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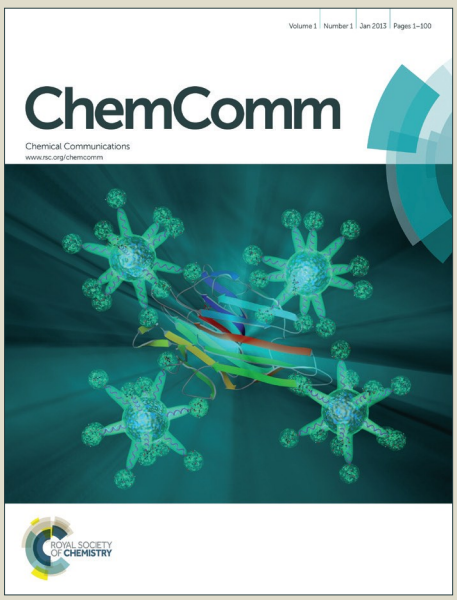

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Synthesis of Di-, Tri- and Tetracyclopropylhydrazines

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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.[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[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.[3,4] An improved procedure for the multigram scale synthesis of cyclopropylhydrazine was published very recently.[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**.[6,7] 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.

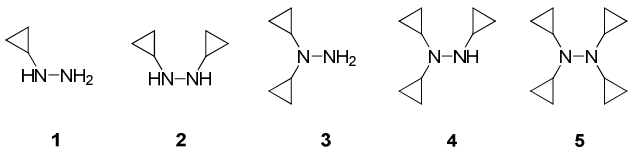
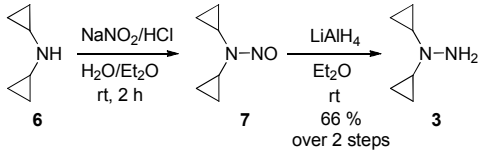


Figure 1. Cyclopropylhydrazines

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 N-nitrosodicyclopropylamine **7** with $LiAlH_4$ (Scheme 1). Starting amine **6** was obtained in four steps following the known literature procedure.[8] 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 of **7** 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[9] of the Kulinkovich reaction. This method is an adaptation of the original Kulinkovich protocol for the preparation of substituted cyclopropanols[10]



Scheme 1. Synthesis of 1,1-dicyclopropylhydrazine

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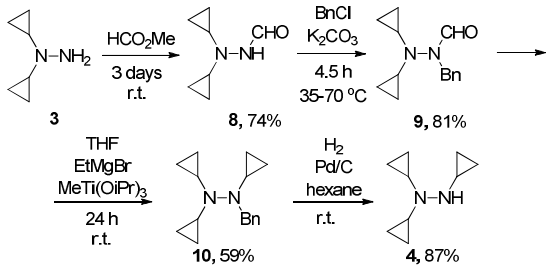
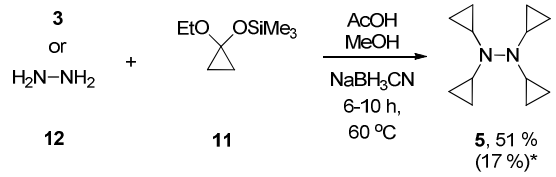


Scheme 2. Synthesis of tricyclopropylhydrazine

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** → **10** provided benzyl protected tricyclopropylhydrazine in fair 59% isolated yield (Scheme 2).

Next, we sought to apply the same strategy to prepare tetracyclopropylhydrazine **5** starting from tricyclopropyl-hydrazine **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 $NaBH_3CN$ and molecular sieves in the mixture of acetic acid and methanol at 60 °C during 6 hours led to the formation of desired tetracyclopropyl-hydrazine **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).

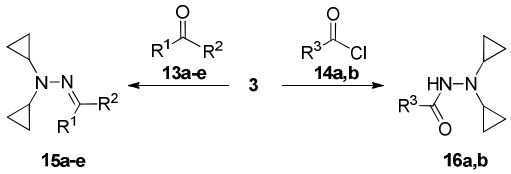
After successful synthesis of all three previously unknown cyclopropylhydrazines we set about to gain insights into their chemical properties and utility for the synthesis of heterocycles. As tricyclopropylhydrazine didn't react with methyl formate and tetracyclopropylhydrazine can't react without breaking of N-N or C-N bonds, we focused on transformations of the less substituted 1,1-dicyclopro-pylhydrazine **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 veratric aldehyde **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



*Starting from hydrazine **12**

Scheme 3. Synthesis of tetracyclopropylhydrazine

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

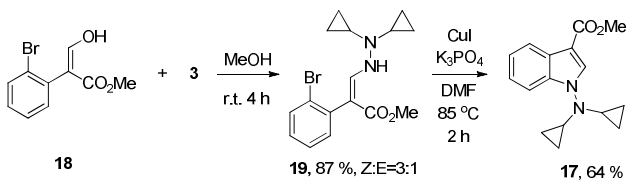


Comp.	R^1	R^2	Yield, %
15a[a]	H	Me	76
15b[a]	H	Ph	84
15c[a]	H	Ar[b]	89
15d[c]	Me	Me	91
15e[d]	Me	Ph	72
16a[e]	Me[f]	—	81
16b[e]	Ph[f]	—	74

[a]**3** (1 mmol), **13a-c** (1 mmol), Et_2O, rt, 6h. [b]Ar = 3,4-$(MeO)_2C_6H_3$. [c]**3** (1 mmol), **13d** (0.5 ml), 60 °C, 3h. [d]**3** (1 mmol), **13e** (1 mmol), benzene, reflux, 6h.[e]**3** (1 mmol), **14a,b** (1 mmol), Et_3N, Et_2O, rt, 2h. [f]R^3.

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 acetophenone **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*:*E*=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-aminoindole was performed according to a known procedure[15] in DMF at 85 °C with CuI as a catalyst, K_3PO_4 as a base and resulted in formation of the product **17** in fair 64 % yield (Scheme 4).



Scheme 4. Synthesis of 1-aminoindole 17

In summary, we have synthesized all previously unknown cyclopropylhydrazines – 1,1-dicyclopropylhydrazine **3**, tricyclopropylhydrazine **4** and tetracyclopropylhydrazine **5.** We presented the anticipated reactivity of **3** in reactions with carbonyl compounds and showed its utility in the synthesis of 1-aminoindole derivative. Tricyclopropylhydrazine **4** was synthesized in a 31% yield over four synthetic steps starting from 1,1-dicyclopropylhydrazine **3**. Tetracyclopropylhydrazine **5** was prepared by reductive amination of the synthetic equivalent of cyclopropanone 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-aminoindole**

1,1-Dicyclopropylhydrazine (**3**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.49-0.51 (m, 8H, 4 CH_2), 2.02-2.08 (m, 2H, 2 CH), 3.24 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 5.7 (CH_2), 41.4 (CH); HRMS (ESI) calcd for $C_6H_{13}N_2$ $[M+H]^+$ 113.1073, found 113.1069.

Tricyclopropylhydrazine (**4**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.41-0.66 (m, 12H, 6 CH_2), 2.17-2.22 (m, 2H, N-1-CH), 2.53-2.58 (m, 1H, N-2-CH), 2.98 (br s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz); δ 5.7 ($4CH_2$), 6.5 ($2CH_2$), 29.5 (CH), 39.0 (2CH); HRMS (ESI) calcd for $C_9H_{17}N_2$ $[M+H]^+$ 153.1386, found 153.1394.

Tetracyclopropylhydrazine (**5**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.43-0.45 (m, 16H, 8 CH_2), 2.45-2.50 (m, 4H, 4 CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.5 (CH_2), 34.6 (CH); HRMS (ESI) calcd for $C_{12}H_{20}N_2$ $[M+H]^+$ 193.1699, found 193.1700.

Methyl 1-(dicyclopropylamino)-1*H*-indole-3-carboxylate (**17**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.56-0.62 (m, 8H, 4 CH_2), 2.92-2.97 (m, 2H, 2 CH), 3.93 (s, 3H, CH_3), 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); ^{13}C NMR ($CDCl_3$, 100 MHz, 296 K): δ 6.7 (CH_2, br), 39.1 (CH), 51.2 (CH_3), 105.9 (C), 110.3 (CH), 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 $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 271.1441, found 271.1447.

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