidines. Organic Letters, American Chemical Society, 2017, 19 (3), pp.722-725. <10.1021/acs.orglett.7b00014>. <hal-01533766>

HAL Id: hal-01533766
https://hal.archives-ouvertes.fr/hal-01533766
Submitted on 6 Jun 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Organocatalytic Activation of Diethyl Glutaconate for the Diastereo- and Enantioselective Assembly of NH-Free 2,3,4-Trisubstituted Pyrrolidines
Adrien Quintard* and Jean Rodriguez

ABSTRACT: Organocatalyzed enantioselective consecutive Michael addition of diethyl glutaconate to a nitro-olefin/reductive cyclization sequence has been developed, directly providing NH-free trans,trans-2,3,4-trisubstituted pyrrolidines with typically >88:12 dr and >90% ee. The obtained structures are closely related to several molecules with high biological profiles, holding great promise for medicinal chemistry. In addition, their potential as direct organocatalysts in the enantioselective Michael addition promoted by enamine activation is also reported.

Pyrrolidines are unique heterocyclic scaffolds present in a broad range of biologically active molecules. In addition to this marked bioactivity, the pyrrolidine backbone has been abundantly used to build efficient chiral ligands and organocatalysts. Given the prevalence of this particular motif, the development of innovative direct enantioselective access to these structures from widely available substrates is highly desirable with strong potential for medicinal chemistry and catalytic applications.

Among the most straightforward and efficient routes to chiral pyrrolidines, (3 + 2) cycloadditions notably catalyzed by copper complexes largely lead the way. Unfortunately, most of them provide products with substituents on both the 2- and 5-positions of the pyrrolidine ring. This considerably limits the potential of these approaches because the 2,3,4-trisubstituted pyrrolidine chiral backbone is present in numerous highly biologically active molecules such as in kainic acid or endothelin receptors ETα antagonists shown in Scheme 1.

To develop an alternative rapid approach to this particular heterocyclic motif, we hypothesized that a new selective organocatalyzed (cat) dialkyl glutaconate addition to nitro-olefins followed by a zinc-promoted reductive cyclization should efficiently provide the desired five-membered ring (Scheme 1). Among the main advantages of this methodology, the highly functionalized NH-free pyrrolidines would be directly obtained without the requirement for any protecting groups and with two ester functions as well as an easily adjustable R′ group. As a result, the strategy should provide both a unique opportunity to access rapidly new drug leads and a powerful synthetic platform to build structurally different ligands or organocatalysts.

The main challenge of developing such a strategy lies in the selective activation of the dialkyl glutaconate toward the designed nucleophilic addition. Indeed, to promote such condensation, the pro-nucleophile must be efficiently deprotonated at the α-position of the ester due to the cooperation of the second ester through vinylogous delocalization. To our knowledge, the unique example of catalytic enantioselective activation of dialkyl glutaconates involved highly basic phase transfer catalysis. In 2009, the group of Bernardi and Fini showed that, under phase transfer catalysis, a cycloaddition with nitrones occurred, providing N–O heterocycles such as isoxazolidines. While efficient, this strategy using aqueous base could hardly be applied to the proposed Michael addition, and alternatively, we hypothesized that bifunctional Bronsted base/acid catalysis might promote with success the proposed vinylogous activation. Herein, we present our efforts at successfully developing this new enantioselective one-pot strategy and illustrate its synthetic interest by applying the obtained NH-free pyrrolidines in aminocatalyzed Michael addition.

To develop the most straightforward access to chiral pyrrolidines, we focused our efforts on using commercially available substrates.

Scheme 1. Proposed Strategy and Interest for Enantioselective 2,3,4-Trisubstituted Pyrrolidines

1) Proposed strategy towards enantioenriched 2,3,4-trisubstituted pyrrolidines:

2) Examples of biologically active 2,3,4-trisubstituted pyrrolidines:
available diethyl glutamate 1 and nitrostyrene 2a (Table 1). The reaction was best performed in m-xylene at $-20 \, ^\circ\text{C}$ using

**Table 1. Optimization of the Pyrrolidine Synthesis**

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from the &quot;standard&quot; conditions</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>cat1 in toluene at rt, 1.5 h</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>cat1 in toluene at rt, 10 h</td>
<td>59</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>cat4 in toluene at rt, 1.5 h</td>
<td>74</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>cat1 in toluene at rt, 1.5 h</td>
<td>64</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>cat1 in toluene at 4 $^\circ\text{C}$, 2 h</td>
<td>74</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>cat1 in toluene at $-20 , ^\circ\text{C}$, 18 h</td>
<td>79</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>cat1 in toluene at $-20 , ^\circ\text{C}$, 18 h</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>cat1 in toluene at $-40 , ^\circ\text{C}$, 22 h</td>
<td>48</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>cat1 in THF at $-20 , ^\circ\text{C}$, 22 h</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>cat1 in DCM at $-20 , ^\circ\text{C}$, 16 h</td>
<td>67</td>
<td>82</td>
</tr>
</tbody>
</table>

*Isolated yield after silica gel chromatography. *2Enantioemeric excess measured by HPLC in all cases for both diastereomers (90:10 dr for all entries).

bifunctional cat1. After completion of the Michael addition, acetic acid and Zn were directly added to the reaction mixture, providing cleanly the expected pyrrolidine 3a in 78% yield. In addition, the three newly created contiguous stereocenters were controlled in 90:10 dr and 90% ee (Table 1, entry 1). When the reaction was performed at rt in toluene (Table 1, entries 2–5), among the organocatalysts tested, both cat1 and cat4 provided the best levels of enantiocontrol (80% ee); however, when the temperature was decreased to $-4 \, ^\circ\text{C}$, $-20 \, ^\circ\text{C}$, or $-40 \, ^\circ\text{C}$ (Table 1, entries 6–9), cat1 gave the best enantiocontrol (90% ee at $-20 \, ^\circ\text{C}$, Table 1, entry 8). Finally, m-xylene allows the best reactivity and selectivity to be obtained, whereas other solvents, such as THF or dichloromethane, provided lower enantiocontrol (Table 1, entry 1 vs entries 10 and 11).

With these optimized conditions in hand, we then scrutinized the scope of the consecutive Michael addition/cyclization sequence (Scheme 2). Gratifyingly, a broad range of substitution patterns from functionalized aromatics to aliphatic chains were well-tolerated, providing the expected substituted pyrrolidines in usually good yields (42−84% yield) and good stereosecontrol (88:12 to 99:1 dr and 81 to 94% ee).

For example, a fluorinated aromatic, a thiophene, or a phenol could be incorporated with success, providing structures 3b–d. Starting from the nitro-olefin possessing a nitro-substituent in the para-position of the aromatic, as expected, the corresponding aniline 3e was directly obtained with enantiocontrol decreased to 83%. Insertion of electron-donating substituents (OMe) yielded either 3f (67% yield, 91% ee) or 3h (75% yield, 94% ee), with the same good diasterecontrol around 90:10. The absolute configuration of pyrrolidine 3h was assigned as (2R,3S,4R) based on an X-ray crystallographic study, and the configurations of all other pyrrolidines were assigned accordingly. Incorporating sterically demanding anthracene was also possible, yielding 3g in excellent 84% yield and good 88% ee. Interestingly, in this case, the initial 91:9 dr observed could be increased to >99:1 dr by performing the reaction at $-40 \, ^\circ\text{C}$ with cat4.

Finally, an aliphatic nitroalkene could also be used efficiently in this sequence, even though the reaction had to be run at room temperature to obtain full conversion, and product 3i was formed in slightly decreased enantiocontrol (82% ee) with still high 92:8 dr.

Mechanistically, the final trans-2,3-diastereocentric in the pyrrolidines seem to be fixed during the Michael addition, as shown by the difference in enantiocontrol observed between both diastereomers in molecules 3b and 3c and the diastereocent control observed for the Michael adduct from 1 and 2b prior to reductive cyclization (see Supporting Information). This means that the cyclization (aza-Michael) creating the third stereocenter at C2 is totally trans-diastereoselective and under kinetic control because, for example, the >99:1 dr in 3g does not evolve upon prolonged time (Scheme 2).

To evaluate the practical applicability of this novel approach, reactions using 2b and 2h were conducted on the gram scale (Scheme 3). Interestingly, the catalyst loading could be reduced to 2 mol % without noticeable loss of catalytic activity. Indeed, both products 3b and 3h were easily formed on the gram scale with more than 90% ee.

Given the rapid access to key NH-free pyrrolidine scaffolds, we were intrigued to test them as organocatalysts in enamine
approach bears some promise for the syntheses of therapeutic biologically active molecules possessing this motif, the developed development of other enantioselective methods.

Typically >88:12 dr and >90% ee. This consecutive reaction allowing after in situ reductive cyclization the key chiral NH-free condensation between diethyl glutarate and nitro-ole

Michael adduct 5a was formed in 96:4 dr and 88% ee, meaning that virtually a perfect enantiomterization was observed in the Michael transition state. The proposed transition state for this Michael addition involves the formation of the s-cis conformation of the C–N single bond between the enamine (alkenyl substituent less hindered than the alkyl substituent), with addition to the electrophile from the less shielded bottom face. Higher enantiocontrol observed using the pyrrolidine 3g possessing the anthracenyl substitution might possibly arise from a change in the conformation of the pyrrolidine, pushing the ester function to efficiently shield the upper face of the enamine (Scheme 4).

In conclusion, we have disclosed the first organocatalyzed condensation between diethyl glutarate and nitro-olefins, allowing after in situ reductive cyclization the key chiral NH-free trans,trans-2,3,4-trisubstituted pyrrolidines to be created with typically >88:12 dr and >90% ee. This consecutive reaction implies an innovative vinylogous-type activation of diethyl glutarate that should readily find applications in the development of other enantioselective methods.

Given the close proximity of the obtained pyrrolidines with biologically active molecules possessing this motif, the developed approach bears some promise for the syntheses of therapeutic agents and should readily find applications in medicinal chemistry.

Finally, we have shown that the pyrrolidines directly accessed from our methodology could serve as efficient organocatalysts for enamine activation. This highly promising result opens new avenues to modify structurally the obtained heterocycles and potentially access new families of ligands and organocatalysts for enantioselective catalysis.

**ACKNOWLEDGMENTS**

The Agence Nationale pour la Recherche (ANR-13-PDOC-0007-01), the Centre National de la Recherche Scientifique (CNRS), and the Aix-Marseille Université are gratefully acknowledged for financial support. The authors warmly thank Marion Jean and Nicolas Vanthuyne (Aix-Marseille Université-CNRS) for chiral-phase HPLC analysis. Michel Giorgi (Aix-Marseille Université-CNRS) is acknowledged for X-ray analysis of 3h.

**REFERENCES**


(9) Among all possible diastereomers of the pyrrolidines, only two were observed.

(10) The X-ray structure was deposited on the Cambridge database under the number CCDC 1518760.


(12) See Supporting Information for results with other pyrrolidines.