MULTIGRAM SCALE SYNTHESIS OF SPIROCYCLIC PYRROLIDINONES

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Hallmarks of the MedChem

- “scaffold hopping”
- “escape from flatland”
- “conformational restriction”

MedChem
relevant molecules:
Complexity ↑
Natural-likeness ↑


DDT: Technologies, 2004, 1, 217-224
The Practice of Medicinal Chemistry, 2015, 279–299. doi:10.1016/b978-0-12-417205-0.00011-0.

But MedChem still prefer to use
Limited set of the reaction

Source of complexity?

J. Med. Chem. 2016, 59, 4443−4458
Source of complexity

Complex structures

\[ \downarrow \]

simple robust procedures

Complex Building Blocks

Enamine BB stock collection:
160 000 compounds

“It’s hard to compete dollar for dollar with China and India, but time is equally important to researchers. Chemists are very impatient.”

Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?

Miniperspective

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Modern Challenges

- New Reactions
- New methods for well-known reactions
  - Expand of the scope
  - Increase the yield
  - Scale up
  - Non expensive reagents
The story of one project

1-Azaspiro[4. n]alkanes and their hetera-analogues
A = C\(X_2\), O, S\((O_2)\), NPG
\(x = 0-3, y = 1\) or 2

\(K_i\) (nAChR) = 4.79 nM, antagonist

\(EC_{50}\) (CFTR) < 3 mM, allosteric modulator

\(EC_{50}\) (CB2) = 1.8 nM, agonist

\(EC_{50}\) (FFA) = 0.2 nM, agonist

\(EC_{50}\) (ET-1) = 6.9 nM, antagonist

The story of one project

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th># of biologically active derivatives</th>
<th># of patents / papers</th>
<th># of syntheses described</th>
<th>Known N-protected derivative(s)</th>
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<tr>
<td>1</td>
<td>1a</td>
<td>11</td>
<td>14/0</td>
<td>0</td>
<td>Bn</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>15</td>
<td>7/0</td>
<td>0</td>
<td>Boc</td>
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<tr>
<td>3</td>
<td>1c</td>
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<td>4/1</td>
<td>0</td>
<td>Boc, Ts</td>
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<tr>
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<td>1d</td>
<td>23</td>
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<td>2</td>
<td>Boc, Ts, CO₂Et</td>
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<tr>
<td>5</td>
<td>1e</td>
<td>2</td>
<td>3/0</td>
<td>1</td>
<td>Boc, CO₂Et</td>
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<tr>
<td>6</td>
<td>1i</td>
<td>5</td>
<td>12/0</td>
<td>0</td>
<td>–</td>
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<tr>
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<td>839</td>
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<td>8</td>
<td>1r</td>
<td>81</td>
<td>69/11</td>
<td>0</td>
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</table>
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• New Reactions
• New methods for well-known reactions
  • Expand of the scope
  • Increase the yield
  • Scale up
  • Non expensive reagents
Literature methods

Um, C. et al *Org. Lett.* **2016**, *18*, 2515–2518. https://doi.org/10.1021/acs.orglett.6b01259,
Literature methods


Expensive Reagents. Complicated scale-up.

Moderate yield of the last step. Need optimization.
Approach I

**Literature procedure**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>BnNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>BnN&lt;sub&gt;Bn&lt;/sub&gt;</td>
<td>96%</td>
</tr>
<tr>
<td>BrMg&lt;sub&gt;alkyne&lt;/sub&gt;</td>
<td>BnN&lt;sub&gt;H&lt;/sub&gt;Bn&lt;sub&gt;N&lt;/sub&gt;</td>
<td>92%</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;, Pd/C, Boc&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>BocN&lt;sub&gt;N&lt;/sub&gt;Boc</td>
<td>38%</td>
</tr>
</tbody>
</table>

**Problems**
- Low yield on the last step
- 2 Chromatographic purification.

**Advantages**
- Non expensive starting materials.
- Scale up is possible.
- Good yields on all steps (exclude last)

1p
- 27%
- Lit. 30%
Approach I

Modifications
- Compounds type 3 were used in the next step without purification
- Steps iii and iv were carried out in a one-pot manner
- Compounds type 6 were used in the next step without purification
- The reduction of compounds 6 were carried out in 2 steps, but the overall yield became better.

Scope
- Compounds with additional functionality (N-PG – low yields; S – doesn’t form)
Approach II

PhCH₂OC(O)NH₂, AllylSiMe₃, BF₃·Et₂O, CH₂Cl₂, 0 °C to rt

(vii)

2b, 2d, 2e, 2o

CbzHN

1. THF, NaBH₄, I₂

2. H₂O₂, NaOH

(viii)

9b, 9d, 9e, 9o

(x)

MsCl, i-Pr₂NEt, CH₂Cl₂, 0 °C to rt

1b·HCl, 1d·HCl, 1e·HCl, 1o·HCl

H₂, Pd-C, MeOH, rt, 1 atm

(xi)

11b, 11d, 11e, 11o

NaH, THF

60 °C

(x)

10b, 10d, 10e, 10o

H₂, Pd-C, MeOH, rt, 1 atm

(xii)

11m

NaO₄, RuCl₃, MeCN, rt

1m

Molecular structure of (R)-1n·HCl

Pavel Nosik
Approach II

Advantages
- More stable organometallics was used
- S-containing compounds can be obtained
- Non expensive starting materials.
- No flammable or toxic reagents.
- Scale up is possible.

Problems
- Low yields (lower than approach I)
- Limited number of protection groups.
Approach III

Kostyantyn Melnykov
Approach III

Advantages
• Any protection groups can be used
• Suitable for all types of substrates where the corresponding cyclic ketone is available
• Non expensive starting materials.
• Scale up is possible.
• Non toxic flammable reagents

Problems
• Slightly lower yields (compare to approach I)
Approach IV

Advantages
• Any protection groups can be used
• Suitable for substrates where the corresponding cyclic ketone is not available
• Non expensive starting materials.
• Scale up is possible.

Problems
• Low yields & many steps.
Guide for spiropyrrolidines synthesis

- Is the corresponding cyclic ketone available?
  - Yes
  - No
    - Approach IV

- Is any functionalities available?
  - Yes
    - Approach III
  - No
    - Approach I
Organic synthesis provides opportunities to transform drug discovery

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