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Radical Intermediates in the Decomposition of Substituted Coumarins

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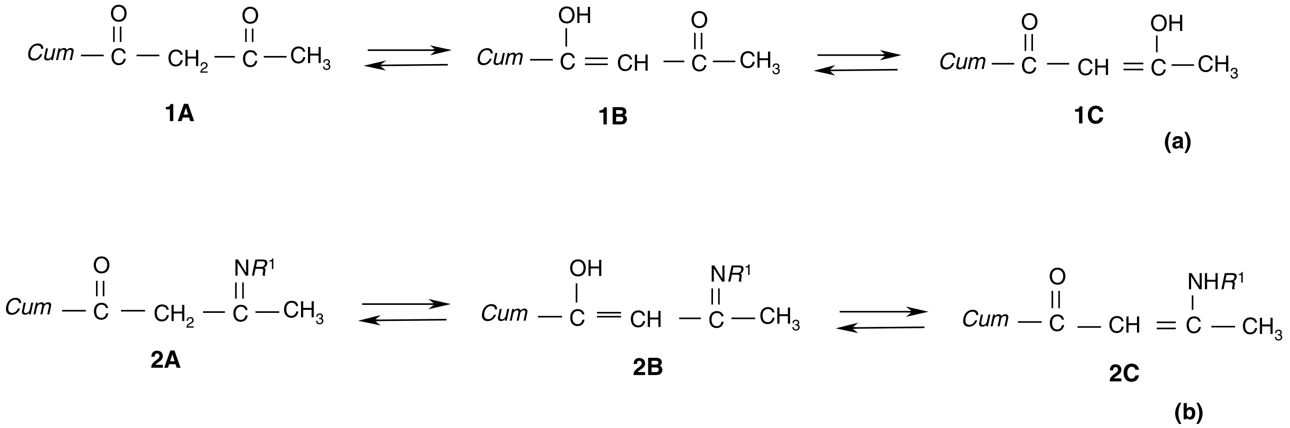
Summary. A series of coumarin derivatives containing substituents with an acidic CH_2 group in 3-position was decomposed on the surface of PbO_2. The radical intermediates were identified by EPR spectroscopy. Although the occurrence of several tautomeric forms is possible, the application of the spin trapping technique confirmed the formation of only one radical product, namely the C-radical resulting from the homolytic splitting of the C–H bond of the methylene group.

Keywords. Coumarin; C-Radicals; EPR; Spin trapping.

Introduction

Strategies based upon free-radical reactions have become a powerful tool for the construction of various types of carbocyclic and heterocyclic compounds and also of complex target molecules. Radical chemistry is now playing an important role in organic synthesis due to several advantages, such as mild reaction conditions, high functional group tolerance, high stereoselectivities, and the possibility of cascade processes. Recently, we have reported a preparative route to substituted benzopyrano[4,3-*b*]pyridines [1]. The cyclization proceeded through 3-acetoacetylcoumarin, which appears to be a valuable intermediate in heterocyclic synthesis. The methylene group in this 1,3-diketone could be prone to homolysis of the active C–H bond to form the corresponding α-acyl radical. Generation and detection of the α-keto radicals arising from this precursor and related compounds can open a way for the further synthetic utility of these coumarins.



$$Cum-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons Cum-\overset{OH}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons Cum-\overset{O}{\overset{\|}{C}}-CH=\overset{OH}{\overset{|}{C}}-CH_3$$

$$Cum-\overset{O}{\overset{\|}{C}}-CH_2-\overset{NR^1}{\overset{\|}{C}}-CH_3 \rightleftharpoons Cum-\overset{OH}{\overset{|}{C}}=CH-\overset{NR^1}{\overset{\|}{C}}-CH_3 \rightleftharpoons Cum-\overset{O}{\overset{\|}{C}}-CH=\overset{NHR^1}{\overset{|}{C}}-CH_3$$

Scheme 1

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Results and Discussion

The homolysis of the C–H bond mediated by agents like PbO_2 or NiO_x characterizes the behaviour of numerous compounds containing a CH_2 or CHR group in α-position to the carbonyl group. The generated carbon centred radicals can be detected by EPR spectroscopy only with the help of spin-trapping technique. Different β-diketones, carboxylic acids, and their esters have been studied this way [2–4].

In coumarins **1a**–**1c**, where keto-enol tautomerism (tautomeric forms **1A**, **1B**, and **1C** in Scheme 1a) has to be considered, the methylene group in the 3-acetoacetyl substituent (tautomer **1A**) also shows a tendency towards homolytic scission of the C–H bond. Moreover, a similar mechanism is expected to operate in analogous structures **2a**–**2d** (occurring in tautomeric forms **2A**, **2B**, and **2C**, Scheme 1b) and related derivatives **3** and **4** as well.

In the absence of a spin trap no EPR signal was observed after the addition of PbO_2 to a benzene solution of coumarins **1a**–**1c**. It was also found that a low concentration of radical adducts is generated in a benzene solution containing only coumarin and spin trap. According to *Booth et al.* [5], consecutively confirmed by *Omelka et al.* [6], these are formed by the reaction of 1,3-diketones with nitroso spin traps, which proceeds through an intermediary hydroxylamine anion. However, a many times higher concentration of radical adducts was detected immediately after the addition of PbO_2 to a coumarin-spin trap binary system.

Table 1. EPR parameters of radical adducts **6a**–**6c**, **7a**–**7c**, **8a**–**8c** ($g = 2.0055$) prepared by the reaction of different spin traps *Y*-NO with the corresponding radicals **5a**–**5c**

	Y	Splitting constant/mT			
		a_N(NO)	a_H(CH)	$a_H(Y)$	
6a	C_6H_5	1.009	0.488	0.260(3H)[a]	0.096(2H)[b]
6b	C_6H_5	1.018	0.467	0.258(3H)[a]	0.086(2H)[b]
6c	C_6H_5	1.030	0.460	0.270(3H)[a]	0.090(2H)[b]
7a	2-CH_3-C_6H_4	1.095	0.400	0.175(2H)[a] 0.180(3H)[c]	0.080(2H)[b]
7b	2-CH_3-C_6H_4	1.109	0.395	0.180(5H)[a,c]	0.080(2H)[b]
7c	2-CH_3-C_6H_4	1.094	0.380	0.180(5H)[a,c]	0.080(2H)[b]
8a	$(CH_3)_3$-C	1.338	0.441	–	–
8b	$(CH_3)_3$-C	1.325	0.437	–	–
8c	$(CH_3)_3$-C	1.326	0.424	–	–

[a] Splitting constants of protons in *o*- and *p*-positions
[b] Splitting constants of protons in *m*-position
[c] Splitting constants of protons of CH_3 group

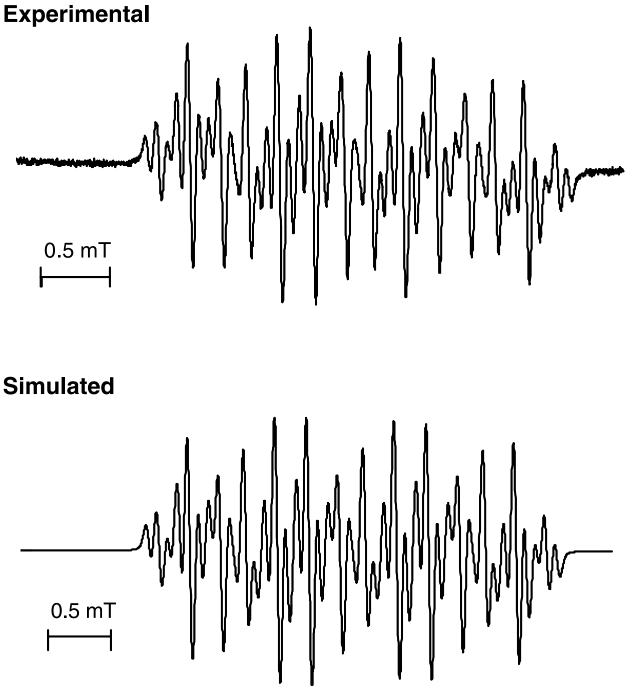
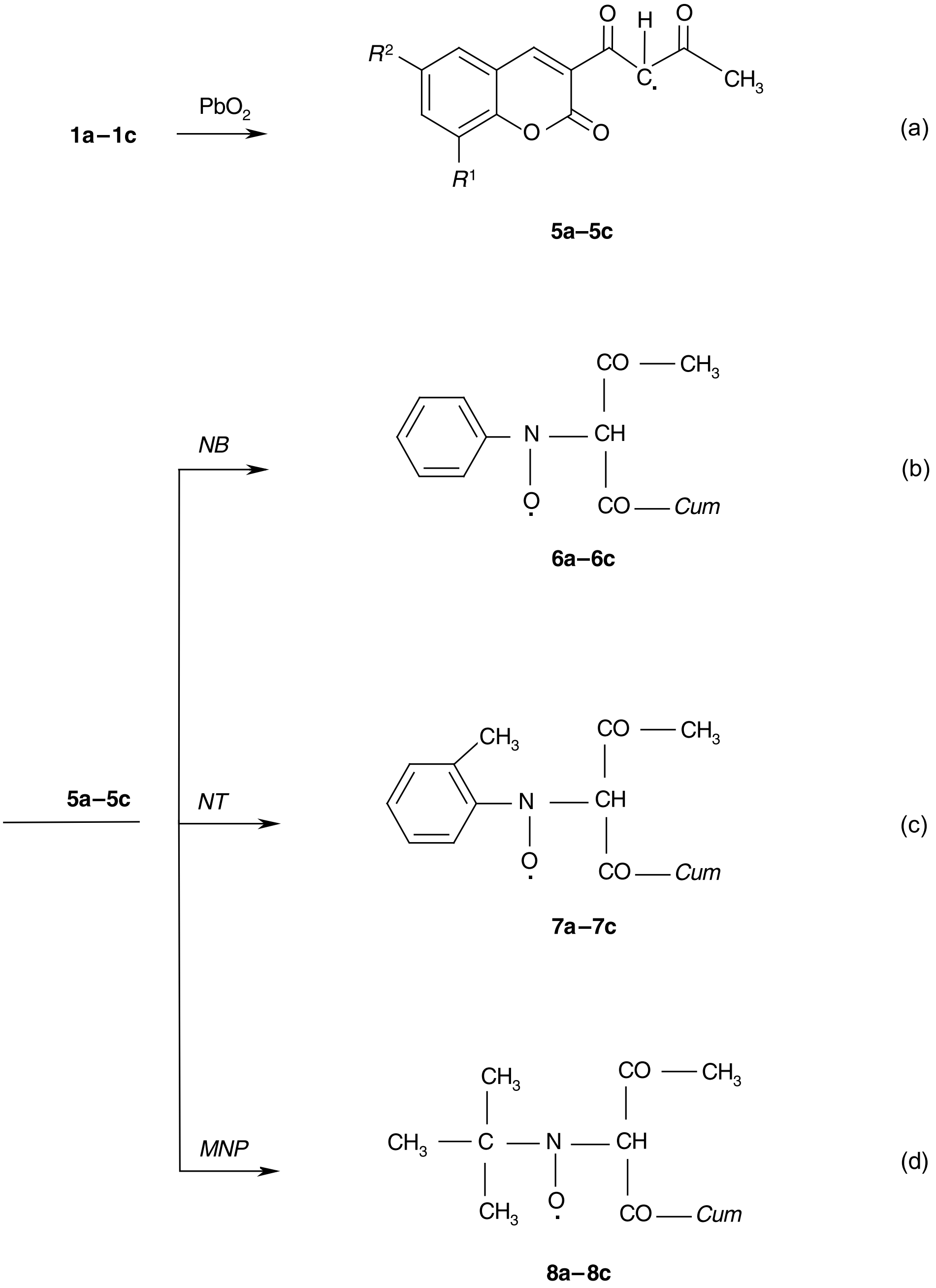


Fig. 1. Experimental and simulated EPR spectra of radical adduct **6a**

Taking into account the EPR parameters of the adducts with nitrosobenzene (*NB*), nitrosotoluene (*NT*), and 2-methyl-2-nitrosopropane (*MNP*) (Table 1) it is evident that the added radical contains one hydrogen atom in the α-position. Based on the structures of the investigated coumarins **1a**–**1c**, this fact can be interpreted as a result of the generation of C-radicals **5a**–**5c** due to the abstraction of a hydrogen atom from the methylene group of the 3-acetoacetyl substituent (Scheme 2a) followed by the consecutive addition to aromatic nitroso spin traps (adducts **6a**–**6c**, **7a**–**7c**, **8a**–**8c**, Scheme 2b–d, Fig. 1).

The experimental results also imply that the radical adducts are derived from the keto form **1A** of coumarins **1a**–**1c**. No radicals arising from the enol forms **1B** and **1C** were detected from the PbO_2 decomposition of **1a** in $CHCl_3$, wherein approximately 93% of coumarin derivative should be present in this tautomeric form [1].

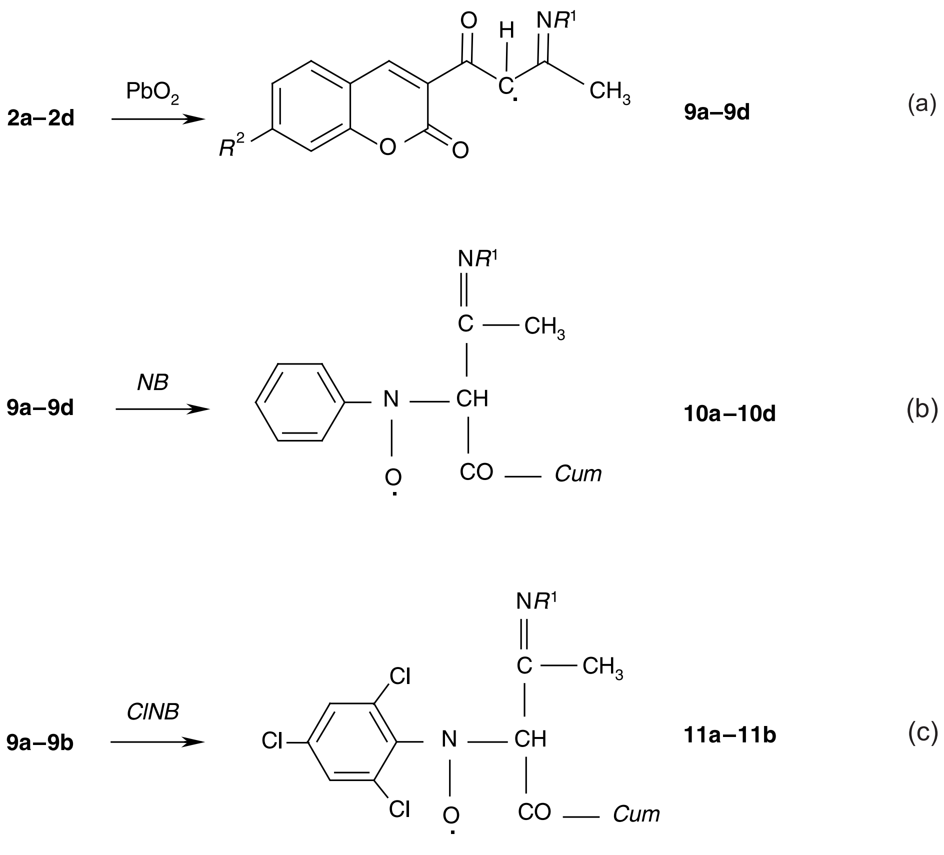
The extension of the coumarin skeleton (**4**) has no influence on the character of the decomposition with PbO_2. Also in this case carbon centred radicals are produced and trapped by nitroso compounds. This fact is confirmed *e.g.* by comparison of the EPR parameters observed by spin adducts with nitroso-



Scheme 2

benzene ($1 \times a_N(NO) = 1.009$ mT, $1 \times a_H$ (CH) = 0.495 mT, $3 \times a_H(o, p) = 0.262$ mT, $2 \times a_H(m) = 0.090$ mT) with those for **6a**–**6c** in Table 1.

The unambiguous tendency towards the formation of C-radicals from 3-acetoacetyl substituted coumarins was confronted with the behaviour of coumarin derivatives **2**. Their structure can theoretically be expressed by tautomeric forms **2A**, **2B**, and **2C** (Scheme 1b). NMR analysis performed with **2a** in dimethylsulfoxide-d$_6$ [1] prefers the structure **2C** to **2B** (structure **2A** is not reported). The question arises, which tautomeric form is involved in the radical producing reaction with PbO_2. The EPR spectrum obtained from the reaction of **2a** in presence of nitrosobenzene suggests that the C-Radical **9a** bearing one hydrogen atom in the α-position is trapped by the



Scheme 3

–N=O group (Scheme 3a), which points to a hydrogen abstraction from the tautomeric form **2A** ($R^1 = \text{H}$).

Nevertheless, the indirect route for the generation of **9a** based on the formation of intermediary oxygen centred radical from **2B** or the nitrogen centred radical from **2C**, cannot be fully excluded. In this case the consecutive inner stabilization of both radicals by unpaired electron transfer is assumed. The addition of radical **9a** was proved also by application of other nitroso spin traps, such as nitrosotoluene (*NT*), 2,4,6-trichloronitrosobenzene (*ClNB*) and nitrosodurene (*ND*). Especially, the EPR spectra

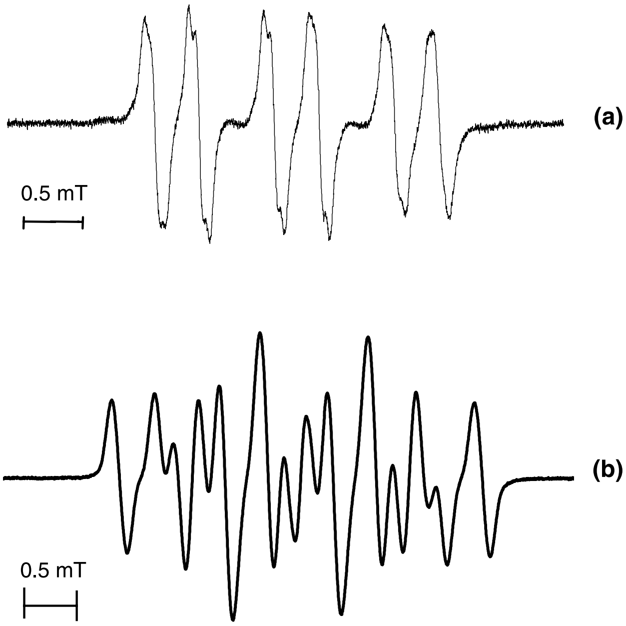


Fig. 2. Experimental EPR spectra of the radical adducts **11a** (a) and **15** (b)

Table 2. EPR parameters of radical adducts **10a–10d**, **11a–11b** ($g = 2.0055$) prepared by the reaction of different spin traps *Y*-NO with the corresponding radicals **9a–9d**

	Y	Splitting constant/mT			
		a_N(NO)	a_H(CH)	a_H(*Y*)	
10a	C_6H_5	1.022	0.513	0.255(3H)[a]	0.080(2H)[b]
10b	C_6H_5	1.012	0.540	0.261(3H)[a]	0.085(2H)[b]
10c	C_6H_5	1.029	0.525	0.249(3H)[a]	0.087(2H)[b]
10d	C_6H_5	1.025	0.516	0.261(2H)[a]	0.088(2H)[b]
11a	2,4,6-$Cl_3C_6H_2$	1.085	0.401	–	–
11b	2,4,6-$Cl_3C_6H_2$	1.085	0.531	–	–

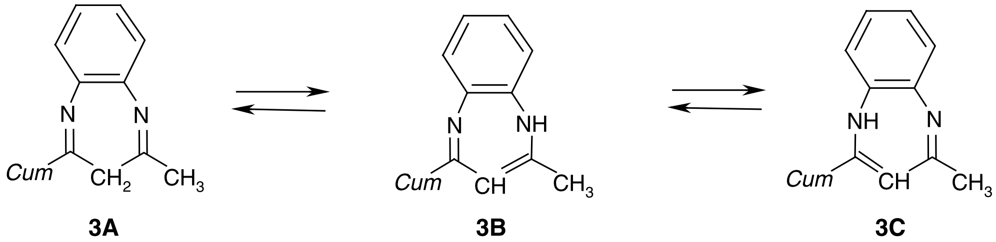
[a] Splitting constants of protons in *o*- and *p*-positions
[b] Splitting constants of protons in *m*-position

obtained with *ClNB* and *ND* enable an unambiguous interpretation of the added radical (Table 2), due to their simplicity (besides the basic nitrogen splitting only the interaction with one hydrogen atom was observed, Fig. 2a).

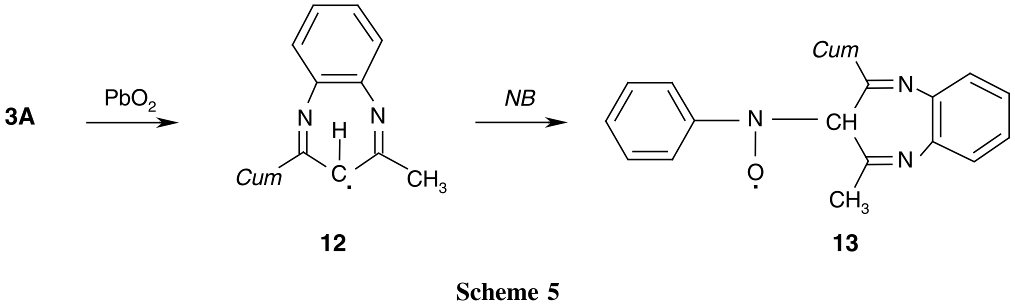
A similar mechanism is expected also with N-substituted derivatives **2b**–**2d**. EPR experiments carried out in the system coumarin (**2b**–**2d**) – nitrosobenzene – PbO_2 confirmed the addition of C-radicals **9b**–**9d**, since the only radical products observed were the nitroxide radicals **10b**–**10d** (Scheme 3b, Table 2). The explanation of experimental EPR spectra of the nitrosobenzene adducts from **2b**–**2d** based on the addition of N-centred radicals (hydrogen abstraction from tautomer **2C**), was also taken into account. The simulated EPR spectra for both alternatives are very similar (in the second instance the splitting constant used for nitrogen atom is one half of a_H(CH) splitting) and they differ only in the intensity ratio of lines. To differentiate between both alternatives, 2,4,6-trichloronitrosobenzene (*ClNB*) was applied for the identification of the radical intermediate from **2b**. Similarly as with **2a**, *ClNB* provided the radical adduct **11b** (Scheme 3c, Table 2). Therefore, it can be concluded that the addition of carbon instead of nitrogen centred radicals characterizes the PbO_2 decomposition of coumarin derivatives **2a**–**2d** in the presence of the aromatic nitroso spin traps.

In the presence of nitrosobenzene and PbO_2 the coumarin derivative **3**, probably occurring in tautomeric forms **3A**, **3B**, and **3C** (Scheme 4) provides a radical adduct whose EPR parameters do not substantially differ from those characterizing **6a**–**6c** and **10a**–**10d** (Tables 1, 2).

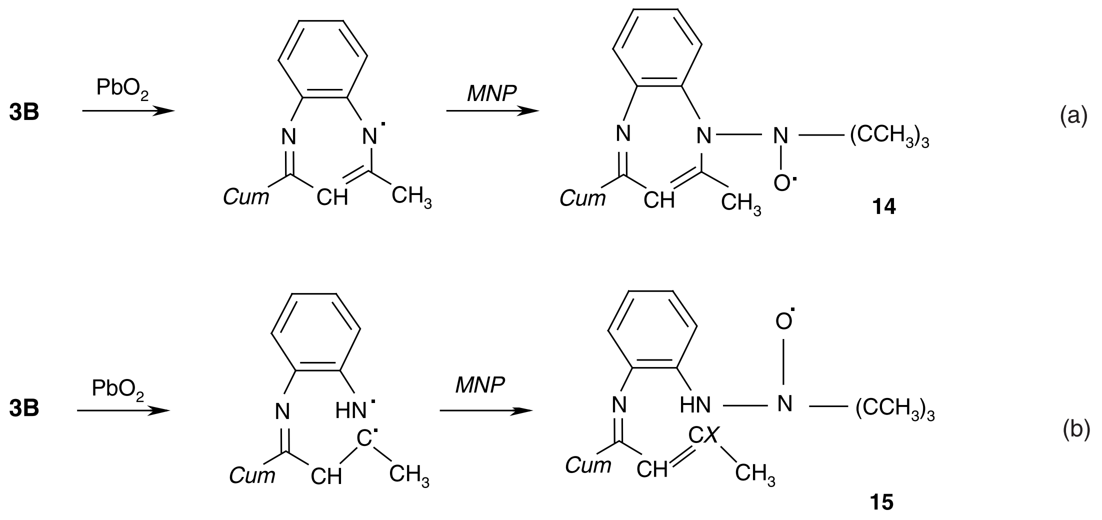
This allows us to interpret the spin trapping reaction in a similar way as with coumarins **1** and **2**, *i.e.* the abstraction of hydrogen atom from the methylene group (radical **12**) proceeds also in this case (Scheme 5). This radical is trapped by *NB* under formation of adduct **13** with the following EPR parameters: $1 \times a_N(\text{NO}) = 1.030\,\text{mT}$, $1 \times a_H(\text{CH}) = 0.511\,\text{mT}$, $3 \times a_H(o, p) = 0.256\,\text{mT}$, $2 \times a_H(m) = 0.090\,\text{mT}$. A substantially different behaviour of coumarin **3** was observed when *MNP* was applied as a spin trap. Instead of the expected triplet to doublet splitting, the EPR spectrum shown in Fig. 2b was obtained. Its simulation confirmed the interaction of the unpaired electron with two nitrogen atoms and one hydrogen atom ($1 \times a_N(\text{NO}) = 1.340\,\text{mT}$, $1 \times a_N = 0.530\,\text{mT}$, $1 \times a_H = 0.720\,\text{mT}$). This result evidently points out the addition of the nitrogen centred radical to the spin trap. There are two possible explanations of this fact. The first one is based on the addition of an aminyl radical from the tautomeric form **3B** (Scheme 6a, adduct **14**). The second one suggests homolysis of the C–N single bond in tautomeric form **3B** to produce an unstable biradical,



Scheme 4



Scheme 5



Scheme 6

which adds consequently to the spin trap through an $-HN^{\cdot}$ fragment (Scheme 6b, adduct **15**, *X* represents a hydrogen atom abstracted from surroundings). In favour of this alternative a similar mechanism can be proposed also for the formation of **3C**.

Experimental

The substituted coumarins **1**–**3** and the related compound **4** were synthesized according to the procedure described in literature [1]. Solvents (benzene, $CHCl_3$) and PbO_2 were commercially available (Fluka), so were the spin traps *MNP* and *NB* (Aldrich).

Decomposition of ***1–3*** *and the Related Compound* ***4*** *with* PbO_2

To 0.3 cm^3 of a 0.1 *M* benzene solution of substituted coumarin an identical volume of a 0.1 *M* solution of spin trap was added in an EPR tube. To this solution 10 mg PbO_2 were added. Subsequently N_2 was bubbled through the suspension formed for 30 sec. Using this procedure an effective contact of solid phase with solution was achieved. On the other hand, the bubbling with inert gas enables to obtain optimal conditions for the registration of high quality EPR spectra. EPR spectra were measured at laboratory temperature using an EPR spectrometer SpectraNova. The simulation of the experimental EPR spectra was performed using the simulation programme Simphonia.

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