A Comparative Study in Oxidative Free Radical Reactions between 9-Benzylidene-9-H Fluorene Derivatives and β-Dicarbonyl Compounds in the Presence of $Mn(OAc)_3$ and CAN

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Abstract: The reactions of some 1,3-dicarbonyl compounds with 9-benzylidene-9-H-fluorene derivatives in the presence of manganese(III)acetate and ceric ammonium nitrate (CAN) were searched. 9-benzylidene-9-H-fluorene compounds form mainly [2+3] dipolar cycloaddition products such as dihydrofuran and lactone which are spirally attached to the C-9 position of flourene ring with manganese(III)acetate and oxidative addition products with CAN. The best yield of cyclization products was obtained from the reaction between **2c** and **1a-c** in both oxidants. The stereochemistry of the products **3d**, **4d** and **5d** was only transformed which has coupling constant 13 Hz.

Keywords: 9-benzylidene-9H-fluorene, cerium(IV) ammonium nitrate (CAN), manganese(III) acetate, radicalic oxidation, β-dicarbonyl compounds.

INTRODUCTION

Free radical and oxidative cyclization reactions have become increasingly important in the synthesis of useful and complex molecules in organic synthesis for a long time [1]. The oxidative addition of carbon centered radicals to double bond mediated by transition metal salts such as Mn^{+3}, Ce^{+4}, Co^{+3}, Cu^{+2} has received considerable attention for the formation of carbon-carbon bond in organic synthesis. Among these, manganese(III)acetate [2] and cerium(IV) ammonium nitrate (CAN) [3], one electron oxidant, have been used most efficiently. Enolizable β-diketones or β-ketoester or β-ketoamide can be oxidized by the salts to generate α-carbon radicals which can attack double or triple bonds [4]. These reactions can be performed intramolecularly or intermolecularly and prepared functionalized products such as furans [5], γ-lactones [1b, 6], β-lactams [7], biologically active compounds and natural products [8].

Fluorene and its derivatives are important compounds and have different types of biological activities, such as anti-inflammatory [9] and antitumor activities [10]. The compounds are important intermediate materials, which are widely used for the synthesis of advanced pigments, dyes, polymers and drugs [8a, 11]. Fluorene-based derivatives have been applied in electronic, photonic and these applications are light emitting diodes, sensors, field effect transistors, two-photon absorbing materials and charge transfer agents [12].

In this paper, we synthesized firstly 9-benzylidene-9H-fluorene derivatives (**1a-c**) by reacting substituted benzaldehydes and fluorene with tert-BuOK in EtOH [13, 14] and described the reaction of some 1,3-dicarbonyl compounds **2a-c** in the presence of $Mn(OAc)_3$ in acetic acid and CAN in methanol with **1a-c** [15] and the reaction is shown in Scheme **1**. Acetic acid and methanol were used as a solvent because they have good solubility for $Mn(OAc)_3$ and CAN respectively.

RESULTS AND DISCUSSION

Dihydrofuran and lactone derivatives of fluorene were prepared by the [2+3] oxidative cycloaddition of 1,3-dicarbonyl compounds to 9-benzylidene-9H-fluorene derivatives by $Mn(OAc)_3/Cu(OAc)_2$ and CAN in which a substituted dihydrofuran unit or lactone is attached to the C-9 position of the fluorene ring. Methoxyl, hydroxyl, nitrate substituted acyclc addition products were obtained when CAN was used as an oxidant. Recommended radicalic cyclization mechanism of **4e** and **5e** with 9-benzylidene-9H-fluorene derivatives (**1a-c**) is given in Scheme **2** and the results of the experiment are given in Table **1** and **2**.

According to the mechanism shown in Scheme **2**, $Mn(OAc)_3$ and acetylacetone give Manganase(III)-enolate complex [5b]. Then Mn^{+3} is reduced to Mn^{+2}. A radical intermediate product is obtained by the addition of the α-carbon radical which is stable and this radical is added to 9-benzylidene-9H-fluorene derivatives. The intermediate product is oxidized to the carbocation with the equivalent of $Mn(OAc)_3$. And the intramolecular cyclization can lead to the products **4e** and **5e**.

A plausible mechanism for additional products is proposed in Scheme **3**. A radical cation forms firstly with CAN and then it turns to stable radical intermediate by nucleophilic addition. The radical intermediate is oxidized to the carbocation with the equivalent of CAN [16] and finally nücleophilic addition occurs. Additionally, these products are depending on alcohol used as a solvent [17]. When methanol or ethanol was used as a solvent, methoxy or ethoxy substituted addition products were obtained.

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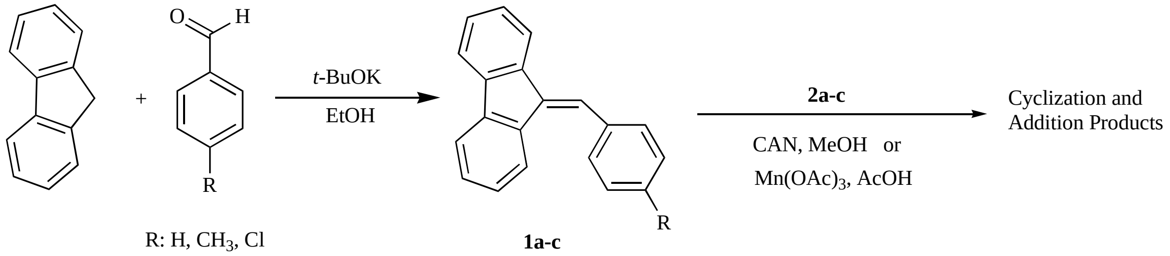
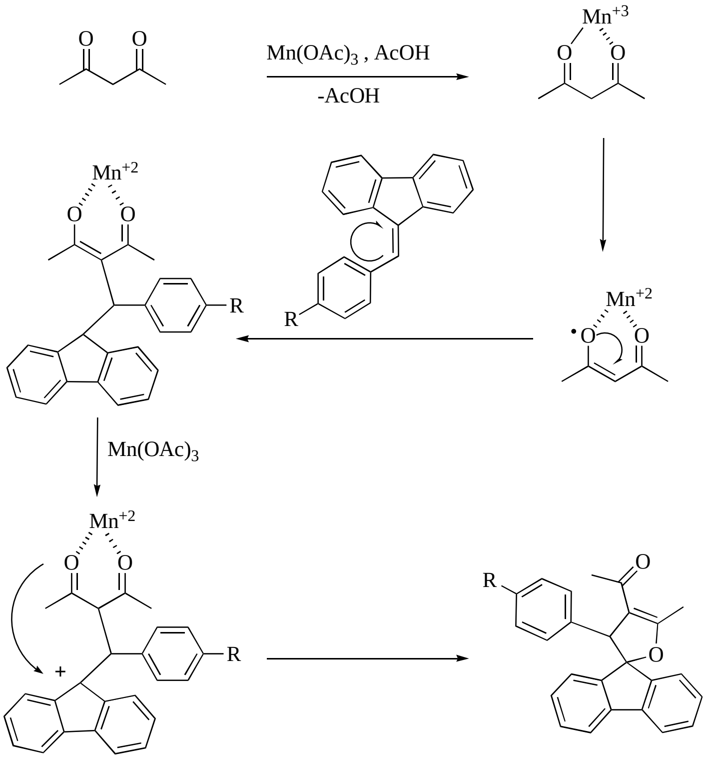
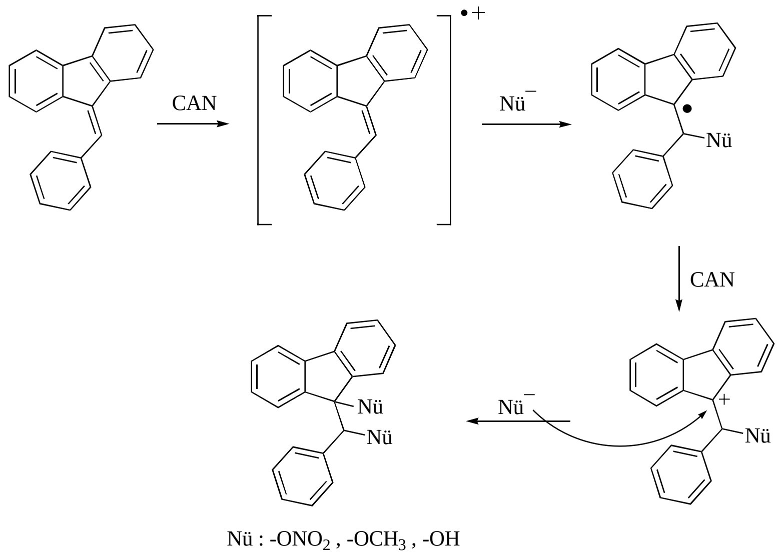


Scheme 1.

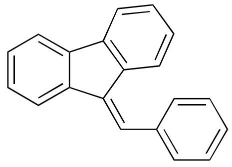
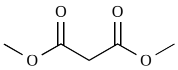
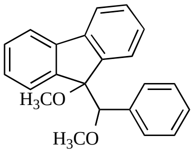
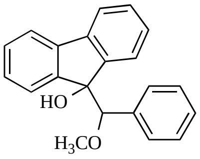
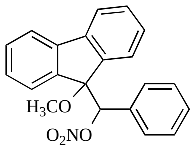
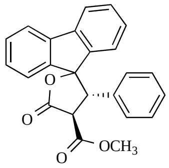
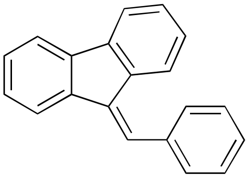
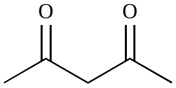
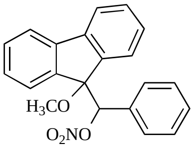
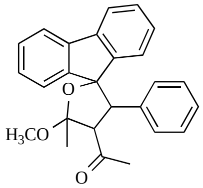
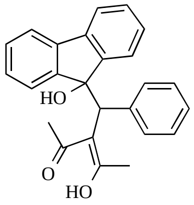
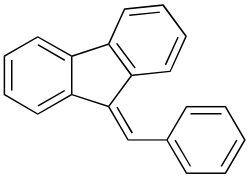
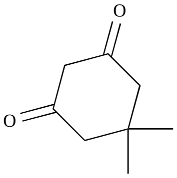
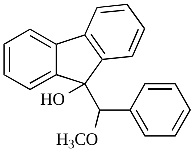
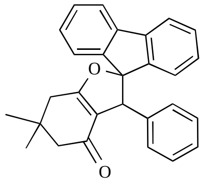
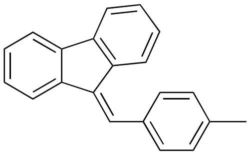
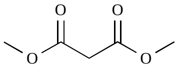
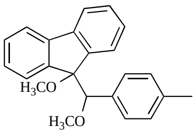
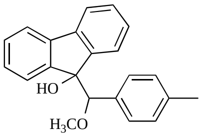
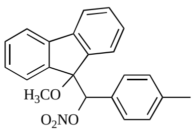
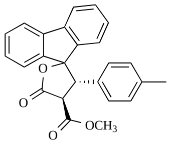
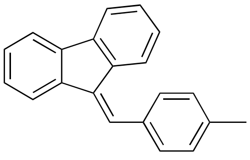
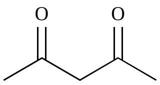
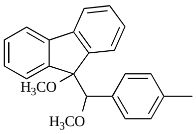
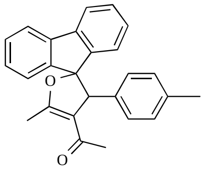
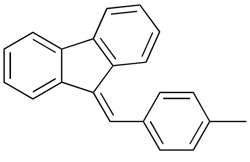
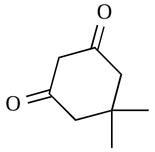
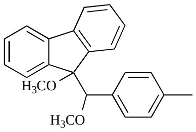
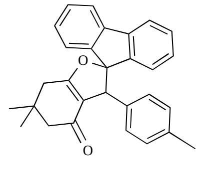
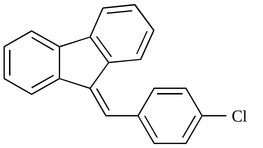
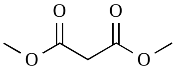
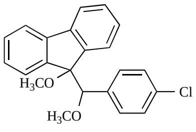
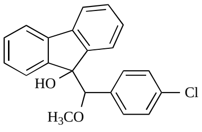
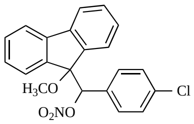
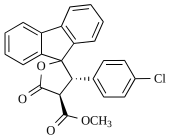


Scheme 2.



Scheme 3.

Table 1. Oxidative Addition of Dimethylmalonate, Acetylacetone and Dimedone to 9-Benzylidene 9H-Fluorene Derivatives in the Presence of CAN

9-benzylidene-9H-fluorene derivative	1,3-Dicarbonyl compound	Products/ Isolated yields (%)			
 **1a**	 **2a**	 **3a** (32%)	 **3b** (7%)	 **3c** (13%)	 **3d** (28%)
 **1a**	 **2b**	 **3c** (5%)	 **3e** (34%)	 **3f** (36%)	-
 **1a**	 **2c**	 **3b** (4%)	 **3g** (61%)	-	-
 **1b**	 **2a**	 **4a** (49%)	 **4b** (4%)	 **4c** (4%)	 **4d** (28%)
 **1b**	 **2b**	 **4a** (5%)	 **4e** (65%)	-	-
 **1b**	 **2c**	 **4a** (5%)	 **4f** (65%)	-	-
 **1c**	 **2a**	 **5a** (20%)	 **5b** (5%)	 **5c** (4%)	 **5d** (46%)

(Table 1). Contd…..

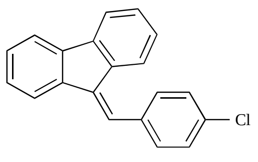
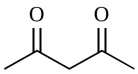
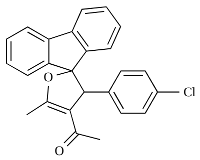
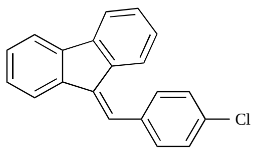
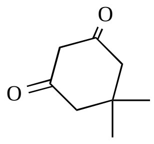
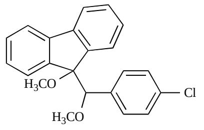
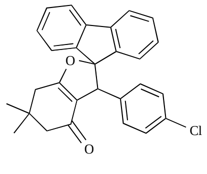
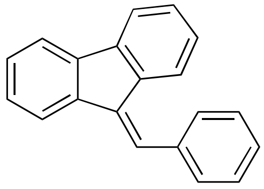
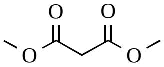
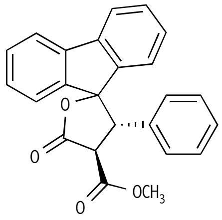
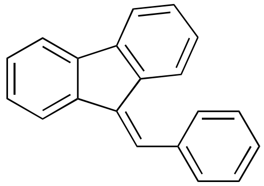
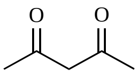
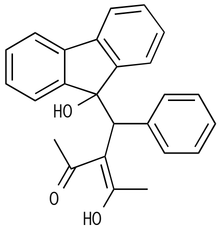
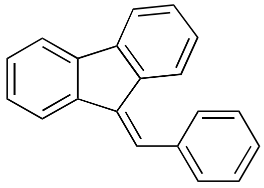
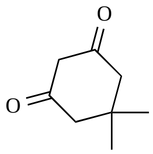
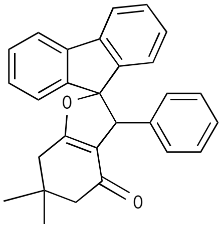
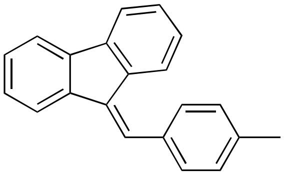
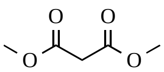
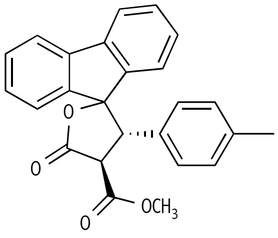
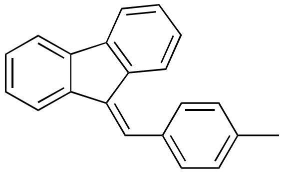
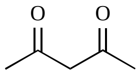
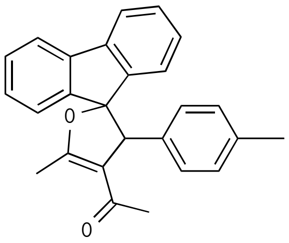
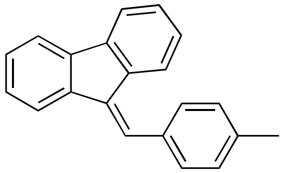
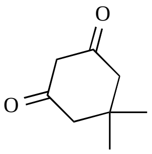
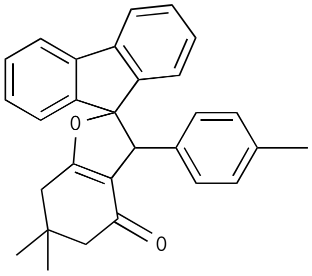
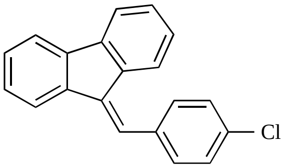
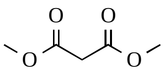
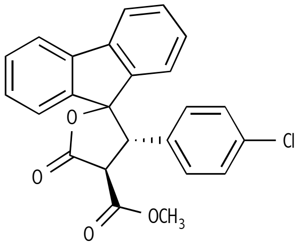
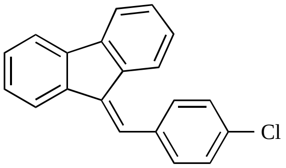
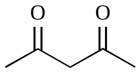
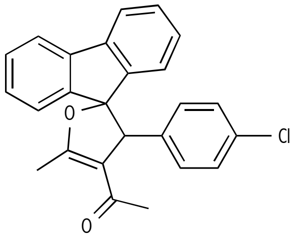
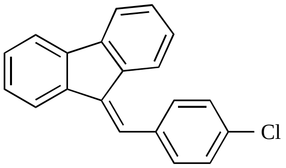
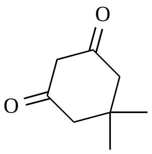
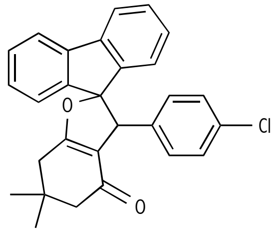
9-benzylidene-9H-fluorene derivative	1,3-Dicarbonyl compound	Products/ Isolated yields (%)			
 **1c**	 **2b**	 **5e** (40%)	-	-	-
 **1c**	 **2c**	 **5a** (15%)	 **5f** (45%)	-	-

Table 2. Oxidative Addition of Dimethylmalonate, Acetylacetone and Dimedone to 9-Benzylidene-9H-Fluorene Derivatives in the Presence of $Mn(OAc)_3$ /$Cu(OAc)_2$

9-benzylidene-9H-fluorene derivative	1,3-Dicarbonyl compound	Products/Isolated yields (%)
 **1a**	 **2a**	 **3d** (40%)
 **1a**	 **2b**	 **3f** (85%)
 **1a**	 **2c**	 **3g** (95%)
 **1b**	 **2a**	 **4d** (65%)

(Table 2). Contd…..

9-benzylidene-9H-fluorene derivative	1,3-Dicarbonyl compound	Products/Isolated yields (%)
 **1b**	 **2b**	 **4e** (81%)
 **1b**	 **2c**	 **4f** (97%)
 **1c**	 **2a**	 **5d** (75%)
 **1c**	 **2b**	 **5e** (90%)
 **1c**	 **2c**	 **5f** (95%)

In the radical cyclization, dimethyl malonate, acetylacetone and dimedone were used as 1,3-dicarbonyl compounds. When dimethyl malonate was used, cyclization products were lactones. On the other hand when acetylacetone or dimedone were used, cyclization products were dihydrofuran units. Besides lactone units which are formed with dimethyl malonate and 9-benzylidene-9H-fluorene derivatives were obtained in lower yield than dihydrofuran units. **3d** (28 %), **4d** (28%) and **5d** (46%) were obtained with **1a-c** and **2a** in the presence of CAN, but these products were obtained with 40%, 65% and 75% yield in the presence of $Mn(OAc)_3/Cu(OAc)_2$ respectively. Similarly, **4e** (65%) and **5e** (40%) were obtained by mediated CAN, although these products were formed with 81% and 90% yield mediated

$Mn(OAc)_3/Cu(OAc)_2$. The reactions of **2c** with **1a-c** exhibited high yield especially in the presence of $Mn(OAc)_3/Cu(OAc)_2$ because of high reactivity of dimedone.

The product distribution in the reactions is influenced by the nature of another salt addition. Heiba and Dessau found that $Cu(OAc)_2$ oxidizes secondary radicals 350 times faster than $Mn(OAc)_3$ does and two reagents can be used together [2b]. Çalışkan et. al. [18] and Hulcoop et. al. [19] showed that salt such as $Cu(OAc)_2$ has affected dipolar cycloaddition reactions between 1,3-dicarbonyl compounds and double bonds in the presence of $Mn(OAc)_3$.

The stereochemistry of lactone annulation is not so pronounced and is highly dependent on the nature of the alkene utilized and generally Jtrans > Jcis for vicinal ring hydrogens [20]. The products **3d**, **4d** and **5d** were obtained by only trans-fused lactones and the coupling constant was J = 13 Hz.

CONCLUSIONS

Consequently, simple, novel and efficient method for the oxidative cyclizations and additions of β-dicarbonyl compounds mediated $Mn(OAc)_3$/ $Cu(OAc)_2$ and CAN with 9-benzylidene-9H-fluorene derivatives have comparatively been studied. As a result, we determined spiro-configurated cyclization products (dihydrofuran and lactone derivatives) in the presence of $Mn(OAc)_3$/ $Cu(OAc)_2$ and either cyclization or addition products in the presence of CAN. Addition products were obtained by using **2a**. The stereochemistry of the products **3d**, **4d** and **5d** was only transconfiguration which had a coupling constant 13 Hz.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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[14] *Typical procedure for coupling reactions of 9-benzylidene-9-H fluorene derivatives with 1,3-dicarbonyl compounds in the presence of CAN*: 9-benzylidene-9-H fluorene derivatives (6 mmol) were stirred in methanol (20 ml) until dissolved at room temperature. 1,3- dicarbonyl compounds (6 mmol) which were dissolved in methanol (10 ml) were added under argon atmosphere and stirred for 0.5 h. CAN (18 mmol) was added with dropping funnel under argon atmosphere too. The mixture was stirred in ice bath or at room temperature until color of reaction had disappeared Alcohol was removed by rotary evaporator. Then, the mixture was worked-up with chloroform. Further purification of the products was carried out by column chromtography on silica gel using hexane:ethylacetate.

[15] *Typical procedure for coupling reactions of 9-benzylidene-9-H fluorene derivatives with 1,3- dicarbonyl compounds in the presence of Mn(OAc)$_3$:* Mn(OAc)$_3$ (16.2 mmol) was dried in benzene (50 ml) by azeotropic destillation system and was dissolved in acetic acid. Then, Cu(OAc)$_2$(1.8 mmol) was added to the flask. 1,3-dicarbonyl compounds (6 mmol) which were dissolved in acetic acid were added under argon atmosphere and stirred for 0.5 h at room temperature. 9-benzylidene-9-H fluorene derivatives (6 mmol) were added slowly by dropping funnel. Temperature was regulated to 80 ^{o}C. The mixture was stirred until color of reaction had disappeared. Then, the mixture was worked-up with dichloromethane. Solvent was evaporated. Further purification of the products was carried out by column chromtography on silica gel using hexane:ethylacetate.

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