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A Simple Radical Addition−Elimination Route to Geometrically Pure (*E*)-Alkene and Chromanone Derivatives via *β*-Nitrostyrene

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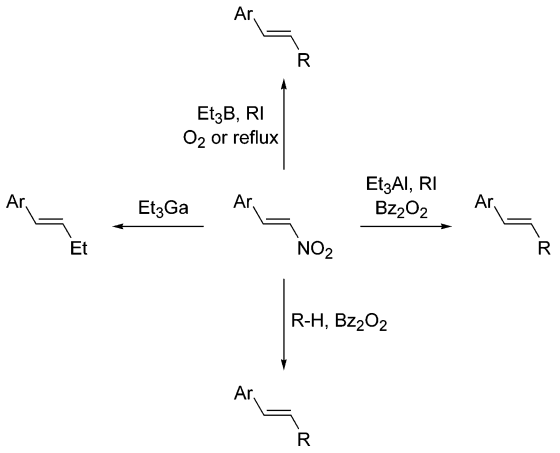
Abstract: Various geometrically pure (*E*)-*β*-alkyl-styrenes have been synthesized by the radical NO_2 substitution of alkyl moieties generated via hydrogen abstraction followed by decarbonylation from aliphatic aldehydes. These reactions, which involve a high chemical selectivity and regioselectivity constitute a new route to (*E*)-*β*-alkylstyrenes. Both aliphatic and aromatic aldehydes can be used in this novel reaction. When 2-allyloxybenzaldehyde was used, the benzoyl radical added directly to the double bond without decarbonylation to give the 3-cinnamylchroman-4-one. This unique difference between aliphatic and aromatic aldehydes represents a simple route for the synthesis of biologically important chromanones.

(*E*)-*β*-Alkylstyrenes are important industrial compounds and are useful intermediates in organic synthesis. A variety of protocols are available for their preparation from (*E*)-*β*-nitrostyrenes **1**. The four major radical addition−elimination methods that are typically used to prepare (*E*)-*β*-alkylstyrenes each utilize a different source for the alkyl radical species R•. An alkyl radical species R• can be produced by the deiodonation of alkyl iodides by ethyl radicals, generated from triethylborane.[1a,b] This type of ethyl radical can also be induced by the reaction of triethylaluminum with benzoyl peroxide.[1c−e] A third method involves the abstraction of hydrogen from alkanes with benzoyl peroxide.[1f] Finally, similar to the other two Group 13 elements mentioned above, triethylgallium can be employed to generate ethyl radicals (Scheme 1).[1g] One of the disadvantages of Scheme 1 is that a large excess of alkyl iodides must be used to suppress competition by ethyl radicals, and the lower molecular weight alkanes are gases, making their use in general laboratory processes inconvenient. In connection with our ongoing program directed at the use of (*E*)-*β*-nitrostyrenes **1**, we herein describe a facile and practical method for producing (*E*)-*β*-alkylstyrenes and 3-cinnamylchromanone, the details of which have not been reported previously.[2]

SCHEME 1



In our continuing effort to understand the origin of (*E*)-selectivity, we recently reported on a range of radical sources that can be used in radical substitution reactions with (*E*)-*β*-nitrostyrenes **1**.[1a−f] Our previous findings indicate that (*E*)-*β*-nitrostyrenes **1** are good radical acceptors and react with alkyl radicals from different sources to generate (*E*)-alkenes under a variety of conditions and the reaction mechanism appears to involve a free-radical addition−elimination reaction.[1b] In this paper, we wish to report on a modified and effective method, based on our previous studies, for the synthesis of a number of (*E*)-alkenes via the reaction of (*E*)-*β*-nitrostyrenes **1** with various alkyl radicals, generated by the α-fragmentation of an acyl radical.

The chemistry of acyl radicals has a long history that can be traced back to the early part of the last century.[3] Nevertheless, the application of acyl radicals in current organic synthesis, such as addition reactions of acyl radicals and olefins, has lagged behind that of simple alkyl and even vinyl radicals until relatively recently. The first radical aldehyde−olefin addition compounds described in the literature were reported by Kharasch and co-workers.[4] The method employed by these authors involved treatment of an aldehyde with the inconvenient radical initiator, acetyl peroxide. However, they specifically state that, to prepare these adducts, certain conditions must be met. Thus, to prepare addition products in acceptable yields it is necessary to start with both long-chained aldehydes and alkyl alkenes. In part, this must be due to the difficulty in abstracting the aldehydic hydrogen atom by the nucleophilic *β*-oxocarbon radicals that result from the hydroacylation of simple alkenes with aldehydes.[5] Nevertheless, in the past decade, this field has expanded enormously. A number of polarity-reversal catalysts, such as *N*-hydroxyphthalimide and methyl thioglycolate, have been reported and these advances have particularly focused on the hydroacylation

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TABLE 1. Benzoyl Peroxide Mediated Radical Substitution of Nitroolefin 1 with Secondary or Tertiary Alkyl Aldehyde 2

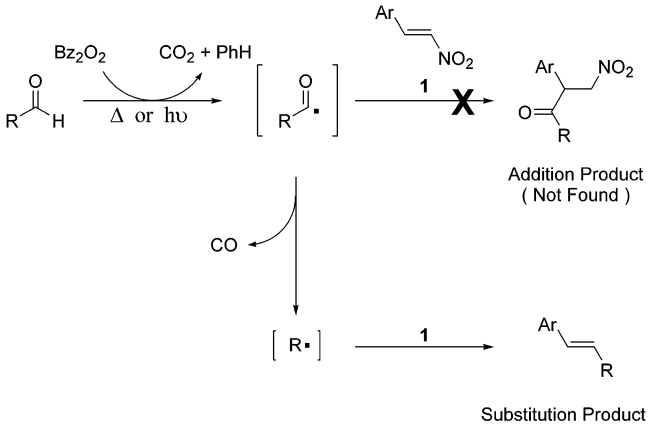
entry	1 (equiv)	2 (equiv)	Bz_2O_2 (equiv)	solvent	time (h)	3	yield (%)[a] under reflux	yield (%)[a] under UV[b]
1	**1a** (1.0)	**2f** (5)	2.5	benzene	5	**3af**	79	44
2	**1b** (1.0)	**2f** (5)	3	benzene	6	**3bf**	84	62
3	**1c** (1.0)	**2f** (5)	2.5	benzene	8	**3cf**	38	19
4	**1d** (1.0)	**2f** (5)	2.5	benzene	3	**3df**	40	34
5	**1e** (1.0)	**2f** (5)	2.75	benzene	4	**3ef**	56	46
6	**1a** (1.0)	**2g** (5)	2.75	benzene	6	**3ag**	68	22
7	**1b** (1.0)	**2g** (5)	2.75	benzene	6	**3bg**	71	28
8	**1c** (1.0)	**2g** (5)	2.5	benzene	6	**3cg**	39	15
9	**1d** (1.0)	**2g** (5)	2.5	benzene	4	**3dg**	41	10
10	**1e** (1.0)	**2g** (5)	2.5	benzene	4	**3eg**	55	17
11	**1a** (1.0)	**2h** (5)	2.5	benzene	6	**3ah**	51	5
12	**1b** (1.0)	**2h** (5)	2.5	benzene	5	**3bh**	63	15
13	**1c** (1.0)	**2h** (5)	2.5	benzene	6	**3ch**	NR	NR
14	**1d** (1.0)	**2h** (5)	2.5	benzene	4	**3dh**	NR	NR
15	**1e** (1.0)	**2h** (5)	2.5	benzene	4	**3eh**	NR	NR
16	**1a** (1.0)	**2i** (5)	2.25	benzene	4	**3ai**	80	83
17	**1b** (1.0)	**2i** (5)	2.25	benzene	5	**3bi**	89	89
18	**1c** (1.0)	**2i** (5)	2.5	benzene	5	**3ci**	45	46
19	**1d** (1.0)	**2i** (5)	2.25	benzene	6	**3di**	51	54
20	**1e** (1.0)	**2i** (5)	2.5	benzene	7	**3ei**	62	59
21	**1a** (1.0)	**2j** (5)	2.5	benzene	6	**3aj**	NR	NR
22	**1a** (1.0)	**2k** (5)	2.5	benzene	6	**3ak**	NR	NR
23	**1a** (1.0)	**2*l*** (5)	2.5	benzene	6	**3a*l***	NR	NR

[a] Isolated yield. [b] UV photolysis was used to initiate the radical process as described in ref 8.

of electron-rich alkenes with aldehydes.[5,6] In contrast, if the alkene contains an electron-withdrawing group, this reaction proceeds smoothly because of the ease of abstracting the aldehydic hydrogen by an electrophilic radical. For example, Neckers reported that the addition of aldehydes to methyl crotonate using *tert*-butyl *p*-benzoylperbenzoate as an initiator produced the corresponding ketones in low to medium yields.[7] According to these authors, it is important that reactions of the electron-poor alkenes, (*E*)-*β*-nitrostyrenes **1**, and aldehydes have not been studied before. This fact prompted us to investigate whether NO_2 substitution or acyl radical addition would be the preferred pathway when these electron-poor alkenes are used as radical acceptors. Details of this chemical selectivity are more fully discussed below.

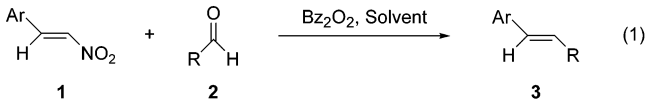
In an initial experiment, (*E*)-*β*-nitrostyrene **1a** was treated with 5 equiv of isobutyraldehyde **2f** and 2.5 equiv of benzoyl peroxide in benzene under reflux for 5 h. To our surprise, (*E*)-**3af** was obtained as the sole product in 79% yield (Table 1, entry 1), and none of the (*Z*)-isomer or acyl-adduct was detected in the crude product. Although acyl radicals are nucleophilic, they do not appear to react with this electrophilic radical acceptor, probably because of the slow acyl radical addition to the C=C bond. Competitive α-fragmentation of the acyl radicals occurs to give alkyl radicals as the major reactive intermediates, which are indeed nucleophilic in nature and were shown to readily react with (*E*)-*β*-nitrostyrenes **1** in our previous studies.[1a−f] In an attempt to verify this viewpoint, benzaldehyde was used in a control experiment under

SCHEME 2



conditions identical with those used to prepare (*E*)-**3af**. Again, none of the benzoyl-adduct or alkene was generated even though the decarbonylation of benzoyl radicals is very slow due to the high resonance energy of the free benzoyl radicals.[4] Therefore, this provides evidence that acyl radicals cannot add to our substrates and that the only pathway for the reactions of acyl radicals and our substrates was substitution, and not addition. Consequently, excellent chemical selectivity can be realized by using this method (Scheme 2).

Similarly, the reaction of **2f** with (*E*)-*β*-nitrostyrene containing an electron-withdrawing group **1b** (Table 1, entry 2) gave the corresponding (*E*)-**3bf** in high yield. On the other hand, the reaction of (*E*)-*β*-nitrostyrene containing an electron-donating group **1c** (Table 1, entry 3) with benzoyl peroxide under analogous reaction conditions led to a decreased yield, which we attribute to the decreased reactivity of (*E*)-*p*-methoxy-*β*-nitrostyrene **1c** due to the electron-donating ability of the methoxy group. In the next two cases (Table 1, entries 4 and 5), the category of substrates was expanded to survey the scope of this reaction. Not surprisingly, low to medium yields were obtained when heteroaromatic substrates **1d**,**e** were used, largely due to the instability of the products. Thus, a practical and efficient methodology has been developed for the synthesis of (*E*)-*β*-alkylstyrenes **3** from nitroalkenes **1** in relative ease. One of the advantages of this protocol is the positive molecular economics, compared with methods in which a large excess of alkyl iodides or alkanes are used,[1] and the excellent chemical and geometrical selectivities are impressive and valuable. In addition, when a number of other secondary and tertiary alkyl aldehydes were used in this method, the reactions proceeded smoothly and the same selectivities were maintained.



1 **2** **3**

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

2, 3 **f.** R = *iso*-propyl; **g.** R = cyclohexyl; **h.** R = 3-cyclohexenyl; **i.** R = *tert*-butyl; **j.** R = ethyl; **k.** R = butyl; **l.** R = hexyl

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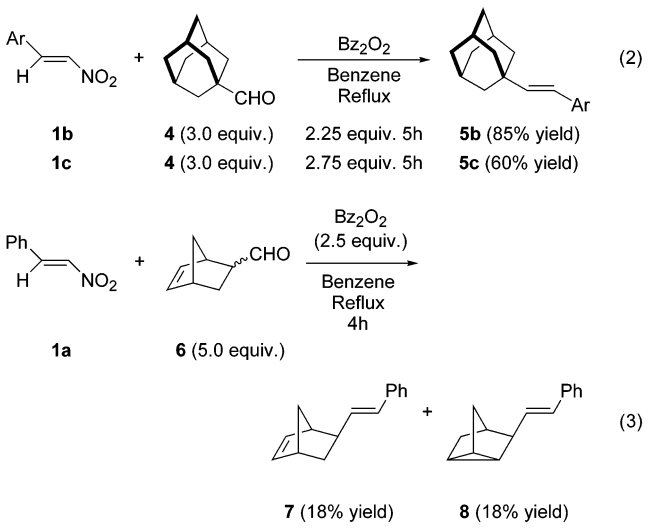
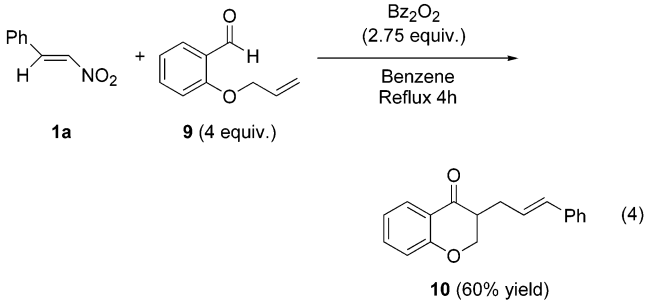
Radical reactivity and stability always play important roles and complement each other in different radical reactions. When other alkyl groups, R, in aldehydes **2** were used, the results were different from that obtained for isobutyraldehyde **2f**. A tendency in which the higher the degree of the radical center the higher its reactivity was observed. For example, the *tert*-butyl radical reacted more efficiently with (*E*)-*β*-nitrostyrenes **1** than isopropyl, cyclohexyl, 3-cyclohexenyl, and norborn-5-en-2-yl radicals (Table 1, entries 16−20, eq 3). It appears that isopropyl and cyclohexyl radicals have approximately the same reactivities and radicals having a double bond at the *β*-position react unfavorably (Table 1, entries 11−15, eq 3). Unfortunately, none of the predicted alkenes was detected in a control experiment when three other primary aldehydes **2j**−***l*** were reacted with (*E*)-*β*-nitrostyrene **1a** (Table 1, entries 21−23). On the basis of Kharasch's experiments,[4] acyl radicals of primary aliphatic aldehydes could be induced, especially in the case of **2*l***, hence the abstraction of the aldehydic hydrogen atom by an initiator is achievable. In other words, it appears that decarbonylation was the problem, which may explain why the use of primary aldehydes was not successful in the reactions.



Alternatively, if UV photolysis[8] was used to initiate the radical process instead of heat, the overall yields of the reaction under the same stoichiometric conditions were decreased in the case of the secondary aldehyde series but were nearly equivalent in the tertiary series (Table 1). On the basis of literature reports,[3] acyl radical fragmentations to form tertiary alkyl radicals are rapid processes even at room temperature. Thus, at least for acyl radicals leading to stabilized C-radicals, α-fragmentation should not be a problem. This led us to suspect that secondary photolysis occurred. It is likely that the product aryl alkene would compete for the absorption of light as it is produced, which would lead to the formation of secondary photoproducts and decreased yields. As a result, all further reactions were conducted under refluxing conditions.

In an extension of our study of the chemistry of alkyl compounds, we investigated the issue of whether aromatic aldehydes could be employed in the synthesis of biologically active compounds using the above strategy. Benzopyran compounds, in a variety of forms, are widespread in the plant kingdom, and many are biologically active.[9] Herein, we provide an improved, easy, and efficient method for the preparation of 3-substituent-1-benzopyran-4-ones (chromanones) by means of direct ring synthesis.[10]

The findings herein show that moderate yields of 3-cinnamylchroman-4-one **10** can be produced by refluxing a mixture of 2-allyloxybenzaldehyde **9** (4 equiv), (*E*)-*β*-nitrostyrene **1a**, and benzoyl peroxide (2.75 equiv) in benzene for 4 h (eq 4).



In conclusion, we demonstrate herein that aldehydes are valuable for the functionality of (*E*)-*β*-nitrostyrenes **1**. This technically simple, radical induced, addition−elimination sequence occurs in a highly chemical-selectively, regioselectively, and stereoselectively manner and provides a new route to the synthesis of biologically active compounds.

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Supporting Information Available: General experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The photochemical reaction was carried out in a benzene solution in a quartz tube using a Rayonet reactor (253.7 nm) at room temperature (23 °C).

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