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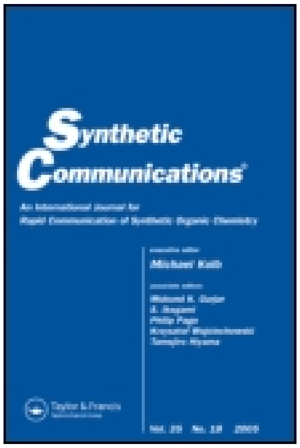

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A NOVEL REDUCTIVE CYCLIZATION OF ARYLMETHYLIDENEMALONONITRILE PROMOTED BY LOW-VALENT TITANIUM

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A NOVEL REDUCTIVE CYCLIZATION OF ARYLMETHYLIDENEMALONONITRILE PROMOTED BY LOW-VALENT TITANIUM

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ABSTRACT

The intermolecular and intramolecular reductive coupling reactions of arylmethylidenemalononitriles induced by low-valent titanium have been studied. A possible reaction mechanism is proposed.

Key Words: Low-valent titanium; Reductive cyclization; Arylmethylidenemalononitrile

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. A lot of other functional groups can also be coupled.[1,2] Although several results have been reported on saturated carbonyl compounds, only a few studies on the coupling

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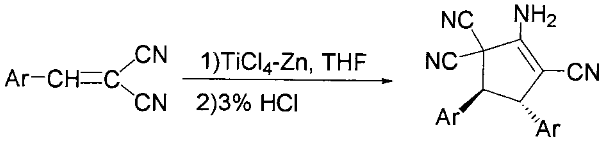


1 **2**

Scheme 1.

α,β-unsaturated cabonyl compounds have been published.[3,4] Recently, we have reported the cyclodimerization of α,β-unsaturated ketones promoted by this reagent to yield cyclopentane derivatives.[5] It has been known that α,β-unsaturated carboxylic acid derivatives are reduced with samarium diiodide to the corresponding saturated compounds,[6] but there is no report on such a reaction using low-valent titanium. Here, we wish to report the novel reductive cyclization of arylmethylidenemalononitriles promoted by treatment with titanium tetrachloride/zinc in anhydrous tetrahydrofuran (THF).

It has been known that the cyano group is relatively more stable to low-valent titanium reagents than the carbonyl group and could not be reduced unless the reaction mixture was refluxed for a long time and only with low yield.[7,8] We considered that the conjugated carbon–carbon double bond could perhaps influence the reactivity of the cyano group. Therefore, we studied the behavior of the cyano group in α,β-unsaturated nitrile derivatives when treated with titanium tetrachloride and zinc in anhydrous THF.

When arylmethylidenemalononitriles **1** were treated with low-valent titanium in THF, the intermolecularly (and reductively) coupled cyclization products, the *trans*-2-amino-1,3,3-tricyano-4,5-diarylcyclopentenes **2**, were formed (Sch. 1).

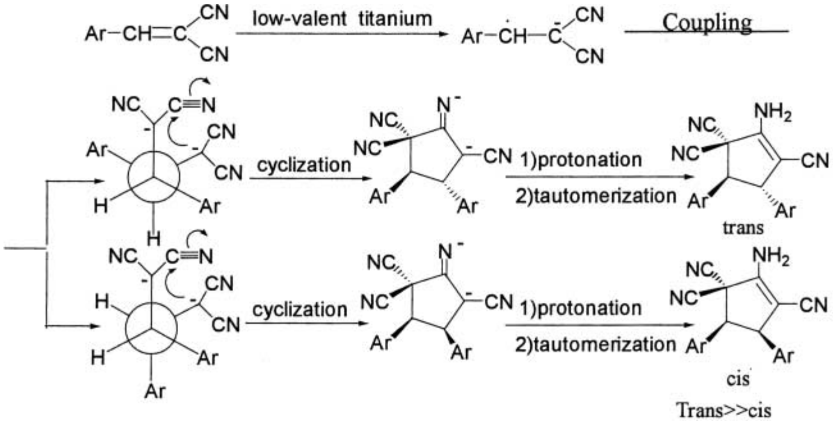
Table 1 summarizes our results of the cyclodimerization of a number of substrates. In the reactions the cleavage takes place at the carbon–nitrogen triple bond and the carbon–carbon double bond. The chloro and alkoxy groups of the substrates could not be reduced under the reaction conditions and have no influence on the rate of cyclodimerization.

Though the detailed mechanism of the above cyclodimerization has not been clarified yet, the cyclopentene formation can be explained by the possible mechanism depicted in Sch. 2.

In the initial step, an electron is transferred from low-valent titanium to substrate (**1**) to form a radical anion which then reacts with another one to produce a dianion. Moreover, the intramolecular nucleophilic addition of the dianion can occur automatically to afford a five-membered ring product due to the stability of the five-membered ring. Considering the stability of

Table 1. Cyclodimerization of Arylmethylidenemalononitriles Induced by Low-Valent Titanium

Entry	Ar	Isolated Yield (%)
A	4-ClC_6H_4	78
B	4-$CH_3C_6H_4$	73
C	C_6H_5	67
D	4-$CH_3OC_6H_4$	72
E	3,4-OCH_2O-C_6H_3	60
F	2-Furyl	64

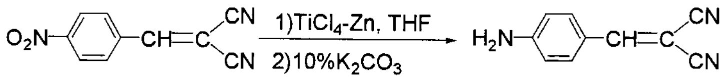


Scheme 2.

the dianion and product, it is obvious that the trans-isomer is easy to form. In support of the mechanism, only the tans-isomer was obtained in this reaction. The relative configuration for C(4)/C(5) in product was determined by analysis of the coupling constrant between H(5)/H(4)($J = 9$–10 Hz, trans).[9,10]

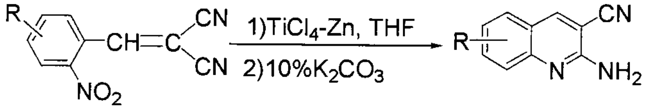
However, treatment of (*p*-nitrobenzylidene)malononitrile (**3**) with titanium tetrachloride and zinc in anhydrous THF under the same reaction conditions was found to afforded only product (**4**) formed by reduction of the nitro group in (**3**) (Sch. 3).

On the other hand, when (*o*-nitrobenzylidene) mlononitrile derivatives (**5**) were subjected to the above procedure, neither products (**3**) nor (**4**) were detected. However, the intramolecular reductive cyclization products, 2-aminoquinoline derivatives (**6**) (Sch. 4), were found in good yields.



3 4

Scheme 3.



5 6

a: R=H

b: R=4,5-OCH_2O

Scheme 4.

In summary, the intermolecular cyclodimerization of arylmethylidenemalononitrile induced by low-valent titanium took place to afford *trans*-2-amino-1,3,3-tricyano-4,5-diarylcyclopentene, while under the same reaction conditions the intramolecular reductive cyclization of *o*-nitrobenzylidene malononitrile derivatives was found, which allowed a facile synthesis of 2-aminoquinoline derivatives.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer. ^{1}H NMR spectra were measured on a R-1500A spectrometer using TMS as internal standard. Elemental analysis were determined using Perkin-Elmer 240C elemental analysers.

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 anhydrous 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 arylmethylidenemalononitrile (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, the reaction was quenched with 3% HCl (50 mL) and extracted with CH_2ClCH_2Cl (3 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), dried (Na_2SO_4), and the solvent was removed in vacuum to give the crude product, which was further purified by column chromatography [silica gel, EtOAc/petroleum ether (b.p. 60–90°C), 1 : 2].

2a: M.p. 158–160°C (Lit.[10] m.p. 158–160°C); IR (KBr, ν, cm^{-1}): 3375, 3190, 2220, 1670, 1625, 1495, 1090, 1015; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.74 (1H, d, $J = 10$ Hz, ArCH), 4.50 (1H, d, $J = 10$ Hz, ArCH), 5.32 (2H, s, NH_2), 6.85–7.40 (8H, m, ArH).

2b: M.p. 186–188°C; (Lit.[10] m.p. 190–192°C); IR (KBr, ν, cm^{-1}): 3375, 3240, 2220, 1670, 1660, 1630, 1515, 1095, 1075, 825; ^{1}H NMR ($CDCl_3$, δ, ppm): 2.24 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.77 (1H, d, $J = 10$ Hz, ArCH), 4.50 (1H, d, $J = 10$ Hz, ArCH), 5.32 (2H, s, NH_2), 6.93–7.38 (8H, m, ArH).

2c: M.p. 130–132°C; (Lit.[10] m.p. 128–130°C); IR (KBr, ν, cm^{-1}): 3375, 3175, 2210, 1675, 1625, 1500, 1450, 1380, 1100, 700; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.82 (1H, d, $J = 9$ Hz, ArCH), 4.58 (1H, d, $J = 9$ Hz, ArCH), 5.21 (2H, s, NH_2), 7.10–7.74 (10H, m, ArH).

2d: M.p. 98–100°C; (Lit.[10] m.p. 95–97°C); IR (KBr, ν, cm^{-1}): 3375, 3240, 2220, 1670, 1630, 1610, 1515, 1260, 1250, 1180, 1035, 830, 810; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.65 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.15 (1H, d, $J = 10$ Hz, ArCH), 4.53 (1H, d, $J = 10$ Hz, ArCH), 5.38 (2H, s, NH_2), 6.71–7.51 (8H, m, ArH).

2e: M.p. 163–165°C; (Lit.[10] m.p. 166–168°C); IR (KBr, ν, cm^{-1}): 3380, 3240, 2220, 1670, 1620, 1505, 1490, 1450, 1380, 1040, 940, 930; ^{1}H NMR ($CDCl_3$, δ, ppm): 4.24 (1H, d, $J = 9$ Hz, ArCH), 4.45 (1H, d, $J = 9$ Hz, ArCH), 5.30 (2H, s, NH_2), 5.97 (4H, s, $2 \times OCH_2O$), 6.30–6.94 (6H, m, ArH).

2f: M.p. 126–128°C; (Lit.[10] m.p. 125–127°C); IR (KBr, ν, cm^{-1}): 3360, 3240, 2220, 1680, 1630, 1510; ^{1}H NMR ($CDCl_3$, δ, ppm): 4.25 (1H, d, $J = 9$ Hz, ArCH), 4.62 (1H, d, $J = 9$ Hz, ArCH), 5.61 (2H, s, NH_2), 6.25–7.52 (6H, m, ArH).

Product 4 and 2-Aminoquinolines 7: General Procedure

A black suspension of low-valent titanium reagents 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 **3** or **5** (10 mmol) in THF (20 mL) was added carefully to the suspension at r.t. 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 CH_2ClCH_2Cl (4 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), dried (Na_2SO_4), and the solvent was removed in vacuum to give the crude product, which was further purified by recrystallization from 95% EtOH.

4: M.p. 202–204°C; yield 88%; IR (KBr, ν, cm^{-1}): 3350, 3250, 2220, 1650, 1610, 1580, 1550, 1520, 1460, 1370, 1350, 1330, 1250, 1175, 820; ^{1}H NMR ($CDCl_3$, δ, ppm): 6.69 (2H, d, $J = 10$ Hz, ArH), 7.63 (2H, d, $J = 10$ Hz, ArH), 7.86 (1H, s, –CH=). Anal. calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.15; H, 4.06; N, 24.78.

6a: M.p. 230–232°C; (Lit.[10] m.p. 226–227°C yield 81%; IR (KBr, ν, cm^{-1}): 3400, 3160, 2230, 1650, 1620, 750; ^{1}H NMR ($CDCl_3$, δ, ppm): 5.45 (2H, s, NH_2), 7.30–7.75 (4H, m, ArH), 8.31 (1H, s, ArH).

6b: M.p. 275–277°C; (Lit.[10] m.p. 280°C); yield 76%; IR (KBr, ν, cm^{-1}): 3400, 3200, 2230, 1650; ^{1}H NMR ($CDCl_3$, δ ppm): 6.14 (2H, s, OCH_2O), 6.65 (2H, s, NH_2), 6.90 (1H, s, ArH), 7.12 (1H, s, ArH), 8.37 (1H, s, ArH).

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