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Intramolecular Titanium-Mediated Aminocyclopropanation of Terminal Alkenes: Easy Access to Various Substituted Azabicyclo[*n*.1.0]alkanes[1]

Gerd-Dieter Tebben, Karsten Rauch, Christian Stratmann, Craig M. Williams, and Armin de Meijere*

Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany

armin.demeijere@chemie.uni-goettingen.de

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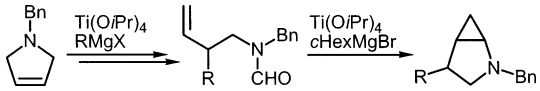
ABSTRACT



A variety of substituted azabicyclo[*n*.1.0]alkanes were synthesized by intramolecular titanium-mediated cyclopropanation of *N*-benzyl-*N*-(2-alkylalk-3-enyl)formamides and *N*-benzyl-*N*-alkadienylformamides. *N*-Benzylpyrroline upon treatment with Grignard reagents undergoes a titanium-mediated carbomagnesiation to yield *N*-benzyl-*N*-(2-alkylbut-3-enyl)amines.

Much attention during the last two decades has been focused on the utilization of organotitanium compounds in organic synthesis.[2] In particular, interest in titanium(IV) alkoxides has significantly increased since the discovery of Kulinkovich et al., who found that a large variety of esters could be converted to cyclopropanols utilizing titanium(II) intermediates generated in situ from Ti(O*i*Pr)$_4$ and alkylmagnesium halides or even with subsequent ligand exchange.[3]

An extrapolation of this methodology has led to a convenient general synthesis of *N*,*N*-dialkylcyclopropylamines from *N*,*N*-dialkylcarboxamides.[4]

The scope of this new cyclopropylamine synthesis has been substantially extended by applying the ligand exchange protocol.[5]

Here we report a further extension of this methodology to a number of intramolecular cases, making azabicyclo[*n*.1.0]alkanes accessible from *N*-benzyl-*N*-alkenylformamides.

Two of the precursors were synthesized starting from *n*-but-3-enol (**1**), the tosylate of which was converted to *N*-benzyl-*N*-but-3-enylamine (**2**) by reaction with benzylamine. Upon reaction of **2** with ethyl formate, *N*-benzyl-*N*-but-3-enylformamide (**3**) was obtained in an overall yield of 60%.

(1) Part 88 in the series *Cyclopropyl Building Blocks for Organic Synthesis*. For Part 87, see: Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, in press. Part 86: de Meijere, A.; Kuchuk, I. D.; Sokolov, V. V.; Labahn, T.; Rauch, K.; Es-Sayed, M.; Krämer, T. *Eur. J. Org. Chem.* **2003**, in press.

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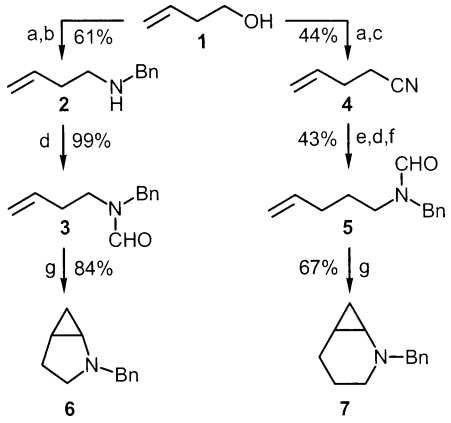
Toward the homologous *N*-benzyl-*N*-pent-4-enylformamide (**5**), the tosylate of **1** was treated with NaCN in DMSO. Reduction of the resulting nitrile **4** with $LiAlH_4$ provided 4-pentenylamine, which was quantitatively converted to the corresponding formamide by reaction with ethyl formate. Deprotonation of the amide and benzylation with benzyl bromide led to **5** in 19% overall yield (Scheme 1).

Scheme 1[a]



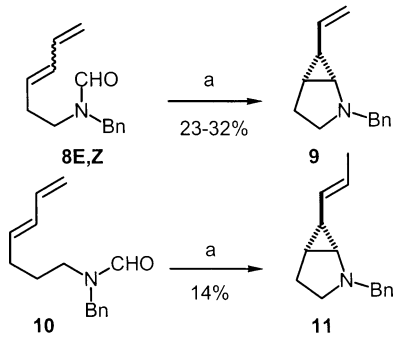
[a] Reaction conditions: (a) TsCl, Py, 0 °C, 3 days; (b) $BnNH_2$ (2.5 equiv), MeCN, 60 °C, 3 h. (c) NaCN, DMSO, 25 °C, 24 h. (d) EtOCHO, 65 °C, 24 h. (e) $LiAlH_4$, Et_2O, 25 °C, 36 h. (f) (1) NaH, DMF, 60 °C, 1 h; (2) BnBr, DMF, 25 °C, 24 h. (g) Ti(O*i*Pr)$_4$ (1.1 equiv), *c*HexMgBr (3.3 equiv), THF, 25 °C, 24 h.

The intramolecular reductive cyclopropanations of **3** and **5** were carried out by adding 3.3 equiv of cyclohexylmagnesium bromide to a THF solution containing 1.1 equiv of titanium(IV) tetraisopropoxide and 1.0 equiv of the respective formamide. Conversion of the *N*-benzyl-*N*-alkenylformamides **3** and **5**, after acid/base workup, gave the expected *N*-benzyl-2-azabicycloalkanes **6** and **7** in good yields (84 and 67% respectively, Scheme 1).[6]

In view of this result and the fact that 1,3-dienes are particularly good ligands on titanium,[5,7] the analogous *N*-benzyl-*N*-alkadienylformamides[8] were also subjected to the established cyclization conditions. In accordance with previous observations that substituted 1,3-dienes with one terminal vinyl group always undergo aminocyclopropanation at the more highly substituted double bond, both the (*E*)- and (*Z*)-isomer of *N*-benzyl-*N*-hexa-3,5-dienylformamide (*E*,*Z*)-**8** gave *exo*-*N*-benzyl-6-vinyl-2-azabicyclo[3.1.0]hexane (**9**) derived from supposed attack on the internal double bond, albeit with yields of only 23 and 32%, respectively.[9] Since, however, the primary attack of the first titanium intermediate most probably occurs at the terminal double bond, the trajectory for intramolecular carbonyl attack is rather disfavored, and this may be one reason for the poor yield.[10]

Surprisingly, the analogous treatment of *N*-benzyl-*N*-hepta-4,6-dienylformamide (**10**) did not yield the expected 2-azabicyclo[4.1.0]heptane derivative but yielded only 15% of *exo*-*N*-benzyl-6-propenyl-2-azabicyclo[3.1.0]hexane (**11**) (Scheme 2).

Scheme 2[a]



[a] Reaction conditions: (a) Ti(O*i*Pr)$_4$ (1.1 equiv), *c*HexMgBr (3.3 equiv), THF, 25 °C, 24 h.

This product most probably arises by initial isomerization of the precursor **10** under the conditions employed.

In another context,[5] we came upon a new synthesis of 2-substituted 3-butenylamines, which were quite welcome as precursors to 4-substituted 2-azabicyclo[3.1.0]hexanes **14**.

Upon treatment of *N*-benzylpyrroline (**12**) with 2.5 equiv of an alkylmagnesium halide in the presence of 1.2 equiv of titanium tetraisopropoxide, *N*-benzyl-*N*-(2-alkylbut-3-enyl)-amines (alkyl = ethyl, isopropyl, *sec*-butyl, cyclopentyl) were obtained. This transformation must arise from a titanium-mediated carbomagnesiation of *N*-benzylpyrroline (**12**) with ring opening. It resembles the zirconium-catalyzed carbomagnesiations discovered by Dzhemilev et al.[11] and further developed by Hoveyda et al. as well as others.[12] However, in those reactions, only isopropyl- and ethylmagnesium halides were used.

Upon reaction of the crude mixtures of the homoallylamines with ethyl formate, the corresponding formamides

(6) A single example of a similar reaction has been reported by Cha et al. leading to 1-methyl-*N*-phenyl-2-azabicyclo[3.1.0]hexane: Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584.

(7) Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett.* **1998**, *39*, 7695 and references therein.

(8) *N*-Benzyl-*N*-alkadienylformamides **8** and **10** were synthesized in an analogous manner as the monoene precursors by using hexa-3,5-dienol as starting material instead of but-3-enol (**1**). Preparation of (*E*)-hexa-3,5-dienol: Martin, S. F.; Tu, C.-y.; Chou, T.-s. *J. Am. Chem. Soc.* **1980**, *102*, 5274. (*Z*)-Hexa-3,5-dienol: Aerrsens, M. H. P. J.; van der Heiden, R.; Heus, S.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3421.

(9) An attempted analogous cyclization of *N*-benzyl-*N*-(3-methylenepent-4-enyl)formamide gave a minute amount (9%) of 2-benzyl-5-methylene-2-azabicyclo[4.1.0]heptane and traces of a second cyclization product, possibly the expected *exo*-*N*-benzyl-5-vinyl-2-azabicyclo[3.1.0]hexane.

(10) In contrast to the unsubstituted azabicycloalkanes **6** and **7**, compounds **9** and **11** upon attempted purification by acid/base workup or distillation underwent rapid polymerization. Therefore, they had to be purified by column chromatography, which probably also contributed to the decreased yields.

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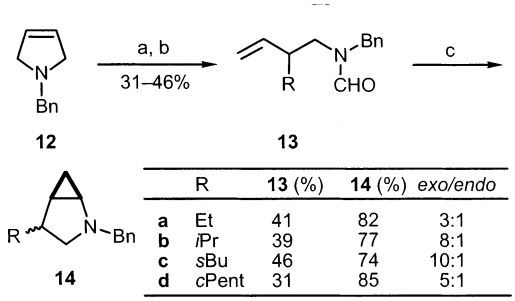
13a−**d** were obtained in overall yields of 31−46%. These were also subjected to the above-mentioned cyclization conditions to afford the 4-substituted 2-azabicyclo[3.1.0]-hexanes **14a**−**d** in good yields as mixtures of exo and endo diastereomers in ratios ranging from 3:1 to 10:1 (Scheme 3).

Scheme 3[a]



	R	**13** (%)	**14** (%)	*exo/endo*
a	Et	41	82	3:1
b	*i*Pr	39	77	8:1
c	*s*Bu	46	74	10:1
d	*c*Pent	31	85	5:1

[a] Reaction conditions: (a) Ti(O*i*Pr)$_4$, RMgBr, Et$_2$O, −20 °C, 4 h. (b) EtOCHO, 65 °C, 24 h. (c) Ti(O*i*Pr)$_4$ (1.1 equiv), *c*HexMgBr (3.3 equiv), THF, 25 °C, 24 h.

In summary, we have demonstrated that a number of variably substituted azabicyclo[*n*.1.0]alkanes are easily accessible by intramolecular titanium-mediated cyclopropanation of carboxylic acid amides. A number of precursors for the cyclization were synthesized by a new titanium-mediated carbomagnesiation reaction of *N*-benzylpyrroline.

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Supporting Information Available: Experimental procedures and characterization for compounds **3**, **5**−**11**, **13a**−**d**, and **14a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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