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# Studies on the titanium-catalyzed cyclopropanation of nitriles

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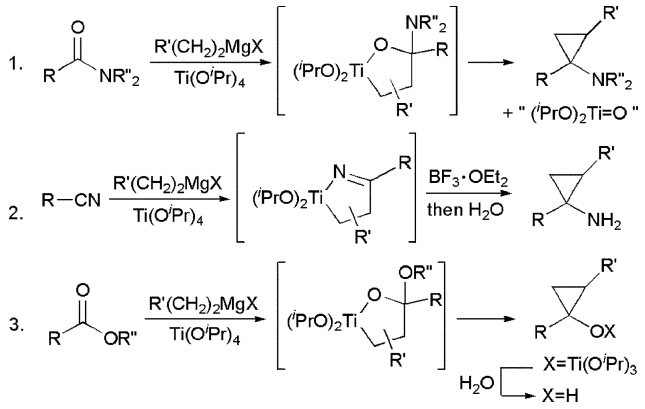
The Ti-mediated reaction of Grignard reagents with nitriles was investigated with sub-stoichiometric amounts of titanium isopropoxide. Cyanoesters were converted to spirocyclopropanelactams in good yields using as low as 0.05 eq of $Ti(O^iPr)_4$. Under similar conditions, cyanocarbonates led to spirocyclopropane oxazolidinones and/or aminocyclopropylcarbinols. A very short synthesis of the naturally occurring aminocyclopropanecarboxylic acid illustrates the usefulness of this methodology.

## Introduction

The aminocyclopropane framework is found in several natural products and many synthetic drugs are endowed with this moiety.[1] For instance, ciprofloxacin is a broad spectrum fluoroquinolone antibiotic[2] and abacavir has found applications as a nucleoside reverse transcriptase inhibitor.[3] Cyclopropylamines are also used as versatile synthetic intermediates[4] but their preparation often requires multistep reactions. Among the most convenient syntheses of cyclopropylamines are the titanium-mediated reactions of Grignard reagents with *N*,*N*-dialkylamides[5,6] or nitriles,[7] leading, respectively, to tertiary or primary cyclopropylamines (Scheme 1, eqns. 1 and 2). The two reactions are somewhat related to the Kulinkovich reaction, *i.e.* the conversion of carboxylic esters to cyclopropanols by the same couple of reagents (eqn. 3).[8] In each of them, a five-membered titanacycle is formed, resulting from the reaction of a transient titanacyclopropane intermediate and the acid derivative. However, the subsequent course leading to cyclopropane derivatives is different. For esters, the ring contraction occurs spontaneously, leading to the three-membered cycle. The reaction works even using catalytic amounts of the titanium complex. Consequently, the asymmetric variant was reported.[9] In the case of *N*,*N*-dialkylamides, the ring contraction also occurs spontaneously, but the formation of a titanium oxide species prevents the use of catalytic amounts of $Ti(O^iPr)_4$.[10] Finally, with nitriles, the addition of a Lewis acid is generally required to induce an efficient ring contraction of the five-membered azatitanacycle. Such a reaction pathway prevents a catalytic reaction as well.

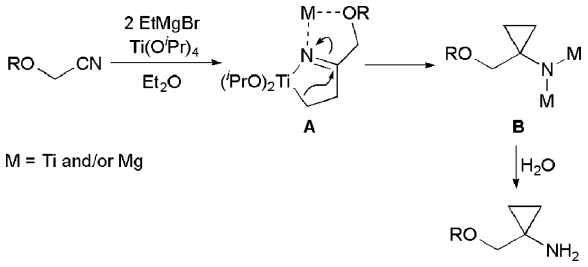



**Scheme 1**

Nevertheless, some nitriles – especially chelating ones – have been noticed to react successfully without an additional Lewis acid (*vide infra*).[7b,c] This allowed us to undertake a preliminary study of the cyclopropanation reaction with sub-stoichiometric amounts of titanium isopropoxide.

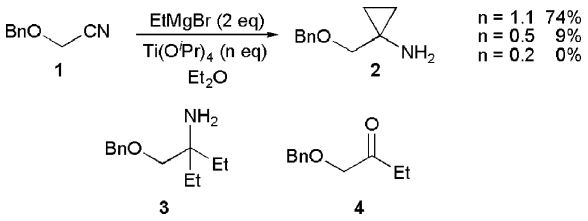
## Results and discussion

The formation of primary cyclopropylamines from nitriles was typically performed with stoichiometric amounts of $Ti(O^iPr)_4$ and a two-fold amount of a Grignard reagent. The addition of a strong Lewis acid affords the primary cyclopropylamine *via* a contraction of the intermediate azatitanacycle (Scheme 1, eqn. 2). However, when using α-hetero-substituted (O, N) nitriles as the substrates, the cyclopropanation reaction proceeds in the absence of any external Lewis acid.[7b] This fact was rationalized by assuming the chelation-controlled process that would involve weak Lewis acid species (M = Mg, Ti) always present in solution (Scheme 2).




**Scheme 2**

Since an additional Lewis acid is not required for the cyclopropanation of benzyloxyacetonitrile (**1**), the reaction was chosen as a model for varying the amount of the titanium complex (Scheme 3). In the presence of the stoichiometric amount of titanium isopropoxide the primary cyclopropylamine




**Scheme 3**

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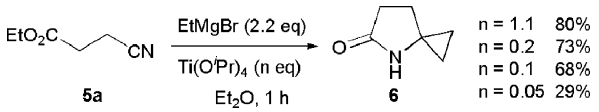
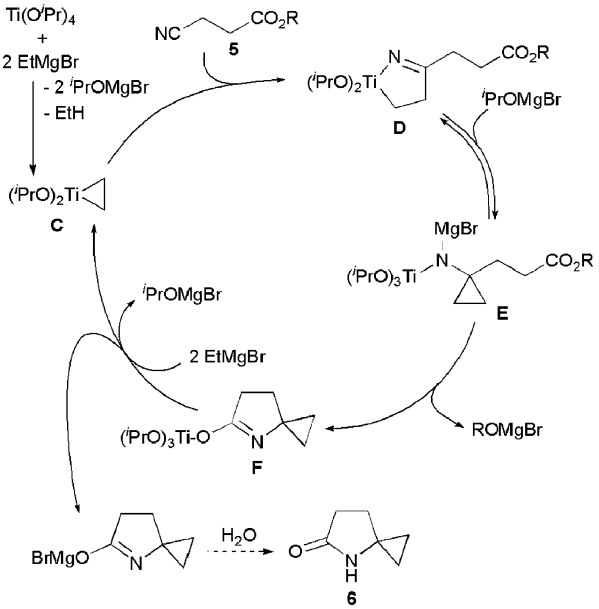
**2** was obtained in good yield, but the use of less than one equiv. of $Ti(O^iPr)_4$ led to a severe decrease in the yield. Even with 0.5 equiv. of titanium complex, almost no cyclopropane-containing product was obtained, the major side products being **3** and **4**.[11] The amine **3** would arise from the addition of the Grignard reagent to the metallacycle **A** [12] (see Scheme 2), and the ketone **4** would derive from the bis-metallated cyclopropylamine intermediate **B** (M = Mg) *via* a ring opening. *N*-Metallated (Li, Mg) cyclopropylamines are indeed known to be unstable.[13]

Another related reaction, *i.e.* the synthesis of spirocyclopropanelactams from cyanoesters,[7c] has been demonstrated to occur without an additional Lewis acid as well. Thus, cyanoester **5a** was transformed into **6** in 80% isolated yield by using 1.1 equiv. of $Ti(O^iPr)_4$ (Scheme 4). We found that this reaction can also be performed efficiently by using a sub-stoichiometric amount of $Ti(O^iPr)_4$. In fact, 10 mol% of the titanium reagent appeared to be sufficient to obtain a good conversion of **5a** to **6**. In this case, a slow introduction of the organomagnesium reagent was proved to be essential.[14]




**Scheme 4**

A tentative mechanism is depicted in Scheme 5 to rationalize both the successful use of a sub-stoichiometric amount of $Ti(O^iPr)_4$ and the fact that a Lewis acid is not necessary. First, the titanacyclopropane **C**, formed *in situ* from EtMgBr and $Ti(O^iPr)_4$,[8] reacts selectively with the nitrile moiety of **5** to afford the azatitanacycle **D**. The ring contraction follows, under the assistance of magnesium salts, leading to the metallated cyclopropylamine **E**. We reasoned that this ring contraction could be reversible, and in this context, the usual role of a Lewis acid would be to shift the equilibrum in favour of the three-membered ring.[7a] Here, the use of a Lewis acid would be avoided due to the subsequent irreversible lactamization step leading to **F**. The reaction of **F** with EtMgBr completes the catalytic cycle by forming the final product and regenerating **C**.




**Scheme 5**

Following this mechanism, one equivalent of the alcoholate (ROMgBr) is released during the lactamization step (**E** → **F**) that can lead to an exchange with isopropoxy ligands on titanium and consequently to a modification of the catalytic activity.[15]

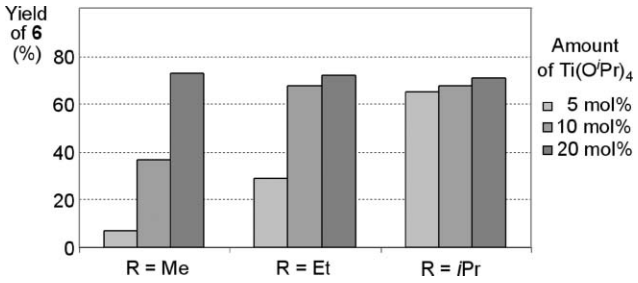


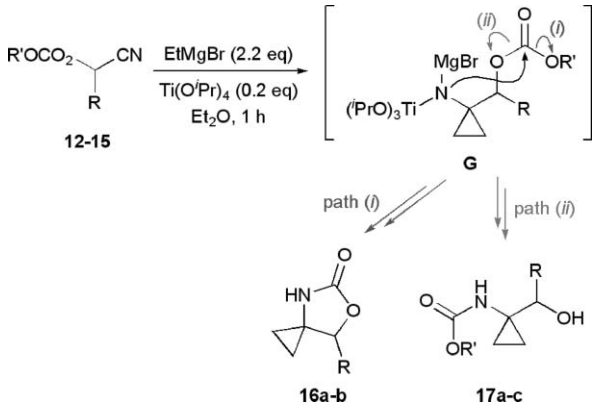

**Fig. 1** Yield of **6** relative to the nature of R in **5a**–**c** and the amount of $Ti(O^iPr)_4$.

In support of the mechanism, the effect of the cyanoester OR group on the reaction was therefore studied (Fig. 1). Starting from the isopropyl ester, the yield of the reaction was good and almost invariable by lowering the amount of $Ti(O^iPr)_4$ from 20 to 5 mol%. In contrast, starting from the methyl or ethyl ester, the yields significantly decreased in these conditions. These results, together with the absence of catalytic activity of $Ti(OEt)_4$, are in accordance with the mechanistic hypothesis in Scheme 5.

The efficient catalytic reaction for **5a** contrasts with the lack of the analogous reaction for **1**. In fact, the lactamization step would lead to a stable amidate in the first case, whereas an unstable bis-metallated cyclopropylamine **B** (M = Mg) would be formed in the second.

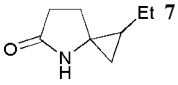
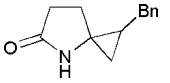
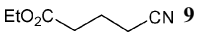
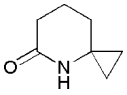
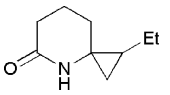
Other spirocyclic lactams can also be obtained by the Ti-catalyzed reaction. Some examples are given in Table 1. The use of Grignard reagents higher than EtMgBr led to the formation of two diastereomeric compounds in good yields and moderate diastereoselectivity. Since two asymmetric carbons are generated in the reaction, an enantioselective variant was tested. In a preliminary experiment **7** was obtained from **5a** in 54% yield, with an increased diastereoisomeric ratio of 93 : 7 and an enantiomeric ratio of 63 : 37 by using 0.2 equiv. of chiral non-racemic titanium bistaddolate[16] instead of $Ti(O^iPr)_4$.

To further explore the catalytic variant we focused on the use of cyanocarbonates **12**–**15** as substrates. Cyanocarbonates **12**–**15** were prepared in one step from NaCN, formaldehyde or propionaldehyde and the resulting cyanhydrin intermediate was quenched with ethyl chloroformate or $Boc_2O$. The results for the cyclopropanation reaction of **12**–**15** are summarized in Table 2. Thus, ethyl cyanomethylcarbonate (**12**) afforded a mixture of oxazolidinone **16a** and alcohol **17a** (entry 1). These products resulted from the non-selective cleavage of the intermediate **G** as shown in Scheme 6. Interestingly, the selectivity of the reaction can be controlled by a subtle modification of the cyanocarbonate structure. The use of the α-substituted nitrile analogue **13** led to the lactam **16b** without traces of the alcohol (entry 2). Increasing the substitution on the carbonate moiety led to a reverse effet, *i.e.* only the alcohol **17b** was obtained from **14** (entry 3). Finally,



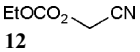
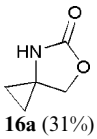
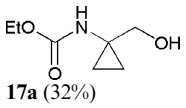
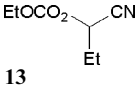
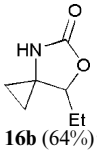
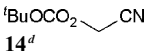
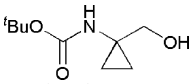
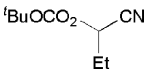
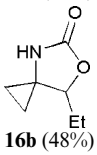
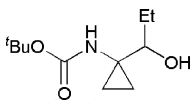

**Scheme 6**

**Table 1** Titanium-catalyzed reaction of cyanoesters with Grignard reagents

| Entry | Nitrile[a] | RMgBr | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **5a** | $^n$BuMgBr |  **7** | 76 (85 : 15) |
| 2 | **5a** | Ph–$(CH_2)_3$MgBr |  **8** | 59 (80 : 20) |
| 3 |  **9** | EtMgBr |  **10** | 72 |
| 4 | **9** | $^n$BuMgBr |  **11** | 50 (78 : 22) |

[a] Reaction performed at rt with 0.2 equiv. of $Ti(O^iPr)_4$ in $Et_2O$. [b] Diastereoisomeric ratio in parentheses.

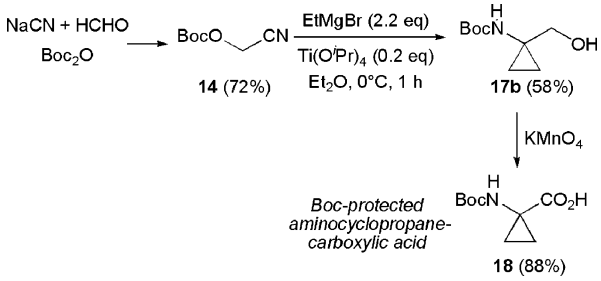
**Table 2** Titanium-catalyzed reaction of cyanocarbonates with EtMgBr

| Entry | Nitrile[a] | Products and yield (%)[b] | |
|---|---|---|---|
| 1 |  **12** |  **16a** (31%) |  **17a** (32%) |
| 2 |  **13** |  **16b** (64%)[c] | |
| 3 |  **14**[d] |  **17b** (64%) | |
| 4 |  **15** |  **16b** (48%) |  **17c** (12%) |

[a] Reaction performed at rt with 0.2 equiv. of $Ti(O^iPr)_4$ in $Et_2O$ unless otherwise stated. [b] Isolated yields. [c] *N*-Ethoxycarbonyl-substituted **16b** derivative was also obtained in 7% yield. [d] Reaction performed at 0 °C.

increasing the substitution on both the nitrile and the carbonate moieties gave a mixture of the two products (entry 4).

Alcohol **17b** was already in use as an intermediate for the synthesis of several biologically active compounds[7b,17] including the naturally occurring aminocyclopropanecarboxylic acid (ACC),[18] and its preparation required several steps. Herein, it was conveniently obtained in only two steps from readily available starting materials (Scheme 7). Since the oxidation of **17b** leads directly to the Boc-protected ACC **18**, the described procedure represents a very short way to obtain this particularly interesting compound.[19]




**Scheme 7**

## Experimental

All reactions were conducted under an atmosphere of dry argon using standard Schlenk techniques. Diethylether and THF were distilled from sodium benzophenone ketyl prior to use. $Ti(O^iPr)_4$ was used as received. Grignard reagents were titrated in THF by menthol in the presence of orthophenanthroline. Cyanoester **9** was prepared according to literature procedure.[20] Flash chromatography was performed with silica gel 60 (Merck, 40–63 μm). $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 spectrometer. Chemical shifts were measured in δ (ppm) and coupling constants *J* in Hz (solvent peak reference: δ = 7.26 for $^1H$, 77.0 for $^{13}C$). IR spectra were recorded on a Nicolet Avatar 320 instrument. Mass spectra were recorded on a ThermoFinnigan Trace MS spectrometer. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V).

### General procedure for the synthesis of cyanoesters 5a–c

Succinonitrile (2.00 g, 25 mmol), chlorotrimethylsilane (3.83 mL, 30 mmol) and the corresponding alcohol (methanol, ethanol or isopropanol, 30 mmol) were stirred at room temperature for 48 h and then water (25 mL) and diethyl ether (50 mL) were added. The mixture was extracted with diethyl ether (50 mL), the organic phase was dried ($MgSO_4$) and filtered. The resulting oil was purified by flash chromatography (petroleum ether–ethyl acetate 80 : 20).

### Ethyl 3-cyanopropionate 5a

Colourless oil (2.15 g, 67%); $R_f$ 0.26 (petroleum ether–ethyl acetate 80 : 20); $\nu_{max}$(film)/cm$^{-1}$ 2985, 2252, 1732, 1421, 1378, 1201 and 1018; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.29 (3 H, t, *J* 7.1 Hz, $CH_3CH_2$), 2.64–2.72 (4 H, m, $CH_2CH_2$) and 4.21 (2 H, q, *J* 7.1, $CH_3CH_2$); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 12.9 (t), 14.0 (q), 29.9 (t), 61.4 (t), 118.4 (s) and 170.0 (s); *m*/*z* (EI) 127 ($M^{+\bullet}$, 32%) and 99 (100).

**Methyl 3-cyanopropionate 5b**

Colourless oil (1.31 g, 46%); $R_f$ 0.24 (petroleum ether–ethyl acetate 80 : 20); $\nu_{max}$(film)/cm$^{-1}$ 2957, 2253, 1739, 1439, 1371, 1210 and 1178; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 2.55–2.70 (4 H, m, C$H_2$C$H_2$) and 3.69 (3 H, s, C$H_3$O); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 12.9 (t), 29.7 (t), 52.3 (q), 118.3 (s) and 170.4 (s); *m/z* (EI) 113 ($M^{+\bullet}$, 3%) and 81 (100).

**Isopropyl 3-cyanopropionate 5c**

Colourless oil (1.70 g, 48%); $R_f$ 0.32 (petroleum ether–ethyl acetate 80 : 20); $\nu_{max}$(film)/cm$^{-1}$ 2985, 2252, 1732, 1422, 1378, 1207 and 1108; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.27 [6 H, d, *J* 6.2 Hz, (C$H_3$)$_2$CH], 2.63–2.66 (4 H, m, C$H_2$C$H_2$) and 5.07 [1 H, hept, *J* 6.2, (CH$_3$)$_2$C*H*]; $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 10.9 (t), 19.5 (q), 28.0 (t), 66.9 (d), 116.5 (s) and 167.4 (s); *m/z* (EI) 141 ($M^{+\bullet}$, 65%), 125 (80) and 99 (100).

**General procedure for the Ti-catalyzed cyclopropanation of cyanoesters and cyanocarbonates (Tables 1 and 2)**

To a solution of the nitrile (1 mmol) and Ti(O$^i$Pr)$_4$ (59 μL, 0.2 mmol) in $Et_2O$ (5 mL) was added under argon at room temperature over 1 h a solution of EtMgBr (1.1 mL, 2 M in $Et_2O$). After additional stirring (1 h), a few drops of water were added to obtain a white precipitate on the walls of the flask. The precipitate was rinsed with diethyl ether. The organic phase was dried ($MgSO_4$). After evaporation of the solvent, the product was purified by flash chromatography on silica gel.

**4-Azaspiro[2.4]heptan-5-one 6**

After purification by flash chromatography on silica gel ($Et_2O$, then $Et_2O$–MeOH 95 : 5), compound **6** was obtained as a white solid (81 mg, 73%); $R_f$ 0.19 ($Et_2O$); $\nu_{max}$(KBr)/cm$^{-1}$ 3241 and 1682; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.64–0.70 (2 H, m, cyclopropyl), 0.84–0.89 (2 H, m, cyclopropyl), 2.15 (2 H, t, *J* 8.1 Hz, C$H_2$CH$_2$CO), 2.54 (2 H, t, *J* 8.1, CH$_2$C$H_2$CO) and 7.32 (1 H, s, N*H*); $^{13}$C NMR $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 11.0 (t), 29.2 (t), 31.5 (t), 39.4 (s) and 178.3 (s); *m/z* (EI) 111 ($M^{+\bullet}$, 58%), 83 (32) and 82 (100); *m/z* (ES) 112.0767 ($MH^+$ $C_6H_{10}NO$ requires 112.0762).

**4-Aza-1-ethylspiro[2.4]heptan-5-one 7**

The diastereomers **7a**,**b** were separated by flash chromatography on silica gel ($Et_2O$).

**7a.** Colourless oil (15 mg, 11%); $R_f$ 0.24 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3208, 1694, 1463, 1366 and 1283; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.43–0.45 (1 H, m, CHC$H_2$), 0.74–0.79 (2 H, m, C$H$C$H_2$) 1.00 (3 H, t, *J* 7.3 Hz, C$H_3$CH$_2$), 1.30–1.41 (2 H, m, CH$_3$C$H_2$), 2.00 (1 H, ddd, *J* 12.6, 8.9, 6.2, C$H_2$CH$_2$CO), 2.12–2.24 (1 H, m, C$H_2$CH$_2$CO), 2.42–2.54 (2 H, m, CH$_2$C$H_2$CO) and 7.21 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 13.9 (q), 16.3 (t), 22.7 (t), 24.6 (d), 30.5 (t), 31.1 (t), 43.3 (s) and 178.8 (s); *m/z* (EI) 139 ($M^{+\bullet}$, 8%), 124 (16) and 110 (100); *m/z* (ES) 140.1079 ($MH^+$ $C_8H_{14}NO$ requires 140.1075).

**7b.** Colourless oil (90 mg, 65%); $R_f$ 0.11 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3215, 1693, 1457, 1361, 1275 and 1239; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.27–0.30 (1 H, m, CHC$H_2$), 0.85–0.93 (2 H, m, C$H$C$H_2$) 0.99 (3 H, t, *J* 7.2 Hz, C$H_3$CH$_2$), 1.12–1.25 (1 H, m, CH$_3$C$H_2$), 1.29–1.42 (1 H, m, CH$_3$C$H_2$), 1.93 (1 H, ddd, *J* 12.8, 9.6, 5.9, C$H_2$CH$_2$CO), 2.15–2.27 (1 H, m, C$H_2$CH$_2$CO), 2.37–2.58 (2 H, m, CH$_2$C$H_2$CO) and 6.55 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 13.5 (q), 17.1 (t), 22.7 (t), 22.9 (d), 24.6 (t), 31.1 (t), 42.8 (s) and 177.5 (s); *m/z* (EI) 139 ($M^{+\bullet}$, 8%), 124 (15) and 110 (100); *m/z* (ES) 140.1079 ($MH^+$ $C_8H_{14}NO$ requires 140.1075).

**4-Aza-1-benzylspiro[2.4]heptan-5-one 8**

The diastereoisomers **8a**,**b** were separated by flash chromatography on silica gel ($Et_2O$).

**8a.** Colourless oil (24 mg, 12%); $R_f$ 0.29 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3180, 1693 and 1457; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.67 (1 H, t, *J* 6.3 Hz, C$H_2$CH), 0.91 (1 H, dd, *J* 9.6, 6.3, C$H_2$CH), 1.02–1.16 (1 H, m, CH$_2$C$H$), 1.97–2.08 (1 H, m, PhC$H_2$), 2.17–2.29 (1 H, m, PhC$H_2$), 2.42–2.49 (2 H, m, C$H_2$CH$_2$CO), 2.63–2.71 (2 H, m, CH$_2$C$H_2$CO), 7.19–7.35 (5 H, m, Ph) and 7.40 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 16.5 (t), 24.0 (d), 30.4 (t), 31.0 (t), 35.0 (t), 43.5 (s), 126.0 (d), 128.1 (d), 128.4 (d), 141.1 (s) and 178.7 (s); *m/z* (EI) 201 ($M^{+\bullet}$, 2%), 128 (3), 117 (6), 115 (10), 110 (100), 91 (15) and 82 (26); *m/z* (ES) 202.1227 ($M^+$ $C_{13}H_{16}NO$ requires 202.1232).

**8b.** White solid (94 mg, 47%); mp 99 °C; $R_f$ 0.21 ($Et_2O$); $\nu_{max}$(KBr)/cm$^{-1}$ 3178, 1693 and 1366; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.46 (1 H, t, *J* 6.1 Hz, C$H_2$CH), 1.06 (1 H, dd, *J* 9.7, 6.1, C$H_2$CH), 1.17–1.39 (1 H, m, CH$_2$C$H$), 1.91–2.02 (1 H, m, PhC$H_2$), 2.15–2.27 (1 H, m, PhC$H_2$), 2.37–2.49 (2 H, m, C$H_2$CH$_2$CO), 2.59–2.63 (2 H, m, CH$_2$C$H_2$CO), 7.19–7.32 (5 H, m, Ph) and 7.91 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 17.5 (t), 21.3 (d), 24.7 (t), 31.2 (t), 35.1 (t), 43.2 (s), 126.0 (d), 127.9 (d), 128.4 (d), 140.6 (s) and 178.0 (s); *m/z* (EI) 201 ($M^{+\bullet}$, 2%), 129 (5), 117 (5), 115 (12), 110 (100), 91 (18) and 82 (38); *m/z* (ES) 202.1225 ($MH^+$ $C_{13}H_{16}NO$ requires 202.1232).

**4-Azaspiro[2.5]octan-5-one 10**

After purification by flash chromatography on silica gel ($Et_2O$, then $Et_2O$–MeOH 95 : 5), compound **10** was obtained as a white solid (90 mg, 72%); mp 124–125 °C; $R_f$ 0.16 ($Et_2O$); $\nu_{max}$(KBr)/cm$^{-1}$ 3183, 3058, 2951, 1655 and 1404; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.58–0.66 (2 H, m, cyclopropyl), 0.69–0.76 (2 H, m, cyclopropyl), 1.61–1.67 (2 H, m, CH$_2$C$H_2$CH$_2$CO), 1.83–1.95 (2 H, m, C$H_2$CH$_2$CH$_2$CO), 2.37 (2 H, t, *J* 6.7 Hz, CH$_2$CH$_2$C$H_2$CO) and 7.08 (1 H, s, NH); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 12.8 (t), 20.0 (t), 30.09 (t), 31.1 (t), 35.8 (s) and 173.5 (s); *m/z* (EI) 125 ($M^{+\bullet}$, 38%), 96 (48) and 82 (100); *m/z* (ES) 126.0922 ($MH^+$ $C_7H_{12}NO$ requires 126.0919).

**4-Aza-1-ethylspiro[2.5]octan-5-one 11**

The diastereomers **11a**,**b** were separated by flash chromatography on silica gel ($Et_2O$).

**11a.** White solid (17 mg, 11%); mp 89 °C; $R_f$ 0.37 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3175, 3059 and 1656; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.24 (1 H, t, *J* 6.0 Hz, CHC$H_2$), 0.71–0.79 (1 H, m, CHC$H_2$), 0.83–0.89 (1 H, m, C$H$CH$_2$), 1.00 (3 H, t, *J* 7.2, C$H_3$CH$_2$), 1.18–1.33 (2 H, m, CH$_3$C$H_2$), 1.36–1.48 (2 H, m, C$H_2$CH$_2$CH$_2$CO), 1.80–1.92 (2 H, m, CH$_2$C$H_2$CH$_2$CO), 2.41–2.46 (2 H, m, CH$_2$CH$_2$C$H_2$CO) and 5.42 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 13.9 (q), 17.7 (t), 20.0 (t), 21.6 (t), 26.1 (d), 30.9 (t), 32.3 (t), 39.4 (s) and 174.0 (s); *m/z* (EI) 154 ($M^{+\bullet}$, 7%), 138 (11), 124 (63) and 96 (100); *m/z* (ES) 154.1234 ($MH^+$ $C_9H_{16}NO$ requires 154.1232).

**11b.** White solid (60 mg, 39%); mp 93 °C; $R_f$ 0.21 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3174, 3070 and 1665; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.29–0.32 (1 H, m, CHC$H_2$), 0.77–0.81 (2 H, m, C$H$C$H_2$), 1.00 (3 H, t, *J* 7.3 Hz, C$H_3$CH$_2$), 1.21–1.29 (2 H, m, CH$_3$C$H_2$), 1.41–1.47 (2 H, m, C$H_2$CH$_2$CH$_2$CO), 1.86–1.95 (2 H, m, CH$_2$C$H_2$CH$_2$CO), 2.38–2.42 (2 H, m, CH$_2$CH$_2$C$H_2$CO) and 5.74 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 13.6 (q), 18.7 (t), 20.0 (t), 22.1 (t), 25.9 (d), 26.2 (t), 31.2 (t), 39.1 (s) and 173.3 (s); *m/z* (EI) 154 ($M^{+\bullet}$, 20%), 138 (26), 124 (100) and 96 (96); *m/z* (ES) 154.1234 ($MH^+$ $C_9H_{16}NO$ requires 154.1232).

**Ethyl cyanomethylcarbonate 12**

To a solution of sodium cyanide (4.90 g, 100 mmol) in methanol (50 mL) was added dropwise at 0 °C an aqueous solution of formaldehyde (16.2 mL, 200 mmol, 37 wt%). Stirring was carried out until the sodium salt was totally dissolved. Ethyl chloroformate (14.3 mL, 150 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then water (50 mL) and diethyl ether (100 mL) were added. The mixture was extracted with diethyl ether (50 mL), the organic phase was dried ($MgSO_4$) and filtered. The resulting oil was purified by flash chromatography (petroleum ether–ethyl acetate 80 : 20), giving a colourless oil (10.3 g, 80%); $R_f$ 0.26 (petroleum ether–ethyl acetate 90 : 10); $\nu_{max}$(film)/cm$^{-1}$ 2989, 1763, 1431, 1380, 1263 and 1011; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.35 (3 H, t, *J* 7.1 Hz, C$H_3$CH$_2$), 4.30 (2 H, q, *J* 7.1, CH$_3$C$H_2$) and 4.78 (2 H, s, C$H_2$CN); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 14.0 (q), 51.3 (t), 65.6 (t), 114.1 (s) and 153.7 (s); *m*/*z* (EI) 129 (M$^{+\bullet}$, 98%) and 101 (100).

**2-(Ethoxycarboxy)butanenitrile 13**

The procedure described for the synthesis of **12** was used with the use of propionaldehyde (10.8 mL, 150 mmol) instead of formaldehyde. The crude **13** was purified by flash chromatography (petroleum ether–ethyl acetate 90 : 10), giving a colourless oil (10.5 g, 67%); $R_f$ 0.45 (petroleum ether–ethyl acetate 90 : 10); $\nu_{max}$(film)/cm$^{-1}$ 2984, 1759, 1374, 1303, 1257 and 1007; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.14 (3 H, t, *J* 7.4 Hz, C$H_3$CH$_2$CH), 1.35 (3 H, t, *J* 7.2, C$H_3$CH$_2$O), 1.99 (2 H, quint, *J* 7.4, CH$_3$C$H_2$CH), 4.28 (2 H, q, *J* 7.2, CH$_3$C$H_2$O) and 5.17 (1 H, t, *J* 7.4, CH$_3$CH$_2$C*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 8.8 (q), 14.4 (q), 25.9 (t), 65.3 (t), 65.7 (d), 116.4 (s) and 153.6 (s); *m*/*z* (EI) 157 (M$^{+\bullet}$, 62%), 130 (53), 117 (41) and 89 (100).

***tert*-Butyl cyanomethylcarbonate 14**

In a procedure analogous to that employed for the synthesis of **12**, but with di-*tert*-butyl dicarbonate (32.7 g, 150 mmol) instead of ethyl chloroformate, **14** was obtained as a colourless oil (11.3 g, 72%); $R_f$ 0.39 (petroleum ether–ethyl acetate 90 : 10); $\nu_{max}$(film)/cm$^{-1}$ 2984, 1755, 1372, 1281, 1259, 1157 and 1109; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.52 [9 H, s, (C$H_3$)$_3$C] and 4.71 (2 H, s, C$H_2$CN); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 27.5 (q), 50.6 (t), 84.7 (s), 114.3 (s) and 151.8 (s); *m*/*z* (EI) 157 (M$^{+\bullet}$, 5%), 142 (100) and 98 (97).

**2-(*tert*-Butoxycarboxy)butanenitrile 15**

In a procedure analogous to that employed for the synthesis of **13**, but with di-*tert*-butyl dicarbonate (32.7 g, 150 mmol) instead of ethyl chloroformate, **15** was obtained as a colourless oil (14.4 g, 78%); $R_f$ 0.53 (petroleum ether–ethyl acetate 90 : 10); $\nu_{max}$(film)/cm$^{-1}$ 2982, 1752, 1372, 1299, 1277, 1257, 1161 and 1107; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.12 (3 H, t, *J* 7.2 Hz, C$H_3$CH$_2$CH), 1.52 [9 H, s, (C$H_3$)$_3$C], 1.97 (2 H, quint, *J* 7.2, CH$_3$C$H_2$CH) and 5.11 (1 H, t, *J* 7.2, CH$_3$CH$_2$C*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 8.8 (q), 25.9 (t), 27.5 (q), 64.9 (d), 84.3 (s), 116.6 (s) and 151.6 (s); *m*/*z* (EI) 185 (M$^{+\bullet}$, 17%), 170 (19), 157 (6), 130 (100), 112 (47) and 84 (14).

**Cyclopropanation of cyanocarbonate 12**

By following the general procedure, cyanocarbonate **12** gave a mixture of **16a** and **17a** after flash chromatography on silica gel ($Et_2O$).

**4-Aza-6-oxaspiro[2.4]heptan-5-one (16a).** Colourless oil (35 mg, 31%); $R_f$ 0.42 ($Et_2O$); $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.70–0.76 (2 H, m, cyclopropyl), 0.97–1.02 (2 H, m, cyclopropyl), 4.37 (2 H, s, C$H_2$O) and 6.73 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 10.2 (t), 37.8 (s), 71.3 (t) and 160.1 (s); *m*/*z* (EI) 113 (M$^{+\bullet}$, 100%), 110 (10) and 85 (8); *m*/*z* (ES) 114.0551 (MH$^+$ $C_5H_8NO_2$ requires 114.0555).

**[1-(*N*-Ethoxycarbonylamino)cyclopropyl]methanol (17a).** Colourless oil (51 mg, 32%); $R_f$ 0.37 ($Et_2O$); $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.82–0.86 (4 H, m, cyclopropyl), 1.24 (3 H, t, *J* 7.0 Hz, C$H_3$CH$_2$), 3.60 (2 H, s, C$H_2$O), 4.10 (2 H, q, *J* 7.0, CH$_3$C$H_2$) and 5.52 (1 H, s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 12.4 (t), 14.4 (q), 35.1 (s), 61.1 (t), 68.8 (t) and 158.0 (s); *m*/*z* (EI) 159 (M$^{+\bullet}$, 10%), 141 (62), 112 (100), 96 (48) and 86 (98); *m*/*z* (ES) 160.0970 (MH$^+$ $C_7H_{14}NO_3$ requires 160.0974).

**7-Ethyl-4-aza-6-oxaspiro[2.4]heptan-5-one 16b**

After purification by flash chromatography on silica gel ($Et_2O$), compound **16b** was obtained as a colourless oil (90 mg, 64%); $R_f$ 0.47 ($Et_2O$); $\nu_{max}$(film)/cm$^{-1}$ 3270, 2973, 2940, 1747, 1464, 1375, 1240, 1004 and 975; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.60 (2 H, ddd, *J* 11.5, 6.8, 5.1 Hz, cyclopropyl), 0.79–0.91 (2 H, m, cyclopropyl), 0.92–1.00 (1 H, m, cyclopropyl), 1.04 (3 H, t, *J* 7.4, C$H_3$CH$_2$), 1.43–1.71 (2 H, m, CH$_3$C$H_2$), 4.48 (1 H, dd, *J* 7.8, 3.9, EtC*H*) and 7.05 (1 H, br s, N*H*); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 6.8 (t), 8.6 (q), 9.2 (t), 24.6 (t), 41.0 (s), 81.6 (d) and 159.2 (s); *m*/*z* (EI) 141 (M$^{+\bullet}$, 8%), 126 (15), 113 (100) and 98 (40); *m*/*z* (ES) 164.0687 (MNa$^+$ $C_7H_{11}NO_2Na$ requires 164.0690).

**[1-(*N*-*tert*-Butoxycarbonylamino)cyclopropyl]methanol 17b**

By following the general procedure, except that the reaction was performed in a 20 mmol scale and conducted at 0 °C, the cyanocarbonate **14** gave a crude material which was purified by flash chromatography on silica gel ($Et_2O$) giving **17b** as a white solid (2.39 g, 64%), mp 61 °C.[7b,17]

**Cyclopropanation of cyanocarbonate 15**

By following the general procedure, cyanocarbonate **15** gave **16b** and **17c** which were separated by flash chromatography on silica gel ($Et_2O$).

**16b** was obtained as a colourless oil (68 mg, 48%).

**[1-(*N*-*tert*-Butoxycarbonylamino)cyclopropyl]propan-1-ol (17c).** White solid (26 mg, 12%); mp 76 °C; $R_f$ 0.14 ($Et_2O$); $\nu_{max}$(KBr)/cm$^{-1}$ 3355, 2974, 2932, 2876, 1693, 1513, 1366, 1251, 1167 and 1077; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.61–0.79 (3 H, m, C$H_2$C$H_2$), 0.81–0.87 (1 H, m, CH$_2$C$H_2$), 0.90 (3 H, t, *J* 7.4 Hz, C$H_3$CH$_2$CH), 1.36 [9 H, s, (C$H_3$)$_3$C], 1.53 (2 H, quint, *J* 7.0, CH$_3$C$H_2$CH), 2.82 (1 H, t, *J* 6.8, CH$_3$CH$_2$C*H*), 4.05 (1 H, br s, OH) and 4.91 (1 H, br s, NH); $\delta_C$(67.8 MHz; $CDCl_3$; $Me_4Si$) 10.6 (q), 13.4 (t), 27.6 (t), 28.3 (q), 36.8 (s), 79.7 (d), 80.3 (s) and 158.2 (s); *m*/*z* (EI) 159 (M–$^t$Bu, 3%), 141 (8), 126 (10), 113 (35) and 100 (100); *m*/*z* (ES) 238.1419 (MNa$^+$ $C_{11}H_{21}NO_3Na$ requires 238.1417).

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