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Tetrahedron Letters 45 (2004) 3685–3687

Tetrahedron Letters

Radical reactions in esters with alkoxy functionality chemistry an unusual alcohol moiety hydrogen abstraction

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Received 8 January 2004; revised 9 February 2004; accepted 27 February 2004

Abstract—Various geometrically pure (*E*)-alkenes have been synthesized by radical substitution of alcohol moieties generated via hydrogen abstraction within ethyl esters. These reactions occurred with high regioselectivity and gave a new access to 1-methyl-3-aryl-allyl esters.

This last decade has witnessed an increased interest in the radical chemistry of β-nitrostyrenes **1**, especially in how to enlarge the diversity of functional groups belonged to the radical donors.[1] It is known from the literature that 3-aryl-allyl ester units are often used as precursors in synthesizing important fused aromatic compounds such as benzofurans, benzothiophenes.[2] In addition, these substrates are valuable for stereochemical studies on the transition metal-catalyzed allylic alkylation,[3] and they have found wide application in organic synthesis as versatile active intermediates. However, examples of radical designs for the preparation of these units have been limited. In connection with our ongoing program related to the utilities of β- nitrostyrenes **1**, we here describe an efficient synthesis of 1-methyl-3-aryl-allyl ester derivatives based on regio-, and stereoselective substitution reactions of β-nitrostyrenes **1** with simple ethyl esters using a common radical initiator—benzoyl peroxide.

It is well known that with carboxylic esters and lactones, radical hydrogen abstraction can occur either α to the carbonyl or at the alkoxy group, but generally esters have been predominately alkylated at the α-position of the acid moiety.[4] For high regioselectivities and yields at the position next to the carbonyl, esters with an additional electron-withdrawing substituent should be used. Therefore, this leads to more electrophilic radicals, which preferentially react with electron-rich alkenes.[5] Against the background presented above, we assume our starting materials (β-nitrostyrenes **1**) are electron-poor nitroalkenes and have high potential for trapping electron-rich radicals. Thus an extraordinary design for preparing 1-methyl-3-aryl-allyl esters involving the alkoxy moiety C–H abstraction followed by radical substitution is build.

First, we began our studies with the benzoyl peroxide mediated reactions shown in Eq. 1 and Table 1. When (*E*)-β-nitrostyrene **1a** was treated with 2.5 equiv of benzoyl peroxide in ethyl acetate **2f** under refluxing condition for 6 h, (*E*)-1-methyl-3-phenyl-allyl acetate **3af** was obtained as the sole product in 50% yield (Table 1, entry 1). The mechanism of this reaction is presumably similar to our previous study in the radical addition–elimination reaction of β-nitrostyrenes **1** and different alkyl radicals.[1] Initiation occurs with the alkoxy moiety C–H abstraction of **2f** with the benzoyl or phenyl radical species generated from benzoyl peroxide. The resulting radical species undergo intermolecular addition to the β-nitrostyrene **1a** followed by elimination of $NO_2\cdot$ to yield (*E*)-alkene because the product stability of (*E*)-alkene is much stable than (*Z*)-alkene in energy. In addition to (*E*)-**1a**, a series of (*E*)-nitroalkenes with various aromatic parts owning different electron demand were examined, and the results revealed the tendency toward the higher electrophilic ability of the functional group in nitroalkenes the higher reactivity of it (Table 1, entries 1–5). This phenomenon led us to believe that our starting substrates (β-nitrostyrenes **1**) were excellent

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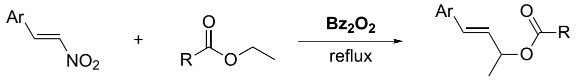
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.02.158

radical acceptors and had great capacity for trapping electron-rich radicals.



1 **2** **3**

1 , 3 **a.** Ar = Ph
b. Ar = *p*-Cl-Ph
c. Ar = *p*-MeO-Ph
d. Ar = 2-thienyl
e. Ar = 2-furyl

2 , 3 **f.** R = methyl
g. R = *iso*-propyl
h. R = *tert*-butyl

(1)

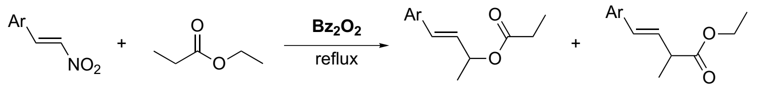
Table 1. The preparation of 1-methyl-3-aryl-allyl ester **3** from the reaction of β-nitrostyrenes **1**, ethyl ester **2**, and benzoyl peroxide under refluxing condition

Entry	**1**	**2**, R	Bz_2O_2 [equiv]	Time [h]	**3** Isolated yield [%]
1	**1a**	Methyl	2.5	6	50
2	**1b**	Methyl	2.25	6	61
3	**1c**	Methyl	2.75	6	47
4	**1d**	Methyl	2.75	6	43
5	**1e**	Methyl	2.5	6	33
6	**1a**	*iso*-Propyl	2.5	6	55
7	**1b**	*iso*-Propyl	2.25	6	69
8	**1c**	*iso*-Propyl	2.5	6	49
9	**1d**	*iso*-Propyl	2.5	5	48
10	**1e**	*iso*-Propyl	2.5	5	33
11	**1a**	*tert*-Butyl	2.5	5	60
12	**1b**	*tert*-Butyl	2.25	6	74
13	**1c**	*tert*-Butyl	2.75	5	48
14	**1d**	*tert*-Butyl	2.5	5	50
15	**1e**	*tert*-Butyl	2.5	5	33

In view of the above results, we decided to examine generality of this radical NO_2-substitution procedure, by replacing **2f** with other esters **2**, since the acetic acid moiety can be introduced first, increasing the likelihood that the chemistry of the new introduced acid moiety in **2** can be analyzed (Table 1, entries 6–15). Ethyl isobutyrate **2g** and ethyl trimethylacetate **2h** were chosen as readily available models for this purpose. As expected, not only similar products were obtained from these two bulkier esters, but NO_2-substitution with them were also found to proceed slightly efficiently than **2f** without loss of configurational integrity at the double bond as indicated by their yields. The success of these two reactions could be attributed to the fact that the boiling points of these two esters are higher than that of **2f**, thus facilitating the hydrogen abstraction and NO_2-substitution reaction; moreover, the increase of alkyl groups on the acid moiety would inhibit the hydrogen abstraction α to the carbonyl group and promote the opportunities of abstraction at the alkoxy moiety.

After successfully establishing the desired C–H abstraction preferentially on alkoxy moiety, attention was given to the difference between the alkoxy and acid moiety in regioselectivity. It is well known that the degree of the carbon radical center always plays important roles in different radical reactions. To study this selectivity for more precisely, the substrates, which generate radical centers with equal degree (‘secondary’ radicals) must be employed. Toward this purpose, we decided to investigate in more detail the reactions with the ester **4** in similar conditions (Eq. 2). As shown, products **6** were obtained as minor products together with the predicted products **5** in moderated yields. Not beyond our expectations, no matter what kind electron demand of substituents in the benzene ring the C–H abstraction at the alkoxy moiety always slightly predominated over the acid moiety. At this stage, we believe the nature of nitroalkenes **1** are mainly influenced by the NO_2-group, making these substrates good electron-rich radical trappers.

To expand the versatility and synthetic value of the reaction for the preparation of geometrically pure (*E*)-styryl esters, we used the conditions resembled in Eq. 2 to examine substitutions of the NO_2-group with the other ester containing longer alkoxy chain (Eq. 3).

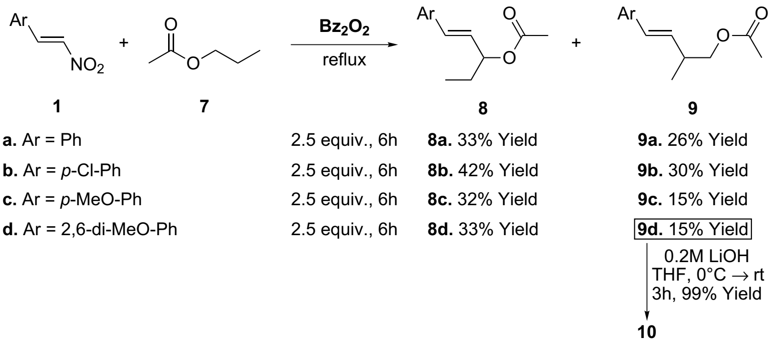


1 **4** **5** **6**

a. Ar = Ph	2.5 equiv., 5h	**5a.** 37% Yield	**6a.** 33% Yield
b. Ar = *p*-Cl-Ph	2.25 equiv., 5h	**5b.** 39% Yield	**6b.** 31% Yield
c. Ar = *p*-MeO-Ph	2.5 equiv., 5h	**5c.** 27% Yield	**6c.** 24% Yield

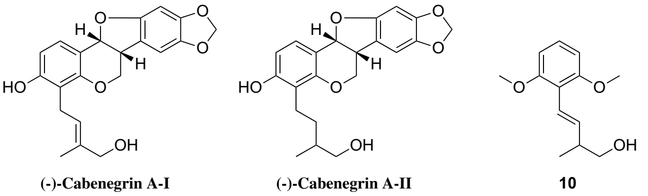
(2)

Not only the reaction of the ethyl ester proceeded in nice yields, but also that of the propyl ester resulted in good yields. The reaction of β-nitrostyrene **1a** and propyl acetate **7** in analogous conditions gave the corresponding propyl acetate derivative isomers **8a** as well as unexpected **9a** in 33% and 26% yields, respectively (Eq. 3). This special type of regioselectivity about the C–H functionalized radical reaction of ester was never seen before,[6] and we presumed that it resulted from the reasons: [1] the difference in the rate of hydrogen abstraction on the alkoxy moiety between α- and β-positions to oxygen; [2] the preeminent radical trapping ability of β-nitrostyrenes **1**. Owing mainly to the excellent electron-rich radical trapping ability of our acceptors as mentioned above, once a radical formed (no matter α- or β-radicals) after hydrogen abstraction, it added to the very reactive β-nitrostyrenes **1**, so that the regioselectivity of hydrogen abstraction process led to the present selectivity of the reactions. On the other hand, the β-hydrogen abstraction rate factor was so small in ethyl ester **2** series that we cannot observe any β-products in the crude GC–MS analysis.



a. Ar = Ph	2.5 equiv., 6h	**8a.** 33% Yield	**9a.** 26% Yield
b. Ar = *p*-Cl-Ph	2.5 equiv., 6h	**8b.** 42% Yield	**9b.** 30% Yield
c. Ar = *p*-MeO-Ph	2.5 equiv., 6h	**8c.** 32% Yield	**9c.** 15% Yield
d. Ar = 2,6-di-MeO-Ph	2.5 equiv., 6h	**8d.** 33% Yield	**9d.** 15% Yield

(3)



(-)-Cabenegrin A-I **(-)-Cabenegrin A-II** **10**

Scheme 1.

Pterocarpans are naturally occurring plant products carrying a *cis*-fused benzofuranyl-benzopyran ring system, and many of them exhibit various biological effects, most particularly antifungal, antibacterial, and anti-HIV activity.[7] In 1982, Darko had demonstrated that two representatives of these natural products, cabenegrin A-I and A-II (Scheme 1) are the active components of a Brazilian folk medicine used against snake venoms.[8] Although the pharmacophore of these two molecules and the synthetic route to some structural analogues were established by Gulacsi and co-workers, the yields of these multistep procedures are too low to be suitable for industrial production: for instance, the structural analogue **10** possessing similar inhibitory effects to cabenegrin A-I on the LPS-induced TNF-α production in the plasma because of carrying a phenylbutenol side chain with *E*-geometry was prepared only in trace yield after five steps (less than 3%).[9]

The above results[10] prompted us to investigate the synthesis of **10** via propyl acetate mediated substitution and subsequent hydrolysis of the resulting β-form ester **9d** based on the present methodology (Eq. 3). Then, a simple two-steps procedure has been developed in which 4-(2,6-dimethoxy-phenyl)-2-methyl-but-3-en-1-ol **10** was synthesized from cheap and easily accessible materials in greatly increasing yield by comparison.

In conclusion, we demonstrated a variety of simple alkyl esters were regioselectively and stereoselectively converted to (*E*)-styryl esters by the reaction with β-nitrostyrenes **1** in the presence of a common radical initiator—Bz_2O_2. Further studies on the application of this method to synthesize other valuable compounds are under investigation.

Acknowledgements

Financial support of this work by the National Science Council of the Republic of China is gratefully acknowledged.

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10. General procedure for the reaction of esters with β-nitrostyrene—preparation of (*E*)-**3af**, (*E*)-1-methyl-3-phenyl-allyl acetate: β-Nitrostyrene **1a** (149.2 mg, 1.0 mmol) and benzoyl peroxide (605.6 mg, 2.5 mmol) were placed in ethyl acetate **2f** (10 mL). The mixture was stirred for 5 h under refluxing condition and then concentrated in vacuo. After the solvent evaporated, the residue was purified by column chromatography on silica gel and yielded the desired product (*E*)-**3af** in 50% yield.