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Six-membered nitrogen ring formation by radical cyclization of trichloroacetamides with enones. A synthetic entry to *cis*-perhydroisoquinoline-3,6-diones

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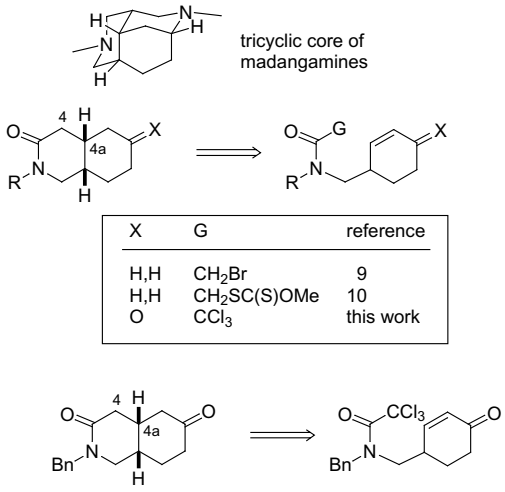
Abstract—Intramolecular reactions between 1-(carbamoyl)dichloromethyl radicals and enones acting as radical acceptors are reported for the first time. The Bu_3SnH promoted 6-*exo* reaction of trichloroacetamides with enones, avoiding the 1,5-hydrogen transfer, constitutes a new synthetic entry to *cis*-perhydoisoquinoline-3,6-diones.

Functionalized *cis*-perhydroisoquinolines are a key architectural feature in a wide array of biologically active natural products (e.g., reserpine,[1] manzamine,[2] and madangamine alkaloids[3]) as well as a number of pharmaceuticals, including several HIV protease inhibitors.[4] Our interest in the madangamine alkaloids[5] has directed our attention to the synthesis of these structural motifs. As envisioned in Scheme 1, our approach to the synthesis of functionalized *cis*-perhydroisoquinolines involves the radical cyclization of trichloroacetamides with enones to give perhydroisoquinoline-3,6-diones,[6] in which both carbonyl groups would be useful in building the backbone of the aforementioned natural products.



X	G	reference
H,H	CH_2Br	9
H,H	$CH_2SC(S)OMe$	10
O	CCl_3	this work

Scheme 1.

The usefulness of the radical processes for the synthesis of nitrogen heterocycles is well established,[7] but there are relatively few examples of six-membered piperidine ring elaboration.[8] Until now there have been reports of two radical approaches[9,10] based on the use of carbamoylmethyl radicals to construct hydroisoquinoline compounds by the formation of the C-4/C-4a bond in the ring closure step, the radical acceptor being an isolated double bond in both Stork's[9] and Zard's work.[10] The isoquinoline derivatives formed in these approaches lack the functionalization at C-6 required for our purposes, but it could be obtained if a radical cyclization upon an enone group were achieved. This type of cyclization, leading to six-membered rings in substrates with a hydrogen atom in the γ-position, is scarce,[11,12] since it is hampered by the competitive process of 1,5-hydrogen transfer, which can totally[13] or partially[14] preclude the formation of the six-membered ring. To avoid this unwanted reaction pathway,[15] we decided to attempt the cyclization using dichloromethylcarbamoyl radical intermediates,

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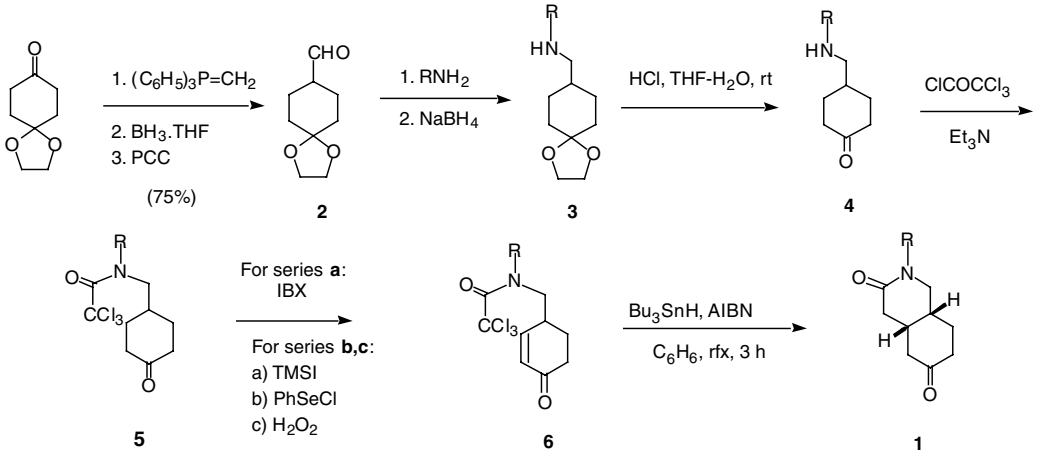


Series		3	4	5	6	1
	a: R = Bn	68%	94%	93%	80%	70%
	b: R = Me	42%	50%	75%	49%	62%
	c: R = CH_2CH_2-indole	82%	88%	81%	36%	60%

Scheme 2. Synthesis of *cis*-perhydroisoquinoline-3,6-diones.

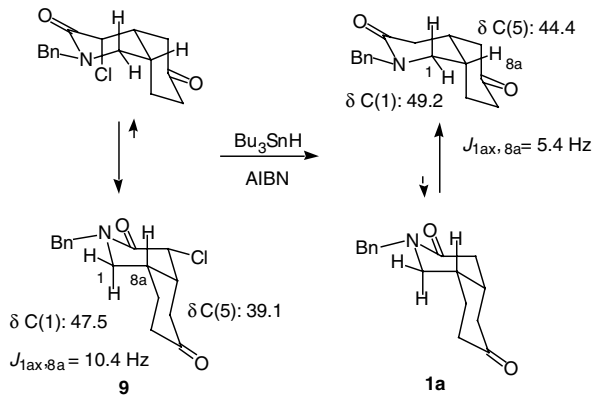
generated from trichloroacetamides, which have given excellent results in the synthesis of 2-azabicyclo[3.3.1]-nonanes by a 6-*exo* radical cyclization.[5,16]

As shown in Scheme 2, we tested this new synthetic entry to *cis*-perhydroisoquinoline-3,6-diones using three different trichloroacetamides. The starting material was aldehyde **2**, which was prepared from the monoethylene acetal of 1,4-cyclohexanedione by Wittig methylenation,[17] followed by hydroboration and oxidation in situ with PCC.[18,19] In the first series, the reductive amination was carried out using benzylamine to form the corresponding imine, which was reduced with $NaBH_4$. The amine **3a**[20,21] was converted into the corresponding trichloroacetamide **5a** by hydrolysis of acetal and trichloroacetylation of the resulting secondary amine **4a**. To generate the enone functionalization of **6a** from **5a** we initially used a classical procedure involving the silyl enol ether formation using TMSI and HMDS followed by phenylselenylation and hydrogen peroxide oxidation of the α-phenylselenyl ketone intermediate. The overall yield was 48%, which was improved up to 80% using IBX as the oxidizing agent for ketone **5a** in a one-step procedure.[22] Treatment of compound **6a** in benzene with Bu_3SnH (3.5 equiv) and AIBN under a reflux temperature provided through a 6-*exo* radical process the isoquinolinedione **1a** as a single diastereoisomer in 70% yield. Under the same reaction conditions, the monochloroacetamide **7** did not give the cyclized compound **1a** but the reduced acetamide **8** was formed.[23] This result again shows that the carbamoylmethyl and carbamoyldichloromethyl radicals behave differently,[5,16a] probably because the two chlorine atoms increase the pyramidalization at the radical center, which in turn increases the rate of radical addition to the alkene.[24] The overall cyclization—full reduction process from **6a** to achieve **1a** was also carried out successfully using TTMSS (66% overall yield).

The promising result in the cyclization of **6a** prompted us to extend this methodology to the synthesis of compounds **1b** and **1c**, which was carried out from trichloroacetamides **6b** and **6c**, prepared in a nonoptimised way following the protocol depicted in Scheme 2. Compound **1c**[25] would be of interest in the field of yohimban indole alkaloids[26] since its functionalization could allow access to the pentacyclic framework of the natural products of this family that bear a *cis*-fused isoquinoline fragment.

The relative stereochemistry of **1a** was elucidated by 2D NMR spectra (COSY, HSQC, NOESY) (Scheme 3).[27] The stereoselective *cis*-perhydroisoquinoline formation agrees with the stereochemical outcome observed in the related radical cyclizations through a 6-*exo* process and with both the steric and electronic preference for a pseudo axial addition of the dichlorocarbamoylmethyl radical to the cyclohexenone moiety.[28] The key evidence for the conformational elucidation of **1a** was found in the ^1H NMR coupling pattern for the methylene protons at C-1, which appear as dd ($J = 12.6$ and 5.4 Hz). The relative configuration for the other azabicyclic compounds **1b** and **1c** is the same as observed in **1a** and their NMR data follows the same pattern of chemical shifts. Interestingly, the monochloro derivative **9**, which was isolated in 56% yield when the cyclization of **6a** was carried out using 2.2 equiv of TTMSS,[29] shows a different preferred conformation to that of **1a** (Scheme 3).[30]

In summary, we report a new method for the synthesis of functionalized *cis*-perhydroisoquinolines consisting of



Scheme 3. Conformational behavior of **1a** and **9**.

Bu_3SnH or TTMSS/AIBN-promoted radical cyclization of trichloroacetamides with enones. This constitutes an example of the otherwise scarce radical process involving a reaction of a carboradical upon enones to generate a six-membered ring. Extension of this methodology to the synthesis of tricyclic skeleton of madangamines is now underway.

Acknowledgements

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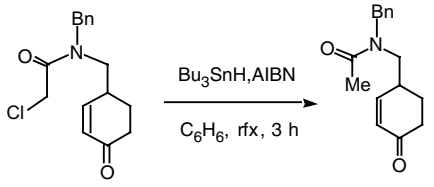

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