A ^{15}N NMR STUDY OF *N*-PHENYLAZOLES

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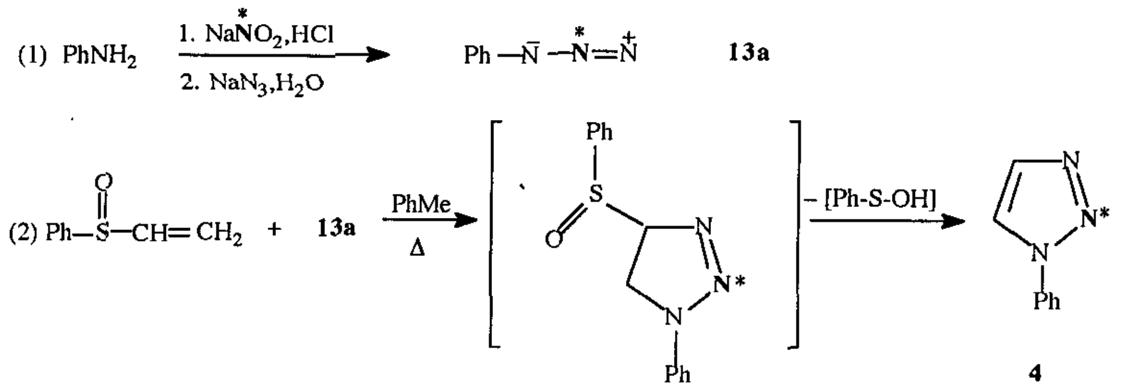
Dedicated to Professor Dr. Rolf Huisgen on the occasion of his 75th birthday.

Abstract - The ^{15}N chemical shifts for a series of eleven *N*-phenylazoles were determined. Assignments for a triazole and four tetrazoles were based on ^{15}N enrichment at specific sites.

Over thirty years ago reports from Professor Huisgen's laboratory presaged his pioneering work in 1,3-dipolar cycloadditions.[2] One of the initial systems investigated was the thermolysis of 2,5-disubstituted tetrazoles.[3] At the same time ^{1}H and later ^{13}C nmr spectroscopy were used to study the sites of alkylation, protonation, and annular tautomerism of tetrazoles.[4,5] Over the past decade ^{15}N nmr spectroscopy has emerged as the method of choice to characterize a variety of azoles, including tetrazoles.[6] In the present work we report ^{15}N nmr spectral data for a series of *N*-phenylazoles. This work extends prior correlations of *N*-methyl- and *N*-aminoazoles.[7,8] The choice of the phenyl derivative stemmed from our early interest in 5-phenyltetrazole thermolysis[9] and from the current interest in angiotensin II antagonists, in which 5-aryltetrazoles are a key structural feature.[10]

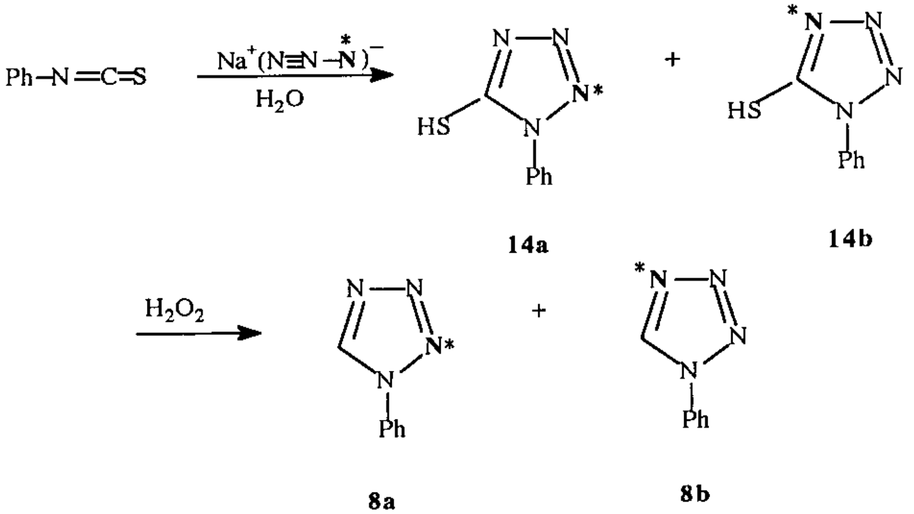
The structures for the ring systems in the present study are shown in Table 1. The chemical shift values for *N*-phenylpyrrole (**1**) and the *N*-phenyldiazoles (**2** and **3**) permit identification of the trigonally-bonded nitrogen atoms and the pyridine type nitrogens. It is also known that the latter type of nitrogen is more deshielding than a trigonal nitrogen.[6a] These interpretations were the basis for assignments in 1-methyl-1,2,3-triazole ($\Delta\delta$ 13 ppm for N-2/N-3).[7a] In linear triazole (**4**) the resonance farthest downfield is similarly assigned to N-2, being flanked by two nitrogen atoms. In this case, however, the difference between N-2 and N-3 is only 4.3 ppm and the assignments are therefore less secure. Accordingly, **4** was prepared with ^{15}N enrichment at N-2. Since prior routes to **4** involved multiple steps and/or sealed tube reactions with acetylene or ethynyltrimethylstannane,[14,15] a new synthesis was devised. We found that phenyl azide was directly converted to **4** by heating with phenyl vinyl sulfoxide (Scheme 1).[16] Although the structure of the intermediate adduct has not been established, the postulated structure is consistent with Hückel calculations.[17] The labelled site in azide (**13**) is known from earlier work.[18] The nmr spectrum of **4** confirmed the assignment for N-2. The chemical shift values for the other triazoles (**5**-**7**) are unambiguous.



Scheme 1

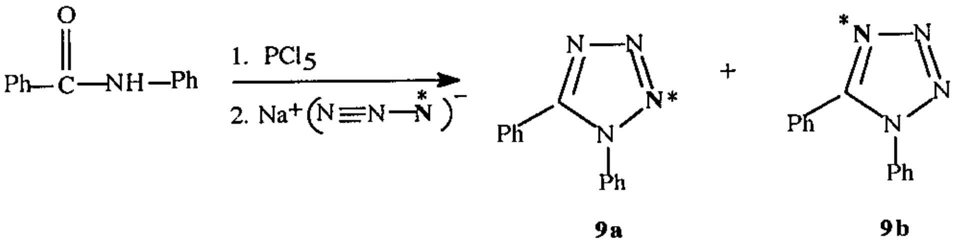
Chemical shift assignments for the 1- and 2-substituted tetrazoles (**8** and **10**, respectively) are not so straightforward. In both systems the pyridine type nitrogens are problematical. In the case of **8** the question is which of the two interior nitrogens (N-2 or N-3) is further downfield, since both are flanked by two nitrogen atoms; it is assumed that N-1 is at highest field and that N-4 is the next highest signal. In the case of **10** the question is which of the two terminal nitrogens (N-1 or N-4) is further downfield; it is assumed that N-2 is at highest field and that N-3 is at lowest field. These questions have been addressed by others in terms of molecular orbital calculations,[7cef] additivity schemes for shielding parameters,[7a] substituent effects,[7e] and protonation effects.[7f] In previous studies of 1-methyltetrazole and 1,5-dimethyltetrazole the lowest field signal was consistently assigned to N-3. With 2-methyltetrazole and 2,5-dimethyltetrazole, however, there was no consensus on the signal at lowest field, which was assigned to N-3 of 2-methyltetrazole[7acf] and to N-4 of 2,5-dimethyltetrazole.[7e]

Given this conflicted situation, we undertook the preparation of tetrazoles enriched with ^{15}N at specific sites. There are two prior studies of ^{15}N enriched tetrazoles, but both systems involved substituents only at C-5. Annular tautomerism therefore equilibrated positions N-1/N-4 and N-2/N-3.[4f,19] Our routes to **8-11** are outlined in Schemes 2-6. The use of sodium azide enriched at one terminus (Schemes 2 and 3) afforded mixtures



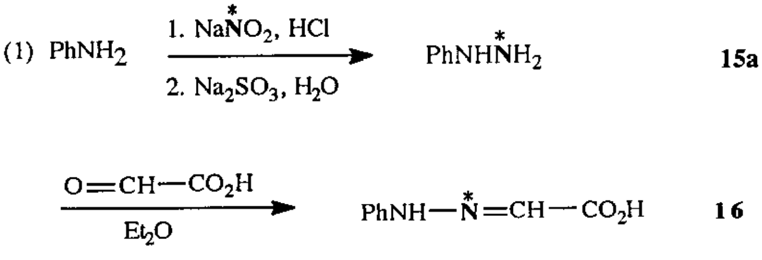
Scheme 2

of products, but each was labelled at only one position. Thus, the ^{15}N spectrum of **8ab** confirmed the N-4 chemical shift and distinguished between N-2 and N-3. Similar deductions were made in the case **9ab**.



Scheme 3

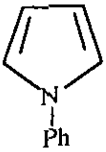
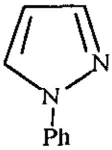
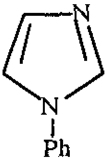
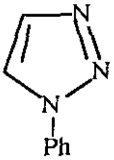
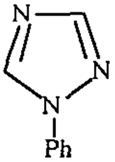
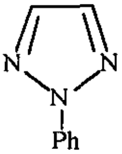
For the 2-substituted tetrazoles (**10** and **11**) doubly-labelled compounds were prepared with different ^{15}N enrichment levels at specific positions. In Scheme 4 step (1) was carried out with 10% ^{15}N and step (2) with 5%

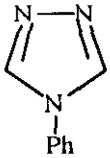
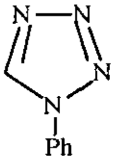
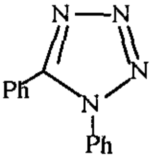
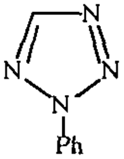
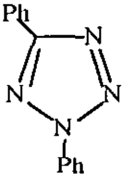
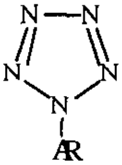


$$\text{(1) } PhNH_2 \xrightarrow[\text{2. } Na_2SO_3,\ H_2O]{\text{1. } Na\overset{*}{N}O_2,\ HCl} PhNH\overset{*}{N}H_2 \qquad \mathbf{15a}$$

$$\xrightarrow[Et_2O]{O{=}CH{-}CO_2H} PhNH{-}\overset{*}{N}{=}CH{-}CO_2H \qquad \mathbf{16}$$

Table 1. ^{15}N Nmr Chemical Shifts of *N*-Phenylazoles

		δ^a				
Compound	S^b	N-1	N-2	N-3	N-4	Ref.^{c}
1 	D	-205.8				
2 	D C B	-159.9 -164.2 -160.1	- 77.3 - 78.2 - 75.3			 6a, 11 12
3 	D	-194.4		-114.4		
4 	D	-125.5	**-20.5***	- 25.0		
5 	D	-154.0	- 89.5		-124.4	
6 	D	- 57.6	-119.1	- 57.6		

7		D	- 58.2	- 58.2		-193.7	
8		D	-133.7	**-17.4***	+ 13.2	**-49.0***	
		D	-134.2	- 17.7	+ 12.7	- 49.6	7f
9		D	-140.6	**- 7.6***	+ 9.7	**-52.5***	
10		D	**-80.6***	- 89.8	**- 6.2***	- 44.2	
11		D	**-90.4***	**-89.9***	**- 4.7***	**-51.3***	
12		C	- 80.0	**-27.1[d]***	+ 4.9	+ 4.9	13

AR = *p*-dimethylaminophenyl

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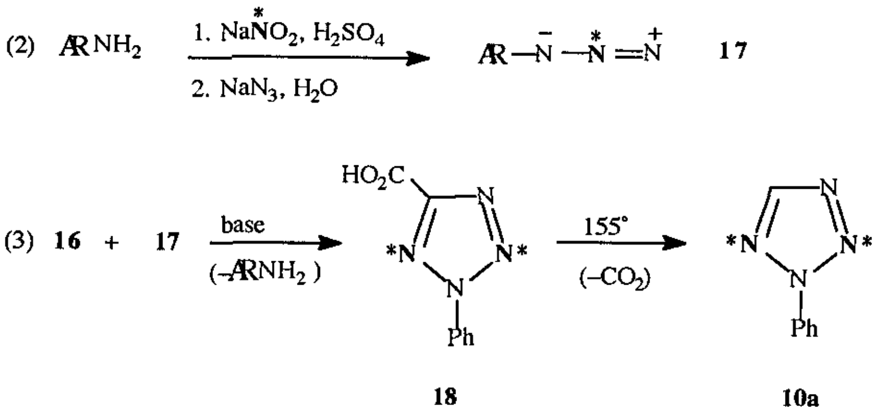
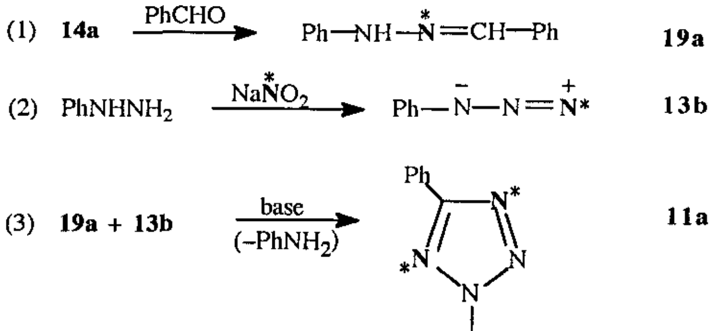
[a] In ppm relative to external neat nitromethane such that a decrease in shielding corresponds to a positive increment. [b] Solvents: D = $(CD_3)_2SO$; C = $CDCl_3$; B = C_6D_6. [c] Present work unless otherwise noted. [d] Also N-5.



AR = 2,4,6-tribromophenyl

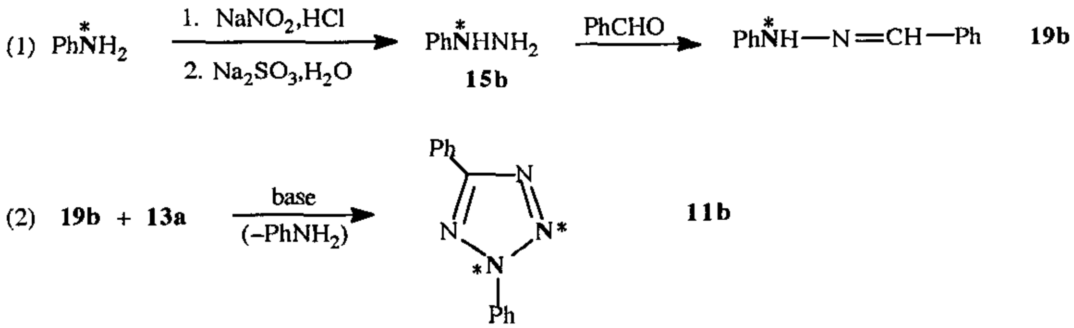
Scheme 4

^{15}N. The base-catalyzed condensation of step (3), followed by thermal decarboxylation, afforded **10a** enriched 10% at N-1 and 5% at N-3. The nmr spectrum exhibited signals of differential height which confirmed the labelled sites and chemical shift assignments. Doubly-labelled **11** was prepared by two different routes. In Scheme 5 steps (1) and (2) were carried out similarly with ^{15}N enrichment levels of 10% and 5%, respectively.



Scheme 5

Step (3) afforded **11a** enriched 10% at N-1 and 5% at N-4, whose chemical shifts were thereby established. Interestingly, however, the spectrum of **11a** exhibited no high field signal for N-2. Suspecting that N-2 and N-4 may be coincident, we sought confirmation of N-2 by further labelling studies. Thus, **11b** was prepared (Scheme 6) with ^{15}N enrichment of 99% at N-2 and *ca.* 32% at N-3. The nmr spectrum of **11b** exhibited labelled peaks



Scheme 6

at -89.9 and -4.7 ppm for N-2 and N-3, respectively. A coupling constant J ($^{15}N2$-$^{15}N3$) of 17.9 Hz was observed, similar to that reported for doubly-labelled **2**.[12] Thus, the assignments for all 15N chemical shifts in tetrazoles(**1**-**11**)have been established.

For completeness of the azole series, Table 1 includes data for the one reported pentazole (**12**); chemical shifts were confirmed by ^{15}N labelling of N-2/N-5.[13]

EXPERIMENTAL

Melting points are uncorrected. GC/MS analyses were performed on a Hewlett-Packard 5890II gas chromatograph (HP-1 crosslinked methyl silicone gum column, 12 m x 200 μm with 33 μm film) and a Hewlett-Packard 5791A mass spectrometer (EI, 70 eV). Liquid chromatography was carried out on short columns of alumina (ICN neutral, Super I) with elution by dichloromethane. Compounds (**1**-**3**) were commercially available. Aniline (98% ^{15}N) and sodium azide (99% ^{15}N-1) were purchased from Cambridge Isotope Laboratories; sodium nitrite (99% ^{15}N) was purchased from C/D/N Isotopes Inc.

Phenyl Azide (**13**). To a stirred solution of aniline (1.12 g, 12.0 mmol) in 4N HCl (8 ml) at 0 °C was added dropwise a solution of $NaNO_2$ (0.913 g, 13.2 mmol; 40% ^{15}N) in H_2O (2 ml). After 15 min a solution of urea (0.10 g, 1.7 mmol) in H_2O (0.5 ml) was added. The solution was treated with decolorizing carbon, cooled to -5 °C and stirred with Et_2O (5 ml) as a solution of NaN_3 (0.858 g, 13.2 mmol) was added dropwise. After 30 min the solution was allowed to warm to room temperature and washed with 3M Na_2CO_3 (3x10 ml); the combined aqueous alkaline wash was extracted once with Et_2O (10 ml). The combined ether solution was dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure. The crude product was evaporatively distilled in a modified Hickman still[20] (block 40 °C, 9 mm) to give **13a** (1.034 g, 72.4%) as a pale yellow liquid.

Phenyl azide (**13b**) was prepared by the modified procedure of Lindsay and Allen.[21] Phenylhydrazine (1.19 g, 11.0 mmol) was dissolved in 2.5N trifluoroacetic acid (10 ml), and Et_2O (4 ml) was added. A solution of $NaNO_2$ (0.897 g, 13.0 mmol; 5% ^{15}N) in H_2O (1.2 ml) was added dropwise to the stirred mixture at 0 °C. After 15 min 3M Na_2CO_3 (10 ml) was added. The mixture was stirred vigorously for 10 min, allowed to warm to room temperature, and steam-distilled. The ether layer was removed and the aqueous phase (40 ml) was extracted with Et_2O (2x10 ml). The combined ether extract was worked up as before to give **13b** (0.705 g, 53.8%) as a pale yellow oil.

1-Phenyl-1,2,3-triazole (**4**). To a solution of phenyl vinyl sulfoxide (0.760 g, 5.00 mmol) in toluene (3.0 ml) was added **13a** (0.536 g, 4.50 mmol), the solution was refluxed 17 h under argon, and the solvent was removed by rotary evaporation at reduced pressure. The residue was boiled with 6N NaOH (5 ml) for 30 min, cooled, and extracted with CH_2Cl_2 (2x5 ml). The combined extract was dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure. The crude brown residue was triturated with boiling hexane (3x5 ml); the combined extract was concentrated and chilled to give yellow crystals, which were vacuum sublimed (105 °C, 9 mm) to give white needles of **4a** (0.22 g, 34%): mp 55 °C (lit.,[15] mp 56 °C).

1-Phenyl-1,2,4-triazole (**5**). The procedure of Micetich, Spevak, Hall and Bains[23] afforded **5** as a pale red oil: bp 115-119 °C, 1.8 mm (lit.,[22] bp 88-90 °C, 0.4 mm); 95.4% pure by GC/MS analysis.

2-Phenyl-1,2,3-triazole (**6**). The procedure of El Khadem and El-Shafei[23] gave crude product which was purified by liquid chromatography to give **6** as a pale yellow liquid; 99.7% pure by GC/MS analysis.

4-Phenyl-1,2,4-triazole (**7**). The method of Olofson[24] gave crude product which was purified by liquid chromatography to give **7** as white crystals: mp 121 °C (lit.,[24] mp 121 °C).

1-Phenyltetrazole-5-thiol (**14a/14b**). The method of Lieber and Ramachandran[25] was followed using sodium azide (0.190 g, 2.92 mmol; 20% ^{15}N-1) to give white crystals of **14a/14b** (0.302 g, 84.8%): mp 150 °C (lit.,[25] mp 150 °C).

1-Phenyltetrazole (**8a/8b**). The method of Stollé and Henke-Stark[26] was modified. To a stirred solution of **14a/14b** (0.302 g, 1.70 mmol) in 1N NH_4OH (1.70 ml) at 0 °C was added dropwise 30% H_2O_2 (0.685 g, 6.04 mmol) and stirring was continued 4 h at 0 °C. The solution was boiled for 10 min and cooled. The solid product was collected by suction filtration, washed, and dried to give white crystals of **8a/8b** (0.150 g, 60.6%): mp 65-

66 °C (lit.,[26] mp 66 °C).

1,5-Diphenyltetrazole (**9a/9b**). The method of Kadaba[27] was followed using NaN_3 (0.182 g, 2.80 mmol; 20% ^{15}N-1) to give **9a/9b** (0.225 g, 67.6%): mp 145-146 °C (lit.,[27] mp 144-146 °C).

Phenylhydrazine (**15**). The procedure of Coleman[28] was followed using $NaNO_2$ (2.21 g, 32.0 mmol; 10% ^{15}N) to give **15a**•HCl (3.0 g, 71%): mp 241-244 °C (lit.,[29] mp 243-246 °C).

The same procedure was used with aniline (0.50 g, 5.4 mmol; 99% ^{15}N) to give **15b**•HCl (0.57 g, 73%): mp 241-244 °C.

2,4,6-Tribromophenyl Azide (**17**). The method of Forster and Fierz[30] was modified. To a stirred solution of 2,4,6-tribromoaniline (7.59 g, 23.0 mmol) in glacial acetic acid (150 ml) and 96% H_2SO_4 (30 ml) at 8 °C was added dropwise a solution of $NaNO_2$ (1.725 g, 25.0 mmol; 5% ^{15}N) in H_2O (5 ml). After 30 min a solution of urea (0.20 g, 3.3 mmol) in H_2O (0.5 ml) was added, followed 10 min later by a solution of NaN_3 (1.725 g, 26.5 mmol) in H_2O (5 ml). The solution was stirred at 8 °C for 1 h and H_2O (200 ml) was added slowly with cooling. The precipitate was collected by suction filtration and recrystallized from 95% EtOH to give pink needles of **17** (7.47 g, 91.2%): mp 70-71 °C (lit.,[30] mp 72 °C).

Glyoxylic Acid Phenylhydrazone (**16**). To a solution of phenylhydrazine (**15a**) hydrochloride (2.17 g, 15.0 mmol) in H_2O (10 ml) was added 1N NaOH (15 ml), the solution was extracted with Et_2O (3x5 ml), and the combined ether exract was dried over Na_2SO_4 and filtered. To a solution of glyoxylic acid monohydrate (1.38 g, 15.0 mmol) in Et_2O (75 ml) under argon was added the ethereal phenylhydrazine solution in one portion. Rotary evaporation of the solvent gave yellow crystals of **16** (2.45 g, 99.3%): mp 133-136 °C (lit.,[4g] mp 134-137 °C). The crude product was used directly in the next step.

2-Phenyltetrazole-5-carboxylic Acid (**18**). The method of Lippmann, Könnecke, and Beyer[4g] was followed to give **18** (1.77 g, 62.0%): mp 136-137 °C (lit.,[4g] mp 137-138 °C).

2-Phenyltetrazole (**10**). The method of Lippmann, Könnecke, and Beyer[4g] afforded **10a** which was evaporatively distilled (block 105 °C, 11 mm) to give a nearly colorless liquid (0.913 g, 66.7%); 99.6% pure by GC/MS analysis.

Benzaldehyde Phenylhydrazone (**19**). The method of Vogel[31] was followed using **15a**•HCl (0.795 g, 5.50 mmol) to give **19a** (1.07 g, 99.0%): mp 156-157 °C (lit.,[31] mp 158 °C).

The same procedure was used with **15b**•HCl (0.567 g, 3.92 mmol) to give **19b** (0.75 g, 97%): mp 156-157 °C.

2,5-Diphenyltetrazole (**11**). The procedure of Huisgen, Sauer, and Seidel[3g] was followed using **19a** (1.07 g, 5.44 mmol) and **13b** (0.675 g, 5.67 mmol) to give **11a** (0.48 g, 41%): mp 100-101 °C (lit.,[3g] 101-103 °C).

The same procedure was used with **19b** (0.750 g, 3.81 mmol) and **13a** (0.473 g, 3.97 mmol) to give **11b** (0.51 g, 58%): mp 100-101 °C.

Nmr Spectra. Measurements were carried out for ^{15}N nuclei on a Brucker WP-200 SY spectrometer at 20.28 MHz in the Fourier transform mode at 298 ±1 °K and using an inverse gated decoupling pulse sequence. Samples (1.0 mmol azole), which were 0.5M solutions in DMSO-d_6 (except **11**, which was 0.3M) containing added Cr(acac)$_3$ (0.1 mmol), were spun in coaxial 10 mm tubes with neat nitromethane as external reference standard. The following spectral settings were used: spectral width, 9300 Hz; data points, 16K (digital resolution of 1.1 Hz per point); and pulse width, 12 μs (flip angle 30°). The relaxation delay was 10s, and the acquisition time was at least 6 h (a minimum of 1800 scans was accumulated for every spectrum).

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