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Novel Reductive Coupling Cyclization of 1,1-Dicyanoalkenes Promoted by Metallic Samarium in Aqueous Media

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Abstract: The reductive coupling cyclization of 1,1-dicyanoalkenes was performed with metallic samarium in saturated aqueous NH_4Cl-THF solution at room temperature. Sub-stoichiometric quantities of samarium could be employed and *trans*-isomer was the major product. © 1998 Elsevier Science Ltd. All rights reserved.

The chemistry of samarium(II) iodide(SmI_2) is of a current interest in organic synthesis. SmI_2 has been developed as a mild, neutral, and ether-soluble one-electron transfer reductant and there have been many examples of its use in the reduction or reductive coupling of various functional groups.[1] However, some problems are incurred when it is used as a reductant. Though SmI_2 is a useful reagent, storage is difficult because it is very sensitive to air oxidation and in general, it has been used invariably in stoichiometric amounts. On the other hand, metallic samarium is stable in air and its strong reducing power(Sm^{3+}/Sm= -2.41V) is similar to that of magnesium(Mg^{2+}/Mg= -2.37V). These properties promoted us to use the more convenient and cheaper samarium directly as a reductant instead of samarium(II) iodide(SmI_2). More recently, there are some reports on the direct use of Sm in organic synthesis.[2] However, to the best of our knowledge, only one paper reported that water could accelerate the reaction of alkyl and aryl iodides with SmI_2 and there was little report of the organic reaction mediated by Sm in aqueous media.[3]

The reductive coupling of compounds containing polar carbon-oxygen and carbon-nitrogen double bonds by means of active metal is one of the most valuable methods for constructing carbon-carbon bonds and in general, the reactions are carried out in anhydrous solvents.[4] Recently, metallic reagents Al(Hg) and Zn-$ZnCl_2$ are reported for the coupling reaction of carbonyl compounds under aqueous conditions,[5] because organic reactions performed in aqueous media offer advantages over those occurring in organic solvents.[6] Herein we wish to report that samarium-mediated reductive coupling cyclization of 1,1-dicyanoalkenes **1** can occur in aqueous media at room temperature to afford functionalized cyclopentenes **2** and **3**. The results are summarized in **Table 1**.

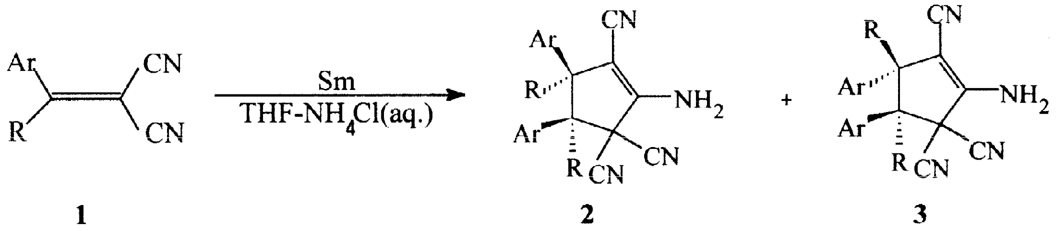

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Table 1 Reductive Coupling Cyclization of 1,1-Dicyanoalkenes[a]

Entry	Ar	R	Temp.(℃)	Time(h)	Yield(%)[b]	**3/2**[c]
a	C_6H_5	H	r.t.	1	80	80/20
			r.t.	4	0[d], 0[e]	--
			r.t.	1	0[f]	--
b	$p\text{-}CH_3C_6H_4$	H	r.t.	1	72	73/27
c	$p\text{-}CH_3OC_6H_4$	H	r.t.	1	63	76/24
d	$p\text{-}BrC_6H_4$	H	r.t.	1	85	81/19
e	$p\text{-}ClC_6H_4$	H	r.t.	1	88	80/20
			r.t.	1	90[g], 88[h], 86[i]	80/20
f	$p\text{-}FC_6H_4$	H	r.t.	1	83	74/26
g	$p\text{-}CF_3C_6H_4$	H	r.t.	1	90	88/12
h	$m\text{-}BrC_6H_4$	H	r.t.	1	82	69/31
i	$o\text{-}BrC_6H_4$	H	r.t.	1	78	71/29
j	C_6H_5	CH_3	r.t.	2	50	60/40
			50	2	71	55/45
k	$p\text{-}BrC_6H_4$	CH_3	r.t.	2	52	60/40
			50	2	73	55/45

a. Reactions were carried out in THF-NH_4Cl(aq.) (4:1, 5 ml) using substrate(1 mmol) and metallic samarium(0.75 mmol). b. Isolated yields and all products were characterized by Elemental Analysis, IR, NMR and MS.[7] c. Ratio determined from the intensities of methenyl protons of products(entry **a-i**) or methyl protons of products(entry **j-k**) in ^1H NMR. d. THF-H_2O(4:1, 5 ml) was used as solvent instead of THF-NH_4Cl(aq.) (4:1, 5 ml). e. THF(anhydrous, 5 ml) was used as solvent instead of THF-NH_4Cl(aq.) (4:1, 5 ml). f. THF-1.0N HCl(4:1, 5 ml) was used as solvent instead of THF-NH_4Cl(aq.) (4:1, 5 ml). g. Metallic samarium(1 mmol) was used. h. Metallic samarium(2 mmol) was used. i. Metallic samarium(0.5 mmol) was used .

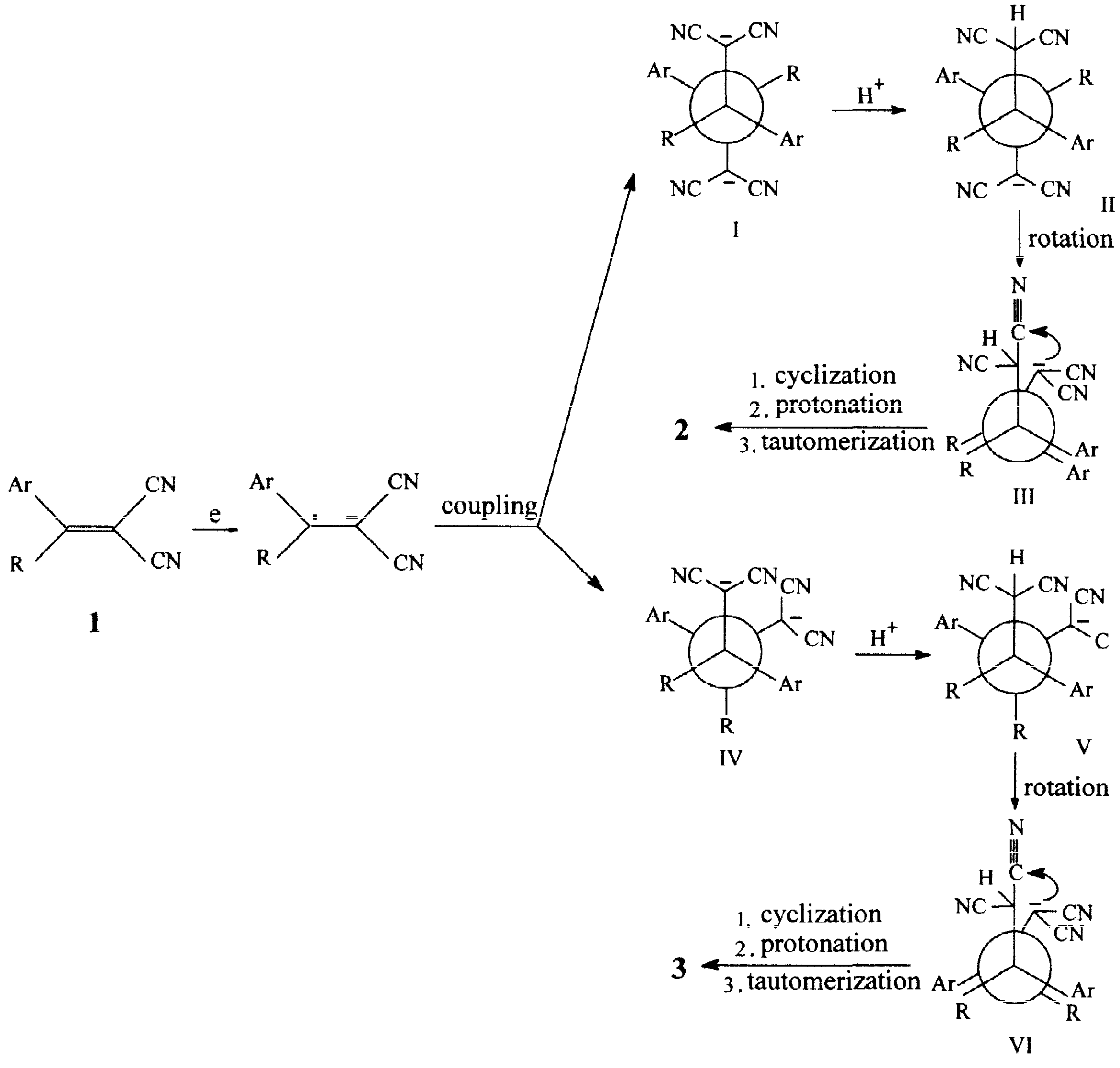
From **Table 1**, we found that substrates **1** derived from aromatic aldehydes give the products **2** and **3** in good to excellent yields within 1 h at room temperature, and the major product is the *trans*-form product **3**. The range of **3/2** ratio is 69/31 to 88/12. Substrates **1** derived from aromatic ketones give **2** and **3** in moderate yields at room temperature, and in good yields at 50 ℃. The range of **3/2** ratio is 55/45 to 60/40. Unfortunately, when **1** derived from aliphatic aldehydes or ketones were used, no reductive coupling cyclization product was isolated.[8]

Since Sm is stable to the neutral THF or THF-H_2O, when the reaction was carried out in THF(anhydrous) or THF-H_2O(4:1), no product was formed, even after longer reaction times(see entry **a**). When the reaction was performed in THF-NH_4Cl(aq.) solution, **2** and **3** were isolated in high yields in a short reaction time. However, when the reaction was carried out in dilute hydrochloric acid-THF solution, no reductive coupling cyclization product was given (see entry **a**).

We have tried to change the quantities of samarium used in the reaction. The results indicated that when the substoichiometric amounts of Sm(substrate/Sm = 2/1 ~ 4/3) were used, the reaction could finish within 1 h in high yield, and when the stoichiometric or superstoichiometric quantities of Sm (substrate/Sm = 1/1 ~ 1/2) were used, the yield of product was not increased.

The configuration of **2** and **3** was determined by ^{1}H NMR and NOE spectra. In the ^{1}H NMR spectra, the coupling constants of the two protons on the ring in substituted cyclopentene **2** and **3** were in the range of 7-8 Hz and 9-10 Hz respectively(entry **a-i**). Thus, we assigned that the two protons whose coupling constant between 7 and 8 Hz are oriented *cis* to each other and there exists strong NOE effect between the *cis*-form protons in NOE spectra, and the two protons whose coupling constant between 9 and 10 Hz are oriented *trans* to each other and no NOE effect was found between the two *trans*-form protons by NOE technique.

The possible mechanism for the formation of **2** and **3** is described in **Scheme 1**. A radical anion of the electron deficient olefin **1** may be formed by a single-electron transfer process under the reaction conditions due to the electron withdrawing property of CN groups, and it reacts with another radical anion of **1** to form a dianion(coupling process). Eventually, dianion gives the functionalized cyclopentene through the protonation, cyclization, protonation and tautomerization. Anion III and VI are key intermediates in the course of the formation of **2** and **3** respectively. Considering the stability of anion III, VI and products, it is obvious that **3** is easy to form. A more detailed study is in progress in our laboratory.



Scheme 1. Possible mechanism of the reductive dimerization cyclization.

In conclusion, we have demonstrated that the Sm/THF-NH_4Cl(aq.) system can be used for reductive coupling cyclization of 1,1-dicyanoalkenes. The notable advantages of this reaction are mild reaction conditions, simple operation, using substoichiometric amounts of Sm, and a high yield.

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7. Spectroscopic data for a mixture of **2a**(*cis*) and **3a**(*trans*). Anal. for $C_{20}H_{14}N_4$: Calc (found) C 77.39(77.57), H 4.55(4.62), N 18.06(17.90)%. IR(KBr) 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). MS(EI) m/z 311(M^++1, 38), 310(M^+, 100), 309(98), 284(15), 283(20), 245(16), 233(22), 156(25), 155(51). ^{1}H NMR($CDCl_3$, 300MHz) δ 3.75(d, J=9.4Hz, 4/5 H, *trans*-CH), 4.59(d, J=9.4Hz, 4/5 H, *trans*-CH), 3.22(d, J=7.2Hz, 1/5 H, *cis*-CH), 4.31(d, J=7.2Hz, 1/5 H, *cis*-CH), 5.31br (s) and 5.45br(s) (2H, NH_2), 7.35 (m, 10H, Ph × 2).

   General procedure is as follows. Under an inert atmosphere of nitrogen, powdered samarium(0.75 mmol) and substrate **1**(1 mmol) were placed in a round bottomed flask, and 4 ml THF was added to it in one portion. After 1 ml saturated NH_4Cl(aq.) was added dropwise to the mixture by syringe over 0.5 h, the mixture was stirred for 0.5 h at room temperature. A dilute HCl(0.5 N, 4 ml) solution was added and the products were extracted with ether(20 ml × 2). After the organic layer was dried with anhydrous Na_2SO_4, the solution was evaporated under reduced pressure. The product was separated from the residue through preparative TLC(silica gel) using cyclohexane-ethyl acetate as the eluent.
8. It is probable that this result may be attributed to the difference in stability of the radical anion intermediate. A benzyl radical anion intermediate from 1,1-dicyanoalkene derived from aromatic aldehyde or ketone is stabilized by the neighboring aromatic ring, so that it is easy to form and has enough time to react with another one to form a dianion and eventually to give product **2** and **3**. The less stable radical anion intermediate from **1** derived from an aliphatic aldehyde or ketone is difficult to form, so that the starting material was recovered.