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$^{1}H–^{15}N$ HMBC as a valuable tool for the identification and characterization of nitrones

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Dedicated to Professor Miguel Yus on occasion of his 60th birthday

Abstract—$^{1}H–^{15}N$ HMBC has been evaluated as an efficient and high-speed method to determine ^{15}N chemical shifts for nitrones, which can be used to identify aromatic nitrones and to extract structural information by comparison with reference data. Substituent effects have been measured on *C* and *N* aryl groups separately, showing up the influence of electronic effects on *C*-aryl groups rather than *N*-aryl groups on the ^{15}N chemical shifts. Steric effects are remarkable in the case of *C*-aryl-*N*-alkyl nitrones. Depending on N or C substitution, chemical shift changes in such an additive way that it is possible to predict chemical shifts for unknown nitrones.

1. Introduction

Nitrones are used extensively both in organic synthesis as building blocks due to their versatile reactivity[1] and as spin traps.[2] New developments in the synthesis of natural compounds have demonstrated that nitrones possess great perspectives as starting products,[3] so there is a growing interest in the synthesis of these compounds.[1,4] In particular, aromatic nitrones (Fig. 1) have received much attention due to their high reactivity which made them suitable for the study of several diverse stereoselective processes.[5] Due to the diversity of methods to synthesize an aromatic nitrone,[6] an easy and fast spectroscopic method to identify the nitrone functional group is required in order to differentiate nitrones from other possible compounds formed in these reactions, such as imines, oxaziridines or amine oxides. In the case of aromatic nitrones, the diagnostic signal for the azomethine nitrone proton is often buried under aromatic proton signals. Also, the assignment of characteristic ^{13}C NMR signals for nitrones is frequently difficult because of its broadening and low sensitivity.

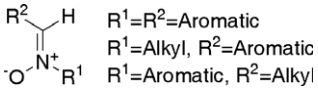

Figure 1. General structure for aromatic nitrones.

In the course of our research directed towards the synthesis of nitrogen containing compounds,[7] we needed a rapid, feasible and efficient technique for identifying nitrone group. In this Letter, we report a versatile spectroscopic method for determining ^{15}N chemical shifts of nitrones. Correlation between chemical shifts and both electronic and steric effects are also presented. We selected for the study the nitrones-type illustrated in Figure 1, R^1 and R^2 being either aromatic or aliphatic groups. To determine ^{15}N chemical shifts we chose HMBC[8] experiments correlating ^{1}H and ^{15}N because of their reliability and speed[9] (typically less than 5 min).[10]

Since nitrones have been scarcely investigated by making use of ^{15}N NMR,[11,12] we pursued an in-depth exploration. After a first screening was made with several nitrones, we decided to carry out studies on electronic and steric effects in an independent way.

2. Results and discussion

In order to study the electronic effects exerted by aromatic groups we selected the nitrones shown in Table 1. The corresponding chemical shifts for these

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Table 1. Nitrones synthesized and ^{15}N NMR chemical shifts (ppm from external liquid NH_3)

Entry	R^1	R^2	Nitrone	δ ^{15}N (ppm)	$\Delta\delta$ (ppm)
1	Bn	Ph	**1**	285.9	—
2	Bn	4-MeOPh	**2**	279.4	−6.5[a]
3	Bn	4-CNPh	**3**	294.2	+8.3[a]
4	Bn	4-NO_2Ph	**4**	295.4	+9.5[a]
5	Bn	5-Imidazole	**5**	270.3	−15.6[a]
6	Bn	2-Thiophene	**6**	274.9	−11.0[a]
7	Bn	2-Furane	**7**	278.1	−7.8[a]
8	Bn	2-Thiazole	**8**	288.2	+2.3[a]
9	Bn	3-Pyridine	**9**	291.2	+5.3[a]
10	Bn	2-Pyridine	**10**	292.9	+7.0[a]
11	Ph	Ph	**11**	285.0	—
12	Ph	4-MeOPh	**12**	278.7	−6.3[b]
13	Ph	4-NO_2Ph	**13**	293.7	+8.3[b]
14	4-MeOPh	Ph	**14**	283.9	−1.1[b]
15	4-CNPh	Ph	**15**	280.0	−5.0[b]
16	4-NO_2Ph	Ph	**16**	279.7	−5.3[b]

[a] Variation over **1**.
[b] Variation over **11**.

compounds showed a strong influence of the electron-donor/acceptor character of the aromatic group when it is linked to the nitrone carbon atom. On the other hand, no significant changes in chemical shifts were observed for different aromatic groups attached to the nitrone nitrogen atom. Due to their synthetic accessibility, nitrones **1**–**10** were quite appropriate to analyse in detail the effects of different substituted aromatic and heteroaromatic rings.

If nitrone **1** (Table 1, entry 1) is taken as reference, when introducing an electronic density donor moiety on R^2 (Table 1, entry 2) chemical shift decreases due to enrichment on electronic density, as well as it increases when acceptor moieties are present (Table 1, entries 3 and 4). This behaviour can be explained if we consider resonance structures for this kind of nitrones. This effect is also observed if substituting R^1 with a heterocycle. For π-exceeding heterocycles (Table 1, entries 5–7) chemical shift is decreased, while for π-deficient cycles it is increased (Table 1, entries 8–10). In all these cases trends in chemical shift can be reasonably predicted, depending on electronic behaviour of the *C*-aryl or *C*-hetaryl moieties.

To evaluate these effects on *N*-phenyl nitrones, nitrones **11**, **12** and **13** bearing a phenyl, a *p*-methoxyphenyl and a *p*-nitrophenyl group at the nitrone carbon, respectively, were studied (Table 1, entries 11–13). The obtained results confirmed the same trend observed for *N*-benzyl nitrones (Table 1, entries 11–13) and no significant effects were observed when the *N*-benzyl group replaces the *N*-phenyl group, thus indicating that variations in the chemical shift of *C*-substituent nitrones are may be separated from N-substitution. In summary whereas replacing the *C*-phenyl group by a *p*-methoxyphenyl resulted in an average decrease of 6.4 ppm, change by a *p*-nitrophenyl group resulted in an increase of the chemical shift by approximately 8.9 ppm.

In the case of *C*-phenyl nitrones (Table 1, entries 14–16), variation of the substituent at the nitrone nitrogen only led to small variations in chemical shift. Moreover, no correlation was found between the electronic character of the substituent and the observed chemical shift.

In order to study steric effects on the chemical shift, we examined nitrones listed in Table 2. For *N*-alkyl substituted nitrones (Table 2, entries 2–4) variations in chemical shifts up to 29 ppm were observed. Chemical shift increased as the number of carbons linked to the α-carbon (β effect) did. A clear correlation between chemical shifts and the number of carbons in β was found (Fig. 2). The point corresponding to 1 carbon in β is get from nitrone 1 (Table 2, entry 1), as an approximated experimental result.

The points of Figure 2 were approximated to a linear regression $y = a + b \cdot x$, for which values are $a = 275.2$ ppm and $b = 9.89$ ($r = 0.9959$). This provides an empirical rule, which can be used to predict ^{15}N chemical shift on *N*-alkyl nitrones, for each carbon on β from nitrogen, 9.9 ppm should be added. On the other hand, changes on substitution degree on *C*-alkyl *N*-benzyl nitrones (Table 2, entries 5 and 6) only induced minor variations in chemical shifts without any predictability (γ effect).

Figure 3 illustrates the application of the described method for nitrone **3**. As indicated in Figure 3a the azomethine proton H_a cannot be assigned because it is in the aromatic range (see enlargement). The experiment

Table 2. ^{15}N NMR chemical shifts (ppm from external liquid NH_3) for nitrones **17**–**21**

Entry	R^1	R^2	Nitrone	δ ^{15}N (ppm)
1	Bn	Ph	**1**	285.9
2	Me	Ph	**17**	274.7
3	^{i}Pr	Ph	**18**	296.6
4	^{t}Bu	Ph	**19**	303.8
5	Bn	^{n}Pr	**20**	284.9
6	Bn	^{i}Pr	**21**	283.3

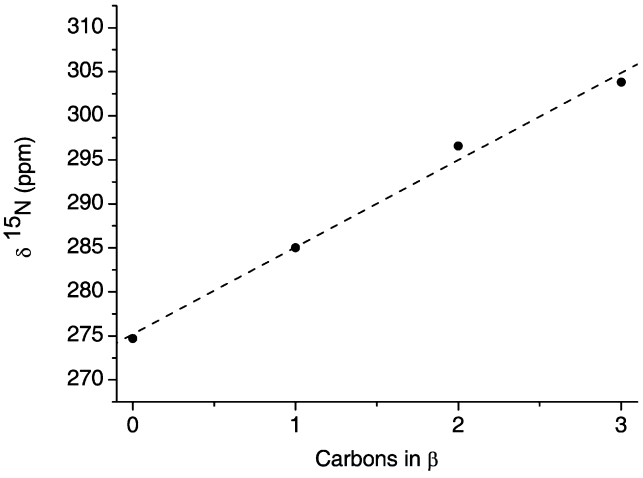

Figure 2. Graph correlating ^{15}N chemical shift and number of carbons in β.

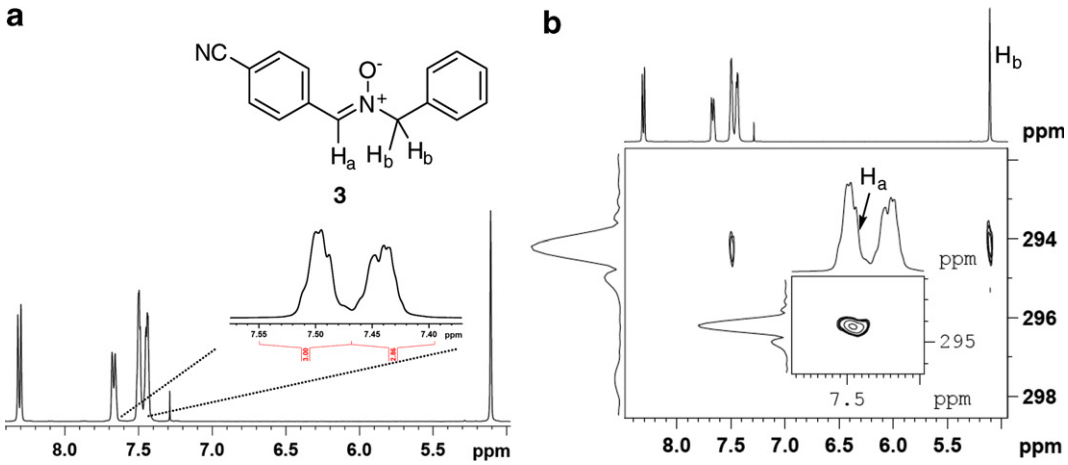

Figure 3. Spectra for nitrone **3**. (a) ^{1}H NMR spectrum. (b) ^{1}H–^{15}N HMBC. Further details in experimental section.

shown in Figure 3b allows as to identify unambiguously the chemical shift of H_a (7.50).

To check if both electronic effects on the carbon and steric effects on the nitrogen are additive, nitrones **22** and **23** were prepared (Fig. 4). In the first case, corresponding to *C*-(*p*-methoxyphenyl)-*N*-methyl nitrone, the chemical shift could be calculated, taking as reference nitrone **1** (*C*-phenyl-*N*-benzyl nitrone) as follows: since the chemical shift of **1** is 285.9 ppm, we should take into consideration that the *C*-*p*-methoxyphenyl group decreases the chemical shift to 6.4 ppm, and the one less carbon in β decreases to 9.9 ppm. Thus, the calculated chemical shift for **22** should be ca. 269.6 ppm. The experimental result showed a chemical shift of 267.7 in good agreement with the prediction. In the other case, for nitrone **23** (*C*-(*p*-nitrophenyl)-*N*-methyl nitrone), application of the above rules, 285.9 + 8.9 (*p*-nitro substituent) – 9.9 (steric effect) gave a value of 283.9 ppm, the experimental result being 283.4 ppm, also in close agreement with the predicted value.

To sum up, we can conclude that (i) ^{1}H–^{15}N HMBC is an optimal experiment to measure ^{15}N chemical shifts of aromatic nitrones; (ii) ^{15}N NMR chemical shift for this kind of nitrones is in the range 270–310 ppm (referenced to liquid NH_3) some structural information being inferred from the chemical shift; (iii) electron density donors or acceptor moieties induce chemical shift variations only when they are linked to the nitrone carbon atom; when they are linked to the nitrone nitrogen their effect is negligible and not predictable; (iv) the number of carbons in β from nitrogen generate a steric hindrance which is translated into an increase of ca. 9.9 ppm for each carbon in β, no steric effects being observed with *C*-substituents; (v) electronic and steric effects are additive, so chemical shift of unknown nitrones can be predicted, and (vi) as the HMBC experiment is able to obtain information from reaction mixtures, it can be adequate for identification in combinatorial nitrone synthesis.

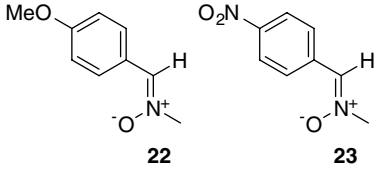

Figure 4. Nitrones **22** and **23**.

3. Experimental

3.1. Compounds

All nitrones were prepared employing the general method reported in the literature.[4a] ^{1}H and ^{13}C NMR data for nitrones **1**–**23** are described in the Supplementary data.

3.2. NMR spectra

All spectra were recorded on a Bruker AVANCE 500 spectrometer operating at 500 MHz (^{1}H), 125.7 MHz (^{13}C) and 50.7 MHz (^{15}N) and a Bruker AVANCE 400 spectrometer operating at 400 MHz (^{1}H), 100.5 MHz (^{13}C) and 40.4 MHz (^{15}N) in deuterochloroform. ^{15}N spectra were measured in $CDCl_3$ solutions at 40 mg ml^{-1} concentration in standard NMR tubes (5 mm o.d.) at 293 K. Chemical shifts are referenced to external liquid ammonia. ^{15}N long-range gHMBC spectra were acquired with pulse field gradients in absolute value mode. The spectral windows for ^{1}H and ^{15}N domains were 12 and 100 ppm, respectively. The multiple-bond delay was adjusted to a coupling constant of 4 Hz. The data were collected in a 1024 × 64 matrix with 2 transients per t_1 increment. The recycle period was 1.0 s. Sine-bell window functions were applied before Fourier transformation in a 1024 × 512 matrix.

Standard procedures of the spectrometer software (Topspin ver. 1.3 and XWinNMR ver. 3.6) were used. A comparison was made between the results of the analysis for a central slice cutting the centre of each correlation peak and two additional neighboring slices which gave the accuracy of ±0.1 ppm. The reproducibility of the

^{15}N chemical shifts values for three spectra recorded at different times of each compound was 0.5–0.7 ppm.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.006.

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