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Synthesis of Di-, Tri- and Tetracyclopropylhydrazines

Aleksandr N. Shestakov\textsuperscript{a}, Mikhail A. Kuznetsov\textsuperscript{a,*}

Previously unknown 1,1-dicyclopropylhydrazine was obtained in two steps starting from dicyclopropylamine. It serves as a convenient starting material to tri- and tetracyclopropylhydrazines, which have not been described in the literature either. Tricyclopropylhydrazine was prepared in an overall four-step sequence featuring the de Meijere – Chaplinski modification of the Kulinkovich reaction as a key step. Tetracyclopropylhydrazine was obtained by the reductive amination of the cyclopropanone ethyl trimethylsilyl acetal with 1,1-dicyclopropylhydrazine or with the parent hydrazine. Synthetic utility of these cyclopropylhydrazine building blocks is presented as well.

Cyclopropyl substituted hydrazines are of great interest for at least two reasons. First, some simplest hydrazines are common rocket propellants that are being researched even nowadays.\textsuperscript{1} Cyclopropylhydrazines are particularly interesting for such applications due to the additional ring strain of the three-membered ring. Second, hydrazine derivatives display a wealth of biological activities\textsuperscript{2} and a combination of hydrazine and cyclopropyl fragments – privileged scaffolds in library design and drug discovery – is very promising towards new pharmaceutically active lead compounds. No wonder there are about 30 patents for pharmaceutical applications of different acyl and alkyl derivatives of cyclopropylhydrazines.\textsuperscript{3,4} An improved procedure for the multigram scale synthesis of cyclopropylhydrazine was published very recently.\textsuperscript{5}

That being said, only two out of the five theoretically possible cyclopropylhydrazines (Figure 1) have been reported to date: monocyclopropylhydrazine 1 and the symmetrical 1,2-dicyclopropylhydrazine 2.\textsuperscript{5,7} The synthesis of the remaining members of the cyclopropylhydrazine family posed a formidable synthetic challenge. We therefore set about to investigate viable practical routes to these target molecules (3 – 5) and report our results herein.

At the onset of our work, we prepared 1,1-dicyclopropylhydrazine 3 in two synthetic steps from dicyclopropylamine 6 according to the “classical way”: nitrosation of dicyclopropylamine followed by the reduction of \textit{N}-nitrosodicyclopropylamine 7 with LiAlH\textsubscript{4} (Scheme 1). Starting amine 6 was obtained in four steps following the known literature procedure.\textsuperscript{6} The NMR spectra of intermediate N-nitrosodicyclopropylamine 7 contain two sets of signals of cyclopropyl rings because of the restricted rotation about the N–N bond that is typical for nitrosoamines. To minimize decomposition during the synthesis, it was prepared in a two phase diethyl ether-water system and the dried ether extract was used in the next reduction step without further purification. The spectral properties of 1,1-dicyclopropylhydrazine 3 are in a full agreement with its structure.

Having established the synthetic route to 3, we explored if it can be used as a platform to introduce additional cyclopropyl rings. Towards this goal we prepared formyl hydrazide 8 in good yield by the reaction of 3 with methyl formate that proceeded at room temperature for 3 days (Scheme 2). To our delight, elaboration of 8 to 4 was successful through the de Meijere – Chaplinski modification\textsuperscript{9} of the Kulinkovich reaction. This method is an adaptation of the original Kulinkovich protocol for the preparation of substituted cyclopropanols.\textsuperscript{10}

Figure 1. Cyclopropylhydrazines

Scheme 1. Synthesis of 1,1-dicyclopropylhydrazine

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enables access to N,N-disubstituted cyclopropylamines from \(N,N\)-dialkylcarboxamides and alkylmagnesium halides in the presence of organotitanium compounds. While benzylation and debenzylation reactions expectedly gave high to excellent yields, the key transformation \(9 \rightarrow 10\) provided benzyl protected tricyclopropylhydrazine in fair 59% isolated yield (Scheme 2).

Next, we sought to apply the same strategy to prepare tetracyclopropyldihydrazine 5 starting from tricyclopropyldihydrazine 4. Unfortunately, the treatment of 4 with methyl formate under various conditions gave no expected hydrazide required for the subsequent elaboration to 5. We therefore adopted the reductive amination reaction of the cyclopropanone ethyl trimethylsilyl acetal 11 as a route to 5.\(^{11}\) Thus, the reaction of 1,1-dicyclopropylhydrazine 3 with a large excess of 11 in the presence of NaBH\(_4\) and molecular sieves in the mixture of acetic acid and methanol at 60 °C during 6 hours led to the formation of desired tetracyclopropyldihydrazine 5 in 51% yield. Encouraged by this result we used the very cheap parent hydrazine 12 as the starting material and, to our delight, isolated the desired product 5 in 17% yield (Scheme 3).

After successful synthesis of all three previously unknown cyclopropyldihydrazines we set about to gain insights into their chemical properties and utility for the synthesis of cyclopropylhydrazines. As tetracyclopropyldihydrazine didn’t react with methyl formate and tetracyclopropyldihydrazine can’t react without breaking of N-N or C-N bonds, we focused on transformations of the less substituted 1,1-dicyclopropyldihydrazine 3. Expectedly, it displays reactions characteristic for unsymmetrical disubstituted hydrazines. For instance, we treated 3 with simple aliphatic and aromatic aldehydes including acetaldehyde \(13a\), benzaldehyde \(13b\), and a less reactive veratraldehyde \(13c\) (Table 1). The latter reaction partner was selected due to the occurrence of its core in many bioactive compounds.\(^{12}\) Reactions with the aforementioned aldehydes proceeded smoothly in diethyl ether at room temperature furnishing corresponding hydrazones \(15a\)-c in good yields. The reaction of 3 with ketones required elevated temperatures. Thus, the condensation with acetone \(13d\) was carried out in neat acetone under reflux, and the reaction with acetonophene \(13e\) proceeded in boiling benzene in the presence of catalytic amount of \(p\)-toluenesulfonic acid. Acetyl and benzoyl derivatives \(16a, b\) were obtained in good yields by treatment of hydrazine 3 with corresponding acyl chlorides \(14a, b\) in diethyl ether at room temperature in the presence of triethylamine.

To further demonstrate the practical utility of novel hydrazine 3 we synthesized 1-aminoindole derivative 17. 1-Aminoindoles represent an important class of heteroaromatic compounds, which have attracted much attention because of their pharmacological properties.\(^{13}\) Starting phenylacetic acid derivative 18 was prepared in five steps according to literature reports.\(^{14}\) Reaction of hydrazine 3 with 18 in methanol at room temperature for 4 h gave enhydrazine 19 as a mixture of two stereoisomers with \(Z:F=3:1\) ratio at equilibrium. It is likely that the intramolecular hydrogen bonding between the NH and the oxygen atom of the carbonyl group in \(Z\)-isomer is responsible for its prevalence. Cyclisation of 19 to the desired 1-aminooindole was performed according to a known procedure\(^{15}\) in DMF at 85 °C with Cul as a catalyst, \(K_2\)PO\(_4\) as a base and resulted in formation of the product 17 in fair 64 % yield (Scheme 4).

\[^3\]Starting from hydrazine 12

**Scheme 3. Synthesis of tetracyclopropyldihydrazine**

**Table 1. Reaction of 1,1-dicyclopropylhydrazine 3 with carbonyl compounds**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Yield, %</th>
</tr>
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<tbody>
<tr>
<td>15a</td>
<td>H</td>
<td>Me</td>
<td>76</td>
</tr>
<tr>
<td>15b</td>
<td>H</td>
<td>Ph</td>
<td>84</td>
</tr>
<tr>
<td>15c</td>
<td>H</td>
<td>Ar(^b)</td>
<td>89</td>
</tr>
<tr>
<td>15d</td>
<td>Me</td>
<td>Me</td>
<td>91</td>
</tr>
<tr>
<td>15e</td>
<td>Me(^b)</td>
<td>Ph</td>
<td>72</td>
</tr>
<tr>
<td>16a</td>
<td>Me(^d)</td>
<td>—</td>
<td>81</td>
</tr>
<tr>
<td>16b</td>
<td>Ph(^e)</td>
<td>—</td>
<td>74</td>
</tr>
</tbody>
</table>

\(3\) (1 mmol), \(13a\)-c (1 mmol), Et\(_2\)O, rt, 6h.\(^b\) \(Ar = 3,4-(MeO)\)_2C\(_6\)H\(_4\).\n
\(3\) (1 mmol), \(13d\) (0.5 ml), 60 °C, 3h.\(^c\) \(3\) (1 mmol), \(13e\) (1 mmol), benzene, reflux, 6h.\(^d\) \(3\) (1 mmol), \(14a, b\) (1 mmol), Et\(_3\)N, Et\(_2\)O, rt, 2h.\(^e\) \(R\).

**Scheme 4. Synthesis of 1-aminoindole 17**
In summary, we have synthesized all previously unknown cyclopropylhydrazines – 1,1-dicyclopentylhydrazine 3, tricyclopentylhydrazine 4 and tetracyclopentylhydrazine 5. We presented the anticipated reactivity of 3 in reactions with carbonyl compounds and showed its utility in the synthesis of 1-aminooindole derivative. Tricyclopentylhydrazine 4 was synthesized in a 31% yield over four synthetic steps starting from 1,1-dicyclopentylhydrazine 3. Tetracyclopentylhydrazine 5 was prepared by reductive amination of the synthetic equivalent of cyclopropane either by 3 or by hydrazine itself. Our current efforts are focused on physico-chemical properties of synthesized compounds and their evaluation as building blocks in synthesis of heterocycles.

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Notes and references

† Characterization data for novel cyclopropylhydrazines and 1-aminooindole

1,1-Dicyclopentylhydrazine 3. 1H NMR (CDCl3, 400 MHz): δ 0.49-0.51 (m, 8H, 4 CH2), 2.02-2.08 (m, 2H, 2 CH), 3.24 (br s, 2H, 2 CH); 13C NMR (CDCl3, 100 MHz): δ 6.7 (CH3), 40.1 (CH); HRMS (ESI) calcd for C18H23N2 [M+H]+ 271.1441, found 271.1447.

Tetracyclopentylhydrazine 5. 1H NMR (CDCl3, 400 MHz): δ 0.43-0.45 (m, 16H, 8 CH2), 2.45-2.50 (m, 4H, 4 CH); 13C NMR (CDCl3, 100 MHz): δ 6.5 (CH3), 34.6 (CH); HRMS (ESI) calcd for C12H10N2 [M+H]+ 193.1699, found 193.1700.

Methyl 1-(dicyclopentylamino)-1H-indole-3-carboxylate (17). 1H NMR (CDCl3, 400 MHz): δ 0.56-0.62 (m, 8H, 4 CH2), 2.92-2.97 (m, 2H, 2 CH), 3.93 (s, 3H, CH3), 7.23-7.26 (m, 2H, CH), 7.37-7.40 (m, 1H, CH), 8.13 (s, 1H, CH), 8.13-8.17 (m, 1H, CH); 13C NMR (CDCl3, 100 MHz, 296 K): δ 6.7 (CH3, br), 39.1 (CH), 51.2 (CH2), 105.9 (C), 110.3 (C), 121.5 (CH), 122.1 (CH), 123.1 (CH), 124.2 (C), 130.7 (CH), 136.9 (C), 165.6 (C=O); HRMS (ESI) calcd for C14H12N2O2 [M+H]+ 271.1441, found 271.1447.