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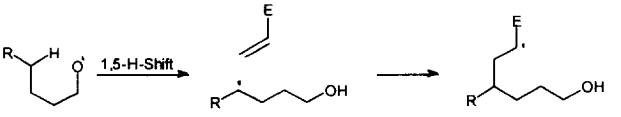
Free Radical Alkylation of the Remote Nonactivated δ-Carbon Atom

Goran Petrović and Živorad Čeković*
Faculty of Chemistry, University of Belgrade, Studentski trg 16, 11001 Belgrade, Serbia, Yugoslavia

Abstract: A free radical introduction of functionalized alkyl chains into the δ-carbon atom (Michael type alkylation) of alkyl nitrites and alkyl benzenesulfenic-O-esters was achieved.

The introduction of a functionalized alkyl chain into remote non-activated carbon atoms is of great synthetic importance. There are several known free radical reactions for the introduction of functional groups into remote non-activated carbon, such as photolysis of alkyl nitrites,[1] lead tetraacetate oxidation of saturated alcohols,[2] and related reactions involving alkoxy,[3] nitrogen[4] or other radical intermediates. The key step in all of these reactions is a 1,5-hydrogen migration from the non-activated carbon to the alkoxy radical[2] **1**. In some of these reactions δ-carbon radicals, generated by 1,5-transposition of the radical center, were intercepted by ligand or electron transfer oxidants and δ-substituted or δ-unsaturated alcohols were obtained, respectively.[5] δ-Carbon radicals possessing an appropriately disposed olefinic bond, formed by the Barton reaction, undergo 5-*exo*-cyclization thus affording the corresponding cyclopentane derivatives[6a] or δ-alkyl radicals undergo intramolecular 3-*exo*-addition to the adjacent keto group giving rearranged products.[6b] δ-Carbon radicals, formed in the lead tetraacetate oxidation of alcohols reacted with carbon monoxide to form δ-lactones.[6c]

We examined the addition of δ-carbon radicals **2**, formed by 1,5-hydrogen migration in alkoxy radical **1**, to electron deficient olefinic bonds. Herein we report a Michael type alkylation of the remote non-activated carbon atom to form radical **3** (Scheme 1, E is an electron withdrawing

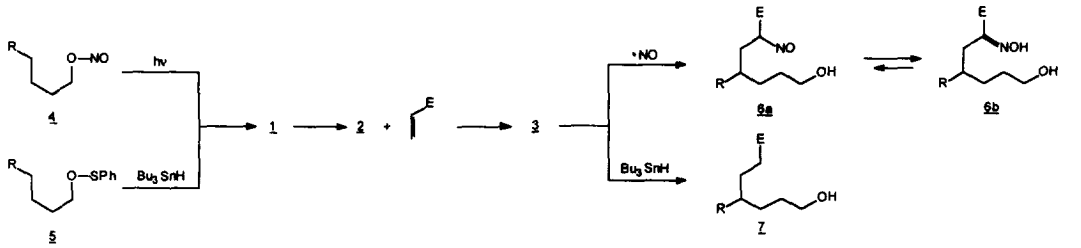


1 2 3

Scheme 1.

group). The introduction of a radicophilic olefin onto the δ-carbon atoms was expected to occur by the following sequence of radical reactions: i) generation of an alkoxy radical, ii) 1,5-hydrogen migration, iii) intermolecular addition to the radicophilic olefin, and iv) termination step (depending on the alkoxy radical precursor and reaction conditions).

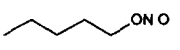
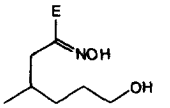
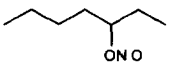
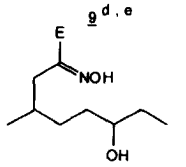
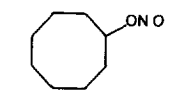
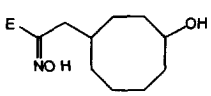
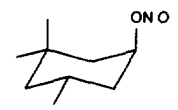
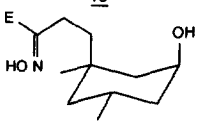
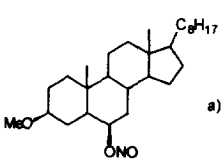
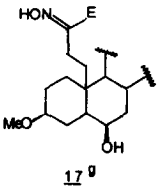
Alkoxy radicals **1**, generated by photolysis of alkyl nitrites **4**, or by reduction of O-alkyl benzenesulfenate esters **5** with Bu_3SnH,[7] undergo the 1,5-hydrogen rearrangement and give δ-carbon radicals **2**. In the presence of a large excess of electron deficient olefins (Michael acceptors) the addition of carbon radical **2** takes place and a new radical **3** is formed (Scheme 2).[8] Radical **3** is quenched by NO giving nitroso compounds **6** or by hydrogen abstraction from Bu_3SnH affording δ-alkylated compounds **7** . Thus two differently functionalized carbon chains could be introduced at the non-activated δ-carbon atom.



Scheme 2.

The first reaction examined was δ-alkylation of 1-pentyl nitrite **8** by Michael acceptors. The reactions were carried out by irradiation of 1-pentyl nitrite (125 W high-pressure mercury lamp)

Table 1. δ–Alkylation of Alkyl Nitrites

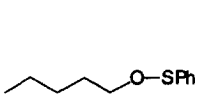
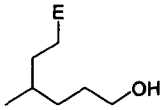
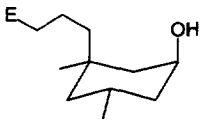
Alkyl Nitrites	Olefins [a]	Products of δ-alkylation	Yields in % [b, c]
 **8**	a) E = CN b) E = CO CH$_3$ c) E = CO OEt	 **9** [d, e]	35 56 55
 **10**	a) E = CN b) E = CO OEt	 **11** [d]	80 49
 **12**	a) E = CN b) E = CO CH$_3$	 **13** [d]	43 36
 **14**	a) E = CN b) E = CO OEt	 **15** [d, f]	41 31
 **16**	a) E = CN	 **17** [g]	22

a) Olefinic compounds were used in 80 molar equiv. excess.
b) Isolated yields.
c) Yields by GC analisys were 60-65%.
d) Exists as a tautomeric mixture with predomination of oxime form.
e) Caracterized also as a diacetate.
f) Dimer of 3,5-dimethyl-3-nitrosomethyl-1-cyclohexanol was also formed.
g) Dimer of 3-methoxy-6β-hydroxy-19-nitroso cholestane was formed.

in the presence of ca. 80 molar equiv. of radicophilic olefins (such as acrylonitrile, methyl vinyl ketone or ethyl acrylate) in benzene solution at r.t., in an argon atmosphere, during 3 h. The reaction products were separated by column chromatography and the δ-alkylated product 2-oximino-4-methyl-7-hydroxyhexyl cyanide (**9a**) was isolated in 35% yield (52% by GC analysis) (Table 1)[9]. In addition to the δ-alkylated product 1-pentanol was also a major by product. Only traces of 4-nitroso-1-pentanol were formed in the Barton reaction. In order to suppress the "normal" Barton reaction a large molar equiv. excess of olefinic compound was needed to favor the intermolecular addition reaction of radical **2** to the olefinic bond. The nitroso groups in **6a** smoothly tautomerised to the corresponding oximes **6b** (Sheme 2.), because there was an electron withdrawing group attached to the same carbon atom.

From 1-pentyl benzenesulfenate **18**, the alkoxy radical was generated by using Bu_3SnH as a reducing reagent. Alkylation was carried out using a 10 molar equiv. excess of radicophilic olefin. The reaction was performed by irradiation of a benzene solution in an argon atmosphere at. r.t during 2 h. The δ-alkylated product **19** was obtained in 32% yield (58% by GC analysis) (Table 2.).[10]

Table 2. δ-Alkylation of Alkyl Benzenesulfenates

Alkyl Benzenesulfenate	Olefins [a] 	Products of δ-alkylation	Yields in % [b,c]
 18	a) E = CN b) E = COOEt	 19	32 56
 20	a) E = CN	 21	34

a) Olefinic compounds were used in 10 molar equiv. excess.
b) Isolated yields.
c) Yields by GC analysis were 58-66%.

In order to survey the scope of these reactions we examined δ-alkylation of different types of saturated alkyl and cycloalkyl nitrites (**10**, **12**, **14**) and O-alkyl benzenesulfenate esters (**18** and **20**). The results are summarized in Tables 1. and 2. and show that this new method for the introduction of Michael acceptors into the remote non-activated δ-carbon atom is a general reaction of alkoxy radicals provided that they can undergo the intramolecular 1,5-hydrogen abstraction and afford free (out of cage) δ-carbon radicals.

This sequence of reactions was applied to a steroid molecule, in order to introduce a functionalized alkyl chain onto the angular 19-methyl group. Thus, by photolysis of 3-methoxy-6β-cholestanyl nitrite (**16**) in the presence of 80 molar equiv, excess of acrylonitrile, in benzene solution, under described[9] experimental conditions the product of alkylation of the 19-methyl group **17** was obtained in 22% isolated yield (Table 1.).

The present results demonstrate a convenient method for the introduction of functionalized alkyl chains at remote non-activated carbon atoms, especially at the difficult to access angular methyl groups. This methodology offers an introduction of two carbon chains bearing different electron withdrawing groups with or without an oximino group. Efforts to expand the scope of this alkylation of non-activated δ-carbon atoms and application in synthetic transformations of natural products, and in further transformations of functional groups of the δ-alkylated products are in progress.

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9. Representative experimental procedure for alkyl nitrite photolysis: A solution of 1-pentyl nitrite (**8**) (0.39 g; 3.33 mmol) and acrylonitrile (14.14 g; 266.4 mmol) in benzene (200 ml) was irradiated at r.t., in an argon atmosphere, by a 125 W high-pressure mercury lamp for 3 h. The solvent was evaporated and the reaction products were separated by chromatography on silica gel (benzene/ethyl acetate 1 : 1) and 0.20 g (35% yield) of product **9** was obtained (by GC analysis of the crude reaction mixture compound **9** was obtained in 52% yield). IR (film): 3251, 2229 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.00 (d, 3H, J = 6.71 Hz), 1.25-1.80 (m, 4H), 1.98 (m, H), 2.47 (ABX system, $\Delta\delta_{AB}$ =33.75 Hz, J_{AB} = 14.52 Hz, J_{AX} = 6.75 Hz, J_{BX} = 7.71 Hz), 3.68 (t, 2H, J = 6.38 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 139.6, 115.2, 63.1, 34.4, 32.6, 30.8, 29.7, 19.6.

   In order to obtain further proof for the structure of the δ-alkylated product, in an additional experiment, the crude reaction mixture was acetylated by acetic anhydride in pyridine. Acetylation of both, hydroxy and oxime, groups took place. The corresponding diacetate was more convenient for purification by chromatography on silica gel (benzene/ethyl acetate 7 : 3) and satisfactory spectral data were obtained.
10. Reduction of 1-pentyl benzenesulfenate by TBTH: A solution of 1-pentyl benzenesulfenate **18** (0.44 g; 2.24 mmol), acrylonitrile (1.2 g; 22.4 mmol) and TBTH (0.73 g; 2.5 mmol) in benzene (200 ml) was irradiated at r.t. by a 125 W high-pressure mercury lamp for 2 h in an argon atmosphere. The course of the reaction was monitored by TLC. Benzene was removed by evaporation, the residue was dissolved in ether, washed with saturated sodium fluoride solution (in order to remove tin compounds) and dried over anh. sodium sulfate. The ether is evaporated and the reaction products were separated by chromatography on silica gel (benzene/ethyl acetate1:1). 4-Methyl-7-hydroxyheptanenitrile **19a** was isolated in 32% yield (by GC analysis 58% yield). IR (film): 3403, 2247 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.94 (d, 3H, J = 6.38 Hz), 1.25-1.80 (m, 7H), 2.35 (m, 2H), 3.65 (t, 2H, J = 6.45 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$)δ: 119.9, 62.8, 32.1, 32.0, 31.7, 29.8, 18.6, 14.8.

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