EurJOC
European Journal of Organic Chemistry

Full Paper
doi.org/10.1002/ejoc.202000329

Nitrogen NMR Spectroscopy

Identification of N- or O-Alkylation of Aromatic Nitrogen Heterocycles and *N*-Oxides Using ^{1}H–^{15}N HMBC NMR Spectroscopy

Kevin J. Sheehy,[a] Lorraine M. Bateman,[a,b,d] Niko T. Flosbach,[c] Martin Breugst,*[c] and Peter A. Byrne*[a,d]

In memoriam of Professor Rolf Huisgen

Abstract: A series of representative diazines and pyridine *N*-oxides were subjected to alkylation using several different alkylating agents. The ^{15}N NMR chemical shifts (δ_N values) of the diazines, pyridine *N*-oxides and derived alkylation products were determined using ^{1}H-^{15}N HMBC NMR spectroscopy at natural ^{15}N abundance. The changes in the ^{15}N NMR chemical shifts ($\Delta(\delta_N)$ values) that occurred on going from starting materials to products in these reactions were analyzed. N-alkylation of diazines resulted in large upfield shifts of the δ_N values of the alkylated nitrogen (of the order of 100 ppm or greater). While O-alkylation of pyridine *N*-oxides resulted in upfield shifts of the δ_N values of the *N*-(alkoxy)pyridinium nitrogen, the $\Delta(\delta_N)$ values were of a much smaller magnitude (*ca.* –42 ppm) than those observed for N-alkylations of diazines. Nitrogen NMR spectroscopic data from the literature of relevance to alkylation of azines, diazines, azine *N*-oxides and diazine *N*-oxides was gathered together, and using this in tandem with our ^{15}N NMR spectroscopic data, we have been able to corroborate our observations on the trends observed in the $\Delta(\delta_N)$ values associated with N- and O-alkylation reactions of aromatic N-heterocycles and *N*-oxides. An analysis protocol that relies on synergistic evaluation of ^{1}H-^{15}N HMBC and ^{1}H-^{13}C HMBC NMR spectra has been developed that enables unambiguous diagnosis of the occurrence of N-alkylation of aromatic N-heterocycles and O-alkylation of aromatic *N*-oxides.

Introduction

In the course of recent preliminary studies on the Lewis basicity of compounds containing multiple Lewis basic sites, we have found in several cases that standard ^{1}H, ^{13}C and two-dimensional NMR correlation spectra do not allow unambiguous establishment of which Lewis basic site of a given compound had undergone reaction with a carbon-centered Lewis acid or electrophile.[1] That is, the structures of the products could not be determined without ambiguity. In order to circumvent this problem, we have endeavored to find other means of establishing the structures of the products of these reactions. Since many of the compounds of interest in our investigations are N-containing aromatic heterocycles (azines, diazines, and derived *N*-oxides) containing one or more Lewis basic nitrogen atoms, exploiting modern nitrogen NMR spectroscopic techniques seemed to be a natural choice to achieve this goal.

To this end, the indirect detection technique of ^{1}H-^{15}N HMBC NMR spectroscopy at natural ^{15}N abundance is of particular interest and potential utility.[2] This technique exploits the sensitivity of measurement of ^{1}H NMR signals to circumvent the difficulties that have typically been associated with direct detection of ^{15}N NMR resonances. Coupled with cryoprobe technology, this enables measurement of ^{15}N NMR chemical shifts with relatively short acquisition times (20–30 minutes), and without any requirement for costly ^{15}N-enrichment of analytes.

However, while modern spectroscopic techniques and instrumentation have removed the barriers that until recently existed to the routine acquisition of ^{15}N NMR spectroscopic data, a problem nonetheless remains with the approach of employing ^{15}N NMR chemical shifts in a diagnostic manner to determine

[a] *K. J. Sheehy, Dr L. M. Bateman, Dr P. A. Byrne*
School of Chemistry, Analytical and Biological Chemistry Research Facility, Kane Building, University College Cork, Cork, T12 K8AF, Ireland
E-mail: peter.byrne@ucc.ie
https://byrnechemistry.wordpress.com
[b] *Dr L. M. Bateman*
School of Pharmacy, University College Cork, Cork, Ireland
[c] *N. T. Flosbach, Dr M. Breugst*
Department für Chemie, Universität zu Köln, Greinstraße 4, 50939 Köln, Germany
E-mail: mbreugst@uni-koeln.de
https://physorg.uni-koeln.de
[d] *Dr L. M. Bateman, Dr P. A. Byrne*
SSPC (Synthesis and Solid State Pharmaceutical Centre), Cork, Ireland

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202000329.

Full Paper
doi.org/10.1002/ejoc.202000329

the identities of alkylation products of aromatic N-heterocycles – in particular if there is more than one possible alkylation site. Although systematic studies have been carried out to establish the manner in which aromatic ^{15}N NMR signals are altered upon N-protonation,[2–4] and coordination of aromatic nitrogen atoms to metals,[2,5] data in the literature indicating how aromatic nitrogen NMR signals change upon N-alkylation of azines and diazines or O-alkylation of aromatic *N*-oxides is somewhat sparse (this data is discussed in detail below). In several instances in publications containing one or more examples of aromatic N-alkylation, statements are made to the effect that N-alkylation of aromatic nitrogen atoms result in large upfield shifts of the δ_N value of the alkylated nitrogen (of the order of 100 ppm). However, frequently in these instances, no references to other relevant publications are cited, and in some others no experimental data is reported. As a result, nitrogen NMR spectroscopic data on aromatic N-heterocycle alkylation reactions is scattered throughout the literature, essentially unconnected in any systematic way to the other relevant pieces of data. Consequently, although important results relating to nitrogen NMR spectroscopic analysis of N-alkylation of aromatic N-heterocycles have been reported in several studies,[2d,4–14] the existence of a systematic trend in how δ_N values change upon N-alkylation of constituents from this rather broad range of compounds (which would be of use in a diagnostic sense) has not been definitively established. Furthermore, only two examples exist indicating the effect on δ_N of O-alkylation of azine or diazine *N*-oxides.[10,15] Hence, at present, one cannot unambiguously diagnose the occurrence of N-alkylation of aromatic N-heterocycles or the occurrence of O-alkylation of aromatic *N*-oxides using nitrogen NMR spectroscopy.

Prompted by this, in carrying out this study, we aimed to achieve the following goals:

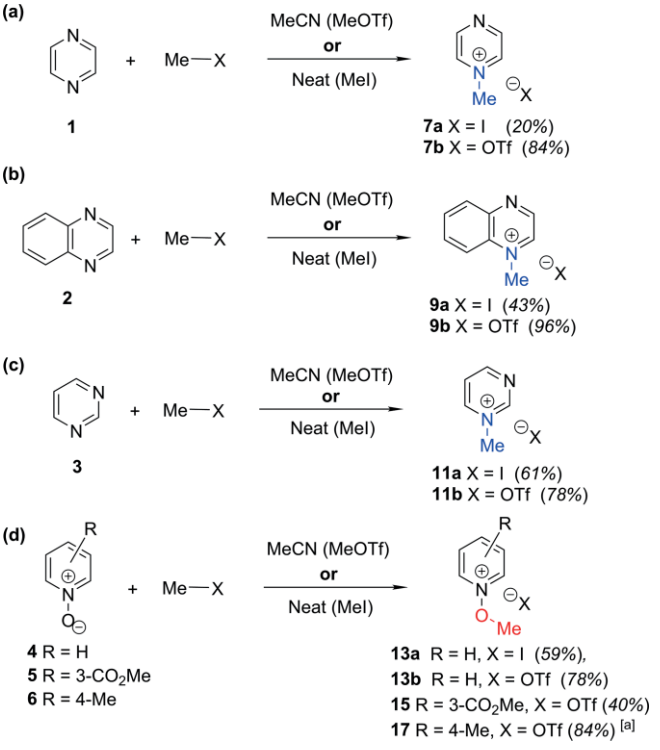
(i) To establish δ_N values for some representative aromatic N-heterocycles and *N*-oxides and N- or O-alkylation products derived from these that had not previously been characterised in order to widen the scope of available data, and to hence establish diagnostic changes in δ_N values (i.e. $\Delta(\delta_N)$ values) for these alkylation reactions.

(ii) To gather together existing relevant data from the literature and combine it with our data in order to establish a systematic basis for understanding the manner in which ^{15}N NMR chemical shifts change during the course of alkylation reactions of N-containing aromatic heterocycles.

As is described in detail below, in this work, $\Delta(\delta_N)$ values that are characteristic of N-alkylation reactions of aromatic N-heterocycles and of O-alkylation of aromatic *N*-oxides have been established. In tandem with multiple-bond correlation data from two-dimensional NMR spectra (^1H-^{15}N HMBC and ^1H-^{13}C HMBC) and certain $^{13}C\{^1H\}$ NMR spectroscopic data, the $\Delta(\delta_N)$ data provides a basis on which to unambiguously diagnose the occurrence (i) of N-alkylation of aromatic N-heterocycles, or (ii) of O-alkylation of aromatic *N*-oxides. It will also enable distinction between products of N-alkylation and O-alkylation in instances where ambiguity exists. The general nature of the approach developed, which involves synergistic application of the ^1H-^{15}N HMBC, ^1H-^{13}C HMBC and $^{13}C\{^1H\}$ NMR spectroscopic techniques, is such that it is sure to find use in a wide range of applications. Long range ^1H-^{15}N NMR correlation techniques have been exploited in previous analogous studies to establish the sites of N-oxidation of various compounds containing multiple nitrogen environments.[16]

Results

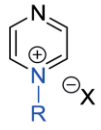
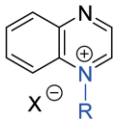
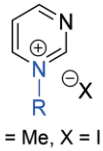
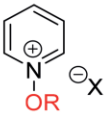
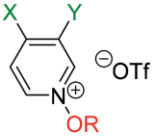
To achieve the goals specified above, we selected diazines **1**–**3** and pyridine *N*-oxides **4**–**6** as our test substrates (see Scheme 1 and Scheme 2 for compound structures), on the basis that they should undergo alkylation reactions with no ambiguity over the site of attachment of the alkyl group in the product. That is, compounds **1**–**3** undergo N-alkylation specifically, while compounds **4**–**6** undergo O-alkylation.



Scheme 1. Use of methylating agents MeI and MeOTf to effect (a)–(c) *N*-methylation of diazines **1**–**3**; (d) O-methylation of pyridine *N*-oxides **4**–**6**. Products were dissolved in DMSO or $[D_6]$DMSO for recording NMR spectra. X = I or OTf throughout. Yields are shown in parentheses. [a] The reaction giving this isolated yield of **17** was carried out in $CDCl_3$ solvent. High conversion was also observed for the reaction in MeCN.[18]

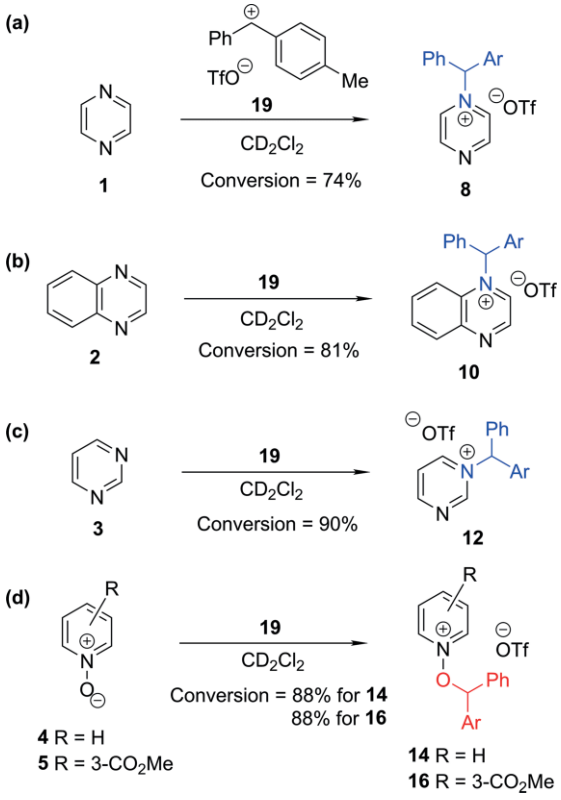
The ^{15}N NMR chemical shifts (δ_N values) of starting compounds **1**–**6** were recorded, as were δ_N values for alkylation adducts derived from **1**–**6**.[17] The alkylation reactions that were conducted are shown in Scheme 1 and Scheme 2,[18] yielding N-alkylation adducts **7**–**12**, and O-alkylation adducts **13**–**17**. As all of the products in Scheme 1 and Scheme 2 are hygroscopic and/or hydrolytically unstable, the reactions were conducted under inert atmosphere.[24] Hydrolytically unstable compounds were characterized by NMR spectroscopy by transferring the reaction mixture directly into an NMR tube under inert atmosphere (i.e. benzhydryl adducts **8**, **10**, **12**, **14** and **16**), and were

Table 1. ^{15}N NMR chemical shift (δ_N) values of starting compounds **1**–**6**, derived N-alkylation products **7**–**12**, and derived O-alkylation products **13**–**17**, and $\Delta(\delta_N)$ values (change in ^{15}N chemical shift) between starting compounds and products upon N- or O-alkylation.[a,c] The δ_N values are referenced to liquid ammonia at 0 ppm (equivalent to referencing to nitromethane at 380.2 ppm). Throughout, Ar = *para*-tolyl group.

Product	#	Reactant	δ_N of reactant (ppm) and NMR solvent		Product	R	X	δ_N of product (ppm) and NMR solvent		$\Delta(\delta_N)$ (ppm)[a]
 **7a** R = Me, X = I **7b** R = Me, X = OTf **8** R = PhArCH, X = OTf	(i)	**1**	DMSO	333.8[b]	**7a**	Me	I	DMSO	357.6 **221.0**	+23.8 **−112.8**
	(ii)	**1**	DMSO	333.8[b]	**7b**	Me	OTf	DMSO	357.4 **220.7**	+23.6 **−113.1**
	(iii)	**1**	CH_2Cl_2	333.0	**8**	$PhArCH^+$	OTf	CD_2Cl_2	364.4 **240.6**	+31.4 **−92.4**
 **9a** R = Me, X = I **9b** R = Me, X = OTf **10** R = PhArCH, X = OTf	(iv)	**2**	[D6]DMSO	329.9[b]	**9a**	Me	I	DMSO	355.5 **208.6**	+25.6 **−121.3**
	(v)	**2**	[D6]DMSO	329.9[b]	**9b**	Me	OTf	DMSO	356.6 **208.7**	+26.7 **−121.2**
	(vi)	**2**	CH_2Cl_2	329.0	**10**	$PhArCH^+$	OTf	CD_2Cl_2	363.7 **225.3**	+34.7 **−103.7**
 **11a** R = Me, X = I **11b** R = Me, X = OTf **12** R = PhArCH, X = OTf	(vii)	**3**	DMSO	295.3[b]	**11a**	Me	I	DMSO	298.7 **199.5**	+3.4 **−95.8**
	(viii)	**3**	DMSO	295.3[b]	**11b**	Me	OTf	DMSO	299.9 **199.4**	+4.6 **−95.9**
	(ix)	**3**	CH_2Cl_2	294.4	**12**	$PhArCH^+$	OTf	CD_2Cl_2	298.8 **218.6**	+4.4 **−75.8**
 **13a** R = Me, X = I **13b** R = Me, X = OTf **14** R = PhArCH, X = OTf	(x)	**4**	DMSO	295.1[c]	**13a**	Me	I	DMSO	256.8	−38.3
	(xi)	**4**	DMSO	295.1[c]	**13b**	Me	OTf	DMSO	252.4	−42.7
	(xii)	**4**	CH_2Cl_2	294.0[c]	**13b**	Me	OTf	CH_2Cl_2	251.0	−43.0
	(xiii)	**4**	CH_2Cl_2	294.0[c]	**14**	$PhArCH^+$	OTf	CD_2Cl_2	246.0	−48.0
 X = H, Y = CO_2Me **15** R = Me **16** R = PhArCH X = Me, Y = H **17** R = Me	(xiv)	**5**	[D6]DMSO	293.2[d]	**15**	Me	OTf	[D6]DMSO	247.3	−40.8
	(xv)	**5**	–	–[e]	**16**	$PhArCH^+$	OTf	CD_2Cl_2	248.3	–[e]
	(xvi)	**6**	[D6]DMSO	284.3[f]	**17**	Me	OTf	[D6]DMSO	247.3	−37.0

[a] $\Delta(\delta_N)$ = The change in the δ_N value of the nitrogen atom of the alkylated compound compared to the δ_N value of that nitrogen in the parent compound. The δ_N and $\Delta(\delta_N)$ values associated with the alkylated nitrogen are highlighted in bold in the table in products containing more than one nitrogen NMR environment. [b] This δ_N value (in [D6]DMSO solvent) was reported in ref. [20]. [c] ^{14}N NMR chemical shift values of 85.64 ppm (in DMSO) and 85.66 ppm (in CH_2Cl_2), referenced to nitromethane at 0 ppm, were reported in ref. [21]. These literature δ_N values equate to 294.6 and 294.5 ppm, respectively, when re-referenced to ammonia at 0 ppm. [d] The δ_N value given for compound **5** is extracted from a ^1H-^{15}N HMBC NMR spectrum of a reaction of the compound. See also ref. [22]. [e] No reference δ_N value for starting compound (**5**) was obtained in CH_2Cl_2. [f] A similar δ_N value (285.2 ppm, relative to nitromethane at 380.2 ppm) was determined in $CDCl_3$ solvent in ref. [23].

Full Paper
doi.org/10.1002/ejoc.202000329



Scheme 2. N- and O-alkylation of nitrogen heterocycles **1**–**5** using benzhydryl triflate **19**, generated in solution from the parent benzhydryl chloride + AgOTf. Throughout the scheme Ar = *p*-tolyl. Conversions of these hydrolytically unstable products were determined from ^{1}H NMR spectra – see the Supporting Information for details.[18,19]

not isolated. Conversions based on integrations of signals in the inert atmosphere ^{1}H NMR spectra of these products are shown in Scheme 2. Moisture-stable compounds were isolated – in some instances this was achieved by carrying out separate reactions on significantly larger scale than that used for the ^{1}H-^{15}N HMBC NMR characterization experiments.[18] Relatively low conversions and yields were observed in some reactions of MeI due to the weak Lewis basicities of some of the diazines or *N*-oxides employed (Scheme 1).[25] Table 1 shows the δ_N values recorded for starting materials **1**–**6**, for derived N-alkylation adducts **7**–**12** and for O-alkylation adducts **13**–**17** using ^{1}H-^{15}N HMBC NMR spectroscopy.

Also shown in Table 1, in the column furthest to the right, are the $\Delta(\delta_N)$ values associated with each of the alkylation reactions. These $\Delta(\delta_N)$ values show the extent to which the chemical shift of a ^{15}N nucleus changes relative to the δ_N value of the starting material (diazine or pyridine *N*-oxide) upon occurrence of an alkylation reaction. If the δ_N value of an alkylation product is upfield of the δ_N value of the corresponding ^{15}N NMR environment in the starting material, this is represented as a negative value of $\Delta(\delta_N)$ in Table 1. Conversely, a positive value of $\Delta(\delta_N)$ indicate that the chemical shift of the ^{15}N environment in question has moved downfield relative to the corresponding environment in the starting material upon alkylation. In Table 1, in each instance in which the starting material and/or product contains more than one nitrogen NMR environment (entries (i) – (ix)), the ^{15}N NMR chemical shift of the nitrogen atom of the starting material that undergoes alkylation and that of the alkylated nitrogen atom of the product are highlighted in bold. The $\Delta(\delta_N)$ value associated with the N-alkylation process is also highlighted in each of these instances. Each of the pyridine *N*-oxides employed contains only one nitrogen environment, and hence there is no potential for ambiguity in instances involving these.

The ^{1}H-^{15}N HMBC NMR spectra of compounds **7**–**12** (N-alkylation adducts of compounds **1**–**3**) indicate that there is a systematic shift upfield of the δ_N value of the alkylated nitrogen environment relative to the δ_N value of the corresponding nitrogen nucleus in the starting material (i.e. the $\Delta(\delta_N)$ value is *negative* – see Table 1 entries (i) – (ix)).[6] That the upfield signal in each case belongs to the alkylated nitrogen is shown by the existence of a correlation in the ^{1}H-^{15}N HMBC NMR spectrum of the product between the upfield ^{15}N signal and the proton(s) of the methyl or benzhydryl groups (i.e. *CH*Ar$_2$ of the latter). The δ_N values of the non-alkylated nitrogen signals move downfield relative to the corresponding δ_N values in the starting materials.[26] The ^{1}H-^{15}N HMBC NMR spectrum of **11b** is shown in

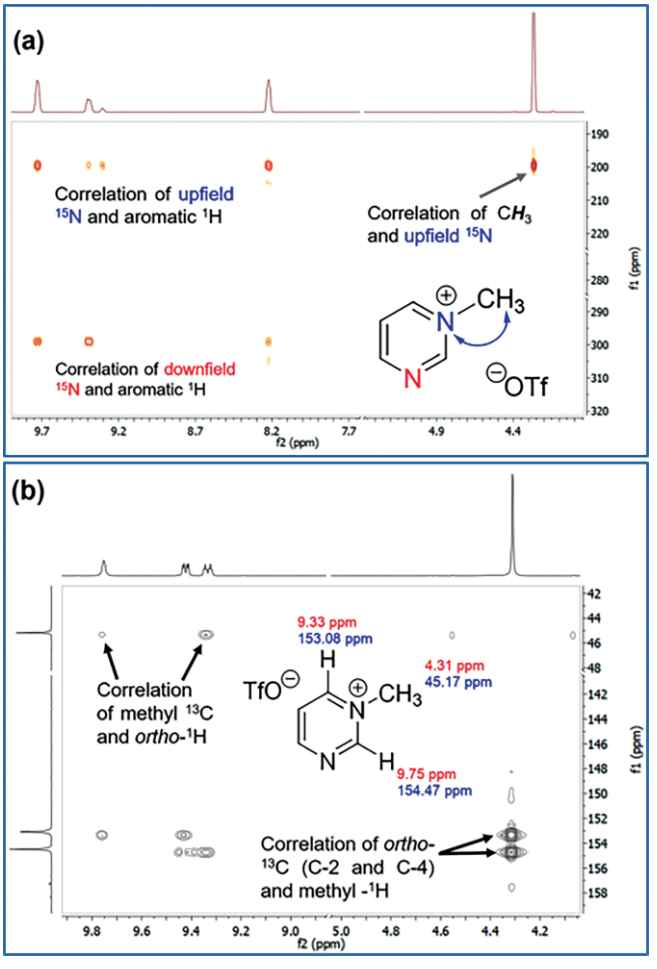


Figure 1. (a) ^{1}H-^{15}N HMBC NMR spectrum of **11b** showing correlation of *N*-methyl ^{1}H signal with upfield ^{15}N signal, (b) ^{1}H-^{13}C HMBC NMR spectrum of **11b** showing correlations between (i) *N*-methyl ^{1}H signal and *ortho*-^{13}C signals, and (ii) *ortho*-^{1}H signals and *N*-methyl group ^{13}C signal.

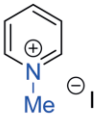
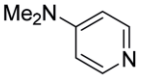
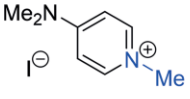
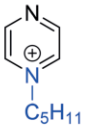
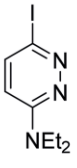
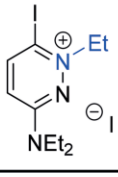
Figure 1a as an example – in this image, one can clearly see the spectral features described above.

The ^{1}H-^{15}N HMBC NMR spectra of compounds **13**–**17** (O-alkylation adducts) also indicate that there is a systematic shift upfield of the δ_N value of the alkoxypyridinium nitrogen of these compounds relative to the δ_N value of the starting material *N*-oxide nitrogen (Table 1 entries (x)–(xiii)). A three-bond coupling interaction is shown to exist for each of these compounds between the alkoxypyridinium nitrogen and the methyl group CH_3 protons or benzhydryl *CH* proton by correlations in the ^{1}H-^{15}N HMBC NMR spectra of the compounds.[27,28]

The data presented in Table 1 make clear that the upfield $\Delta(\delta_N)$ values associated with the alkylated nitrogen atom in N-alkylation reactions are systematically larger than the $\Delta(\delta_N)$ values associated with O-alkylations (e.g. compare Table 1 entries (i) and (x) for methylation reactions, and entries (iii) and (xii) for benzhydrylations).

As alluded to in the introduction, by making reference to previous studies in the literature, we were able to find some additional examples of azines, diazines, azine *N*-oxides and the derived N- and O-alkylation adducts of these compounds for which ^{14}N and/or ^{15}N chemical shifts are known. These are gathered together in Table 2, Table 3 and Table 4. As in Table 1, the δ_N values of the nitrogen atoms of the starting materials or products that are involved in the N- or O-alkylation processes (and the derived $\Delta(\delta_N)$ values) are highlighted in bold in Table 2 and Table 4 in instances in which there are more than one nitrogen NMR environments. A further example, involving methylation of compound **18** to give **19** (see structures in Figure 2) results in an upfield shift in the δ_N value of the methyl-

Table 2. Nitrogen (^{14}N or ^{15}N) NMR chemical shift (δ_N) values of starting compounds and derived alkylation products from literature reports, and $\Delta(\delta_N)$ values (change in ^{15}N chemical shift) between starting compounds and products upon N-alkylation.[a] The δ_N values are referenced to liquid ammonia at 0 ppm (equivalent to referencing to nitromethane at 380.2 ppm), and hence in some instances have been re-calculated from the literature values, which are referenced relative to a different standard.

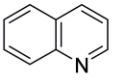
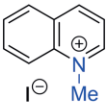
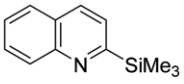
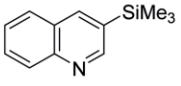
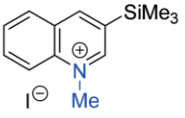
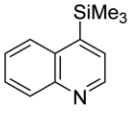
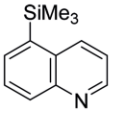
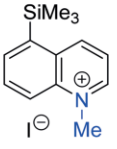
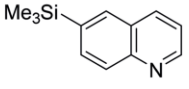
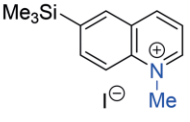
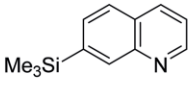
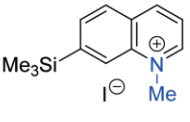
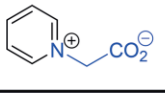
Entry	Starting Compound	Solvent	δ_N of starting compound (ppm)	Product	Solvent	δ_N of product (ppm)	$\Delta(\delta_N)$ (ppm) [a]
(i)		DMSO	316.2[b]		DMSO	200.3[c]	−115.9 [d]
(ii)		$MeNO_2$	**Ring N 275.5**[e]		$MeNO_2$	**Ring N 157.9**[f]	−117.6
(iii)		H_2O	**321.2**[g]		D_2O	351.9[h] **231.4**[h]	+30.7 **−89.8**
(iv)		[D6]DMSO	**403.3**[i] 353.2[i] 91.9[i]		[D6]DMSO	**258.0**[i] 300.5[i] 105.3[i]	**−145.3** −52.7 +13.4

[a] $\Delta(\delta_N)$ = The change in the δ_N value of the alkylated nitrogen compared to the δ_N value of that nitrogen in the parent compound. The δ_N and $\Delta(\delta_N)$ values associated with the alkylated nitrogen are highlighted in bold in the table in products containing more than one nitrogen NMR environment, as are δ_N values of nitrogen atoms of starting materials that undergo N-alkylation. [b] The δ_N value originally reported in ref. [4], referenced relative to nitromethane at 0 ppm, was reported as –64.0 ppm. It has been re-referenced to ammonia at δ_N 0 ppm in the Table to enable comparison with the δ_N values in Table 1. A δ_N value of –63.0 ppm (relative to nitromethane at 0 ppm) has also been reported for this compound in DMSO.[29] δ_N values of 275.2 ppm and –57.6 ppm have also been reported for this compound in DMSO relative to external 2 mol L^{-1} $(Me_4{}^{15}N)Cl$ and external 1 mol L^{-1} HNO_3 in D_2O (enriched in ^{15}N), respectively.[30] A δ_N value of –62.7 ppm (^{14}N NMR spectroscopy; relative to nitromethane at 0 ppm) has also been reported for this compound in nitromethane.[6] [c] The δ_N value originally reported in ref.[4], referenced relative to nitromethane at 0 ppm, was reported as –179.9 ppm. δ_N values of 159.1 ppm and –173.7 ppm have also been reported for this compound in DMSO relative to external 2 mol L^{-1} $(Me_4{}^{15}N)Cl$ and external 1 mol L^{-1} HNO_3 in D_2O (enriched in ^{15}N), respectively.[30] A δ_N value of –179.2 ppm (^{14}N NMR spectroscopy; relative to nitromethane at 0 ppm) has also been reported for this compound in nitromethane.[6] [d] Very similar values of $\Delta(\delta_N)$ (–116.1 ppm in DMSO solvent, –116.5 ppm in $MeNO_2$) are derived from the data reported by Yavari and Roberts,[31] and Costisella *et al.*, respectively.[6] [e] The δ_N value originally reported in ref. [6], referenced relative to nitromethane at 0 ppm, was reported as –104.7 ppm. [f] The δ_N value originally reported in ref.[6], referenced relative to nitromethane at 0 ppm, was reported as –222.3 ppm. [g] The δ_N value originally reported in ref. [31], referenced relative to nitromethane at 0 ppm, was reported as 59.02 ppm. [h] The δ_N value shown was reported in ref.[32] No information was given on the referencing of the ^{15}N NMR spectrum. Note: The identity of the counter-cation of the pyrazinium ion was not specified. [i] The δ_N value shown was reported in ref. [11], referenced relative to ammonia at 0 ppm.

Full Paper
doi.org/10.1002/ejoc.202000329

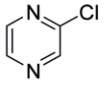
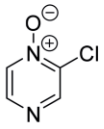
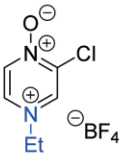
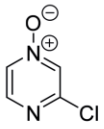
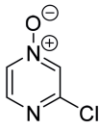
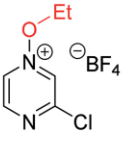
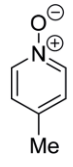
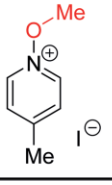
ated nitrogen of $\Delta(\delta_N)$ = –112.4 ppm.[2d,12] Across all of the examples from the chemical literature involving N-alkylation of azines, diazines and diazine *N*-oxides for which nitrogen NMR spectroscopic data is available (16 examples in total – see Table 2, Table 3, and Table 4 and Figure 2), one can discern that N-alkylation of these compounds does result in an upfield shift of the δ_N value of the alkylated nitrogen atom of over 100 ppm (i.e. $\Delta(\delta_N)$ = *ca.* –100 ppm), as indicated in several previous publications on the basis of small numbers of results or without reference to other literature examples.

Table 3. Nitrogen (^{14}N or ^{15}N) NMR chemical shift (δ_N) values of starting compounds and derived alkylation products from literature reports, and $\Delta(\delta_N)$ values (change in ^{15}N chemical shift) between starting compounds and products upon N-alkylation.[a] The δ_N values are referenced to liquid ammonia at 0 ppm (equivalent to referencing to nitromethane at 380.2 ppm), and hence have been re-calculated from the literature values, which were referenced to nitromethane at 0 ppm.

Entry	Starting Compound	Solvent	δ_N of starting compound (ppm)	Product	Solvent	δ_N of product (ppm)	$\Delta(\delta_N)$ (ppm)[a]
(i)		$CDCl_3$	309.1[b]		[D$_6$]DMSO	188.6[c]	−120.5
(ii)		$CDCl_3$	332.3[b]		[D$_6$]DMSO	191.4[c]	−140.9
(iii)		$CDCl_3$	303.6[b]		[D$_6$]DMSO	188.2[c]	−115.4
(iv)		$CDCl_3$	313.2[b]		[D$_6$]DMSO	188.8[c]	−124.4
(v)		$CDCl_3$	310.0[b]		[D$_6$]DMSO	190.0[c]	−120.0
(vi)		$CDCl_3$	307.1[b]		[D$_6$]DMSO	188.1[c]	−119.0
(vii)		$CDCl_3$	310.5[b]		[D$_6$]DMSO	187.4[c]	−123.1
(viii)		DMSO	316.2[d]		[D$_6$]DMSO	207.3[e]	−108.9

[a] $\Delta(\delta_N)$ = The change in the δ_N value of the nitrogen atom of the alkylated compound compared to the δ_N value of that nitrogen in the parent compound. [b] The δ_N values of the quinolines in entries (i) – (vii) originally reported in ref. [9], referenced relative to nitromethane at 0 ppm, were reported as –71.1, –47.9, –76.6, –67.0, –70.2, –72.8, and –69.7 ppm, respectively. [c] The δ_N values of the *N*-methylquinolinium salts in entries (i) – (vii) originally reported in ref. [9], referenced relative to nitromethane at 0 ppm, were reported as –191.6, –188.8, –192.0, –191.4, –190.2, –192.1, and –192.8 ppm, respectively. [d] The δ_N value originally reported in ref. [4], referenced relative to nitromethane at 0 ppm, was reported as –64.0 ppm. A δ_N value of –63.0 ppm (relative to nitromethane at 0 ppm) has also been reported for this compound in DMSO.[29] [e] The δ_N value (^{14}N NMR spectroscopy) originally reported in ref. [7], referenced relative to nitromethane at 0 ppm, was reported as –172.9 ppm (at 0.1 mol L^{-1} concentration; slight concentration dependence of δ_N is reported).

Table 4. Nitrogen (^{14}N or ^{15}N) NMR chemical shift (δ_N) values of starting compounds and derived alkylation products from literature reports, and $\Delta(\delta_N)$ values (change in ^{15}N chemical shift) between starting compounds and products upon N- or O-alkylation.[a] The δ_N values are referenced to liquid ammonia at 0 ppm (equivalent to referencing to nitromethane at 380.2 ppm), and hence have been re-calculated from the literature values, which were referenced to nitromethane at 0 ppm.

Entry	Starting Compound	Solvent	δ_N of starting compound (ppm)	Product	Solvent	δ_N of product (ppm)	$\Delta(\delta_N)$ (ppm)[a]
(i)		[D6]Acetone	324.7[b] **344.5**[b]		[D6]Acetone	345.0[c] **238.5**[c]	+20.3 **−106.0**
(ii)		[D6]Acetone	305.6[b] **307.4**[b]		[D6]Acetone	316.7[c] **201.2**[c]	+11.1 **−106.2**
(iii)		[D6]Acetone	314.4[b] **295.1**[b]		[D6]Acetone	326.3[c] **199.1**[c]	+11.9 **−96.0**
(iv)		[D6]Acetone	**314.4**[b] 295.1[b]		[D6]Acetone	**269.9**[c] 342.9[c]	**−44.5** +47.8
(v)		$CDCl_3$	−284.3[d]		MeOH	245.8[e]	−38.5

[a] $\Delta(\delta_N)$ = The change in the δ_N value of the nitrogen atom of the alkylated compound compared to the δ_N value of that nitrogen in the parent compound. The δ_N and $\Delta(\delta_N)$ values associated with the alkylated nitrogen are highlighted in bold in the table in products containing more than one nitrogen NMR environment, as are δ_N values of nitrogen atoms of starting materials that undergo N-alkylation. [b] The δ_N values of the compounds in entries (i) – (iv) originally reported in ref. [10], referenced relative to nitromethane at 0 ppm, were reported as –55.5 and –35.7 ppm for 2-choropyrazine (entry (i)), –74.6 and –72.8 ppm for 2-chloropyrazine *N*-oxide (entry (ii)), and –65.8 and –85.1 ppm for 3-chloropyrazine *N*-oxide (entries (iii) and (iv)). [c] The δ_N values of the compounds in entries (i) – (iv) originally reported in ref. [10], referenced relative to nitromethane at 0 ppm, were reported as –35.2 and –141.7 ppm (entry (i)), –63.5 and –179.0 ppm (entry (ii)), –53.9 and –181.1 ppm (entry (iii)), and –110.3 and –37.3 ppm (entry (iv)). [d] The δ_N value originally reported in ref. [15], referenced relative to nitromethane at 0 ppm, was reported as 95.9 ppm. [e] The δ_N value originally reported in ref. [15], referenced relative to nitromethane at 0 ppm, was reported as –134.4 ppm.

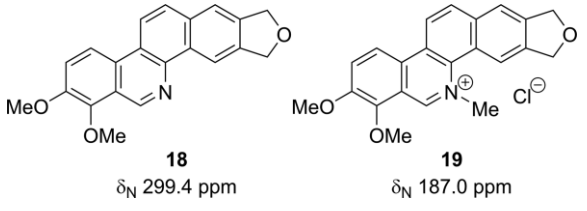


Figure 2. δ_N Values of compounds **18** and **19** (referenced to ammonia at δ_N 0 ppm; solvent not specified).[2d,12]

The compounds involved in these studies were pyridines (3 examples),[4,6,7,8] quinolines (7 examples),[9] pyrazine *N*-oxides (2 examples),[10] a pyridazine,[11] and an isoquinoline alkaloid.[2d,12,13] N-alkylation of purines (which occurs on one of the imidazole nitrogen atoms) has also been reported to result in a large upfield shift in the δ_N value of the alkylated nitrogen ($\Delta(\delta_N)$ = –80 to –90 ppm).[14] Two reports from the literature indicate that O-alkylation of azine and diazine *N*-oxides results in much smaller changes in the δ_N values of the *N*-oxide nitrogen nuclei ($\Delta(\delta_N)$ = *ca.* –40 ppm) – see Table 4 entries (iv) and (v).[10,15]

The data in Table 2, Table 3, and Table 4 has allowed us to establish further $\Delta(\delta_N)$ values associated with N- and O-alkylation processes. Across all of the adducts of N-alkylation (i.e. those in Table 1, Table 2, Table 3, and Table 4 and Figure 2; 26 examples in total), the average upfield $\Delta(\delta_N)$ value associated

Full Paper
doi.org/10.1002/ejoc.202000329

with N-alkylation is –112 ppm. The shift upfield in the *N*-oxide nitrogen δ_N value upon O-alkylation is significantly smaller – i.e. the average $\Delta(\delta_N)$ value across the *N*-oxide O-alkylation adducts shown in Table 1 and Table 4 is –42 ppm (8 examples in total). From this, we can conclude that there is a characteristic $\Delta(\delta_N)$ value associated with N-alkylation of an azine, diazine or diazine *N*-oxide, distinct from (and significantly larger than) the characteristic $\Delta(\delta_N)$ values associated with O-alkylations of azine *N*-oxides or diazine *N*-oxides.

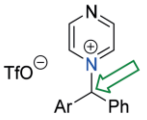
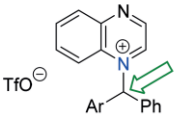
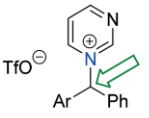
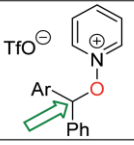
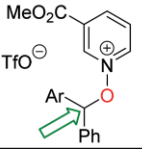
Another very important observation is that in the ^{1}H-^{13}C HMBC NMR spectra of compounds **7**–**12**, the signals of the N-methyl or N-benzhydryl proton(s) are correlated with the ^{13}C NMR signals of the aromatic carbons directly bound to the alkylated nitrogen. Similarly, the N-methyl or N-benzhydryl Ar_2CH ^{13}C NMR signal is correlated with the ^{1}H NMR signals of the aromatic protons on the *ortho*-positions relative to the quaternized nitrogen. These correlations can be seen in the ^{1}H-^{13}C HMBC NMR spectrum of **11b** shown in Figure 1b. The connectivity indicated by the ^{1}H-^{13}C HMBC NMR data for each compound is entirely consistent with the conclusions indicated by the ^{1}H-^{15}N HMBC NMR data. In contrast, in the ^{1}H-^{13}C HMBC NMR spectra of compounds **13**–**17**, the signals of the *O*-methyl or *O*-benzhydryl proton(s) *are not correlated* with the ^{13}C NMR signals of the aromatic carbons directly bound to the *N*-oxide nitrogen. Similarly, the O-methyl or O-benzhydryl Ar_2CH ^{13}C NMR signal is not correlated with the ^{1}H NMR signals of the aromatic protons in the *ortho*-positions relative to the alkoxypyridinium group. Hence, the absence of these correlations (in tandem with ^{15}N NMR spectroscopic data) is indicative of O-alkylation. An example of a ^{1}H-^{13}C HMBC NMR spectrum showing the absence of these four-bond ^{1}H-^{13}C NMR correlations for compound **13b** is shown on page S39 of the Supporting Information (Figure S35).

Furthermore, a thorough examination of the ^{13}C{^{1}H} NMR chemical shifts of the N- or O-alkyl group carbon atoms directly bound to the heteroatoms (in our data and literature data) revealed a systematic trend. On its own, this data does not allow definitive establishment of N- or O-alkylation, but if analysed together with $\Delta(\delta_N)$ and ^{1}H-^{13}C HMBC NMR data, the δ_C values of these carbons can be used to identify N-alkylated aromatic compounds and O-alkylation adducts of aromatic *N*-oxides (alkoxypyridinium ions).

The ^{13}C NMR signals of the N-benzhydryl group NCH carbons of compounds **8**, **10** and **12** exhibit δ_C values in the range 75–80 ppm, as is shown in Table 5 entries (i) – (iii). The δ_C values of the benzhydryl NCH carbons in related benzhydrylpyridinium ions ranges from 65 to 76 ppm.[33,34] The δ_C values of the OCH benzhydryl group carbon signals of **14** and **16** are substantially higher, at 97.1 and 97.8 ppm, respectively (Table 5 entries (iv) and (v)).

The δ_C values of a variety of aromatic N-methylated compounds and alkylation adducts of aromatic *N*-oxides for which ^{13}C NMR spectroscopic data has been reported in the literature are gathered together in Tables S1 and S2 in the Supporting Information.[35] The ^{13}C NMR chemical shifts of the *N*-methyl group carbon in these compounds appear in the range 36–53 ppm,[36,37] while the δ_C values of the O-methyl group

Table 5. ^{13}C NMR chemical shift (δ_C) values of benzhydryl group Ar_2**C**H carbon nuclei (position indicated by arrow in compounds below) of compounds **8**, **10**, **12**, **14** and **16** in CD_2Cl_2 solvent. Ar = *p*-tolyl throughout.

Entry	Compound	Compound Number	δ_C (ppm)
(i)		**8**	79.6
(ii)		**10**	75.2
(iii)		**12**	76.6
(iv)		**14**	97.1
(v)		**16**	97.8

carbons of methoxypyridinium ions are in the range 62–75 ppm.[38,39] Similar systematic trends exist for other N- and O-alkyl groups.[33,40,41]

It is clear from this data that for each alkyl group, there is a well-defined characteristic ^{13}C NMR chemical shift range in which one can expect to observe the signal of the *N*-alkyl group N^+–*C* nucleus of an aromatic N-alkylated compound. Similarly, there is a distinct chemical shift range in which the ^{13}C NMR signal of the *O*-alkyl O–*C* nucleus of an alkoxypyridinium ion can be reliably expected to appear. Although in isolation the ^{13}C NMR chemical shift of a single carbon environment is certainly not uniquely diagnostic, it can be used in tandem with $\Delta(\delta_N)$ and ^{1}H-^{13}C HMBC NMR data to diagnose the occurrence of N- or O-alkylation of aromatic N-heterocycles or *N*-oxides.

Discussion

Since the compounds selected for this study each contain only one Lewis basic site or two equivalent Lewis basic sites, there is no ambiguity over the site of alkylation of these compounds by alkyl electrophiles. Consequently, comparison of the ^{15}N NMR chemical shifts of the alkylation adducts with the chemical shifts of the corresponding nitrogen atoms in the starting materials has enabled diagnostic trends in the magnitudes of the $\Delta(\delta_N)$ values for reactions of these compounds to be associated with N- or O-alkylation. In combination with collected nitrogen NMR spectroscopic data from the literature relating to azine, diazine, or diazine *N*-oxide alkylation (Table 2, Table 3, and

Table 4 and Figure 2), our results clearly show that N-alkylation reactions of these compounds result in very large upfield shifts in the δ_N values of the alkylated nitrogen atoms ($\Delta(\delta_N)$ values of the order of –100 ppm from starting material to product). Given that a similar phenomenon has also been observed for N-alkylation reactions of purines (with $\Delta(\delta_N)$ values of –80 to –90 ppm for the alkylated nitrogen),[14] it is clear that large negative $\Delta(\delta_N)$ values are strongly indicative of N-alkylation of aromatic nitrogen nucleophiles. We have also established that information from $^{13}C\{^1H\}$ and ^1H-^{13}C HMBC NMR spectra of alkylation adducts can be used to compliment the ^{15}N NMR chemical shift data from ^1H-^{15}N HMBC NMR spectra. Hence, analysis of products formed in reactions of aromatic N-heterocycles using the ^1H-^{15}N HMBC, ^1H-^{13}C HMBC and $^{13}C\{^1H\}$ NMR spectroscopic techniques in tandem provides a definitive means of establishing the occurrence or otherwise of N-alkylation in these reactions.

In a similar fashion, our ^1H-^{15}N HMBC NMR spectroscopic data on pyridine *N*-oxides and their O-alkylated derivatives shows that there is a characteristic upfield shift in the δ_N values of aromatic *N*-oxide nitrogen nuclei upon O-alkylation that is of much smaller magnitude ($\Delta(\delta_N)$ = *ca*. –42 ppm) than that observed for the N-alkylations discussed above. This observation aligns closely with the two literature precedents involving O-alkylation of aromatic *N*-oxides in which nitrogen NMR spectroscopic data has been reported Table 4 entries (iv) and (v)).[10,15] ^1H-^{15}N HMBC NMR spectra of *N*-alkoxypyridinium ions (**13**–**17**) show three-bond coupling interactions between the *N*-oxide nitrogen and alkoxy group protons.[27] ^1H-^{13}C HMBC NMR spectra of the O-alkylated adducts show that long-range correlations *are not present* between the O-alkyl protons and carbons and the aromatic carbons and protons.[7] Hence, long-range correlation data obtained from ^1H-^{15}N HMBC and ^1H-^{13}C HMBC NMR spectra can also be used in tandem with $\Delta(\delta_N)$ values and δ_C values (from ^{13}C NMR spectroscopy) to diagnose the occurrence of O-alkylation of aromatic *N*-oxides.

It is appropriate at this point to compare the characteristic $\Delta(\delta_N)$ values associated with formation of N-alkylated adducts of aromatic N-heterocycles and O-alkylated adducts of aromatic *N*-oxides (established above) with some $\Delta(\delta_N)$ values associated with other important chemical transformations of N-heterocycles.

In contrast to the large negative $\Delta(\delta_N)$ value associated with N-alkylation of an aromatic N-heterocycle, N-alkylation of aliphatic or alicyclic N-heterocycles (i.e. amines) results in a comparatively small downfield shift in δ_N of ≤ +10 ppm (small positive $\Delta(\delta_N)$).[42]

N-oxidation of aromatic N-heterocycles results in an upfield shift of δ_N of the oxidised nitrogen of the order of 20–30 ppm (i.e. $\Delta(\delta_N)$ = –20 to –30 ppm).[43] Comparison of the δ_N values of the pyridine *N*-oxides that we have recorded in this project (295.1 and 284.3 ppm, respectively, for **4** and **6** in $[D_6]$DMSO) with the δ_N values of pyridine and 4-methylpyridine (316.2 ppm[4] and 311.0 ppm,[2h] respectively, in $[D_6]$DMSO) indicates $\Delta(\delta_N)$ values for N-oxidation of these pyridines of –21.1 ppm and –26.7 ppm, respectively. In contrast, N-oxidation of aliphatic N-heterocycles (amines) has been reported to result in a relatively large *downfield* shift of the δ_N value of the signal of the nitrogen nucleus involved ($\Delta(\delta_N)$ = *ca*. +68 to +85 ppm).[16a,16b,44]

Conclusions

The diagnostic NMR spectroscopic analytical protocols described above are of general utility, and are likely to prove beneficial in other applications in organic chemistry involving aromatic N-heterocycles and *N*-oxides, especially given the analogous effects observed on δ_N values upon N- or O-protonation[2–4] or oxidation[43] of aromatic N-heterocycles, and upon complexation of aromatic nitrogen atoms to metals.[2,5] In addition, this approach can be used to distinguish between the N- and O-alkylation in reactions in which there is ambiguity over the outcome, e.g. in alkylation reactions of compounds containing both aromatic nitrogen(s) and *N*-oxide(s). The data reported in this article will facilitate our future studies on Lewis basicity and ambident nucleophilicity by enabling us to overcome the previously intractable challenge of unambiguously establishing the structure of products formed in alkylation reactions of aromatic N-heterocycles with multiple Lewis basic and/or nucleophilic nitrogen or oxygen sites.

Importantly, our use of ^1H-^{13}C HMBC NMR spectroscopy alongside ^1H-^{15}N HMBC NMR spectroscopy in this study has enabled the information contained in ^1H-^{13}C HMBC and $^{13}C\{^1H\}$ NMR spectra to take on a new significance. The NMR ^1H-^{13}C HMBC and $^{13}C\{^1H\}$ NMR spectroscopic data, which in isolation was ambiguous up until now, has been rendered diagnostic in the context of the ^1H-^{15}N HMBC NMR spectroscopic data, facilitated by the findings reported herein.

Experimental Data

Supporting Information is available for this article, containing a full set of experimental procedures, characterization data for products and reaction mixtures, general experimental details, and copies of NMR spectra. Selected experimental details are given below.

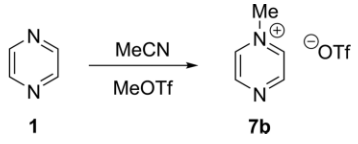
Details on NMR Spectroscopic Experiments: NMR spectra were recorded in 5 mm diameter NMR tubes on Bruker Avance III 600, Bruker Avance I 400 and Bruker Avance III 300 NMR spectrometers. These spectrometers are equipped, respectively, with a Bruker 5 mm Broadband (BBFO) Cryoprobe (Avance III 600), a Bruker 5 mm QNP room temperature probe (Avance I 400), and a Bruker 5 mm Broadband room temperature probe (Avance III 300).

^1H NMR spectra (600 MHz, 400 MHz and 300 MHz respectively), $^{13}C\{^1H\}$ NMR spectra (proton decoupled mode; 150 MHz, 100 MHz and 75 MHz, respectively), COSY, ^1H-^{13}C HSQC and ^1H-^{13}C HMBC NMR spectra were acquired at 300 K on the Avance II 600 spectrometer (cryoprobe coil temperature = 16 K) and Avance III 300 spectrometer and at 293 K on the Avance I 400 spectrometer. Tetramethylsilane (TMS) was employed as the external chemical shift reference standard for these.

^1H-^{15}N HMBC NMR spectra were recorded at 300 K on the Bruker Avance III 600 NMR spectrometer [600.1 MHz (^1H), 60.8 MHz (^{15}N)], equipped with Bruker BBFO cryoprobe (coil temperature 16 K) and referenced externally to ammonia (at 0 ppm), the value of which was uncorrected. ^1H-^{15}N HMBC NMR spectra were acquired using

the Bruker hmbcqpndqf pulse program (2D H-1/X correlation via heteronuclear zero and double quantum coherence optimised on long range couplings), with 4 scans and spectral width of 600–650 ppm. Spectra recorded in non-deuterated solvents were acquired using the Bruker NOESY presat (noesygppr) solvent suppression pulse sequence, using presaturation during the mixing time and relaxation delay.

Preparation of *N*-methylpyrazinium Triflate (7b)



1 **7b**

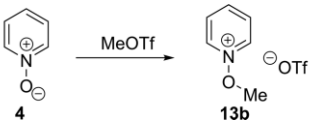
Pyrazine (**1**) (0.142 g, 1.77 mmol) was dissolved in dry MeCN (5 mL) in a N_2-filled Schlenk flask, which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.295 g, 1.79 mmol) was subsequently added dropwise. After *ca.* 18 hours, the MeCN was removed under vacuum – precise details on how this was done are given in Procedure A in the General Procedures section in the Supporting Information. The solid product (**7b**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 mL each) were used in this manner to wash the product (yield = 0.372 g, 86 %; product contained *ca.* 2 % of **1**, therefore yield = 86 % × 0.98 = *84 %*). Dry [D_6]DMSO (ca. 0.9 mL) was added carefully to the Schlenk flask in such a way as to ensure dissolution of only a portion of the solid (ca. 10–20 mg), and the resulting solution was transferred to a NMR tube under inert atmosphere. Full details of the protocol used for preparation of samples for NMR spectroscopy under inert atmosphere are given in Procedure B in the General Procedures section in the Supporting Information. The NMR tube was sealed with a rubber septum (wrapped around the outside with PTFE tape and then Parafilm) under inert atmosphere, and brought to the NMR spectrometer.

^{1}H NMR (400 MHz, [D_6]DMSO) δ = 9.50 (s, 2H), 9.13 (s, 2H), 4.42 (s, 3H).[37a] A very small signal from residual pyrazine is visible at 8.73 ppm.

(b) Pyrazine (**1**) (0.113 g, 1.41 mmol) was dissolved in dry MeCN (5 mL) in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.167 g, 1.02 mmol) was subsequently added dropwise. After ca. 30 minutes, the MeCN was removed under vacuum – precise details on how this was done are given in Procedure A in the General Procedures section in the Supporting Information. This is likely to have also resulted in removal of much of the excess pyrazine (**1**). If any unreacted MeOTf remained, it would also have been removed under vacuum. The solid product (**7b**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 mL each) were used in this manner. The resulting solid was dried under vacuum (again, precise details on this are given in Procedure A in the Supporting Information). The entirety of the solid residue was dissolved in dry DMSO (2 mL), and a portion of this (0.8 mL) was transferred to a NMR tube under inert atmosphere. Full details of the protocol used for preparation of samples for NMR spectroscopy under inert atmosphere are given in Procedure B in the General Procedures section in the Supporting Information. The NMR tube was sealed with a rubber septum (wrapped around the outside with PTFE tape and then Parafilm) under inert atmosphere, and brought to the NMR spectrometer. ^{1}H and ^{1}H-^{15}N HMBC NMR spectra were recorded for the sample using the solvent signal suppression protocol referred to above.

^{1}H NMR (600 MHz, DMSO) δ = 9.47 (s, 2H), 9.10 (d, *J* = 3.2 Hz, 2H), 4.38 (s, 3H).[37a] A small signal from residual pyrazine is visible at 8.73 ppm. ^{15}N NMR (60.8 MHz, DMSO): δ = 357.4, 220.7.

Preparation of *N*-Methoxypyridinium triflate (13b)



4 **13b**

(a) Pyridine *N*-oxide (**4**) (0.220 g, 2.31 mmol) was dissolved in dry MeCN (5 mL) in a N_2-filled Schlenk flask. Methyl triflate (0.384 g, 2.34 mmol) was subsequently added dropwise. After ca. 18 hours, the MeCN was removed under vacuum – precise details on how this was done are given in Procedure A in the General Procedures section in the Supporting Information. The solid product (**13b**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 mL each) were used in this manner to wash the product (yield = 0.469 g, 78 %). The resulting solid was dried under vacuum (again, precise details on this are given in Procedure A in the Supporting Information). Dry [D_6]DMSO (ca. 0.9 mL) was added carefully to the Schlenk flask in such a way as to ensure dissolution of only a portion of the solid (ca. 10–20 mg), and the resulting solution was transferred to a NMR tube under inert atmosphere. Full details of the protocol used for preparation of samples for NMR spectroscopy under inert atmosphere are given in Procedure B in the General Procedures section in the Supporting Information. The NMR tube was sealed with a rubber septum (wrapped around the outside with PTFE tape and then Parafilm) under inert atmosphere, and brought to the NMR spectrometer.

^{1}H NMR (300 MHz, [D_6]DMSO) δ = 9.40 (d, *J* = 6.3 Hz, 2H), 8.61 (t, *J* = 7.8 Hz, 1H), 8.22 (t, *J* = 7.3 Hz, 2H), 4.45 (s, 3H).[39a]

(a) Pyridine *N*-oxide (**4**) (0.064 g, 0.67 mmol) was dissolved in dry MeCN (5 mL) in a N_2-filled Schlenk flask. Methyl triflate (0.111 g, 0.670 mmol) was subsequently added dropwise. After ca. 20 minutes, the MeCN was removed under vacuum – precise details on how this was done are given in Procedure A in the General Procedures section in the Supporting Information. The entirety of the solid product was dissolved in DMSO (0.8 mL), and this solution was transferred to a NMR tube under inert atmosphere.

Full details of the protocol used for preparation of samples for NMR spectroscopy under inert atmosphere are given in Procedure B in the General Procedures section in the Supporting Information. The NMR tube was sealed with a rubber septum (wrapped around the outside with PTFE tape and then Parafilm) under inert atmosphere, and brought to the NMR spectrometer. ^{1}H and ^{1}H-^{15}N HMBC NMR spectra were recorded for the sample using the solvent signal suppression protocol referred to above.

^{1}H NMR (600 MHz, DMSO) δ = 9.41 (d, *J* = 6.3 Hz, 2H), 8.59 (t, *J* = 7.7 Hz, 1H), 8.21 (t, *J* = 7.2 Hz, 2H), 4.41 (s, 3H).[39a] ^{15}N NMR (60.8 MHz, DMSO): δ = 252.4.

(b) Pyridine *N*-oxide (**4**) (0.026 g, 0.27 mmol) was dissolved in dry CH_2Cl_2 (0.8 mL) in a vial inside a glove box under an atmosphere of dry N_2. Methyl triflate (0.040 g, 0.24 mmol) was added to the solution dropwise. The entire reaction mixture was transferred to an NMR tube. The NMR tube was sealed with a rubber septum (wrapped around the outside with PTFE tape and then Parafilm) under inert atmosphere. After ca. 30 minutes, the NMR tube was removed from the glove box, and the sample was analysed by ^{1}H and ^{1}H-^{15}N HMBC NMR spectroscopy (in CH_2Cl_2, using the solvent

signal suppression protocol referred to above). Quantitative conversion to the product was observed based on the ^{1}H NMR spectrum (based on consumption of MeOTf, i.e. the excess of **4** used remains).

^{1}H NMR (600 MHz, CH_2Cl_2) Signals of **13b**: δ = 9.18 (d, J = 6.7 Hz, 2H), 8.57 (td, J = 7.8, 0.8 Hz, 1H), 8.17 (t, J = 7.2 Hz, 2H), 4.47 (s, 3H).[39a] Signals of residual **4**: δ = 8.24–8.21 (m, 2H), 7.45–7.38 (m, 3H). ^{15}N NMR (60.8 MHz, CH_2Cl_2): δ = 251.0 (**13b**). No correlations for signals of **4** were detected.

Acknowledgments

This work was undertaken using equipment provided by Science Foundation Ireland though a research infrastructure award for process flow spectroscopy (ProSpect) (grant: SFI 15/RI/3221) and as part of the Synthesis and Solid-State Pharmaceutical Centre supported by Science Foundation Ireland (grant: SFI SSPC2 12/RC/2275). K. J. S. would like to thank the Irish Research Council for provision of a GOIPG research grant to fund his research (IRC GOIPG/2018/1517). Support from the Fonds der Chemischen Industrie (Liebig scholarship to M. B.) and the University of Cologne within the excellence initiative is gratefully acknowledged. We gratefully acknowledge the excellent analytical services provided in the School of Chemistry and ABCRF in UCC, Prof. Justin Holmes and research group for access to a nitrogen atmosphere glove box, Dr. Denis Lynch for assistance with NMR spectroscopy, and Mick O'Shea for HRMS data. Finally, we would like to acknowledge a very helpful observation from a reviewer on diagnostic trends in our ^{13}C NMR spectroscopic data.

Keywords: Alkylation · Nitrogen heterocycles · ^{1}H–^{15}N HMBC · Nitrogen · NMR spectroscopy

[1] P. A. Byrne, K. J. Sheehy, S. Buckley, H. Mayr, *unpublished results*.
[2] a) G. E. Martin, A. J. Williams, *Annu. Rev. NMR Spectrosc.* **2015**, *84*, 1–76; b) R. Marek, A. Lyčka, E. Kolehmainen, E. Sievänen, J. Toušek, *Curr. Org. Chem.* **2007**, *11*, 1154–1205; c) G. E. Martin, A. J. Williams, *Annu. Rev. NMR Spectrosc.* **2005**, *55*, 1–119; d) R. Marek, A. Lyčka, *Curr. Org. Chem.* **2002**, *6*, 35–66; e) M. Köck, J. Junker, T. Lindel, *Org. Lett.* **1999**, *1*, 2041–2044; f) J. Saurí, A. J. Williams, G. E. Martin in *Modern NMR Approaches to the Structure Elucidation of Natural Products*, Volume 2, (Eds.: A. J. Williams, G. E. Martin, D. Rovnyak), RSC, Cambridge, **2016**, pp. 71–116; g) R. T. Williamson, A. V. Buevich, G. E. Martin, *Tetrahedron Lett.* **2014**, *55*, 3365–3366; h) M. Kline, S. Cheatham, *Magn. Reson. Chem.* **2003**, *41*, 307–314.
[3] a) M. Witanowski, *J. Am. Chem. Soc.* **1968**, *90*, 5683–5689; b) R. L. Lichter, J. D. Roberts, *J. Am. Chem. Soc.* **1971**, *93*, 5218–5224; c) J. D. Baldeschwieler, E. W. Randall, *Proc. Chem. Soc.* **1961**, 303–304; d) Z. Dega-Szafran, M. Szafran, L. Stefaniak, C. Brevard, M. Bourdonneau, *Magn. Reson. Chem.* **1986**, *24*, 424–427.
[4] E. Haslinger, M. Schlederer, W. Robien, P. Wolschann, *Monatsh. Chem.* **1984**, *115*, 1345–1351.
[5] a) L. Pazderski, *Magn. Reson. Chem.* **2008**, *46*, S3–S15; b) R. M. Shanahan, A. Hickey, L. M. Bateman, M. E. Light, G. P. McGlacken, *J. Org. Chem.* **2020**, *85*, 2585–2596; c) R. Kleinmaier, S. Arenz, A. Karim, A.-C. C. Carlsson, M. Erdélyi, *Magn. Reson. Chem.* **2013**, *51*, 46–53; d) See ref.[2c]; e) L. Pazderski, T. Pawlak, J. Sitkowski, L. Kozerski, E. Szłyk, *Magn. Reson. Chem.* **2010**, *48*, 417–426; f) L. Pazderski, *Annu. Rep. NMR Spectrosc.* **2013**, *80*, 33–179.
[6] B. Costisella, J. Schulz, H. Teichmann, C. Donaths, M. Meisels, *Phosphorus Sulfur Silicon Relat. Elem.* **1990**, *53*, 367–371.
[7] M. Szafran, Z. Dega-Szafran, A. Katrusiak, G. Buczak, T. Głowiak, J. Sitkowski, L. Stefaniak, *J. Org. Chem.* **1998**, *63*, 2898–2908.
[8] Approximate δ_N values for the *N*-alkylpyridinium salts produced by N-alkylation of pyridines with bromoalkyl nitriles have also been reported. Derived $\Delta(\delta_N)$ values are of the order of –100 ppm, but as exact δ_N values are not reported, precise $\Delta(\delta_N)$ values cannot be determined: K. C. Lethesh, K. Van Hecke, L. Van Meervelt, P. Nockemann, B. Kirchner, S. Zahn, T. N. Parac-Vogt, W. Dehaen, K. Binnemans, *J. Phys. Chem. B* **2011**, *115*, 8424–8438.
[9] E. Lukevics, E. Leipiņš, I. Segal, M. Fleisher, *J. Organomet. Chem.* **1991**, *406*, 283–298.
[10] P. Cmoch, *Magn. Reson. Chem.* **2003**, *41*, 693–698.
[11] A. R. Katrizky, B. E.-D. M. El-Gendy, B. Draghici, D. Fedseyenko, A. Fadli, E. Metais, *Magn. Reson. Chem.* **2010**, *48*, 397–402.
[12] R. Marek, O. Humpa, J. Dostál, J. Slavík, V. Sklená, *Magn. Reson. Chem.* **1999**, *37*, 195–202.
[13] Some further examples involving isoquinolines and related but not directly derived *N*-methylisoquinolinium ions also demonstrate this principle qualitatively: a) See ref.[12]; b) A. Czyrski, U. Girreser, T. Hermann, *J. Mol. Struct.* **2013**, *1036*, 111–114; c) See ref. 2d.
[14] a) R. Marek, J. Brus, J. J. Toušek, L. Kovács, D. Hocková, *Magn. Reson. Chem.* **2002**, *40*, 353–360; b) A. K. Bakkestuen, L. L. Gundersen, D. Petersen, B. T. Utenova, A. Vik, *Org. Biomol. Chem.* **2005**, *3*, 1025–1033; c) H. Roggen, L. L. Gundersen, *Eur. J. Org. Chem.* **2008**, 5099–5106; d) M. Hocek, R. Pohl, I. Císařová, *Eur. J. Org. Chem.* **2005**, 3026–3030.
[15] Z. Dega-Szafran, M. Szafran, J. Sitkowski, L. Stefaniak, *J. Phys. Org. Chem.* **1996**, *9*, 746–750.
[16] a) K. A. Farley, P. B. Bowman, J. C. Brumfield, F. W. Crow, W. K. Duholke, J. E. Guido, R. H. Robins, S. M. Sims, R. F. Smith, T. J. Thamann, B. S. Vonderwell, G. E. Martin, *Magn. Reson. Chem.* **1998**, *36*, S11–S16; b) G. E. Martin, C. E. Hadden, J. R. Blinn, M. H. M. Sharaf, A. N. Tackie, P. L. Schiff Jr., *Magn. Reson. Chem.* **1999**, *37*, 1–6; c) C. E. Hadden, W. K. Duholke, J. E. Guido, R. H. Robins, G. E. Martin, M. H. M. Sharaf, P. L. Schiff Jr., *J. Heterocycl. Chem.* **1999**, *36*, 525–531.
[17] The ^{15}N NMR chemical shift values are referenced to liquid ammonia at 0 ppm (equivalent to referencing to nitromethane at 380.2 ppm) as per the convention specified in ref.[2a].
[18] See experimental details in the Supporting Information on pages S8 to S22.
[19] Details of the conversion calculations are given in the Supporting Information – see pages S8–S22 for experimental details.
[20] A. Dokalik, H. Kalchhauser, W. Mikenda, G. Schweng *Magn. Reson. Chem.* **1999**, *37*, 895–902. In addition to ^{15}N NMR spectroscopic data for diazines and other heterocycles in [D_6]DMSO solvent, similar data in $CDCl_3$ is also given.
[21] M. Witanowski, W. Sicinska, S. Biernat, G. A. Webb, *J. Magn. Reson.* **1989**, *83*, 351–357.
[22] M. Sawada, Y. Takai, S. Yamano, S. Misumi, T. Hanafusa, Y. Tsuno, *J. Org. Chem.* **1988**, *53*, 191–194.
[23] D. Sanz, A. Perona, R. M. Claramunt, J. Elguero, *Tetrahedron* **2005**, *61*, 145–154.
[24] A detailed description of how inert NMR spectral analysis was carried out is given on page S5 of the Supporting Information.
[25] Methylation of pyridine *N*-oxide (**10**) by MeI, for example, has been shown to be reversible in MeCN (equilibrium favours starting materials): V. P. Andreev, *Chem. Heterocycl. Compd.* **2010**, *46*, 184.
[26] For ^{15}N NMR chemical shift data of N-alkylation adducts of diazines (taken from ^{1}H-^{15}N HMBC NMR spectra), see pages S8 to S15 in the Supporting Information, and pages S23 – S48 of the Supporting Information for copies of NMR spectra.
[27] For ^{15}N NMR chemical shift data of O-alkylation adducts of *N*-oxides (taken from ^{1}H-^{15}N HMBC NMR spectra), see pages S16 to S22 in the Supporting Information, and pages S23–S48 of the Supporting Information for copies of NMR spectra, including ^{1}H-^{15}N HMBC NMR spectra showing multiple bond correlations between N and N-alkyl or N and O-alkyl groups.
[28] Similar correlations (in ^{1}H-^{15}N HMBC NMR spectra) have been used to establish structures of nitrogen-containing products of reactions: a) P. H. Vasconcelos Vontobel; R. dos Santos Fuscaldo, F. P. dos Santos, J. Sobieski da Costa *Magn. Reson. Chem.* DOI: https://doi.org/10.1002/mrc.4980; b) A. Salgado, C. Varela, A. M. García Collazo, P. Pevarello, *Magn. Reson. Chem.* **2010**, *48*, 614–622.

[29] W. Städeli, W. von Philipsborn, *Helv. Chim. Acta* **1980**, *63*, 504–522.
[30] I. Yavari, J. D. Roberts, *Org. Magn. Reson.* **1979**, *12*, 87–91.
[31] M. Witanowski, W. Sicinska, S. Biernat, G. A. Webb, *J. Magn. Reson.* **1991**, *91*, 289–300.
[32] V. Kolman, M. Babinský, P. Kulhánek, R. Marek, V. Sindelar, *New J. Chem.* **2011**, *35*, 2854–2859.
[33] δ_C for benzhydrylpyridinium bromide = 75.4 ppm: A. R. Katrizky, Z. Dega-Szafran, *Magn. Reson. Chem.* **1989**, *27*, 1090–1105. This publication contains NMR spectroscopic data for many other *N*-alkylpyridinium ions .
[34] For δ_C values of various benzhydyrl derivatives of *N*′,*N*′-dimethylaminopyridine, see: F. Brotzel, B. Kempf, T. Singer, H. Zipse, H. Mayr, *Chem. Eur. J.* **2007**, *13*, 336–345.
[35] Tables S1 and S2 may been seen on page S48 to S51 of the Supporting information.
[36] See Table S1 on page S48–49 of the Supporting Information.
[37] a) R. A. Newmark, A. Tucker, L. C. Hardy, *Magn. Reson. Chem.* **1996**, *34*, 728–729; b) F. B. Mortzfeld, J. Pietruszka, I. R. Baxendale, *Eur. J. Org. Chem.* **2019**, 5424–5433; c) H. Chaumeil, P. Jacques, V. Diemer, D. L. Nouën, C. Carré, *J. Mol. Struct.* **2011**, *1002*, 70–75; d) D. Jun, M. Paar, J. Binder, J. Marek, M. Pohanka, P. Stodulka, K. Kuca, *Lett. Org. Chem.* **2009**, *6*, 500–503; e) E. Lukevics, E. Leipiņš, I. Segal, M. Fleisher, *J. Organomet. Chem.* **1991**, *406*, 283–298; f) J. Eberhard, K. Peuntinger, R. Fröhlich, D. M. Guldi, J. Mattay, *Eur. J. Org. Chem.* **2018**, 2682–2700; g) R. Marek, J. Toušek, J. Dostál, J. Slavík, R. Dommisse, V. Sklenář, *Magn. Reson. Chem.* **1999**, *37*, 781–787; h) T. Brünig, K. Krekić, C. Bruhn, R. Pietschnig, *Chem. Eur. J.* **2016**, *22*, 16200–16212; i) G. Feng, X. Luo, X. Lu, S. Xie, L. Deng, W. Kang, F. He, J. Zhang, C. Lei, B. Lin, Y. Huang, Z. Nie, S. Yao, *Angew. Chem. Int. Ed.* **2019**, *58*, 6590–6594; *Angew. Chem.* **2019**, *131*, 6145.
[38] See Table S2 on page S50–51 of the Supporting Information.
[39] a) X. Ma, S. B. Herzon, *J. Am. Chem. Soc.* **2016**, *138*, 8718–8721; b) X. Gao, S. Han, M. Zheng, A. Liang, J. Li, D. Zou, Y. Wu, Y. Wu, *J. Org. Chem.* **2019**, *84*, 4040–4049.
[40] See Table S3 on page S52–53 of the Supporting Information.
[41] a) F. Brotzel, B. Kempf, T. Singer, H. Zipse, H. Mayr, *Chem– Eur. J.* **2007**, *13*, 336–345; b) A. R. Katritzky, Z. Dega-Szafran, *Magn. Reson. Chem.* **1989**, *27*, 1090–1093; c) M. L. Bennasar, T. Roca, M. Monerris, C. L. Juan, J. Bosch, *Tetrahedron* **2002**, *58*, 8099–8106; d) M. L. s. Bennasar, T. Roca, E. Zulaica, M. Monerris, *Tetrahedron* **2004**, *60*, 6785–6789; e) W. Huang, J. Guo, Y. Xiao, M. Zhu, G. Zou, J. Tang, *Tetrahedron* **2005**, *61*, 9783–9790; f) M. Sabbah, L. Soulère, S. Reverchon, Y. Queneau, A. Doutheau, *Bioorg. Med. Chem.* **2011**, *19*, 4868–4875; g) J. Kabatc, K. Kostrzewska, R. Dobosz, Ł. Orzeł, K. Jurek, *J. Polym. Sci., Part A J. Polym. Sci. A1.* **2017**, *55*, 2840–2850; h) D. Shukla, S. P. Adiga, W. G. Ahearn, J. P. Dinnocenzo, S. Farid, *J. Org. Chem.* **2013**, *78*, 1955–1964; i) I. Kim, B. Park, G. Kang, J. Kim, H. Jung, H. Lee, M.-H. Baik, S. Hong, *Angew. Chem. Int. Ed.* **2018**, *57*, 15517–15522; *Angew. Chem.* **2018**, *130*, 15743; j) A. Fuentes, R. Martínez-Palou, H. A. Jiménez-Vázquez, F. Delgado, A. Reyes, J. Tamariz, *Monatsh. Chem.* **2005**, *136*, 177–192; k) T. S. Balaban, I. Tămăşan, C. Deleanu, *Liebigs Ann. Chem.* **1992**, 173–175.
[42] a) The ^{15}N NMR chemical shift of *N*,*N*-dimethylpiperidinium iodide in $CDCl_3$ is 8.1 ppm downfield of that of *N*-methylpiperidine: F. Potmischil, H. Duddeck, A. Nicolescu, C. Deleanu, *Magn. Reson. Chem.* **2007**, *45*, 231–235; b) The ^{15}N NMR chemical shift of tetramethylammonium bromide in H_2O is 5.3 ppm downfield of that of trimethylamine: O. Vogl, A.-u. Rehman, P. Zarras, *Monatsh. Chem.* **2000**, *131*, 437–449.
[43] See for example: a) C. Sakuma, M. Maeda, K. Tabei, A. Ohta, A. Kerim, T. Kurihara, *Magn. Reson. Chem.* **1996**, *34*, 567–570; b) N. S. Rao, G. B. Rao, B. N. Murthy, N. M. Das, T. Prabhakar, M. Lalitha, *Spectrochim. Acta Part A* **2002**, *58*, 2737–2757.
[44] P. Brough, C. Klumpp, A. Bianco, S. Campidelli, M. Prato, *J. Org. Chem.* **2006**, *71*, 2014–2020.

Received: March 12, 2020