Low-Valent Titanium Induced Novel Reductive Cyclizations of α,β-Unsaturated Nitrile Compounds

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Abstract: The intermolecular and intramolecular reductive coupling reactions of α,β-unsaturated nitrile derivatives induced by a low-valent titanium reagent prepared from titanium tetrachloride and zinc powder were studied. The configuration of cyclodimerization product was confirmed by X-ray analysis.

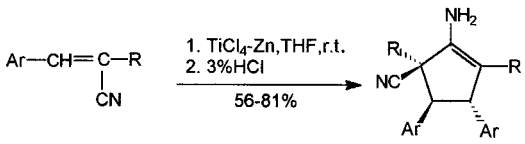
Key words: cyclopentenes, reductive cyclization, 2-aminoquinolines, low-valent titanium, α,β-unsaturated nitriles

Low-valent titanium reagents have an exceedingly high ability in promoting the reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis. A lot of other functional groups can also be coupled.[1, 2] 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 cyclodimerization of α,β-unsaturated ketones promoted by this reagent to yield cyclopentane derivatives.[3] It has been known that α,β-unsaturated carboxylic acid derivatives are reduced with samarium diiodide to the corresponding saturated compounds,[4] but there is no report on such a reaction using low-valent titanium. Here, we wish to report the novel reductive cyclization of α,β-unsaturated nitrile derivatives promoted by treatment with titanium tetrachloride/zinc in anhydrous tetrahydrofuran.

It has been known that the cyano group is relatively more stable to low-valent titanium reagent than the carbonyl group and could not be reduced unless the reaction mixture was refluxed for a long time and only with low reaction yield in our previous reports.[5, 6] We considered that the conjugated carbon–carbon double bond could perhaps influence the reactivity of the cyano group. Therefore, we have studied the behavior of the cyano group in α,β-unsaturated nitrile derivatives when treated with titanium tetrachloride and zinc in anhyd tetrahydrofuran.

As expected, the reactivity of the cyano group of the α,β-unsaturated nitrile compounds is much higher than that of the saturated nitriles. When α,β-unsaturated nitrile derivatives **1** were treated with titanium tetrachloride and zinc in tetrahydrofuran, the cyclodimerization products **2**, which are different from the products of the saturated nitrile compounds,[5, 6] were obtained.

The reaction for various α,β-unsaturated nitrile compounds promoted by low-valent titanium reagent was examined and our cyclization results are summarized in the Table. In all the reactions, the cleavage takes place selectively at the cyano group, rather than at the alkoxycarbonyl group. At the same time, chloro, bromo, and alkoxy groups in the aromatic ring could not be reduced under the



1 **2**

2	Ar	R	**2**	Ar	R
a	4-ClC_6H_4	CO_2Et	**f**	3,4-$OCH_2OC_6H_3$	CO_2Et
b	2-ClC_6H_4	CO_2Et	**g**	3-OH,4-$OMeC_6H_3$	CO_2Et
c	4-MeC_6H_4	CO_2Et	**h**	4-ClC_6H_4	CN
d	4-BrC_6H_4	CO_2Et	**i**	Ph	Ph
e	Ph	CO_2Et			

reaction conditions and have no influence on the rate of cyclodimerization (**1a–f**). Substrate **1g** which contains a hydroxy group is not as reactive as the other substrates examined and requires longer reaction times. (*p*-Chlorobenzylidene)malononitrile (**1h**) and α-phenylcinnamonitrile (**1i**) can also give the corresponding cyclodimerization products. However, **1h** has higher reactivity, while **1i** has lower reactivity and needs longer reaction times. When ethyl cinnamate was treated with the same reagent under the same reaction conditions, the reductive cyclization could not take place, even under refluxing conditions overnight, and the substrate could be recovered. All cyclodimerization reactions are highly stereoselective as only one isomer was obtained and the careful analysis of the reaction mixture indicated the absence of the other stereoisomer. This could be confirmed by the X-ray crystal structure analysis of the product **2a**, which clearly demonstrate the *trans-trans* stereochemistry of the product (Figure). The atoms C(7), C(8), C(9), C(10), and C(11) form a central 5-ring. The alkoxycarbonyl group at C(8) is in the equatorial position. The phenyl groups at C(7) and C(11) are in equatorial positions and form angles of 70.67 and 66.74° with the central 5-ring respectively. The two phenyl groups form an angle of 92.68° with each other. The delocalization between the donor N(1) and the acceptor alkoxy carbonyl group (1) is reflected in the molecular dimensions: the C(9)–C(10) distance of 1.359(5)Å is significantly longer than the C=C bond in ethylene (1.336(2)Å.[7] There is a corresponding shortening of the C(9)–N(1) [1.350 (5)Å] bond relative to the normal C(sp^2)–N (1.426Å) bond.[8]

However, treatment of ethyl α-cyano-α-(*p*-nitrobenzylidene)acetate (**3**) with titanium tetrachloride and zinc in anhyd tetrahydrofuran under the same reaction condi-

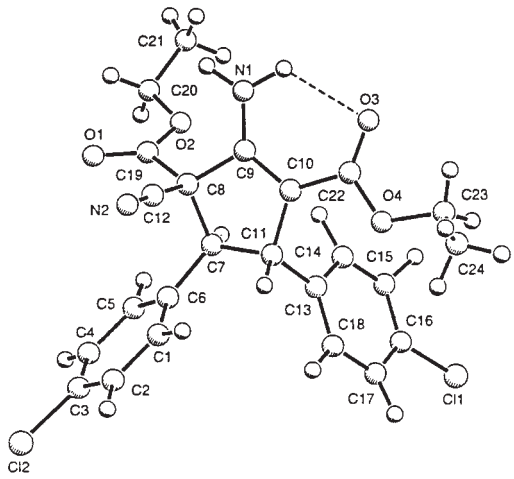
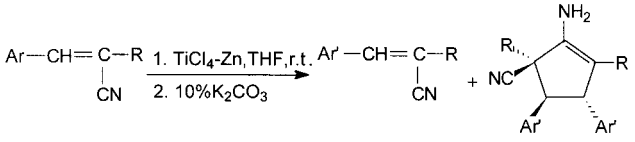


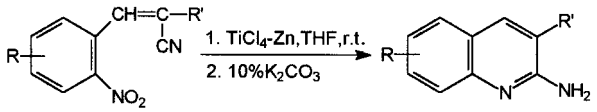
Figure. X-ray Crystallographic Structure of **2a**.[13]



Ar=4-$NO_2C_6H_4$, **Ar'**=4-$NH_2C_6H_4$, **R**=$COOC_2H_5$

tions afforded cyclopentene **5** along with the corresponding product **4** formed by reduction of the nitro group in **3**.

On the other hand, when α-cyano-α-(*o*-nitrobenzylidene)acetate or (*o*-nitrobenzylidene)malononitrile derivatives **6** were subjected to the above procedure, no products **4** or **5** were detected. However, the intramolecular reductive cyclization product, 2-aminoquinoline derivatives **7**, were found in good purity and high yields.



6, 7	R	R′
a	H	CO_2Et
b	H	CN
c	4,5-$OCH_2OC_6H_3$	CO_2Et
d	4,5-$OCH_2OC_6H_3$	CN

In summary, we have found a novel cyclodimerization of α,β-unsaturated nitrile compounds promoted by low-valent titanium reagent and a facile synthesis of 2-aminoquinoline derivatives with this reagent.

THF was distilled from $LiAlH_4$ prior to use. All mps are uncorrected. IR spectra were recorded in KBr disks using a FTIR-8101 spectrophotometer. The ^1H NMR spectra were recorded on a JOEL JNMFX-90Q or Bruker AZ-300 spectrometer with $CDCl_3$ as solvent and TMS as internal standard, chemical shifts are reported in δ units (ppm). MS were recorded on a ZAB-HS spectrometer. Microanalyses were carried out on a Perkin–Elmer 240C instrument. X-ray diffraction was recorded on a Rigaku AFC7R diffractometer.

Cyclopentenes 2: General Procedure:

$TiCl_4$ (2.2 mL, 20 mmol) was added dropwise using a syringe to a stirred suspension of Zn powder (2.6 g, 40 mmol) in freshly distilled anhyd THF (20 mL) at r.t. under N_2. On completion of the addition, the mixture was refluxed for 2 h. The black suspension of the low-valent titanium reagent formed was allowed to cool to r.t. and a solution of α,β-unsaturated nitrile (10 mmol) in THF (10 mL) was added dropwise over ca. 20 min. The mixture was stirred at r.t. under N_2. When the reaction was complete, most of the solvent was removed under reduced pressure. The residue was quenched with 3% HCl (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product, which was further purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 60–90 °C),1:4] (Table).

Products 4 and 5:

A black suspension of low-valent titanium reagent was prepared with $TiCl_4$ (40 mmol) and Zn powder (80 mmol) in THF (40 mL) using the same procedure mentioned above. A solution of ethyl α-cyano-α-(*p*-nitrobenzylidene)acetate (3) (10 mmol) in THF (20 mL) was added carefully to the suspension at r.t. The mixture was stirred for 1 h at r.t. under N_2, and most of the solvent was then removed in vacuo. The residue was poured into 10% K_2CO_3 (200 mL), and extracted with $CHCl_3$ (4 × 50 mL). The combined extracts were washed with water (2 × 30 mL), dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product, which was further purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 60–90° C),1:1] (Table).

2-Aminoquinolines 7: General Procedure:

A solution of the appropriate substrate **6** (10 mmol) in anhyd THF (20 mL) was added carefully at r.t. to a suspension of low-valent titanium reagent (40 mmol) prepared as mentioned above. When the reaction was complete (at r.t. under N_2), most of the solvent was removed in vacuo. The residue was poured into 10% K_2CO_3 (200 mL), and extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product. This was further purified by recrystallization from the appropriate solvent (Table).

Crystal Structure Analysis of 2a:[13]

Crystal data: $C_{24}H_{22}Cl_2N_2O_4$, colorless; approximate dimensions: 0.20 × 0.20 × 0.30 mm^3, *Mr* = 473.35 $gmol^{-1}$, monoclinic, space group $P2_1/c$ (#14), *a* = 6.923(1), *b* = 33.178(5), *c* = 10.644(3)Å, β = 99.86(2)°, *V* = 2408.8(8)Å^3, *Z* = 4, D_c = 1.305 g·cm^{-3} M_0-K_α radiation, λ = 0.71069Å (graphite monochromator), $\mu(M_0K_\alpha)$ = 3.01 cm^{-1}.

Data Collection: The intensity data for the compound were collected on a Rigaku AFC7R diffractometer, using the ω-2θ technique at 20°C. 3367 reflections were measured, of which 3308 were independent reflections with 2θ in the range of 6 ~49.8°, 2147 reflections having $I>3\sigma(I)$. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods (SHELXS-86)[10] and expanding using Fourier techniques (DIRDIF-92).[11] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement converged with unweighted and weighted agreement factors of *R* = 0.052 and R_w = 0.067. The maximum and the minimum peak on the final difference Fourier map corresponded to 0.28 and –0.26 e/Å^3, respectively. All calculations were performed using TEXSAN program package.[12]

Table. Cyclopentenes **2**, Compounds **4** and **5**, and 2-Aminoquinolines **7** Prepared

Product	Time (h)	Yield (%)[a]	mp (°C)	Molecular Formular[b] or Lit. mp (°C)	IR (KBr) υ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (M^+)
2a	1.5	81	176–178	$C_{24}H_{22}Cl_2N_2O_4$	3340, 3300, 2250, 1740, 1680, 1580, 830	0.92 (t, 3H, J = 7.1, CH_3), 1.33 (t, 3H, J = 7.1, CH_3), 3.89 (d, 1H, J = 8.5, ArCH), 3.92 (dd, 2H, J = 7.1, OCH_2), 4.35 (dd, 2H, J = 7.1, OCH_2), 4.37 (d, 1H, J = 8.5, ArCH), 5.93 (br s, 2H, NH_2), 7.02–7.29 (m, $8H_{arom}$)	472
2b	1	76	171–173	$C_{24}H_{22}Cl_2N_2O_4$	3450, 3300, 2250, 1750, 1680, 1630, 1580, 750	0.98 (t, 3H, J = 7.1, CH_3), 1.20 (t, 3H, J = 7.1, CH_3), 4.05 (dd, 2H, J = 7.1, OCH_2), 4.24 (dd, 2H, J = 7.1, OCH_2), 4.60 (d, 1H, J = 6.0, ArCH), 4.96 (d, 1H, J = 6.0, ArCH), 6.05 (br s, 2H, NH_2), 6.95–7.75 (m, $8H_{arom}$)	472
2c	1.5	78	165–167	$C_{26}H_{28}N_2O_4$	3430, 3320, 2250, 1740, 1660, 1565, 810	0.90 (t, 3H, J = 7.2, CH_3), 1.30 (t, 3H, J = 7.2, CH_3), 2.25 (s, 3H, $ArCH_3$), 2.31 (s, 3H, $ArCH_3$), 3.92 (d, 1H, J = 8.5, ArCH), 3.98 (dd, 2H, J = 7.2, OCH_2), 4.32 (dd, 2H, J = 7.2, OCH_2), 4.43 (d, 1H, J = 8.5, ArCH), 5.92 (br s, 2H, NH_2), 7.00–7.52 (m, $8H_{arom}$)	432
2d	1	74	194–196	$C_{24}H_{22}Br_2N_2O_4$	3430, 3330, 2250, 1740, 1680, 830	0.90 (t, 3H, J = 7.1, CH_3), 1.30 (t, 3H, J = 7.1, CH_3), 3.85 (d, 1H, J = 8.5, ArCH), 3.95 (dd, 2H, J = 7.1, OCH_2), 4.30 (dd, 2H, J = 7.1, OCH_2), 4.34 (d, 1H, J = 8.5, ArCH), 6.00 (br s, 2H, NH_2), 6.88–7.50 (m, $8H_{arom}$)	562
2e	1	74	175–177	$C_{24}H_{24}N_2O_4$	3430, 3330, 2250, 1740, 1670, 700	0.86 (t, 3H, J = 7.2, CH_3), 1.29 (t, 3H, J = 7.2, CH_3), 3.90 (d, 1H, J = 8.4, ArCH), 4.00 (dd, 2H, J = 7.2, OCH_2), 4.30 (dd, 2H, J = 7.2, OCH_2), 4.45 (d, 1H, J = 8.4, ArCH), 5.98 (br s, 2H, NH_2), 6.85–7.58 (m, $10H_{arom}$)	404
2f	3.5	75	188–189	$C_{26}H_{24}N_2O_8$	3410, 3310, 2250, 1745, 1665, 1570, 1495, 930, 815	0.98 (t, 3H, J = 7.2, CH_3), 1.32 (t, 3H, J = 7.2, CH_3), 3.85 (d, 1H, J = 8.5, ArCH), 4.00 (dd, 2H, J = 7.2, OCH_2), 4.30 (dd, 2H, J = 7.2, OCH_2), 4.35 (d, 1H, J = 8.5, ArCH), 5.85 (s, 2H, OCH_2O), 5.93 (s, 2H, OCH_2O), 5.98 (br s, 2H, NH_2), 6.60–7.08 (m, $6H_{arom}$)	492
2g	24	73	190–192	$C_{26}H_{28}N_2O_8$	3450, 3320, 2250, 1740, 1680	0.95 (t, 3H, J = 7.2, CH_3), 1.30 (t, 3H, J = 7.2, CH_3), 3.74 (s, 3H, OCH_3), 3.82 (d, 1H, J = 8.5, ArCH), 3.85 (s, 3H, OCH_3), 3.92 (dd, 2H, J = 7.2, OCH_2), 3.98 (d, 1H, J = 8.5, ArCH), 4.30 (dd, 2H, J = 7.2, OCH_2), 5.45 (s, 1H, ArOH), 5.65 (s, 1H, ArOH), 5.95 (br s, 2H, NH_2), 6.50–7.10 (m, $6H_{arom}$)	496
2h	1	78	158–160	$C_{20}H_{12}Cl_2N_4$	3380, 3240, 2260, 2240, 1680, 1630, 1500, 730	3.62 (d, 1H, J = 9.5, ArCH), 4.51 (d, 1H, J = 9.5, ArCH), 5.46 (br s, 2H, NH_2), 6.85–7.40 (m, $8H_{arom}$)	378
2i	24	56	239–241	$C_{30}H_{24}N_2$	3420, 3310, 2250, 1680, 1600	3.80 (br s, 2H, NH_2), 3.95 (d, 1H, J = 8.0, ArCH), 4.63 (d, 1H, J = 8.0, ArCH), 6.60–7.60 (m, $20H_{arom}$)	412
4	1	17	167–168	$C_{12}H_{12}N_2O_2$	3450, 3360, 2250, 1690, 830	1.38 (t, 3H, J = 7.2, CH_3), 4.33 (dd, 2H, J = 7.2, OCH_2), 4.40 (br s, 2H, NH_2), 6.67 (d, 2H, J = 9.2, $2H_{arom}$), 7.85 (d, 2H, J = 9.2, $2H_{arom}$), 8.08 (s, $1H_{arom}$)	216
5	1	35	196–197	$C_{24}H_{26}N_4O_4$	3430, 3360, 3330, 2250, 1680, 830	0.92 (t, 3H, J = 7.2, CH_3), 1.28 (t, 3H, J = 7.2, CH_3), 3.24 (br. s, 4H, 2 × $ArNH_2$), 3.78 (d, 1H, J = 8.6, ArCH), 3.93 (d, 1H, J = 8.6, ArCH), 3.95 (dd, 2H, J = 7.2, OCH_2), 4.27 (dd, 2H, J = 7.2, OCH_2), 5.85 (br s, 2H, NH_2), 6.42–7.13 (m, $8H_{arom}$)	434

Table. (continued)

Product	Time (h)	Yield (%)[a]	mp (°C)	Molecular Formular[b] or Lit. mp (°C)	IR (KBr) υ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (M^+)
7a	1	91	134–135[c]	135[7]	3440, 3300, 1690, 750, 700	1.42 (t, 3H, J = 7.2, CH_3), 4.40 (dd, 2H, J = 7.2, OCH_2), 6.57 (br s, 2H, NH_2), 7.12–7.68 (m, $4H_{arom}$), 8.65 (s, $1H_{arom}$)	216
7b	2	90	227–228[d]	$C_{10}H_7N_3$	3400, 3160, 2230, 1650, 1620, 750	5.46 (br s, 2H, NH_2), 7.32–7.42 (m, $1H_{arom}$), 7.62–7.71 (m, $3H_{arom}$), 8.30 (s, $1H_{arom}$)	169
7c	1.5	92	204–205[e]	$C_{13}H_{12}N_2O_4$	3440, 3280, 1680, 1620, 1500	1.41 (t, 3H, J = 7.1, CH_3), 4.38 (dd, 2H, J = 7.1, OCH_2), 6.03 (s, 2H, OCH_2O), 6.56 (br s, 2H, NH_2), 6.90 (s, $1H_{arom}$), 6.95 (s, $1H_{arom}$), 8.46 (s, $1H_{arom}$)	260
7d	2	86	280 (dec)[f]	$C_{11}H_7N_3O_2$	3400, 3200, 2230, 1650	6.14 (s, 2H, OCH_2O), 6.66 (br s, 2H, NH_2), 6.91 (s, $1H_{arom}$), 7.12 (s, $1H_{arom}$), 8.37 (s, $1H_{arom}$)	213

[a] Yield of pure isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.19, N ± 0.25.
[c] Solvent: EtOH.
[d] Solvent: EtOAc/Acetone.
[e] Solvent: EtOAc.
[f] Solvent: EtOH/EtOAc.

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