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Tetrahedron Letters 44 (2003) 2485–2487

TETRAHEDRON LETTERS

Titanium-mediated synthesis of bicyclic cyclopropylamines from unsaturated nitriles

Christophe Laroche, Philippe Bertus* and Jan Szymoniak*

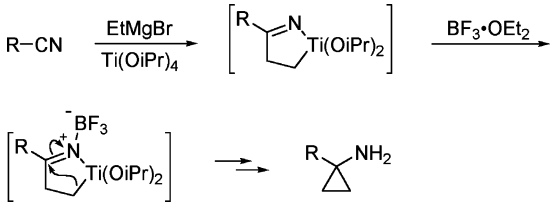
UMR 6519-Réactions Sélectives et Applications, CNRS-Université de Reims Champagne-Ardenne, UFR Sciences, BP 1039, 51687 Reims Cedex 2, France

Received 11 December 2002; revised 3 February 2003; accepted 3 February 2003

Abstract—Here we report an easy synthesis of bicyclic primary cyclopropylamines directly from unsaturated nitriles. The described reaction involves Ti(II)-mediated intramolecular coupling of alkene and nitrile moieties.

The cyclopropane ring is encountered in a variety of biologically active compounds.[1] In particular, the aminocyclopropyl moiety is present in natural aminocyclopropane carboxylic acids (ACC),[2] and in several synthetic drugs.[3] We recently reported a new synthetic method for preparing primary cyclopropylamines from nitriles and Grignard reagents in the presence of $Ti(OiPr)_4$.[4,5] The described reaction is similar to the Kulinkovich or de Meijere reactions which allow to the preparation of cyclopropanols and tertiary cyclopropylamines respectively from carboxylic esters and *N*,*N*-dialkylamides.[6] However, in our case, the subsequent addition of a Lewis acid is important for the reaction to occur (Scheme 1).

Since the development of the ligand-exchange methodology for the generation of titanacyclopropane intermediates,[7–10] the scope of the Kulinkovich and de Meijere reactions had been extended. In this way, a number of bicyclic cyclopropanols[8,9] and tertiary cyclopropylamines[10–12] were obtained by the intramolecular cyclopropanation of unsaturated esters and amides. However, de Meijere et al. had very recently reported[12] that bicyclic cyclopropylamines were not formed efficiently[13] from δ,ε-unsaturated nitriles, under the conditions described previously.[4] These results prompted us to report our work relating to the preparation of bicyclic cyclopropylamines by intramolecular cyclization of unsaturated nitriles.



Scheme 1.

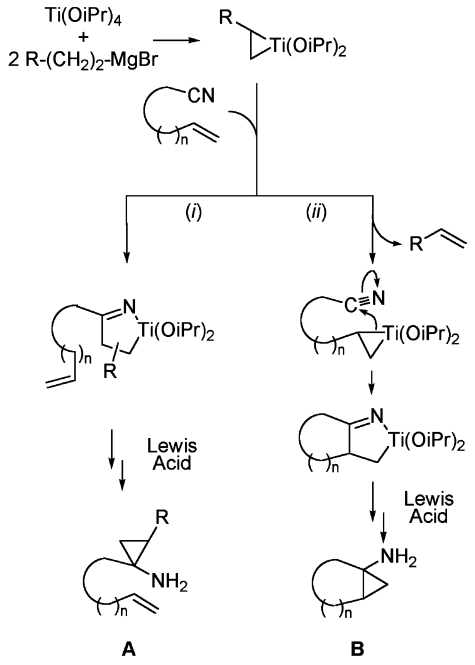
First, competing inter- and intramolecular reactions, as shown in Scheme 2, were considered. In fact, the initially formed titanacyclopropane can directly insert the C≡N bond to afford **A** as a final product (path (*i*)). Alternatively, the alkene exchange with the C=C bond of the nitrile can result in the intramolecular reaction to afford **B** (path (*ii*)). Since the alkene exchange may be greatly influenced by the nature of the Grignard reagent, we thus investigated several organomagnesium halides with the aim of favoring the intramolecular cyclopropanation (path (*ii*)). In these preliminary experiments, Grignard reagents were added to a mixture of the unsaturated nitrile **1** and $Ti(OiPr)_4$ in Et_2O. The results are summarized in Table 1.

By using EtMgBr,[7] only the product **2a** was obtained, resulting from a direct addition to the nitrile moiety (entry 1). With higher Grignard reagents such as *n*-BuMgBr[8] or iPrMgCl[9] (entries 2 and 3), the bicyclic product **3** is obtained, albeit in poor yield and accompanied by a large amount of cyclopropylamines **2b** and **2c**. Cyclic organomagnesium halides[8b,10–12] have proven to be efficient in the preparation of low-valent titanium

Keywords: bicyclic compounds; cyclizations; cyclopropanes; nitriles; titanium.

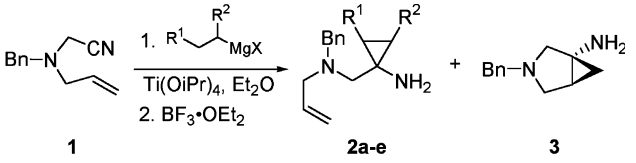
* Corresponding authors. Fax: +33 326 913 166; e-mail: philippe.bertus@univ-reims.fr; jan.szymoniak@univ-reims.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00325-3



Scheme 2.

Table 1.



Entry	R^1	R^2	Yield (%)[a]	Ratio of products	
1	H	H	60	**2a**/**3**	100/0
2	Et	H	67	**2b**/**3**	84/16
3	H	Me	61	**2c**/**3**	78/22
4	-$(CH_2)_3$-		60	**2d**/**3**	83/17
5	-$(CH_2)_4$-		69[b]	**2e**/**3**	<2/98

Conditions: $Ti(OiPr)_4$ 1.1 equiv., Grignard reagent 2.2 equiv. in Et_2O, then $BF_3{\cdot}OEt_2$ 2 equiv.
[a] Overall yield of **2** and **3**.
[b] 66% yield without addition of Lewis acid.

and minimization of undesired intermolecular process. We then tested cyclopentyl- and cyclohexylmagnesium chlorides. Whereas a mixture of **2d** (major) and **3** was formed in the first case, the intramolecular product **3** was solely obtained in the second (entries 4 and 5). Interestingly, **3** was also obtained without the addition of $BF_3{\cdot}OEt_2$, with only a slight decrease of the yield (66%).[14] The amount of Grignard reagent used is important. A lower yield of **3** (37%) was observed when using 3 equiv. of the reagent.[15]

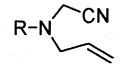
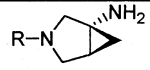
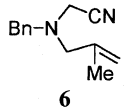
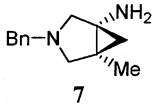
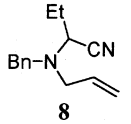
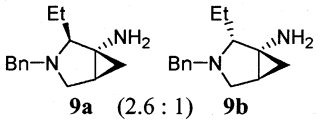
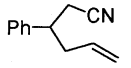
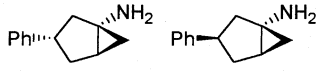
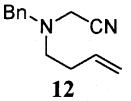
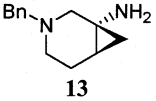
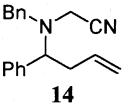
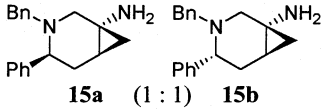
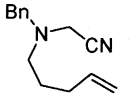
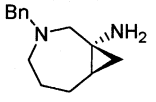
With these optimal conditions in hands, we next studied the scope of the reaction with various unsaturated nitriles.[16] As shown in Table 2, the reaction employing cyclohexylmagnesium chloride proceeded smoothly to afford the corresponding bicyclic cyclopropylamines.[17]

The 3-azabicyclo[3.1.0]hex-1-ylamine framework can be constructed efficiently using the optimized procedure (entries 1–4). An additional double bond in **4** did not interfere with the reaction (entry 2). Starting from the nitrile **6** bearing a *gem*-disubstituted double bond, the cyclopropylamine **7** was obtained without decrease of the yield (entry 3).[18] To our knowledge, this is the first example for the insertion of a disubstituted alkene in Ti-mediated intramolecular cyclopropanation. All-carbon bicycles can also be obtained as shown by the synthesis of diastereomeric 3-phenylbicyclo[3.1.0]hex-1-ylamines **11a** and **11b** (entry 5).

The reaction is not limited to the elaboration of cyclopropylamines with a five-membered ring. Thus, the bicyclo[4.1.0]heptane framework can be formed (entries 6–7).[13,18] In these cases, Lewis acid is required to obtain a good yield of cyclopropylamine. The seven-membered ring homologue **17** can also be obtained, albeit in poor yield (entry 8).

In summary, the Ti-mediated intramolecular coupling of unsaturated nitriles was investigated. The described reaction makes it possible to prepare various bicyclic primary cyclopropylamines.

Table 2. Ti-mediated synthesis of bicyclic cyclopropylamines[17]

Entry	Nitrile	Product	Yield (%)[a]
1	 **1** (R = Bn)	 **3**	69 (66)
2	**4** (R = Allyl)	**5**	67 (58)
3	 **6**	 **7**	69 (62)
4	 **8**	 **9a** (2.6 : 1) **9b**	67 (59)
5	 **10**	 **11a** (2 : 1) **11b**	62 (58)
6	 **12**	 **13**	60 (11)
7	 **14**	 **15a** (1 : 1) **15b**	62 (36)
8	 **16**	 **17**	27

a: Isolated yield; yields without addition of $BF_3{\cdot}OEt_2$ are given in brackets.

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13. In the paper cited in Ref. 12, the reaction of **1** with cyclohexylmagnesium chloride led only to traces of product **3**, under the conditions described in Ref. 4. Moreover, the bicyclo[4.1.0]heptane framework could not be formed from the corresponding nitriles.
14. At this stage, other titanium complexes such as $ClTi(OiPr)_3$ and $Cl_2Ti(OiPr)_2$ were tried, but without improving the yield of **3**.
15. This is in contrast to the reaction employing esters or amides. In the latter cases, the Grignard reagent is generally used in excess. See Refs. 8–12.
16. Several attempts to prepare cyclopropylamines intermoleculary from nitriles and alkenes (styrene, 1-octene) via ligand exchange were unsuccessful.
17. Typical procedure for the synthesis of cyclopropylamines: To a solution of the nitrile (1 mmol) in Et_2O (5 mL) were added successively at room temperature $Ti(OiPr)_4$ (0.33 mL, 1.1 mmol) and cyclohexylmagnesium chloride (1.1 mL, 2.2 mmol, 2 M in ether). After stirring for 0.5 h, $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added at once. Stirring was continued over a period of 30 min. A solution of 10% NaOH (ca. 1 mL) was added and the mixture was extracted with ether. The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography on silica gel.
18. Selected data for **7** and **13**: *3-benzyl-5-methyl-3-azabicyclo[3.1.0]hept-1-ylamine (**7**)*: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.25 (m, 1H), 1.10 (m, 4H), 1.50 (s, 2H), 2.20 (d, $J=8.4$ Hz, 1H), 2.25 (d, $J=8.4$ Hz, 1H), 2.90 (d, $J=8.3$ Hz, 1H), 3.05 (d, $J=8.3$ Hz, 1H), 3.55 (s, 2H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 14.2, 20.6, 26.1, 43.0, 59.2, 60.6, 68.8, 126.7, 128.0, 128.5, 139.1; MS (EI) m/z (%): 202 ($M^{+\bullet}$, 13), 147 (2), 120 (4), 111 (14), 91 (100). *3-Benzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**13**)*: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.65 (m, 2H), 0.95 (m, 1H), 1.65 (m, 3H), 1.95 (dt, $J=17.5$ Hz, $J=5.2$ Hz, 2H), 2.20 (d, $J=10.4$ Hz, 1H), 2.45 (m, 1H), 2.95 (d, $J=10.4$ Hz, 1H), 3.45 (s, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 18.4, 19.3, 24.7, 34.4, 50.9, 61.2, 62.7, 126.8, 128.1, 128.7, 138.8; MS (EI) m/z (%): 202 ($M^{+\bullet}$, 10), 187 (10), 161 (11), 132 (15), 120 (25), 91 (100).