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The use of a germene for the synthesis of esters of α-germyl-substituted α-amino acid and α-aminophosphonic acid†

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The first α-germyl-substituted α-amino ester and α-germyl-substituted α-aminophosphonic ester have been synthesized by a one-pot reaction between the germene $Mes_2Ge{=}CR_2$ (CR_2 = fluorenylidene) and the iminoester or iminophosphonate $Ph(H)C{=}NCH_2{-}Y$ (Y = COOMe, $P(O)(OEt)_2$).

There is a great deal of interest in the synthesis and the use of α-amino acids and α-aminophosphonic acids which bear unnatural side chains which could modify their biological activities. For example, the introduction of organometallic moieties such as triorganosilyl (or germyl) groups known for their non polar, hydrophobic properties and large volume (relative to the corresponding hydrocarbon groups) is particularly attractive. However, if some β-silyl[1] (or germyl[1gh]) α-amino acids have been described, only one α-silyl α-amino acid **I** (M = Si) has been reported[2a] and its α-germanium analogues are still unknown (Chart 1). Some α-silyl esters **II** (M = Si)[2b] have been described but to the best of our knowledge, their α-germanium analogues **II** (M = Ge), precursors of the corresponding α-amino acids **I** (M = Ge), do not exist. The main reason is the absence of a suitable method for their synthesis.

In the field of α-aminophosphonic acids, the α-silyl- or germyl-substituted derivatives **III** (R = H) are still unknown, as well as the corresponding germylphosphonates (R = alkyl, aryl); only a few examples of α-silyl compounds have been described so far.[3]

We report here the nearly quantitative one-step synthesis, using a germanium–carbon doubly bonded derivative, of the first α-germyl-substituted α-amino ester of type **II** and α-germyl α-aminophosphonic ester **III**.

Addition of iminoester **2**[4] or iminophosphonate **3**[5] to an ethereal solution of germene **1**[6] followed by overnight stirring at room temperature afforded nearly quantitatively the 3-germapyrrolidines **4** or **5** respectively which were purified by fractional crystallization as air stable compounds (Scheme 1).

The structures of **4** and **5** were deduced from their NMR data‡ and that of **4** was unambiguously established through an X-ray crystal diffraction study (Fig. 1).§

One of the main features of this reaction is its complete regioselectivity and complete diastereoselectivity leading to the isomer with the Ph and Y groups in a pseudo equatorial position and therefore *cis*.

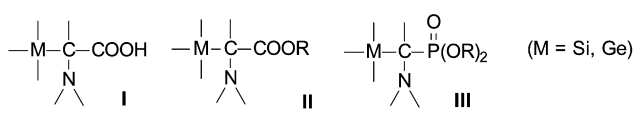


Chart 1

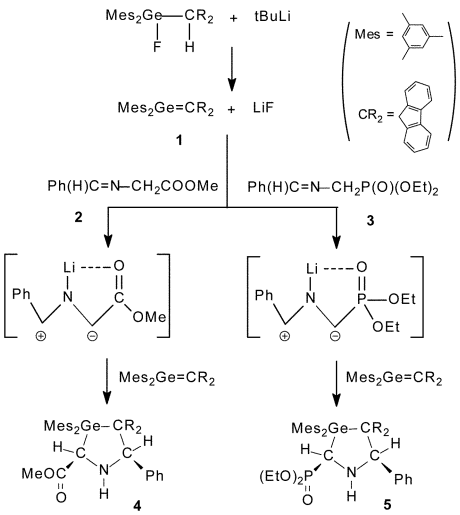
† Electronic supplementary information (ESI) available: molecular structure of **4**; crystal data and structure refinement for **4**. See http://www.rsc.org/suppdata/cc/b3/b303661h/

The stereochemical outcome of the process suggested that the most reasonable mechanism should be a [3 + 2] cycloaddition reaction between the germene and the 1,3-dipole azomethine ylide. The latter could arise from **2** or **3** by a prototropic shift (perhaps catalyzed by the germene[7]). The complete diastereoselectivity could be explained by the presence of one equivalent of LiF in the crude solution of germene prepared from $Mes_2Ge(F)CHR_2$. Such types of diastereoselective reactions from iminoesters R(H)C=N–CH(R′)COOR″ have already been described.[8]

Due to the hindered rotation of the two nonequivalent mesityl groups caused by the great steric hindrance, the four *ortho* methyl groups of the mesityls appear as broad signals. They are spread over a very large range (from 0.96 to 2.97 ppm) since the steric hindrance and the cyclic structure induce a special blocked position relative to the CR_2 group. The spectroscopic data for **4** and **5** feature very surprising extremely low-field shifts (8.80 and 8.76 ppm respectively) of one proton of the fluorenylidene group. From the X-ray structure, it appears that it corresponds to the $C_{22}H$ which is close to one mesityl group. This low-field shift is in good agreement with calculations from the Johnson and Bovey π-effect tables.[9]

The X-ray structure does not deserve any special comment; we have only to mention the elongation of the two intracyclic Ge–C bonds: Ge–C(1) (2.027(1) Å) and particularly Ge–C(11) (2.041(1) Å) (generally 1.95 to 1.98 Å for standard Ge–C bonds),[10] due to the high steric hindrance.

The straightforward formation of α-germyl-substituted α-amino ester **4** and α-aminophosphonic ester **5** illustrates the



Scheme 1 *Reagents and conditions*: **1** (500 mg) in Et_2O; **2** or **3** (1 equiv.) slowly added at rt, stirring 15 h, recrystallization from Et_2O, white crystals of **4** (605 mg, 87%) and **5** (710 mg, 92%).

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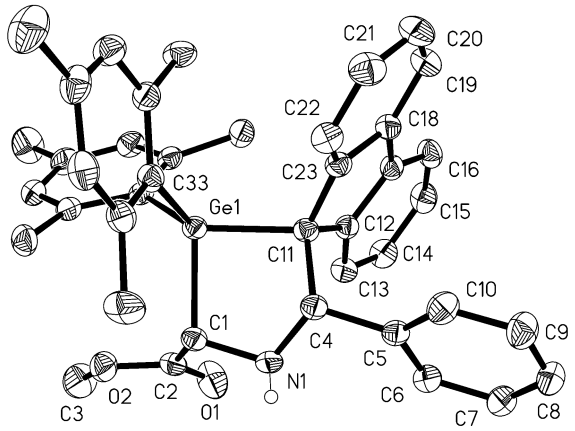

Fig. 1 Molecular structure of **4** (thermal ellipsoids at 50% probability level, H atoms and a molecule of diethyl ether are omitted for clarity). Selected bond lengths (Å) and angles (°): Ge–C(11) 2.041(1), C(4)–C(11) 1.567(2), C(4)–N 1.464(2), N–C(1) 1.459(2), Ge–C(1) 2.027(1), Ge–C(24) 1.980(1), Ge–C(33) 1.984(2), C(11)–C(12) 1.513(2), C(11)–C(23) 1.509(2), C(1)–Ge–C(11) 89.16(6), C(24)–Ge–C(33) 107.39(6), Ge–C(11)–C(4) 97.63(9).

synthetic potential and rich chemistry of germene **1**.[7,11] This method constitutes an original route to α-amino esters which contain large hydrophobic moieties. The hydrolysis of these esters to the corresponding α-germanium (phosphonic) amino acids is now under active investigation.

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Notes and references

‡ Data for **4**: white crystals (Et_2O), mp 198–199 °C; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.96 and 1.12 (2 br s, 2 × 3H, *o*-Me of Mes), 1.21 (t, $^3J_{HH}$ = 6.9 Hz, 6H, Me of Et_2O), 2.11 (s, 3H, *p*-Me of Mes), 2.17 (br s, 3H, *o*-Me of Mes), 2.31 (s, 3H, *p*-Me of Mes), 2.97 (br s, 3H, *o*-Me of Mes), 3.30 (s, 3H, OMe), 3.48 (q, $^3J_{HH}$ = 6.9 Hz, 4H, C*H*$_2$ of Et_2O), 5.12 (d, $^3J_{HH}$ = 8.8 Hz, 1H, C*H*COOMe), 5.34 (d, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*Ph), 6.37 (br d, $^3J_{HH}$ = 7.8 Hz, 1H, H of CR_2), 6.50, 6.56 and 6.62 (3 br s, 3 × 1H, *m*-H of Mes), 6.74–6.78 (m, 5H, Ph), 6.81 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, H of CR_2), 7.04 (br s, 1H, *m*-H of Mes), 7.11 and 7.23 (2td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 2 × 1H, H of CR_2), 7.35 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, H of CR_2), 7.54 (2 br d, $^3J_{HH}$ = 7.5 Hz, 2H, H of CR_2), 8.80 (br d, $^3J_{HH}$ = 7.5 Hz, 1H, H of CR_2), ^{13}C {^{1}H} NMR δ = 15.3 (CH_3 of Et_2O), 20.8 and 21.0 (2s, *p*-Me of Mes), 23.0, 23.3, 24.3 and 24.6 (4s, *o*-Me of Mes), 51.4 and 55.7 (*C*HCOO*C*H$_3$), 60.1 (*C*R$_2$), 65.9 (OCH$_2$ of Et_2O), 71.0 (*C*HPh), 119.2 and 119.3 (2s, C(4)C(5) of CR_2), 124.4, 125.3, 125.7 and 126.0 (4s, CH of CR_2), 126.6, 126.7, 126.9, 127.2, 127.9 (5s, CH of Ph and CR_2), 128.4, 128.6, 130.0 and 130.4 (4s, *m*-CH of Mes), 134.7, 135.4, 137.1, 138.4, 139.0, 140.9, 141.9, 142.9, 144.4, 144.8, 146.2 (arom C of Ph, Mes and CR_2), 175.0 (CO). IR ν cm^{-1} 3323 (NH), 1706 (CO). MS (EI, 70 eV) *m*/*z* 653 (M$^+$, 25), 533 (M − Mes − 1, 20), 476 ($Mes_2Ge{=}CR_2$, 42), 399 (M − R_2CCHPh, 96), 311 (Mes_2Ge − H, 100), 254 (R_2CCHPh, 93), 192 (MesGe − H, 50), 177 (M − Mes_2GeCR_2, 20).

5: white crystals (Et_2O), mp 224–225 °C; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 1.00 and 1.06 (2 br s, 2 × 3H, *o*-Me of Mes), 1.22 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HP}$ = 9.2 Hz, 6H, C*H*$_3$CH$_2$O), 2.08 (s, 3H, *p*-Me of Mes), 2.15 (br s, 3H, *o*-Me of Mes), 2.29 (s, 3H, *p*-Me of Mes), 2.73 (br s, 1H, NH), 2.93 (br s, 3H, *o*-Me of Mes), 3.48–3.68 (m, 1H, CH$_2$OP), 3.82–4.02 (m, 3H, CH$_2$OP), 4.84 (dd, $^3J_{HH}$ = 5.9 Hz, $^2J_{HP}$ = 10.2 Hz, 1H, CHP), 5.24 (s, 1H, C*H*Ph), 6.31 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H of CR_2), 6.48, 6.50 and 6.61 (3 br s, 3 × 1H, *m*-H of Mes), 6.71–6.81 (m, 5H, Ph), 6.89 (t, $^3J_{HH}$ = 7.8 Hz, 1H, H of CR_2), 7.00 (br s, 1H, *m*-H of Mes), 7.14 (t, $^3J_{HH}$ = 7.1 Hz, 1H, H of CR_2), 7.23–7.31 (m, 2H, H of CR_2), 7.50–7.56 (m, 2H, H of CR_2), 8.76 (br d, $^3J_{HH}$ = 6.8 Hz, 1H, H of CR_2). ^{13}C {^{1}H} NMR δ = 16.5 (*C*H$_3$CH$_2$O), 21.0 (*p*-Me of Mes), 23.3, 24.3 and 25.6 (s, *o*-Me of Mes), 48.5 (*C*HPh), 61.2 (*C*R$_2$), 62.1 (d, $^2J_{CP}$ = 7.2 Hz, OCH$_2$), 69.5 (d, $^1J_{CP}$ = 17.0 Hz, CHP), 118.9 and 119.0 (2s, C(16)C(19) of CR_2), 125.0, 125.7, 125.9, 126.7, 127.0, 127.6, 128.2, 128.7, 129.4, 130.4 (s, arom CH of Ph, Mes and CR_2), 138.1, 138.2, 138.7, 140.8, 144.5, 146.3 (arom C of Ph, CR_2 and Mes). ^{31}P NMR δ = 28.6. IR ν cm^{-1} 3379 (NH), 1245 (P=O). MS (EI, 70 eV) *m*/*z* 593 (M$^+$ − P(O)(OEt)$_2$ − 1, 35), 476 ($Mes_2Ge{=}CR_2$, 10), 312 (Mes_2Ge, 60), 253 (R_2CCPh, 71), 192 (MesGe − 1, 100).

§ Crystal structure determination of **4**, $C_{45}H_{51}GeNO_3$, M = 726.46, triclinic, space group *P*1, *a* = 11.9777(7), *b* = 12.1155(7), *c* = 14.5540(8) Å, α = 101.825(1), β = 95.774(1), γ = 108.611(1)°, *V* = 1927.5(2) Å^3, *Z* = 2, *T* = 193(2) K, crystal size 0.5 × 0.7 × 0.7 mm^3, ρ = 1.252 g cm^{-3}, 12972 reflections (9290 independent, R_{int} = 0.0247) were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97)[12] and all non hydrogen atoms were refined anisotropically using the least-squares method on F^2.[13] Largest electron density residue: 0.493 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0316 and wR_2 = 0.0864 (all data) with $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR_2 = (\Sigma w (F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$. CCDC 207496. See http://www.rsc.org/suppdata/cc/b3/b303661h/ for crystallographic data in .cif format.

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