Ti-Mediated Chemoselective Conversion of Cyanoesters and Cyanoamides into β-Aminoesters and 1-Aza-spirolactams Bearing a Cyclopropane Ring.

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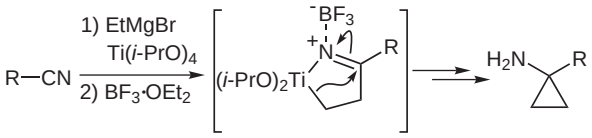
Abstract: α-Cyanoesters or tertiary α-cyanoamides react with Grignard reagents and Ti(*i*-PrO)$_4$ to afford respectively β-amino esters or amides, bearing a cyclopropane ring. Starting from β- or γ-cyanoesters, spirocyclopropanelactams are formed via an in situ cyclopropanation-lactamization sequence.

Key words: cyclizations, cyclopropanes, nitriles, spiro compounds, titanium

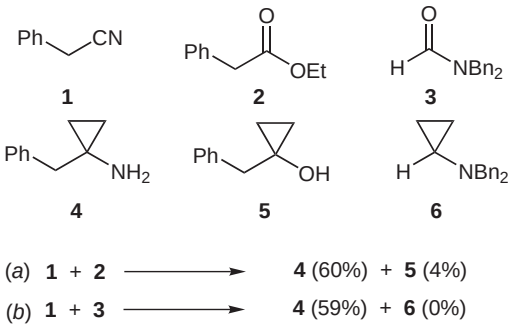
Recently, we developed a new synthetic method for preparing primary cyclopropylamines from nitriles and Grignard reagents in the presence of Ti(*i*-PrO)$_4$ (Scheme 1).[1,2] The described reaction is somewhat similar to the Kulinkovich synthesis of cyclopropanols from carboxylic esters[3,4] or carbonates,[5] and the de Meijere reaction which allows for the preparation of tertiary cyclopropylamines from *N*,*N*-dialkyl carboxamides.[6] In the Kulinkovich and de Meijere reactions the intermediate oxatitanacycle rearranges spontaneously, whereas in our reaction the intermediate azatitanacycle contracts under Lewis acid activation conditions (Scheme 1). However, despite this difference, similar reagents and conditions are involved in all reactions.



Scheme 1

In this context, we attempted to study the chemoselectivity of the reaction employing nitriles in the presence of an additional ester or amide groups.

Our investigation began with comparative intermolecular tests of chemoselectivity. Thus, the reactions employing nitrile **1**, ester **2** and amide **3** were performed as depicted in Scheme 2. Two reactions (*a* and *b*) were carried out involving equimolar amounts of **1** and **2** or **1** and **3**, respectively. We noticed that cyclopropylamine **4** was the highly major (reaction *a*) or even unique (reaction *b*) cyclopropane-containing product in these cross experiments.[7,8]



Scheme 2 Conditions: Ti(*i*-PrO)$_4$ 1.1 equiv, EtMgBr 2 equiv in Et$_2$O, then BF$_3$·OEt$_2$ 2 equiv.

Since the reaction from nitriles had tolerated the presence of an external ester or amide group, we next carried out a series of reactions from functionalized nitriles, bearing an ester, carbonate or amide group. The results are summarized in Table 1.

Starting from α-cyanoesters **7** and **9**, the cyclopropane-derived β-alanine analogues **8** and **10** could be obtained (entries 1 and 2).[9] Similarly, α-cyanoamide **11** was converted into the corresponding amide **12** (entry 3).[10] There is an increasing interest for new synthesis of substituted β-amino acids.[11] Readily available α-cyanoesters or -amides appear as suitable starting materials for a direct preparation of β-amino acids bearing a cyclopropane ring.

As for α-cyanoesters and -amides, the chemoselective cyclopropanation reaction also took place with the γ-cyanoamide **13** to afford the corresponding aminocyclopropane derivative **14** (entry 4). In contrast, when using cyanoesters **15**, **17** and **19** and carbonate **21** with a 2 or 3 atom tether between C≡N and C=O groups, subsequent cyclization reactions occurred, even in the absence of additional Lewis acid.[12] As a result, azaspirocyclic lactams **16**, **18** and **20** and oxazolidinone **22** were formed in good yields (entries 5–8). Thus, starting from β-cyanoester **15**, only **16** was obtained in 68% yield, without any trace of the corresponding aminoester.[13,14] Similarly, **17** gave the corresponding spirocyclic lactam **18** in good yield. Interestingly, the dicyanodiester **19** underwent twofold cyclopropanation-lactamization sequence to afford **20** (entry 7). Also the nitrile **21** bearing a carbonate group reacts only on the cyano moiety giving directly the oxazolidinone **22** in 72% yield (entry 8).

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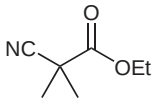
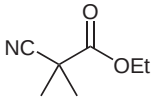
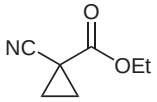
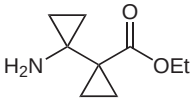
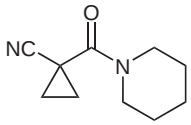
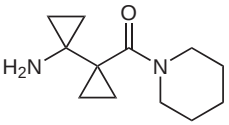
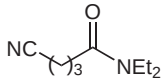
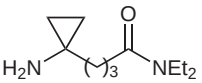
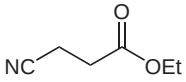
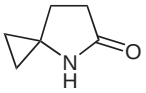
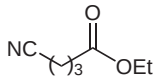
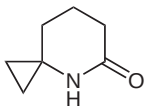
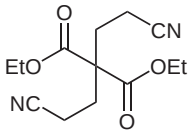
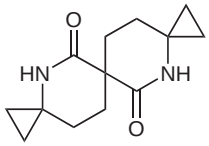
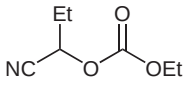
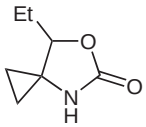
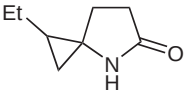
Table 1 Reaction of Grignard Reagents with Cyanoesters, Cyanoamides and Carbonates Mediated by Ti(*i*-PrO)$_4$

Entry	Nitrile	Product	Yield[a]
1	 **7**	 **8**	35%
2	 **9**	 **10**	51%
3	 **11**	 **12**	40%
4	 **13**	 **14**	46%[b]
5	 **15**	 **16**	68%[c]
6	 **17**	 **18**	63%[c]
7[d]	 **19**	 **20**	60%[b,c]
8	 **21**	 **22**	72%[c]
9[e]	**15**	 **23**	74%[c,f]

[a] Isolated yields.
[b] Reaction performed in THF.
[c] Lewis acid is not required.
[d] 2 equiv of Ti(*i*-PrO)$_4$ and 4 equiv of EtMgBr were used.
[e] *n*-BuMgBr was used instead of EtMgBr.
[f] Diastereoisomeric ratio 82:18.

More substituted cyclopropanes can also be obtained by employing higher Grignard reagents. As an example, ethyl-substituted cyclopropane **23** was obtained by using *n*-BuMgBr instead of EtMgBr (entry 9 vs. 5).

In summary, by using the title reaction, we have presented a new and easy access to cyclopropane-containing β-amino acid derivatives and azaspirolactams.

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(7) Carboxylic esters have been demonstrated to be generally more reactive towards the cyclopropanation reaction than the corresponding amides, see: Cho, S. Y.; Lee, J.; Lammi, R. K.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 8235.
(8) Under the same cyclopropanation conditions, the ester **2** alone or the amide **3** alone give cyclopropanol **5** (66% yield) or cyclopropylamine **6** (40%) respectively, irrespective of the addition of $BF_3{\cdot}OEt_2$.
(9) No cyclopropane-containing product was obtained from ethyl cyanoacetate, probably due to the presence of acidic hydrogens.
(10) Typical procedure for the synthesis of **8**, **10**, **12** and **14**: *Ethyl 1′-aminobicyclopropyl-1-carboxylate* **10**: To a solution of nitrile **9** (139 mg, 1 mmol) and Ti(*i*-PrO)$_4$ (0.33 mL, 1.1 mmol) in anhydrous Et_2O (5 mL), was added dropwise at room temperature a solution of EtMgBr in Et_2O (2 mmol). After the mixture was stirred for 1 h, $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added. After additional stirring for 30 min, water (1 mL) was added, followed by 10% aq HCl (10 mL) and CH_2Cl_2 (20 mL). A 10% aq NaOH 10% solution was added to the resulting clear mixture until the pH became basic. The product was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4). After evaporation of the solvent, the product was purified by flash chromatography on silica gel (Et_2O, then acetone) to afford 83 mg (49%) of **10** as a pale yellow oil. IR (KBr): 3373, 1719, 1311 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.35–0.39 (m, 2 H), 0.60–0.69 (m, 4 H), 1.15–1.21 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 2.15 (s, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.1, 14.2, 14.7, 30.5, 34.9, 60.5, 174.8. MS (EI, 70 eV), *m/z* (%): 169 (4, M$^+$),154 (18), 140 (34), 123 (60), 112 (78), 94 (100).
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(12) Typical procedure for the synthesis of **16**, **18**, **20** and **22**: *4-Azaspiro[2.5]octan-5-one* **18**: To a solution of nitrile **17** (141 mg, 1 mmol) and Ti(*i*-PrO)$_4$ (0.33 mL, 1.1 mmol) in anhydrous Et_2O (5 mL), was added dropwise at room temperature a solution of EtMgBr in Et_2O (2 mmol). After the mixture was stirred for 1 h, water (1 mL) was added, followed by CH_2Cl_2 (20 mL). The resulting precipitate was removed and washed with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4). After evaporation of the solvent, the product was purified by flash chromatography on silica gel (Et_2O, then Et_2O–MeOH, 95:5) to afford 80 mg (63%) of **18** as a white solid, mp 124–125 °C. IR (KBr): 3183, 3058, 2951, 1655, 1404 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.58–0.66 (m, 2 H), 0.69–0.76 (m, 2 H), 1.61–1.67 (m, 2 H), 1.83–1.95 (m, 2 H), 2.37 (t, *J* = 6.7 Hz, 2 H), 7.08 (s, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.8, 20.0, 30.9, 31.1, 35.8, 173.5. MS (EI, 70 eV), *m/z* (%): 125 (38, M^+), 96 (48), 82 (100).

(13) These spirocyclopropanelactams cannot be directly prepared from cyclic imides using the same procedure (Grignard reagent and titanium isopropoxide), since the resulting titanaoxacyclopentanes do not lead to cyclopropane formation. See: Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127.

(14) The spirolactam **16**, being a γ-aminobutyric acid (GABA) analogue, has already been prepared, in several steps. See: Kordes, M.; Winsel, H.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 3235.