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One pot synthesis of important retinoid synthon by the catalytic regioselective bi-functionalization of acetylenes, alcohol and carbon monoxide

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ABSTRACT

Base free $Fe(CO)_5$ catalyzed one-pot synthesis of *E/Z* alkyl 3-formyl-3-alkyl/aryl/ferrocenyl-2-propenoates (retinoid esters) was achieved by the photolysis of alcoholic solution of terminal acetylenes and carbon monoxide. 8–10 Mol% of ironpentacarbonyl was used as a catalyst for significant transformations of retinoid esters. During the photolysis, alkynes reduced by the simultaneous double functionalization esterification and formylation and resulted in regioselective *E/Z* isomers of alkyl 3-formyl-3-alkyl/aryl/ferrocenyl-2-propenoates. The bi-functionalization of acetylene is quite unusual and is not observed frequently. The highest yield of the retinoid esters was achieved with 3° alcohols (96%, for *E* and *Z* isomers) while the least yield was observed with 1° alcohols (25%, for *E* and *Z* isomers). All retinoid esters are regiospecific and have exceptional biological significance to serve as key structural motifs in drug and pharmaceutical applications.

Introduction

Alkyl/aryl derivatives of *E/Z* 3-formyl-3-alkyl/aryl/ferrocenyl-2-propenoates (retinoic acids) are an important metabolite of vitamin A (retinol).[1] These are essentially required for growth and development and also mediates the functions of vitamin A which is essential to maintain the normal growth and epithelial cell differentiations.[2] Recent studies indicate that retinoic acids are highly necessary for cell-cell signalling during the organogenesis in vertebrates.[3,4] Retinoid esters are also needed for the development of eyes and organs in vertebrates and non-vertebrates.[5] Retinoic acids and their analogues used for the treatment of skin disorders and serve as potential cancer chemotherapeutic agents.[6] The tretinoin or all trans retinoic acid or ATRA is a commercially available drug of retinoic acid. It is one of the several retinoids which consists of the carboxylic acid form of vitamin A and is used for the treatment of acne vulgaris,[7] keratosis pilaris[8] and acute promyelocytic leukaemia (APL).[9] It is one of the most important medicines required for the basic health system as it is listed in the essential list of medicines published by WHO.[10]

In addition to the biological relevance of retinoid esters, these are equally important in synthesis and work as versatile intermediates in organic synthesis and are used as dienophile[11] and diene precursor for the synthesis of alkavinone and dihydropyranones.[12] Several methods for the synthesis of the *E/Z* alkyl 3-formyl-3-alkyl/aryl-2-propenoates have been reported[13,14] but these are largely suffer from the limitation of being multistep, need vigorous reaction conditions and traditional organic synthetic methods, moreover, the reactant must contain easily transformable functionalities.[15] Sisido and co-workers reported the multistep synthesis of the *trans*-β-formylcrotonic acids by acid hydrolysis of arylnitrone to aldehyde or Krohnke's procedures.[16] Curley et al.[17] reported the synthesis of ethyl *trans*-3-formyl-2-butenoate via two stages SeO_2 mediated oxidation of ethyl 3-methyl-2-butenoate. Laugraud et al.[18] synthesized (*E*)-3-alkyl-4-oxo-2-butenoic acid esters by condensation of aliphatic aldehyde, enamines and glyoxylic acids.

Metal catalyzed carbonylation reactions are still proactive area of research.[19] Double carbonylation reactions are specifically high in demand as they can transform highly unusual molecules which may otherwise require multiple synthetic processes.[20] Moreover, carbonylation reactions have huge potential in synthetic organic chemistry.[21] Among various metals, specifically the iron-complexes are very much useful in organometallic catalysis for carbonylation reactions.[22–24] Easy availability, huge abundance, low toxicity and biomimetic properties of iron make it an ideal metal for catalysis.[25] Fe-catalyzed hydro-esterification, lactonization, succinimide formation has been reported in the recent past.[26,27]

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To the best of our knowledge, there is no method available for one pot direct synthesis of retinoid esters. Here, in this report, we demonstrate a one pot direct route for the catalytic synthesis of *E/Z* alkyl 3-formyl-3-alkyl/aryl/ferrocenyl-2-propenoate by the photolysis of terminal acetylenes, alcohols and carbon monoxide.

Results and discussion

Earlier the selective one pot synthesis of α,β-vinyl esters (**1**) and γ-lactones (**2**) was reported[26] in 30–180 min photolysis of an alcoholic solution of terminal acetylene and CO (Scheme 1). $Fe(CO)_5$ catalyzed selective formation of the desired product was achieved by controlled UV irradiations and careful selection of alcohols. In continuation of the same, when a methanol solution of ferrocenylacetylene was exposed for a much shorter UV exposure on slightly modified reaction conditions (12–15 min, −5 °C and 8–10 mol% of $Fe(CO)_5$), two new *E/Z* isomers of methyl 3-formyl-3-ferrocenyl-2-propenoates (**3**) were isolated in average to good amount (Scheme 2).

The reaction was further optimized to obtain the best yield of these value-added regioselective organic products (Table 1). In a blank reaction, 15–30 min photolysis of ferrocenylacetylene in methanol was not able to produce the desired products (Table 1, entry 1 and 2), while 30 min photolysis of the same solution with continuous CO purging resulted in a negligible amount of previously reported[26] α,β-vinyl esters (Table 1, entry 4). On addition of $Fe(CO)_5$, the formations of two new *E/Z* isomers of retinoid ester were obtained in low yield (Table 1, entry 5). In the present reaction, methanol used as a solvent is also working as an important reagent for current transformations. During the solvent optimization, it was noted that the reaction works well for all alcohols while the transformation of retinoid is highly influenced by the nature of alcohols (Table 1, entry 5–8). Solvent optimizations have been studied further and have been discussed separately in the manuscript. The time of photolysis also played an important role for selective transformation of reaction products. Transformation of products was investigated for 3–30 min photolysis of ferrocenylacetylene in 2-propanol solvent/reagent. During the photolysis, formation of products was not detected in first 3 min (Table 1, entry 9), while 8% transformation resulted in 6 min, further 9, 12 and 15 min photolysis yielded 26, 54 and 76% retinoid esters respectively (Table 1, entry 10–12 and 7). Further photolysis of reactants significantly reduced the yield of desired products (Table 1, entry 13–14). Moreover, continuous 30 min photolysis of the reactants did not transform the desired products (Table 1, entry 15). During the optimizations of catalyst amount of $Fe(CO)_5$, it was noted that the reaction needs more than 2 mol% of $Fe(CO)_5$ (Table 1, entry 16) and increasing mol% of $Fe(CO)_5$ considerably increases the yield of products i.e. 4, 6, 8 and 10 mol% of $Fe(CO)_5$ transformed the 12, 34, 71 and 76% products respectively (Table 1, entry 17–20). Further addition of $Fe(CO)_5$ results in unwanted $Fe_2(CO)_6$ clusters of ferrocenylacetylenes[28] and also the yield of desired products decreased significantly (Table 1, entry 21).

Table 1
Optimization and formation of retinoid esters.

Entry	Solvent	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	Methanol	Nil	15[b]	nd
2	Methanol	Nil	30[b]	nd
3	Methanol	Nil	15	nd
4	Methanol	Nil	30	Nd[c]
5	Methanol	$Fe(CO)_5$ (8)	15	25
6	Ethanol	$Fe(CO)_5$ (8)	15	38
7	2-Propanol	$Fe(CO)_5$ (8)	15	76
8	*tert*-Butylalcohol	$Fe(CO)_5$ (8)	15	96
9	2-Propanol	$Fe(CO)_5$ (8)	3	nd
10	2-Propanol	$Fe(CO)_5$ (8)	6	8
11	2-Propanol	$Fe(CO)_5$ (8)	9	26
12	2-Propanol	$Fe(CO)_5$ (8)	12	54
13	2-Propanol	$Fe(CO)_5$ (8)	20	27
14	2-Propanol	$Fe(CO)_5$ (8)	25	09
15	2-Propanol	$Fe(CO)_5$ (8)	30	nd
16	2-Propanol	$Fe(CO)_5$ (2)	15	nd
17	2-Propanol	$Fe(CO)_5$ (4)	15	12
18	2-Propanol	$Fe(CO)_5$ (6)	15	34
19	2-Propanol	$Fe(CO)_5$ (8)	15	71
20	2-Propanol	$Fe(CO)_5$ (10)	15	76
21	2-Propanol	$Fe(CO)_5$ (15)	15	7[d]
22	2-Propanol	$Ru(CO)_5$ (8)	15	nd
23	2-Propanol	$Mo(CO)_6$ (10)	15	nd
24	2-Propanol	$Cr(CO)_6$ (10)	15	nd
25	2-Propanol	$W(CO)_6$ (10)	15	nd
26	2-Propanol	$Fe_2(CO)_9$ (10)	15	16
27	2-Propanol	$Fe_3(CO)_{12}$ (10)	15	nd
28	2-Propanol	$Ru_3(CO)_{12}$ (10)	15	nd
29	2-Propanol	$Os_3(CO)_{12}$ (10)	15	nd

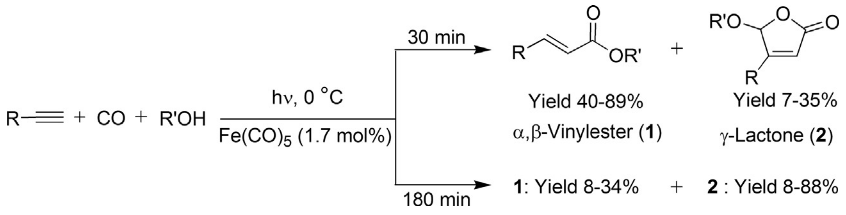
Reaction conditions: 60 mL of alcohol, 1.5 mmol of ferrocenylacetylene, −5 °C, Photolysis, 12–15 min, continuous CO purging.

[a] Yield of both the regioselective isomers.

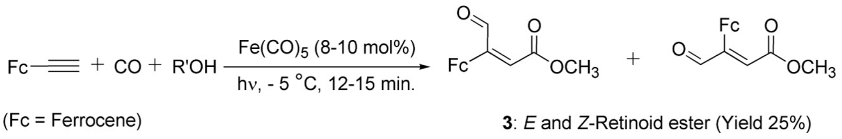
[b] In Ar/N_2atmosphere.

[c] Trace of α,β-vinyl esters obtained.

Various other monometallic carbonyl complexes $Ru(CO)_5$ and $M(CO)_6$ (M = Cr, Mo, W), and multimetalcarbonyls $M_3(CO)_{12}$ (M = Ru, Os and Fe) were screened for catalytic/stoichiometric transformations of retinoid ester, but all failed together to reproduce the



Scheme 1. Selective formation of α,β-vinyl esters and γ-lactones from terminal acetylenes, alcohols and carbon monoxide.



Scheme 2. Photolysis of ferrocenylacetylene, methanol and carbon monoxide in the presence of $Fe(CO)_5$ catalyst.