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# Intermolecular reductive coupling cyclisation of 1,1-diaryl-2,2-dicyanoethylenes with aldehydes or ketones to synthesise polysubstituted 2, 3-dihydrofurans and cyclopentenylamines promoted by samarium metal in DMF

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The intermolecular reductive coupling and cyclisation of 1,1-diaryl-2,2-dicyanoethylenes with carbonyl compounds promoted by metallic samarium in DMF afforded functionalised 2,3-dihydrofurans and cyclopentenylamines.

**Keywords:** intermolecular reductive coupling, cyclisation, 1,1-diaryl-2,2-dicyanoethylenes, samarium diiodide

As a powerful, versatile, and ether-soluble one-electron transfer reducing agent, samarium diiodide ($SmI_2$) has played an ever-increasing role in organic synthesis since its introduction by Kagan and his group.[1] However, though $SmI_2$ is a useful reductive reagent, its storage is difficult and $Sm^{2+}$ has only one electron to donate, which seriously restricts its application on a large scale. Therefore, the direct use of metallic samarium as a reducing agent in organic transformations has attracted the attention of many organic chemists.[2] However, in most cases, the reactions promoted by samarium are usually carried out in THF.[3, 4]

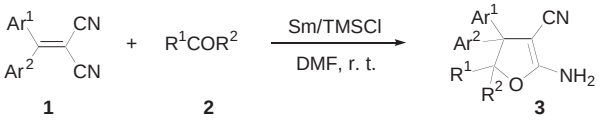
1,1-Diaryl-2,2-dicyanoethylenes can form radical anions just like diaryl ketones.[5,6] Correspondingly, the reductive coupling reactions of 1,1-diaryl-2,2-dicyanoethylenes and nitriles[7] proceed as successfully as those of ketones and nitriles.[8]

The above consideration prompted us to investigate the reductive coupling reaction of 1,1-diaryl-2,2-dicyanoethylenes and ketones, aldehydes or chalcones promoted by metallic samarium. Herein our study was initiated by examining the reactivity of samarium metal by using *N*,*N*-dimethylformamide (DMF) as a solvent instead of THF.

*Synthesis of 2,3-dihydrofuran derivatives by Sm/TMSCl in DMF:* Dihydrofuran and its derivatives are found in many biologically active natural products.[9] They can also serve as versatile building blocks in organic synthesis[9] and several methods have been developed for the preparation of dihydrofurans.[10] Although unsubstituted dihydrofurans are relatively easily derived from furan, preparation of polysubstituted dihydrofurans is much more difficult. Therefore, the development and introduction of more convenient and efficient methods for the preparation of polysubstituted dihydrofurans is of practical importance and these are still in demand.

When 1,1-diaryl-2,2-dicyanoethylenes **1** and ketones (or aldehydes) **2** were treated with Sm/TMSCl in dry DMF, the intermolecular reductive cross-coupling cyclisation products, polysubstituted 2,3-dihydrofurans **3**, were obtained (Scheme 1).

As shown in Table 1, substrates **1** could react readily with aliphatic ketones, acetophenone, aliphatic aldehydes or aromatic aldehydes **2** to produce polysubstituted 2,3-dihydrofurans **3** in moderate to good yields and the structures of the products were confirmed by $^1$H NMR, $^{13}$C NMR, IR, MS and elemental analyses.




**1** **2** **3**

**Scheme 1**

Interestingly, aldehydes, especially aromatic aldehydes, which are usually reactive toward samarium reagents and immediately afford pinacolic coupling products when the reactions are performed in other solvents,[1] were inert towards such a Sm/TMSCl/DMF system thus and their cross-coupling reactions with the substrates go smoothly to afford products **3** in relatively high yields (entries 8, 9 and 10). However, unlike the aliphatic ketones or acetophenone, which react smoothly with substrates **1** in this reaction, when diphenyl ketone is used as the substrate, the desired functionalised 2, 3-dihydrofuran could not be obtained under the same conditions or even at –10°C and only a complex mixture was obtained. In addition, phenylmethylidenemalononitrile failed to react with cyclohexanone to give the corresponding product 2,3-dihydrofuran under the same reaction conditions, and only the reductive dimerisation cyclisation product of the phenylmethylidenemalononitrile was isolated (entry 11).

According to the literature,[5-8, 11] a possible mechanism (two pathways) for the formation of polysubstituted 2,3-dihydrofurans may be postulated as shown in Scheme 2.

In path A, a radical anion **A** of the electron-deficient olefin may be easily formed by a one-electron transfer from metallic samarium under the reaction conditions due to the electron withdrawing property of the cyano groups, and it reacts with ketyl **B** to form the carbon-carbon bond and generates a dianion intermediate **C** (coupling process). Then the oxygen anion of intermediate **C** attacks a cyano group intramolecularly to result in the formation of a carbon–oxygen bond and produce intermediate **D** which is then protonated. Eventually, tautomerisation forms a carbon-carbon double bond due to the stabilisation effect of the cyano group and to give product **3**.

In path B, a one-electron transfer process in the presence of metallic Sm may form the radical anion **A** of the electron-deficient olefin. This then attacks the carbonyl group of ketone **2** to form the carbon–carbon bond and generates an intermediate **E**, which accepts an electron to give **C**, which undergoes the same process as that in pathway A to give the product **3**.

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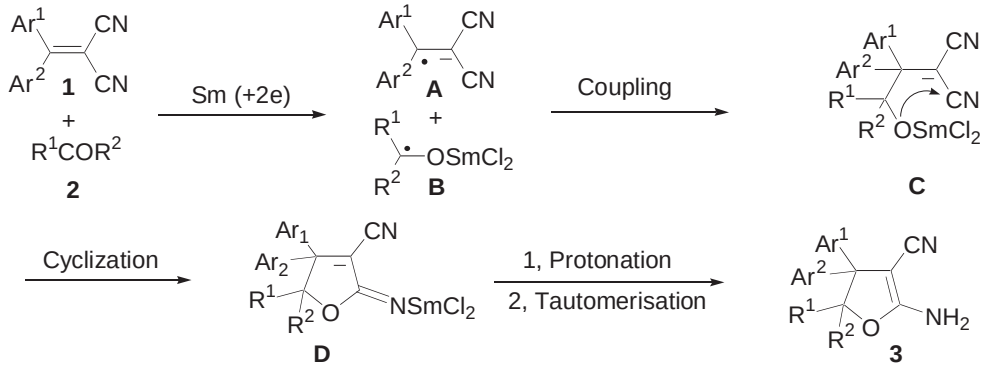
**Table 1** Synthesis of polysubstituted 2,3-dihydrofuran promoted by Sm/TMSCl in DMF

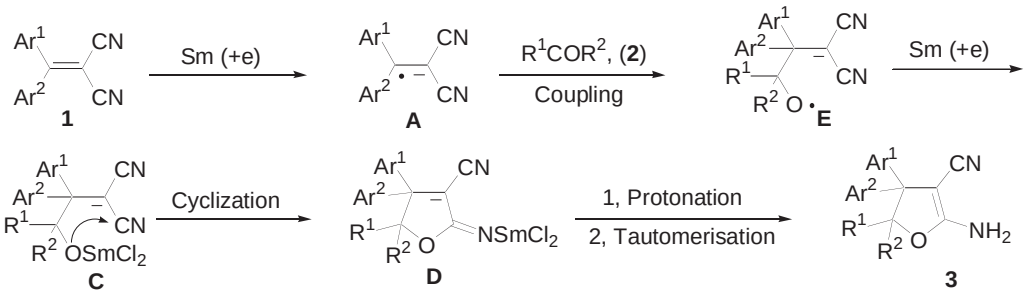
| Entry | $Ar^1$ | $Ar^2$ | $R^1$, $R^2$ | Yield/%[a, b] of **3** |
|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | $-(CH_2)_5-$ | 78 (**3a**) |
| 2 | $C_6H_5$ | $C_6H_5$ | $CH_3$, $CH_3(CH_2)_4$ | 71 (**3b**) |
| 3 | $C_6H_5$ | $C_6H_5$ | $CH_3$, $CH_3(CH_2)_3$ | 73 (**3c**) |
| 4 | $C_6H_5$ | $C_6H_5$ | $CH_3CH_2$, $CH_3CH_2$ | 60 (**3d**) |
| 5 | $C_6H_5$ | $C_6H_5$ | $C_6H_5$, $CH_3$ | 81 (**3e**) |
| 6 | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | $-(CH_2)_5-$ | 82 (**3f**) |
| 7 | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | $CH_3$, $CH_3(CH_2)_4$ | 74 (**3g**) |
| 8 | $C_6H_5$ | $C_6H_5$ | H, $CH(CH_3)_2$ | 84 (**3h**) |
| 9 | $C_6H_5$ | $C_6H_5$ | H, $CH_2CH(CH_3)_2$ | 69 (**3i**) |
| 10 | $C_6H_5$ | $C_6H_5$ | H, 4-Cl-$C_6H_4$ | 92 (**3j**) |
| 11 | $C_6H_5$ | H | $-(CH_2)_5-$ | 0[c] |
| 12 | $C_6H_5$ | $C_6H_5$ | $C_6H_5$, $C_6H_5$ | 0 |

[a]About 3–5 hours are required for the completion of the reaction at r. t.. [b]Isolated yields based on substrates **1**. [c]Only the reductive dimerisation cyclisation product of 1,1-dicyanoalkene was obtained.

**Path A:**

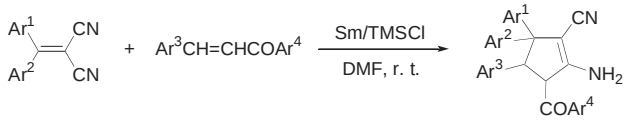



**Path B:**




**Scheme 2**

*Synthesis of polysubstituted cyclopentenylamines by Sm/TMSCl in DMF:* The enamine is an important synthetic intermediate in organic synthesis.[12] It is not only an intermediate for the directly selective alkylation or acylation of an aldehyde or a ketone,[13] but also it can be converted into a carbonyl compound, or into a carboxylic acid or one of its derivatives.[14] It is well known that the Thorpe-Ziegler method is an effective synthetic route to enamino-nitriles.[15] The base-catalysed condensation of two molecules of nitriles, or cyclization of a dinitrile yields imines which tautomerise to enamines, but usually a strong base such as sodium ethoxide or sodium methyl anilide is needed in the reaction. Therefore, it is desirable to develop milder methods for the preparation of enamines. With the successful synthesis of functionalised 2,3-dihydrofurans from 1,1-diaryl-2,2-dicyanoethylenes and aldehydes or ketones, we further investigated the reaction between 1,1-diaryl-2,2-dicyanoethylenes and chalcones promoted by the Sm/TMSCl/DMF system, in an attempt to synthesise the type of enamine **5** (Scheme 3).




**Scheme 3**

A variety of chalcones **4** was used to undergo the cross-coupling cyclisation reactions with 1,1-diaryl-2,2-dicyanoethylene **1**, and the anticipated products **5** were obtained in good yields (Table 2). The reaction was carried out at room temperature in 3–4 hours.

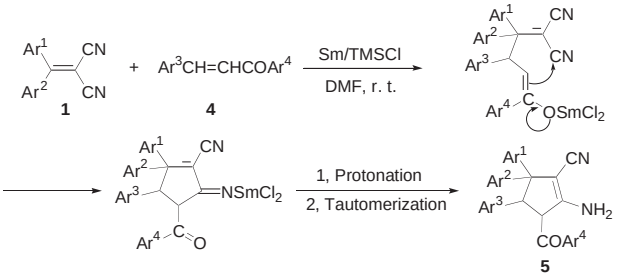
As shown in Table 2, chloro, bromo and alkoxyl groups could not be reduced under the reaction conditions and have no obvious influence on the yields of intermolecular reductive cyclisation products. Also isolated from the reaction mixture were the byproducts resulting from the self-coupling of chalcones.

Though the detailed mechanism of the reaction has not been clarified yet, [5-8, 11, 16] we assume that the formation of polysubstituted cyclopentenylamines may be described by the possible mechanism presented in Scheme 4.

**Table 2** Synthesis of polysubstituted cyclopentenylamines by Sm/TMSCl in DMF

| Entry | $Ar^1$ | $Ar^2$ | $Ar^3$ | $Ar^4$ | Isolated yield of **5**/%[a] |
|---|---|---|---|---|---|
| 13 | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 77 (**5a**) |
| 14 | $C_6H_5$ | $C_6H_5$ | 4-$CH_3C_6H_4$ | $C_6H_5$ | 81 (**5b**) |
| 15 | $C_6H_5$ | $C_6H_5$ | 4-$ClC_6H_4$ | $C_6H_5$ | 78 (**5c**) |
| 16 | $C_6H_5$ | $C_6H_5$ | 3-$BrC_6H_4$ | $C_6H_5$ | 64 (**5d**) |
| 17 | $C_6H_5$ | $C_6H_5$ | 4-$ClC_6H_4$ | 4-$CH_3C_6H_4$ | 76 (**5e**) |
| 18 | $C_6H_5$ | $C_6H_5$ | 4-$CH_3C_6H_4$ | 4-$BrC_6H_4$ | 67 (**5f**) |
| 19 | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | $C_6H_5$ | $C_6H_5$ | 68 (**5g**) |
| 20 | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | $C_6H_5$ | 4-$CH_3C_6H_4$ | 72 (**5h**) |

[a] Isolated yields based on substrates **1**.




**Scheme 4**

In conclusion, the application of metallic samarium, with the activation of TMSCl in DMF, in the preparation of polysubstituted 2,3-dihydrofuran and cyclopentenylamine derivatives has been studied. The advantages of our method are atom economy, convenient manipulation, easily accessible starting materials and moderate to good yields. Further studies to develop other new reactions using samarium metal in DMF are now in progress in our laboratory.

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