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Substitution of β-nitrostyrenes by electrophilic carbon-centered radicals

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Abstract—Various *trans*-β-alkylstyrenes (55–90% yield) were isolated from the free radical addition/elimination process of α-iodocarboxylic acid derivatives with β-nitrostyrenes using dilauroyl peroxide as initiator. The corresponding xanthates give low yields of the alkene under similar conditions.
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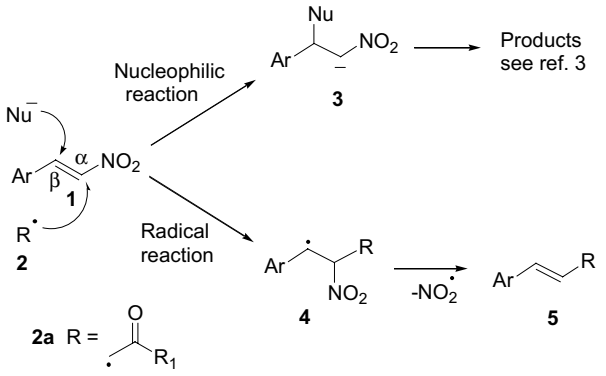
The development of practical methods for intermolecular carbon–carbon bond formation is of great interest since such new strategies can greatly facilitate the synthesis of complex molecular structures. In this context, the radical vinylation of alkyl radicals has emerged as a powerful synthetic tool, with the sulfone moiety being the most explored functional group for this purpose.[1] β-Nitrostyrenes are very important synthetic intermediates, which can be used in the construction of a wide variety organic compounds.[2] Due to the strong electron-withdrawing property of the nitro group, conjugated nitroalkenes are excellent Michael acceptors, and many classes of compounds have been prepared through this process.[3] Yao and co-workers[4] have recently reported the Et_3B-mediated radical reaction of alkyl iodides with nitrostyrenes to generate alkenes. In this reaction the nitro group is substituted by an alkyl moiety through attack of the radical α to the nitro group followed by the loss of NO_2 from the radical **4** so obtained (Scheme 1).[5] Thus, while nucleophilic additions occur at the β-site of the nitrostyrene, the corresponding radical reaction takes place at the α-carbon. Whereas the addition of nucleophilic radicals to nitrostyrenes has been well studied, no information exists regarding the corresponding process using electrophilic radicals (e.g., the α-acetyl radical **2a**).



Scheme 1. Radical and nucleophilic reactions of nitrostyrenes.

In this preliminary report we demonstrate that under dilauroyl peroxide (DLP) mediated radical conditions, the intermolecular substitution of various β-nitrostyrenes by electrophilic carbon-centered radicals can be effected in preparatively useful yields.

The utility of (DLP) as a cheap and efficient initiator of radical reactions has been amply demonstrated not only in xanthate based processes[6] but also commencing from α-iodocarboxylic acid derivatives, in both the inter- and intra-molecular modes.[7]

The xanthate **8** and the iodide **9**, required for this study, were synthesized in good yield from the corresponding chloride as shown in Scheme 2.

Keywords: Radicals; Nitrostyrenes; Xanthates; Substitution.
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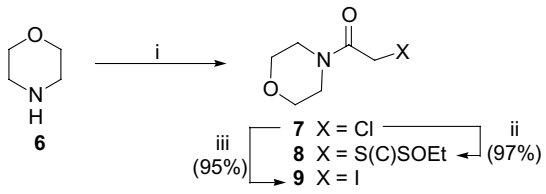


Scheme 2. Synthesis of radical precursors. Reagents and conditions: (i) $ClCH_2COCl$, Et_3N, CH_2Cl_2, rt, 2 h; (ii) $EtOC(S)S^-K^+$, CH_3CN, rt; (iii) NaI, acetone, rt, 3 h.

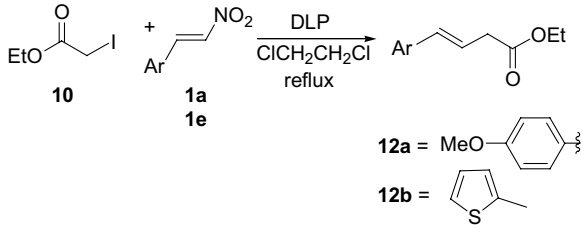
Initial experiments were carried out using the xanthate **8** (Scheme 3). Thus, portionwise addition of DLP (1.8 equiv, over 15 h) to a boiling solution of the nitrostyrene **1a** (2 equiv) and xanthate **8** in 1,2-dichloroethane (2 mL/mmol), lead to substitution of the nitro group and furnished **11a**. In these experiments, we observed that the reaction ceased after addition of only part (~0.7 equiv) of the required DLP and the desired product was isolated in low to moderate yield along with considerable starting material **1a** (Table 1, entries 1–3). Further addition of peroxide (2 equiv) resulted in only slightly higher product yields and the starting material was still not consumed. Reactions using toluene and benzene as the solvent gave similar results. The nature of this presumed inhibition is not understood, but it caused us to turn our attention to the corresponding iodides as the radical source.[8] Thus, reaction of iodide **9** with **1a** gave the expected *trans*-β-alkylstyrene in good yield in a cleaner reaction under the above-described conditions (Scheme 3). The nitrostyrenes **1b–e** also reacted with iodide **9** providing the alkylstyrenes **11b–e** in moderate to good yields (Table 1, entries 4–8). Similarly **12a** and **b** were isolated in good yields in the reaction of ethyl iodoacetate **10** with the nitrostyrenes **1b** and **e**, respectively (Scheme 4, Table 1, entries 9 and 10).

It is noteworthy that the best product yields were obtained from those nitrostyrenes bearing electron-releasing groups in the aryl moiety (Table 1, entries 5 and 7). The α-carbon of the nitrostyrene is electronically

Table 1. Free radical addition/elimination process on β-nitrostyrenes using dilauroyl peroxide as initiator[a]

Entry	Nitrostyrene	Radical precursor	Product	Yield (%)
1	**1a**	**8**	**11a**	42
2	**1b**	**8**	**11b**	35
3	**1c**	**8**	**11c**	29
4	**1a**	**9**	**11a**	67
5	**1b**	**9**	**11b**	75
6	**1c**	**9**	**11c**	40
7	**1d**	**9**	**11d**	90
8	**1e**	**9**	**11e**	60
9	**1b**	**10**	**12a**	70
10	**1e**	**10**	**12b**	70

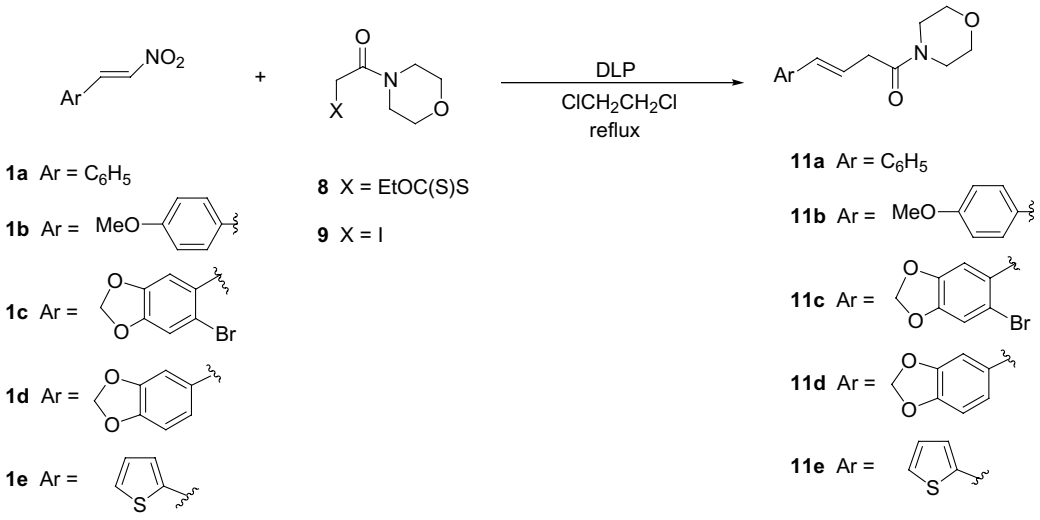
[a] The reaction was conducted under deaerated atmosphere.



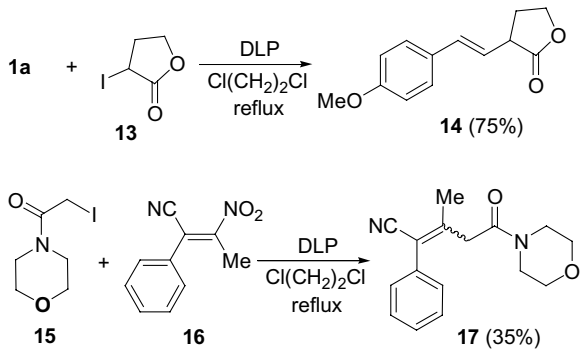
Scheme 4.

affected by the nature of the group on the aromatic system. In the present case, electron-releasing groups give rise to a polarity-matched combination with an electrophilic radical such as **2a**, whereas reaction at the β-carbon would generate an unfavorable polarity-mismatched combination.[9] The presence of a bromine atom in the *ortho* position of **1c** resulted in a lower product yield (Table 1, entry 6).

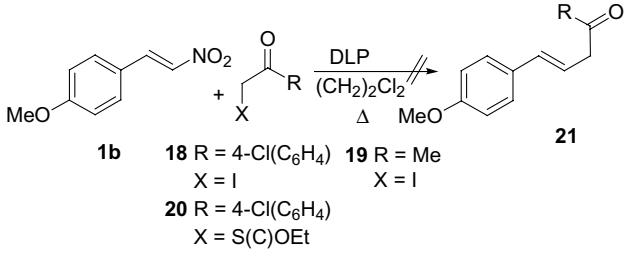
The secondary radical derived from **13** also reacted with **1a** to efficiently produce **14**. Surprisingly, however, the fully substituted nitrostyrene **16** was not a good substrate for the radical derived from**15** (Scheme 5), pro-



Scheme 3. Substitution of β-nitrostyrenes by electrophilic carbon-centered radicals.



Scheme 5.



Scheme 6. Free radical addition/elimination process of α-iodoacetone with β-nitrostyrene.

ducing the expected olefin **17** in low yield as an inseparable 3:1 mixture of the *E* and *Z* isomers. This result may well be explicable as another example of a polarity-mismatched situation.

So far, attempts to extend the process to the α-keto radicals derived from the iodides **18** and **19** or the xanthate **20** and the β-nitrostyrene **1b**, have failed. The thermally sensitive iodides decompose under the reaction conditions while the xanthate produces complex mixtures not containing the expected enone **21** (Scheme 6).

In closing, we have demonstrated that the substitution of β-nitrostyrenes by appropriate electrophilic carbon-centered radicals, mediated by DLP, can be effected in preparatively useful yields. The process has the distinct advantage of using near stoichiometric quantities of the reagents, in contrast to the related Et_3B method.[4] The results also once again demonstrate the synthetic potential of nitrostyrenes in radical vinylation reactions, and the products have considerable synthetic potential for the synthesis of even more complex molecular entities. Work along these lines is underway.

Acknowledgements

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8. *Typical experimental procedure*: To a deaerated solution of the iodide (1 mmol) and nitrostyrene (2 mmol) in refluxing 1,2-dichloroethane (2 mL/mmol), dilauroyl peroxide (1.8 mmol) was added portionwise over a 15 h period. The reaction was monitored by TLC. The solvent was removed under reduced pressure and the crude residue purified by chromatography on a silica gel column (ethyl acetate/hexane) to furnish the desired product. *Selected spectroscopic data:* **11a** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.31 (dd, $J = 1.0$, 6.3 Hz, 2H), 3.53–3.7 (m, 8H), 6.31 (dt, $J = 6.0$, 15.8 Hz, 1H), 6.49 (d, $J = 16.0$ Hz, 1H), 7.22–7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 136.8, 133.0, 128.5, 127.6, 126.2, 122.6, 66.8, 66.6, 46.3, 42.0, 37.7. IR (cm^{-1}) ν: 2966, 2920, 1632,1436, 1113. MS (EI) $m/z = 114$ (100%; M^+), 231 (56% M^+). **11b** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.28 (dd, $J = 1.4$, 6.7 Hz, 2H), 3.49–3.70 (m, 8H), 3.80 (s, 3H), 6.16 (dt, $J = 6.7$, 16.1 Hz, 1H), 6.42 (d, $J = 15.8$ Hz,

1H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.29 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 159.2, 132.3, 129.6, 127.3, 120.3, 113.9, 66.9, 66.7, 55.2, 46.3, 42.0, 37.7. IR (cm^{-1}) v: 2927, 2858, 1636, 1607, 1511, 1115. MS (EI) $m/z = 147$ (100%; M^+), 261 (61% M^+). **11c** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.32 (dd, $J = 1.4$, 6.6 Hz, 2H), 3.50–3.71 (m, 8H), 5.97 (s, 2H), 6.13 (dt, $J = 6.6$, 15.8 Hz, 1H), 6.72 (dt, $J = 1.6$, 15.8 Hz, 1H), 6.98 (s, 1H), 7.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 147.8, 147.6, 131.4, 130.0, 124.1, 114.2, 112.4, 106.3, 101.7, 66.7, 46.2, 42.0, 37.6. IR (cm^{-1}) v: 3002, 2967, 2917, 2859, 1640, 1497, 1470, 1239, MS (EI) $m/z = 355$ (M^++2) 353 (M^+, 5%), 274 (100%). **11d** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.27 (dd, $J = 1.4$, 6.8 Hz, 2H), 3.51–3.66 (m, 8H), 5.95 (s, 2H), 6.13 (dt, $J = 6.6$, 15.8 Hz, 1H), 6.39 (d, $J = 15.8$ Hz, 1H), 6.71–6.81 (m, 2H), 6.91 (d, $J = 1.2$ Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): IR (cm^{-1}) v: 2971, 2925, 2860, 1636, 1445, 1115. MS (EI) $m/z = 131$(100%; M^+), 275 (95% M^+). **11e** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.27 (dd, $J = 1.6$, 6.8 Hz, 2H), 3.53–3.70 (m, 8H), 6.14 (dt, $J = 6.7$, 15.6 Hz, 1H), 6.61 (dt, $J = 1.6$, 15.6 Hz, 2H), 6.90–6.97 (m, 2H), 7.12–7.15 (dd, $J = 1.6$, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 141.7, 127.2, 126.1, 125.3, 124.1, 122.1, 66.7,46.3, 42.1, 27.5. IR (cm^{-1}) v: 2855, 1646, 1436, 1115. MS (EI) $m/z = 237$ (100%; M^+). **12a** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.28 (t, $J = 7.0$ Hz, 3H), 3.22 (dd $J = 1.2$, 7.0 Hz, 2H), 3.80 (s, 3H), 4.16 (q, $J = 7.0$ Hz, 2H), 6.15 (dt, $J = 7.2$, 15.8 Hz, 1H), 6.43 (d, $J = 15.8$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.31 (d, $J = 6.6$ Hz, 2H). IR (cm^{-1}) v: 2926, 2854, 1735, 1608, 1512, 1250. MS (EI) $m/z = 220$ (100%; M^+). **14** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.15–2.28 (m, 1H), 2.43–2.53 (m, 1H), 3.29–3.38 (m, 1H), 3.74 (s, 3H), 4.18–4.26 (m, 1H), 4.32–4.39 (m, 1H), 6.03 (dd, $J = 6.6$, 16.0 Hz, 1H), 6.44 (dd, $J = 1.3$, 16.0 Hz, 1H), 6.78 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.5, 159.4, 132.8, 129.0, 127.6, 121,6, 113.9, 66.6, 55.2, 42.7, 29.2. IR (cm^{-1}) v: 2926, 2855, 1771, 1718, 1607, 1512, 1252. MS (EI) $m/z = 218$ (100%; M^+). **17** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.03 (s, 2.25H), 2.33 (s, .75H), 3.22 (s, .5H), 3.51–3.73 (m, 8H), 4.06 (s, 1.5H), 7.31–7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2, 166.9, 151.9, 151.4, 133.6, 133.3, 129.0, 128.8, 128.7, 128.6, 118.3, 113.9, 66.8, 66.6, 66.5, 66.3, 46.7, 46.3, 46.0, 42.2, 40.5,38.8, 29.3, 23.4, 20.5. IR (cm^{-1}) v: 2955, 2920, 2853, 2210, 1650, 1441, 1116. MS (FAB+) $m/z = 271$ (100%; M^++1).

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