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Synthesis and cytotoxic activity of new hexaazadibenzotetracenes derived from *trans*-1,2-diaminocyclohexane

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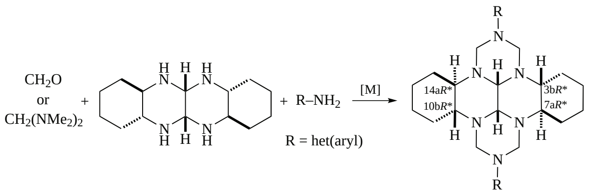
A one-pot synthesis of *N,N′*-disubstituted (3b*R,7a*R**,10b*R**,14a*R**)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes *via* the catalytic heterocyclization of *trans*-1,6,7,12-tetraazaperhydrotetracene with formaldehyde or $CH_2(NMe_2)_2$ and anilines has been accomplished. Preliminary screening of thus obtained perhydro hexaazadibenzotetracenes for cytotoxic activity has been performed.**

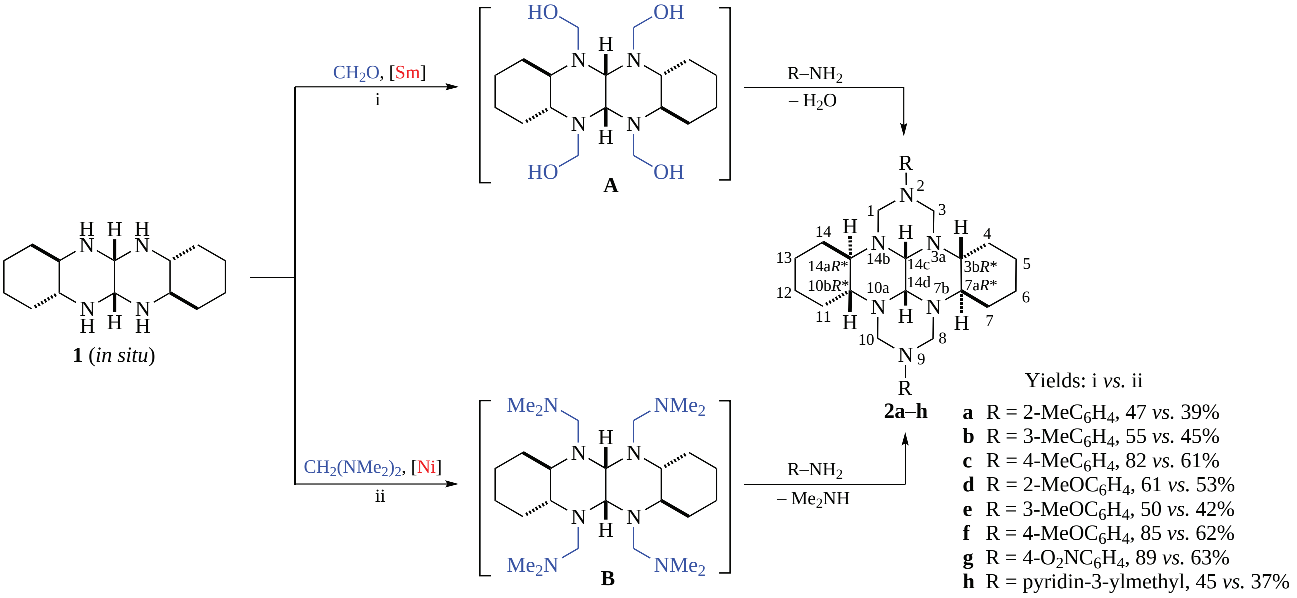


cytotoxic activity on human cancer cell lines HepG2, HTC116, SH-SY5Y, MCF-7, A549, Jurkat, THP-1

Keywords: catalysis, heterocyclization, *trans*-1,2-diaminocyclohexane, anilines, polycyclic compounds, hexaazadibenzotetracenes, cytotoxic activity.

Methods for synthesizing cyclic derivatives based on *trans*-1,2-diaminocyclohexane,[1,2] including poly- and macrocyclic compounds,[3–5] have been reported in the world literature. Heterocycles comprising the *trans*-1,2-diaminocyclohexane moiety can serve as N-containing chiral ligands,[6] bifunctional organocatalysts[7,8] and catalytic systems for enantioselective reactions.[9,10] On the other hand, they possess antitumor[11–15] and antiproliferative activity.[16] A series of *N,N′*-disubstituted perhydro hexaazabenzotetracenes with *in vitro* anticancer activity against the human histiocytic lymphoma cell line U937 have recently been synthesized from (±)-*trans*-1,2-diaminocyclohexane.[17] In view of this, our experiments were aimed at determining whether a selective synthesis of new potentially biologically active representatives of the perhydro tetracene series is possible.

Considering the previous results on the synthesis of disubstituted (3b*R**,7a*R**,10b*R**,14a*R**-*cis*-14c,14d)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzotetracenes,[18,19] we paid attention to the catalytic heterocyclization of the starting building block, namely, perhydro-1,6,7,12-tetraazatetracene **1** with formaldehyde and substituted anilines. Compound **1** is readily formed *in situ* from (±)-*trans*-1,2-diaminocyclohexane and



Yields: i *vs.* ii
a R = 2-MeC_6H_4, 47 *vs.* 39%
b R = 3-MeC_6H_4, 55 *vs.* 45%
c R = 4-MeC_6H_4, 82 *vs.* 61%
d R = 2-$MeOC_6H_4$, 61 *vs.* 53%
e R = 3-$MeOC_6H_4$, 50 *vs.* 42%
f R = 4-$MeOC_6H_4$, 85 *vs.* 62%
g R = 4-$O_2NC_6H_4$, 89 *vs.* 63%
h R = pyridin-3-ylmethyl, 45 *vs.* 37%

Scheme 1 *Reagents and conditions*: i, CH_2O (aq., 4 equiv.), $Sm(NO_3)_3{\cdot}6H_2O$ (5 mol%), then RNH_2 (2 equiv.), MeOH, room temperature, 3 h; ii, $CH_2(NMe_2)_2$ (4 equiv.), $NiCl_2{\cdot}6H_2O$ (5 mol%), then RNH_2 (2 equiv.), MeOH, room temperature, 3 h.

Table 1 Yields of compound **2c** in the presence of 5 mol% lanthanide catalysts.

Catalyst	Yield (%)	Catalyst	Yield (%)
$Yb(NO_3)_3 \cdot 6H_2O$	60	YbF_3	72
$EuCl_3 \cdot 6H_2O$	62	$YbCl_3 \cdot 6H_2O$	75
$LaCl_3 \cdot 6H_2O$	65	$SmCl_3 \cdot 6H_2O$	80
$Er(NO_3)_3 \cdot 6H_2O$	65	$Sm(NO_3)_3 \cdot 6H_2O$	82
SmF_3	69		

glyoxal. Previously,[18–20] we used salts of rare-earth elements possessing ‘hard’ Lewis acidity for activation of the starting compounds under three-component cyclocondensation conditions.[21] Using the model reaction of compound **1** with formaldehyde and *p*-toluidine as an example (Scheme 1), we studied the effect of rare-earth element salts on the yield of the target perhydro hexaazadibenzotetracene **2c**. The highest activity in this reaction was shown by catalysts based on samarium(III) salts (Table 1). Increasing the catalyst loading to 10 mol% did not boost the yield of the target polycycle to any considerable extent.

Under optimum conditions [5 mol% $Sm(NO_3)_3 \cdot 6H_2O$, 20 °C, 3 h, MeOH], *trans*-perhydro-1,6,7,12-tetraazatetracene **1** reacts with formaldehyde and isomeric toluidines or anisidines to selectively give 2,9-disubstituted perhydro hexaazadibenzotetracenes **2a**–**f** in 47–85% yields (see Scheme 1). It should be noted that spatially hindered *ortho*/*meta*-substituted toluidines and anisidines were found to be less reactive in comparison with their *para*-substituted analogues. Heterocyclization of compound **1** with formaldehyde and *p*-nitroaniline in the presence of 5 mol% $Sm(NO_3)_3 \cdot 6H_2O$ as the catalyst results in product **2g** in 89% yield. An attempt to involve *o*- and *m*-nitroanilines into this multicomponent condensation failed. According to experimental data, the yield of perhydro hexaazadibenzotetracenes increases in the series: *p*-Me (**2c**, 82%) < *p*-OMe (**2f**, 85%) < *p*-NO_2 (**2g**, 89%). Electron-donating groups (Me, OMe) present in the aniline molecule decrease the desired yield of the target perhydro tetracenes **2**. The largest yield is observed if an electron-withdrawing group (NO_2) is present (the pK_a value of *p*-nitroaniline is 1.02, while those for *p*-toluidine and *p*-anisidine are 5.12 and 5.29, respectively).

Recently,[18] we synthesized perhydro hexaazadibenzotetracenes with pyridine moieties. We herein performed a one-pot catalytic condensation of compound **1** with formaldehyde and 3-(aminomethyl)pyridine, which gave product **2h** in 45% yield (see Scheme 1).

Apparently, the condensation of perhydro-*trans*-1,6,7,12-tetraazatetracene **1** with formaldehyde involves the stage of the formation of tetrakis(hydroxymethyl) derivative **A** (see Scheme 1).[18,22] Previously,[20] MALDI TOF/TOF mass spectrometry showed that the reaction mixture contained molecular ions of similar compounds formed in reactions of secondary amino groups with formaldehyde.

The ability of *N*,*N*,*N'*,*N'*-tetramethylmethanediamine $CH_2(NMe_2)_2$ to form new C–N bonds in the catalytic synthesis of heterocyclic compounds was reported.[23] With this in mind, we studied if $CH_2(NMe_2)_2$ could be used as a synthetic equivalent of formaldehyde in the synthesis of perhydro hexaazadibenzotetracenes **2**. Really, the condensation of compound **1** with $CH_2(NMe_2)_2$ and substituted anilines was accomplished in the presence of nickel(II) chloride as the most reactive catalyst (see Scheme 1, conditions ii). It was observed that under these conditions (5 mol $NiCl_2 \cdot 6H_2O$, MeOH, 20 °C, 3 h), compound **1** reacted with $CH_2(NMe_2)_2$ and the corresponding amines to afford the same 2,9-disubstituted perhydro hexaazadibenzotetracenes **2a**–**h** in 37–63% yields. Apparently, the condensation of compound **1** with $CH_2(NMe_2)_2$ involves a stage of the formation of intermediate tetrakis(dimethylaminomethyl) derivative **B** similar to tetrakis(hydroxymethyl) derivative **A**. According to the hard/soft acids/bases principle,[24,25] nickel(II) chloride hexahydrate as an ‘intermediate’ Lewis acid would prefer coordination with the intermediate N-donor ligand to give the most stable acid–base complex. The possible pathway of cyclocondensation involves the initial coordination of a nitrogen atom in intermediate **B** with the ion of the central catalyst atom, nucleophilic addition of the primary amine to the resulting carbocation, and subsequent heterocyclization that results in perhydrotetracenes.

The NMR spectra of all the compounds **2a**–**h** obtained show a spectral pattern typical of the stereochemical features of perhydro hexaazadibenzotetracenes.[17–19] The approaches that we developed make it possible to convert (±)-*trans*-1,2-diaminocyclohexane to perhydrotetracenes with *R**,*R**,*R**,*R** relative configuration of chiral centers at the C^{3b}, C^{7a}, C^{10b} and C^{14a} atoms and with *cis*-articulation of the piperazine rings at the C^{14c}–C^{14d} bond.

Compounds **2a**,**c**–**h** were tested for cytotoxicity in a panel of human cancer cell lines (HepG2, HTC116, SH-SY5Y, MCF-7, A549, Jurkat, THP-1) and in tentatively normal cells (HEK293) by the MTT assay. As shown in Table 2, compounds **2a**,**c**,**d**,**f**, did not demonstrate any activity towards the tested cell lines, whilst compounds **2e**,**g** containing 3-methoxyphenyl and 4-nitrophenyl substituents exhibited a moderate cytotoxicity against tentatively normal HEK293 cells only (IC_{50} 46 μM and IC_{50} 71 μM, respectively). Compound **2h** containing a pyridine substituent was found to be the most active amongst the series inhibiting the viability of cancer and non-cancer cells at IC_{50} values ranging from 25 to 52 μM, depending on cell line tested.

In summary, the heterocyclization of *trans*-1,6,7,12-tetraazaperhydrotetracene **1** with formaldehyde or tetramethylmethanediamine and substituted anilines in the presence of salts of transition and rare-earth metals is an efficient method for synthesizing novel (3b*R**,7a*R**,10b*R**,14a*R**-*cis*-14c,14d)-

Table 2 The effect of perhydro hexaazadibenzotetracenes **2a**,**c**–**h** on the viability of cancer and non-cancer cells *in vitro*.[a]

Compound	HEK293 IC_{50}/μM	HepG2 IC_{50}/μM	HTC-116 IC_{50}/μM	SH-SY5Y IC_{50}/μM	MCF-7 IC_{50}/μM	A549 IC_{50}/μM	Jurkat IC_{50}/μM	THP-1 IC_{50}/μM
2a	>100	>100	>100	>100	>100	>100	>100	>100
2c	>100	>100	>100	>100	>100	>100	>100	>100
2d	>100	>100	>100	>100	>100	>100	>100	>100
2e	46.67 ± 5.70	>100	>100	>100	>100	>100	>100	>100
2f	>100	>100	>100	>100	>100	>100	>100	>100
2g	71.71 ± 3.70	>100	>100	>100	>100	>100	>100	>100
2h	30.83 ± 0.18	52.11 ± 0.77	44.77 ± 0.09	37.90 ± 0.49	25.01 ± 0.17	44.16 ± 0.03	32.19 ± 0.49	34.07 ± 0.24
FU	6.32 ± 0.71	3.86 ± 0.7	2.38 ± 0.9	1.16 ± 0.3	1.0 ± 0.04	0.28 ± 0.02	0.67 ± 0.10	4.3 ± 0.8

[a] Cells were treated with compounds for 48 h. Data are expressed as the mean ± SEM from two independent experiments performed in triplicate. FU is 5-fluorouracil.

perhydro-2,3a,7b,9,10a,14b-hexaazadibenzotetracenes. The compounds obtained may be of interest for their cytotoxic activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.035.

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