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Lei Wang [a] & Yongmin Zhang [a]
[a] Department of Chemistry , Hangzhou University , Hangzhou, 310028, P. R. China

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NOVEL REDUCTIVE DIMERIZATION CYCLIZATION OF 1,1-DICYANOALKENES MEDIATED BY ZINC IN AQUEOUS MEDIA

Lei Wang and Yongmin Zhang*

Department of Chemistry, Hangzhou University, Hangzhou, 310028, P. R. China

Abstract: Zinc-mediated reductive dimerization cyclization of 1,1-dicyanoalkenes **1** occurs to give functionalized cyclopentenes **2**(*cis*) and **3**(*trans*) in good yields under saturated aqueous NH_4Cl-THF solution at room temperature. **3** is major product.

Carbon-carbon bond formation is the essence of organic synthesis and the reductive dimerization of carbonyl derivatives by means of active metal is one of the most valuable method for establishing carbon-carbon bonds. Among its principal variants are the pinacol reduction[1] and acyloin condensation[2]. In a general fashion, the carbonyl derivatives are aldehydes, ketones, carboxylic ester, acid chloride or imines[3], active metals are alkali or alkaline earth metals and the reactions were carried out in anhydrous solvents. Most recently, there are some reports on the reductive dimerization and reductive dimerization cyclization of α,β-unsaturated esters and α,β- unsaturated amides promoted by samarium(II) iodide[4].

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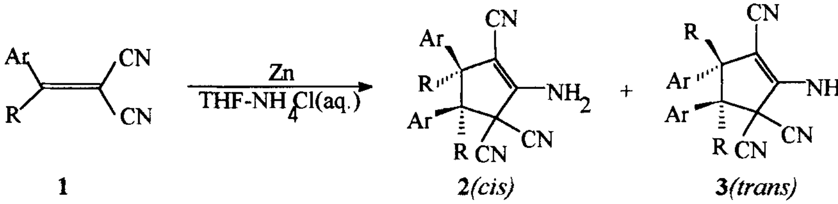
* To whom the correspondence should be addressed

In the last decade, metal-mediated organic reactions in aqueous media have attracted considerable interest in organic synthesis[5]. Such reactions in aqueous media offer a number of advantages over conventional organometallic reaction in organic solvent. There is the practical convenience, possible environmental benefits, of not having to use anhydrous organic solvents and the regio- and stereoselectivity of the reaction may well change from organic to aqueous media[6]. As a cheap and efficient reagent, metallic zinc powder has been adopted for the preparation of homoallylic alcohols by the coupling of allylic halides with carbonyl compounds in aqueous media[7]. However, the type of reactions possible have been somewhat limited and it would seem reasonable to extend the coupling reaction of carbonyl derivatives or other compounds. We report herein that zinc-mediated reductive dimerization cyclization of electron deficient olefin **1** can be carried out in aqueous media at room temperature (**Scheme 1**). The results are summarized in **Table 1**.



Scheme 1

As coupling components, 1,1-dicyanoalkenes have enough reactivity to perform the reductive dimerization cyclization in the presence of zinc under aqueous media due to their carbon-carbon double bonds can be activated by attached cyano groups. From **Scheme 1** and **Table 1**, we found that reductive dimerization cyclization can be completed at room temperature in saturated aqueous NH_4Cl-THF(1:4) within 4 h. We also found that 1,1-dicyanoalkenes **1** derived from aromatic aldehydes give the products with good to excellent yields and those derived from aromatic ketones give the products in moderate yields. Unfortunately, while substrate **1** derived from an aliphatic aldehyde was used, no product was isolated, even in longer reaction time(entry l).

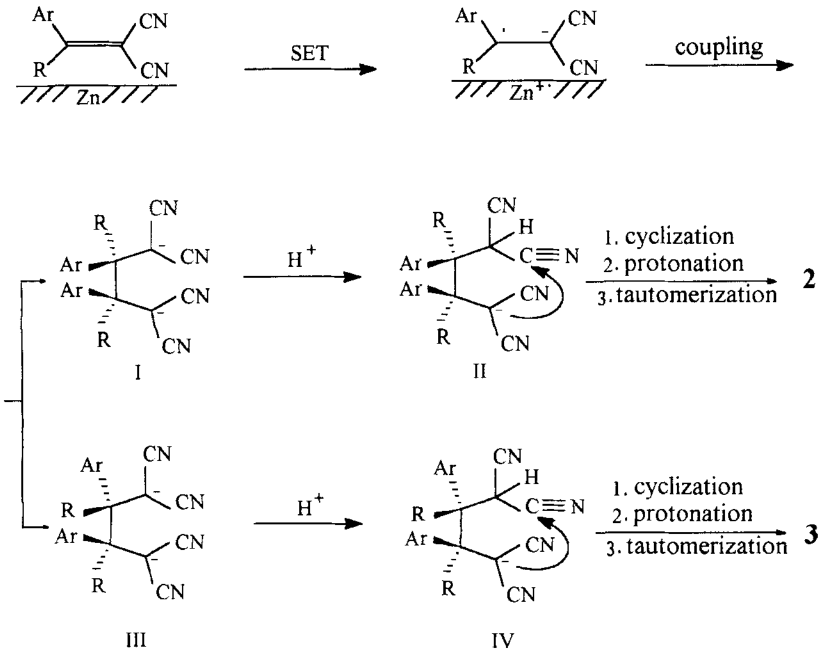
Table 1 Zinc-mediated Reductive Dimerization Cyclization of 1,1-Dicyanoalkenes[a]

Entry	Ar	R	Yield(%)[b]	**3/2** [c]
a	C_6H_5	H	75	80/20
b	p-ClC_6H_4	H	80	84/16
c	p-$CH_3C_6H_4$	H	72	77/23
d	p-$CH_3OC_6H_4$	H	60	75/25
e	m-BrC_6H_4	H	82	79/21
f	o-BrC_6H_4	H	81	74/26
g	p-$CF_3C_6H_4$	H	90	89/11
h	p-BrC_6H_4	H	84	84/16
i	p-FC_6H_4	H	79	81/19
j	C_6H_5	CH_3	54	60/40
k	p-BrC_6H_4	CH_3	57	60/40
l	n-C_3H_7	H	0[d]	--

[a] Reaction conditions: 1 mmol scale, solvent NH_4Cl(aq.)-THF(1 ml-4 ml), r. t., 4 h. [b] Isolated yields and all products were characterized by Elemental Analysis, IR, NMR, and MS. [c] Ratio determined from the intensities of methenyl protons of products (entry **a-i**) or methyl protons of products (entry **j-k**) in ^{1}H NMR.
[d] Reaction time was 8 h.

We have tried to use anhydrous THF, THF-H_2O or H_2O in place of THF-NH_4Cl(aq.). The results show that no product is formed under these solvents. On the other hand, we also have used other metal powder, such as tin and indium to take the place of zinc, the reaction can not occur.

A possible reaction mechanism, involving the intermediate of a radical anionic species and coupling cyclization of radical anion, is outlined in **Scheme 2**. Owing to the electron withdrawing property of CN groups, a radical anion of the electron deficient olefin **1** may be formed by a single-electron transfer process at the zinc surface under the reaction condition[8]. Here the carbon bearing the negative charge should be flanked by cyano groups which are capable of stabilizing the carbanion, so that a radical anion is easy to form and has enough time to react with another one to produce a dianion. Moreover, the intramolecular nucleophilic addition of intermediates can occur automatically to afford a five-membered ring product due to the stability of five-membered ring.



Scheme 2. Possible mechanism of the reductive dimerization cyclization

In **Scheme 2**, we found that anion II and IV are key intermediates in the course of the formation of **2** and **3** respectively. Considering the stability of anion and product, it is obvious that **3**(*trans*) is easy to form. In support of the mechanism, compound **3a** was obtained through the recrystalization from the mixture of **2a** and **3a**(chloroform-ether) and its *trans*-form structure was verified by NOE experiment of NMR technique(the results were shown in **Fig. 1**). The more detailed study is in progress in our laboratory.

In conclusion, it is found that zinc is a useful metal to mediate the reductive dimerization cyclization of 1,1-dicyanoalkenes in aqueous media at room temperature. The remarkable advantages of this reaction are mild and neutral

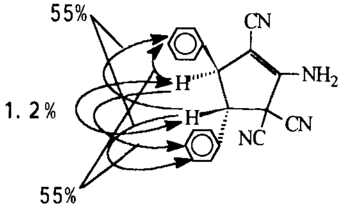


Fig. 1 Observed NOE of **3a.**

reaction condition, simple operation and good yields. It provides a new, simple and practical method for the synthesis of polysubstituted cyclopentene from a simple electron deficient olefin.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JEOL PMX 60 SI instrument. All NMR samples were measured in $CDCl_3$ using TMS as internal standard. IR spectra were obtained on a Perkin-Elmer 683 infrared spectrophotometer as KBr discs. The IR peak intensities were recorded as w (weak), m (medium) and s (strong). Mass spectra were determined on a Finnigan MAT GC-MS spectrometer. Elemental analyses were carried out on a Carlo-Erba 1106 instrument.

General procedure for the syntheses of functionalized cyclopentenes:

1,1-Dicyanoalkene **1** (1.0 mmole) and zinc powder (1.1 mmole) were added to the saturated aqueous NH_4Cl-THF(1 ml-4 ml) solution. The resulting mixture was stirred at room temperature for 4 h. The product was extracted with ether(20 ml × 2). After the organic layer was dried with anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel /hexane-ethyl acetate) to give **2** and **3**.

2a and **3a**: Anal. for $C_{20}H_{14}N_4$: Calc.(found) C 77.40(77.67), H 4.55(4.72), N 18.05(17.80)%. IR υ/cm^{-1} 3378(br), 3217(br), 3052(m), 2940(m), 2212(s), 1678(s), 1670(s), 1660(s), 1630(m), 1503(m), 1460(s), 696(s). ^{1}H NMR δ 3.75(d, J=9.4Hz, 0.80H, **3a**-CH), 4.59(d, J=9.4Hz, 0.80H, **3a**-CH), 3.22(d, J=7.2Hz, 0.20H, **2a**-CH), 4.31(d, J=7.2Hz, 0.20H, **2a**-CH), 5.31 br(s) and 5.45 br(s) (2H, NH_2), 7.35(m, 10H, Ph × 2). MS(EI) m/z 311(M^++1, 25), 310(M^+, 100), 283(13), 156(16), 155(39), 128(16), 102(13), 101(13), 78(15), 77(27), 52(24), 51(49).

2b and **3b**: Anal. for $C_{20}H_{12}Cl_2N_4$: Calc.(found) C 63.34(63.57), H 3.19(3.02), N 14.77(14.90)%. IR υ/cm^{-1} 3375(br), 3200(br), 3070(m), 2950(m), 2220(s), 1685(s), 1660(s), 1630(m), 1500(m), 1460(s), 828(m). ^{1}H NMR δ 3.75(d, J=9.1Hz, 0.84H, **3b**-CH), 4.53(d, J=9.1Hz, 0.84H, **3b**-CH), 3.44(d, J=7.0Hz, 0.16H, **2b**-CH), 4.28(d, J=7.0Hz, 0.16H, **2b**-CH), 5.30 br(s) and 5.42 br(s) (2H, NH_2), 7.30(m, 8H, Ar × 2). MS(EI) m/z 382(M^++4, 13), 380(M^++2, 58), 378(M^+, 100), 345(36), 344(29), 343(52), 156(23), 155(58), 127(21),101(17), 77(26), 76(18), 75(33), 63(17), 52(15), 51(25).

2c and **3c**: Anal. for $C_{22}H_{18}N_4$: Calc.(found) C 78.08(77.87), H 5.36(5.60), N 16.56(16.74)%. IR υ/cm^{-1} 3380(br), 3223(br), 3048(m), 2950(m), 2220(s), 1680(s), 1665(s), 1645(s), 1620(m), 1500(m), 1460(s), 1380(s), 826(m). ^{1}H NMR δ 2.16(s, 3H), 2.21(s, 3H), 3.84(d, J=9.4Hz, 0.77H, **3c**-CH), 4.60(d, J=9.4Hz, 0.77H, **3c**-CH), 3.20(d, J=7.2Hz, 0.23H, **2c**-CH), 4.30(d, J=7.2Hz, 0.23H, **2c**-CH), 5.30 br(s) and 5.40 br(s) (2H, NH_2), 7.17(m, 8H, Ar × 2). MS(EI) m/z 339(M^++1, 16), 338(M^+, 100), 325(12), 324(25), 155(20), 115(14), 91(12), 65(15) 51(12).

2d and **3d**: Anal. for $C_{22}H_{18}N_4O_2$: Calc.(found) C 71.34(71.57), H 4.90(4.66), N 15.13(15.01)%. IR υ/cm^{-1} 3370(br), 3220(br), 3050(m), 2945(m), 2221(s), 1683(s), 1666(s), 1648(m), 1618(m), 1500(m), 1460(s), 1385(s), 820(m). ^{1}H NMR δ 3.66(s, 3H), 3.81(s, 3.75H, CH_3O- and **3d**-CH), 4.42(d, J=9.4Hz, 0.75H, **3d**-CH), 4.06(d, J=7.2Hz, 0.25H, **2d**-CH), 3.13(d, J=7.2Hz, 0.25H, **2d**-CH), 5.30 br(s) and 5.40 br(s) (2H, NH_2), 7.08(m, 8H, Ar × 2). MS(EI) m/z 371(M^++1, 28), 370(M^+, 100), 369(34), 355(22), 339(35), 255(20), 199(30), 184(32), 171(65), 155(51), 142(32), 114(34), 77(38), 63(32), 51(36).

2e and **3e**: Anal. for $C_{20}H_{12}Br_2N_4$: Calc.(found) C 51.31(51.57), H 2.58(2.79), N 11.97(12.20)%. IR υ/cm^{-1} 3375(br), 3210(br), 3080(m), 2960(m), 2222(s), 1685(s), 1665(s), 1640(s), 1500(m), 1460(s), 790(m), 700(m). ^{1}H NMR δ 3.57(d, J=9.4Hz, 0.79H, **3e**-CH), 4.48(d, J=9.4Hz, 0.79H, **3e**-CH), 3.12(d, J=7.2Hz, 0.21H, **2e**-CH), 4.15(d, J=7.2Hz, 0.21H, **2e**-CH), 5.48 br(s) and 5.60 br(s) (2H, NH_2), 7.33(m, 8H, Ar × 2). MS(EI) m/z 470(M^++4, 44), 468(M^++2, 100), 466(M^+, 48), 390(22), 389(48), 388(33), 308(28), 156(18), 155(42), 128(19), 127(23), 101(17), 77(23), 76(33), 75(35), 63(20), 51(32).

2f and **3f**: Anal. for $C_{20}H_{12}Br_2N_4$: Calc.(found) C 51.31(51.65), H 2.58(2.32), N 11.97(11.80)%. IR υ/cm^{-1} 3380(br), 3220(br), 3075(m), 2950(m), 2210(s), 1690(s), 1660(s), 1630(m), 1500(m), 1460(s), 752(m). ^{1}H NMR δ 3.62(d, J=9.0Hz, 0.74H, **3f**-CH), 4.53(d, J=9.0Hz, 0.74H, **3f**-CH), 3.20(d, J=7.0Hz, 0.26H, **2f**-CH), 4.20(d, J=7.0Hz, 0.26H, **2f**-CH), 5.53 br(s) and 5.66 br(s) (2H, NH_2), 7.19(m, 8H, Ar × 2). MS(EI) m/z 470(M^++4, 44), 468(M^++2, 100), 466(M^+, 44), 391(22), 390(37), 389(79), 388(42), 309(25), 308(47), 155(37), 77(24), 76(24), 75(25), 51(23).

2g and **3g**: Anal. for $C_{22}H_{12}F_6N_4$: Calc.(found) C 59.20(59.57), H 2.71(2.62), N 12.55(12.70)%. IR υ/cm^{-1} 3380(br), 3220(br), 3070(m), 2950(m), 2220(s), 1690(s), 1680(s), 1660(s), 1640(m), 1520(m), 1460(s), 832(m). ^{1}H NMR δ 3.80(d, J=9.2Hz, 0.89H, **3g**-CH), 4.63(d, J=9.2Hz, 0.89H, **3g**-CH), 3.33(d, J=7.2Hz, 0.11H, **2g** -CH), 4.33(d, J=7.2Hz, 0.11H, **2g**-CH), 5.33 br(s) and 5.42 br(s) (2H, NH_2), 7.50(m, 8H, Ar × 2). MS(EI) m/z 447(M^++1, 16), 446(M^+, 100), 428(17), 379(8), 378(13), 377(23), 156(10), 155(25), 153(8), 69(11), 51(8).

2h and **3h**: Anal. for $C_{20}H_{12}Br_2N_4$: Calc.(found) C 51.31(51.59), H 2.58(2.62), N 11.97(11.75)%. IR υ/cm^{-1} 3380(br), 3215(br), 3050(m), 2945(m), 2210(s), 1680(s), 1668(s), 1660(s), 1630(m), 1500(m), 1460(s), 830(m). ^{1}H NMR δ 3.71(d, J=9.0Hz, 0.84H, **3h**-CH), 4.50(d, J=9.0Hz, 0.84H, **3h**-CH), 3.35(d, J=7.2Hz, 0.16H, **2h**-CH), 4.21(d, J=7.2Hz, 0.16H, **2h**-CH), 5.29 br(s) and 5.40 br(s) (2H, NH_2), 7.33(m, 8H, Ar × 2). MS(EI) m/z 470(M^++4, 46), 468(M^++2, 100), 466(M^+, 50), 391(25), 390(33), 389(70), 388(35), 309(34), 308(47), 155(44), 77(24), 75(25), 51(27).

2i and **3i**: Anal. for $C_{20}H_{12}F_2N_4$: Calc.(found) C 69.36(69.67), H 3.49(3.62), N 16.18(16.00)%. IR υ/cm^{-1} 3377(br), 3205(br), 3080(m), 2960(m), 2215(s), 1690(s), 1660(s), 1635(m), 1500(m), 1460(s), 820(m). ^{1}H NMR δ 3.60(d, J=9.4Hz, 0.81H, **3i**-CH), 4.42(d, J=9.4Hz, 0.81H, **3i**-CH), 3.13(d, J=7.0Hz, 0.19H, **2i**-CH), 4.12(d, J=7.0Hz, 0.19H, **2i**-CH), 5.28 br(s) and 5.40 br(s) (2H, NH_2), 7.17(m, 8H, Ar × 2). MS(EI) m/z 347(M^++1, 14), 346(M^+, 100), 319(5), 318(5), 252(6), 175(5), 174(8), 173(20), 170(5), 147(5), 146(6), 109(6), 76(5), 75(10), 57(5), 51(5).

2j and **3j**: Anal. for $C_{22}H_{18}N_4$: Calc.(found) C 78.08(77.87), H 5.36(5.12), N 16.56(16.80)%. IR υ/cm^{-1} 3380(br), 3225(br), 3050(m), 2950(m), 2225(s), 1685(s), 1660(s), 1600(m), 1500(m), 1460(s), 1380(s), 690(s). ^{1}H NMR δ 1.21(s, 0.40 × 3H, **2j**-CH_3), 1.46(s, 0.60 × 3H, **3j**-CH_3), 1.88(s, 0.40 × 3H, **2j**-CH_3), 2.01(s, 0.6 × 3H, **3j**-CH_3), 5.37(br, 2H, NH_2), 7.10(m, 10H, Ph × 2). MS(EI) m/z 339(M^++1, 73), 338(M^+, 73), 323(18), 170(19), 169(42), 157(20), 156(45), 155(100), 128(18), 115(28), 103(18), 102(15), 78(25), 77(42), 52(27), 51(48).

2k and **3k**: Anal. for $C_{22}H_{16}Br_2N_4$: Calc.(found) C 53.25(53.57), H 3.25(3.52), N 11.29(11.07)%. IR υ/cm^{-1} 3370(br), 3230(br), 3060(m), 2960(m), 2220(s), 1690(s), 1660(s), 1600(s), 1520(m), 1460(s), 1380(s), 825(m). ^{1}H NMR δ 1.20(s, 0.40 × 3H, **2k**-CH_3), 1.47(s, 0.60 × 3H, **3k**-CH_3), 1.90(s, 0.40 × 3H, **2k**-CH_3), 2.01(s, 0.6 × 3H, **3k**-CH_3), 5.35(br, 2H, NH_2), 7.08(m, 8H, Ar × 2). MS(EI) m/z 498(M^++4, 40), 496(M^++2, 100), 494(M^+, 49), 248(23), 247(20), 170(32), 169(76), 168(32), 140(26), 115(27), 102(26), 77(33), 76(25), 75(23), 51(29).

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