

A novel reductive cyclisation of arylidenecyanoacetate induced by the TiCl₄/Sm system[†]

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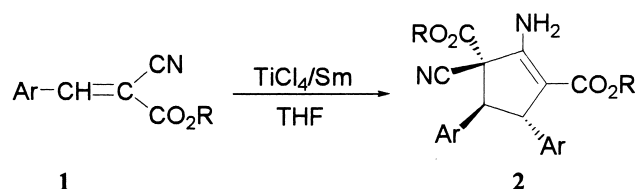
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The intermolecular reductive coupling reaction of arylidenecyanoacetates induced by the TiCl₄/Sm system was studied and the configuration of a cyclodimerisation product was confirmed by X-ray analysis.

Keywords: arylidenecyanoacetate, TiCl₄/Sm system

Low-valent titanium reagents have an exceedingly high ability to promote the reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis.¹ Many other functional groups can also be coupled.^{2–5} Although several results are reported on saturated carbonyl compounds, only a few studies concerning α,β -unsaturated carbonyl compounds have been published. Recently, we reported the cyclodimerisation of α,β -unsaturated ketones promoted by such a reagent to yield cyclopentane derivatives⁶. It has been known that α,β -unsaturated carboxylic acid derivatives are reduced with samarium diiodide to the corresponding saturated compounds,⁷ but there is no report on such a reaction using low-valent titanium. Here, we wish to report the novel reductive cyclisation of arylidenecyanoacetate promoted by treatment with titanium tetrachloride/samarium in anhydrous tetrahydrofuran.

When arylidenecyanoacetates **1** were treated with TiCl₄/Sm, the cyclodimerisation products 3,4-*trans*-4,5-*trans* isomers of 2-amino-3-cyano-1,3-dialkoxy carbonyl-4,5-diaryl cyclopentenes **2** were obtained.



Scheme 1

Table 1 summarises our results on the cyclodimerisation of a number of substrates. In all the reactions, the cleavage takes place selectively at the cyano group, rather than at the alkoxy-carbonyl group. At the same time, chloro and alkoxy groups in the aromatic ring could not be reduced under the reaction conditions and have no influence on the rate of cyclodimerisation. All cyclodimerisation reactions are highly stereoselective as only one isomer was obtained and careful analysis of the reaction mixture indicated the absence of the other stereo isomer. This was confirmed by the X-ray crystal structure analysis of the product **2d**,⁸ which clearly demonstrated the *trans-trans* stereochemistry of the product (Fig. 1). Selected bond lengths and angles are shown in Table 2

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 Yields of the products

Entry	Ar	R	Isolated yield/%
2a	C ₆ H ₅	CH ₃	87
2b	C ₆ H ₅	C ₂ H ₅	83
2c	4-ClC ₆ H ₄	CH ₃	88
2d	4-ClC ₆ H ₄	C ₂ H ₅	82
2e	4-CH ₃ OC ₆ H ₄	CH ₃	79
2f	4-CH ₃ OC ₆ H ₄	C ₂ H ₅	74
2g	4-CH ₃ C ₆ H ₄	C ₂ H ₅	93
2h	2-ClC ₆ H ₄	CH ₃	76
2i	2-ClC ₆ H ₄	C ₂ H ₅	81

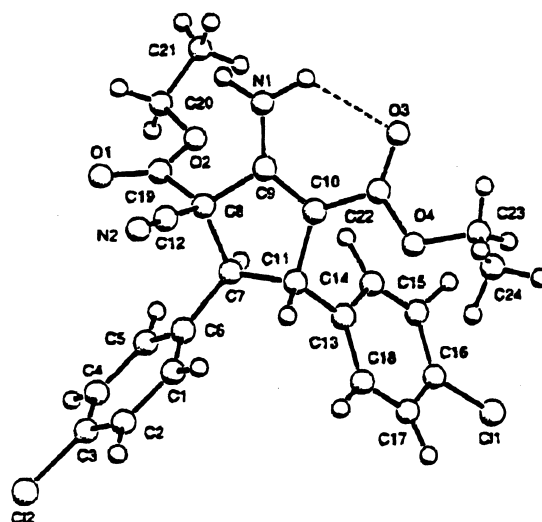


Fig. 1 the X-ray crystal structure of compound **2d**.

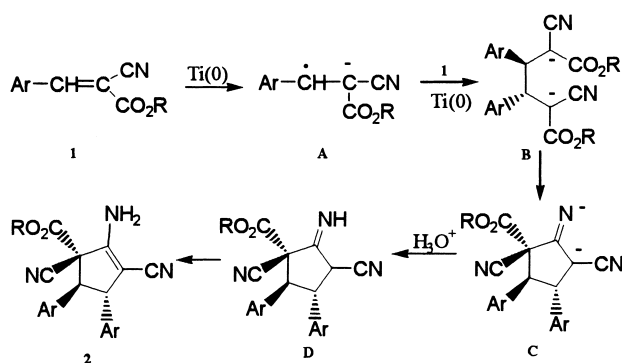
Though the detailed mechanism of the above cyclodimerisation has not been clarified yet, the cyclopentene formation can be explained by the possible mechanism presented in Scheme 2

In the initial step, an electron is transferred from low-valent titanium to substrate **1** to form radical anion **A**, which then attacks another molecule of substrate to form a carbon-carbon bond and generate intermediate **B**. Intermediate **B** then reacts intramolecularly to result in the formation of a new carbon-carbon bond and produce intermediate **C**. Then **C** is converted into **D** which isomerises to give product **2**.

In summary, we have found a novel cyclodimerisation of arylidenecyanoacetates promoted by the TiCl₄/Sm system. Further studies to develop other new reactions using TiCl₄/Sm are now in progress in our laboratory.

Table 2 Selected bond lengths and angles

Bond	Length/Å	Angle/°	
Cl(1)–C(16)	1.748(5)	C(19)–O(2)–C(20)	116.4(4)
Cl(2)–C(3)	1.743(5)	C(22)–O(4)–C(23)	117.9(4)
O(1)–C(19)	1.193(5)	C(7)–C(8)–C(9)	102.2(3)
O(2)–C(19)	1.315(5)	C(7)–C(8)–C(12)	112.3(3)
O(2)–C(20)	1.453(6)	C(7)–C(8)–C(19)	109.9(3)
O(3)–C(22)	1.219(5)	N(1)–C(9)–C(8)	120.0(3)
O(4)–C(22)	1.342(5)	N(1)–C(9)–C(10)	129.4(4)
O(4)–C(23)	1.443(6)	C(8)–C(9)–C(10)	110.2(3)
N(1)–C(9)	1.350(5)	C(9)–C(10)–C(11)	112.6(3)
N(2)–C(12)	1.136(5)	C(9)–C(10)–C(22)	122.4(4)
C(7)–C(8)	1.580(5)	C(11)–C(10)–C(22)	124.7(3)
C(8)–C(9)	1.524(5)	O(1)–C(19)–O(2)	126.1(4)
C(9)–C(10)	1.359(5)	O(1)–C(19)–C(8)	124.0(5)
C(10)–C(11)	1.520(5)	O(2)–C(19)–C(8)	109.9(4)
C(7)–C(11)	1.551(5)	O(2)–C(20)–C(21)	107.8(5)
C(8)–C(12)	1.479(6)	O(3)–C(22)–O(4)	123.0(4)
C(8)–C(19)	1.526(6)	O(3)–C(22)–C(10)	125.6(4)

**Scheme 2****Experimental**

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer in KBr with absorptions in cm^{-1} . ^1H NMR spectra were determined on a Inova-400 or R-1500A spectrometer using CDCl_3 solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Microanalyses were carried out on a Perkin-Elmer 240C elemental analyzer. X-ray diffraction was recorded on a Rigaku AFC7R diffractometer.

General procedure for the synthesis of cyclopentenes 2: TiCl_4 (1.1ml, 10mmol) was added dropwise using a syringe to a stirred suspension of Sm power (1.5g, 10mmol) in freshly distilled anhydrous THF (15ml) at room temperature under a dry nitrogen atmosphere. On completion of the addition, the mixture was refluxed for 2h. The black suspension of the low-valent titanium reagent formed was allowed to cool to room temperature and a solution of arylidene cyanoacetate (5mmol) in THF (10ml) was added dropwise over 20 min. The mixture was stirred at room temperature for 2–4h at 60°C under N_2 , and most of the solvent was then removed *in vacuo*. The residue was poured into 3% HCl (100ml) and extracted with Et_2O (3×50ml). The combined organic layers were washed with water (3×50ml), dried (Na_2SO_4), and the solvent was removed *in vacuo* to give the crude product, which was further purified by column chromatography on silica gel using acetone-petroleum ether (b.p. $60\text{--}90^\circ\text{C}$) (1:3) as eluent.

2a: m.p. $166\text{--}167^\circ\text{C}$; ν/cm^{-1} 3450, 3350, 2250, 1740, 1680, 1570, 1440; ^1H NMR δ_{H} 3.52 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.98 (1H, d, $J=8.5\text{Hz}$, ArCH), 4.49 (1H, d, $J=8.5\text{Hz}$, ArCH), 5.98 (2H, br, s, NH_2), 7.05–7.34 (10H, m, ArH). Anal. Calc. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$: C, 70.20, H, 5.36, N, 7.44; Found: C, 70.35, H, 5.04, N, 7.68%.

2b: m.p. $170\text{--}171^\circ\text{C}$; ν/cm^{-1} 3430, 3340, 2250, 1740, 1670, 1570, 1455; ^1H NMR δ_{H} 0.88 (3H, t, $J=7.1\text{Hz}$, CH_3), 1.30 (3H, t, $J=7.1\text{Hz}$, CH_3), 3.89 (1H, d, $J=8.0\text{Hz}$, ArCH), 4.02 (2H, q, $J=7.1\text{Hz}$, OCH_2), 4.34 (2H, q, $J=7.1\text{Hz}$, OCH_2), 4.48 (1H, d, $J=8.0\text{Hz}$, ArCH), 5.98 (2H, br, s, NH_2), 7.08–7.38 (10H, m, ArH). Anal. Calc. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4$: C, 71.27, H, 5.98, N, 6.93; Found: C, 71.56, H, 5.96, N, 7.18%.

2c: m.p. $146\text{--}148^\circ\text{C}$; ν/cm^{-1} 3450, 3320, 2250, 1760, 1670, 1570, 1490, 1440; ^1H NMR δ_{H} 3.53 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (1H, d, $J=8.0\text{Hz}$, ArCH), 4.39 (1H, d, $J=8.0\text{Hz}$, ArCH), 6.02 (2H, br, s, NH_2), 6.75–7.34 (8H, m, ArH). Anal. Calc. for $\text{C}_{22}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_4$: C, 59.34, H, 4.07, N, 6.29; Found: C, 59.63, H, 3.85, N, 6.52%.

2d: m.p. $172\text{--}174^\circ\text{C}$; ν/cm^{-1} : 3430, 3300, 2250, 1740, 1670, 1580, 1490; ^1H NMR δ_{H} 0.92 (3H, t, $J=7.2\text{Hz}$, CH_3), 1.35 (3H, t, $J=7.2\text{Hz}$, CH_3), 3.92 (1H, d, $J=8.5\text{Hz}$, ArCH), 4.01 (2H, q, $J=7.2\text{Hz}$, OCH_2), 4.35 (2H, q, $J=7.2\text{Hz}$, OCH_2), 4.38 (1H, d, $J=8.5\text{Hz}$, ArCH), 5.95 (2H, br, s, NH_2), 6.99–7.33 (8H, m, ArH). Anal. Calc. for $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4$: C, 60.90, H, 4.68, N, 5.92; Found: C, 61.17, H, 4.71, N, 6.18%.

2e: m.p. $155\text{--}156^\circ\text{C}$; ν/cm^{-1} : 3400, 3300, 2250, 1750, 1670, 1570, 1520, 1490; ^1H NMR δ_{H} : 3.53(3H, s, OCH_3), 3.74(3H, s, OCH_3), 3.79 (3H, s, ArOCH_3), 3.88 (3H, s, ArOCH_3), 3.90(1H, d, $J=8.2\text{Hz}$, ArCH), 4.34 (1H, d, $J=8.2\text{Hz}$, ArCH), 5.93 (2H, br, s, NH_2), 6.65–7.27 (8H, m, ArH). Anal. Calc. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6$: C, 66.04, H, 5.54, N, 6.42; Found: C, 66.13, H, 5.78, N, 6.39%.

2f: m.p. $170\text{--}172^\circ\text{C}$; ν/cm^{-1} : 3400, 3320, 2250, 1740, 1670, 1570, 1510; ^1H NMR δ_{H} 0.93 (3H, t, $J=6.8\text{Hz}$, CH_3), 1.34 (3H, t, $J=6.8\text{Hz}$, CH_3), 3.74 (3H, s, ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.91 (1H, d, $J=8.0\text{Hz}$, ArCH), 4.01 (2H, q, $J=6.8\text{Hz}$, OCH_2), 4.34 (2H, q, $J=6.8\text{Hz}$, OCH_2), 4.38 (1H, d, $J=8.0\text{Hz}$, ArCH), 5.92 (2H, br, s, NH_2), 6.71–7.29 (8H, m, ArH). Anal. Calc. for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_6$: C, 67.23, H, 6.08, N, 6.03; Found: C, 67.50, H, 5.83, N, 5.97%.

2g: m.p. $165\text{--}167^\circ\text{C}$; ν/cm^{-1} : 3430, 3320, 2250, 1740, 1660, 1570; ^1H NMR δ_{H} 0.92 (3H, t, $J=7.2\text{Hz}$, CH_3), 1.32 (3H, t, $J=7.2\text{Hz}$, CH_3), 2.25 (3H, s, ArCH_3), 2.31 (3H, s, ArCH_3), 3.92 (1H, d, $J=8.5\text{Hz}$, ArCH), 3.98 (2H, q, $J=7.2\text{Hz}$, OCH_2), 4.32(2H, q, $J=7.2\text{Hz}$, OCH_2), 4.43(1H, d, $J=8.5\text{Hz}$, ArCH), 5.93 (2H, br, s, NH_2), 6.98–7.32 (8H, m, ArH). Anal. Calc. for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$: C, 72.20, H, 6.52, N, 6.48; Found: C, 72.36, H, 6.29, N, 6.72%.

2h: m.p. $168\text{--}170^\circ\text{C}$; ν/cm^{-1} 3400, 3320, 2250, 1760, 1670, 1570, 1450; ^1H NMR δ_{H} 3.61 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.56 (1H, d, $J=4.2\text{Hz}$, ArCH), 4.94 (1H, d, $J=4.2\text{Hz}$, ArCH), 6.07 (2H, br, s, NH_2), 7.19–7.62 (8H, m, ArH). Anal. Calc. for $\text{C}_{22}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_4$: C, 59.37, H, 4.07, N, 6.29; Found: C, 59.71, H, 4.13, N, 5.98%.

2i: m.p. $164\text{--}166^\circ\text{C}$; ν/cm^{-1} : 3450, 3320, 2250, 1755, 1670, 1630, 1580, 1480; ^1H NMR δ_{H} 0.99 (3H, t, $J=7.2\text{Hz}$, CH_3), 1.24(3H, t, $J=7.2\text{Hz}$, CH_3), 4.07 (2H, dd, $J=7.2\text{Hz}$, OCH_2), 4.24 (2H, dd, $J=7.2\text{Hz}$, OCH_2), 4.60(1H, s, ArCH), 4.96(1H, s, ArCH), 6.01 (2H, br, s, NH_2), 7.11–7.71 (8H, m, ArH). Anal. Calc. for $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4$: C, 60.90, H, 4.68, N, 5.92; Found: C, 61.16, H, 4.37, N, 6.13%.

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- Crystal data for 2d: $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4$, $M = 473.35$, colourless prismatic crystals, $0.2 \times 0.2 \times 0.3\text{mm}$, Monoclinic, space group $P2_1/c$, $a = 6.923(1)$, $b = 33.178(5)$, $c = 10.644(3)\text{Å}$, $\beta = 99.86(2)^\circ$, $V = 2408.8(8)\text{Å}^3$, $Z = 4$, $D_c = 1.305\text{Mg/m}^3$, $\mu = 3.01\text{cm}^{-1}$, $F(000) = 984.00$. Intensity data were collected on Rigaku AFC7R diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71069\text{Å}$) using ω - 2θ scan mode with 2θ max = 49.8° . 3308 unique reflections were measured and 2147 reflection with $I > 3\sigma(I)$ were used in the refinement. Refinement of positions and anisotropic thermal parameters for all non-hydrogen atoms (290 variables) converged to $R = 0.052$ and $\omega R = 0.067$.