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# 4-Isocyano-2,2,6,6-tetramethylpiperidin-1-oxyl: A Valuable Precursor for the Synthesis of New Nitroxides

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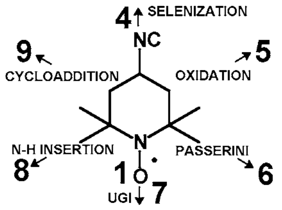
## ABSTRACT

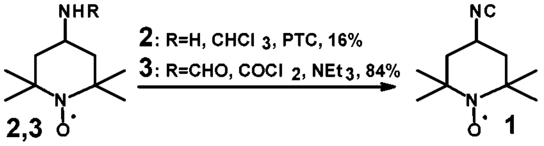


**To enrich the limited set of isonitriles typically employed, 4-isocyano-2,2,6,6-teramethylpiperidin-1-oxyl (1) is proposed as an isonitrile bearing a nitroxyl moiety. Isocyanide 1 was used in some reactions characteristic of isonitriles. Isoselenocyanate, amides (products of Passerini and Ugi reactions), and tetrazole derivative were obtained. The EPR spectra of the urea derivative 5b and a product of an Ugi reaction 7 (both dinitroxides) were analyzed.**

Recently, we described an efficient synthesis of an isonitrile bearing a nitroxyl moiety: 4-isocyano-2,2,6,6-tetramethylpiperidin-1-oxyl (**1**). Formylation of 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl (**2**) with ethyl formate, followed by dehydration of 4-formamido-2,2,6,6-tetramethylpiperidin-1-oxyl (**3**) with phosgene, resulted in the formation of **1** in 84% yield. The Hofmann carbylamine reaction of **2** with chloroform under PTC conditions gave **1**, but with a yield of only 16% (Scheme 1).[1]

The importance of isonitriles has increased in the past few years due to their application in such multicomponent reactions (MCRs) as the Passerini and Ugi reactions.[2−4] They are in turn ideal tools for creating combinatorial libraries. Isonitriles are also used as versatile building blocks for the synthesis of heterocyclic systems.[5] Typical isonitriles commonly used in the above reactions have been limited mainly to aryl, benzyl, cyclohexyl, and *tert*-butyl isocyanides. 4-Isocyano-2,2,6,6-tetramethylpiperidin-1-oxyl (**1**) increases the range of available isonitriles and furthermore allows insertion of a spin-labeled fragment into MCR products. This enables the study of the structures of product libraries created

**Scheme 1.** Synthesis of 4-Isocyano-2,2,6,6-tetramethylpiperidin-1-oxyl (**1**)[1]



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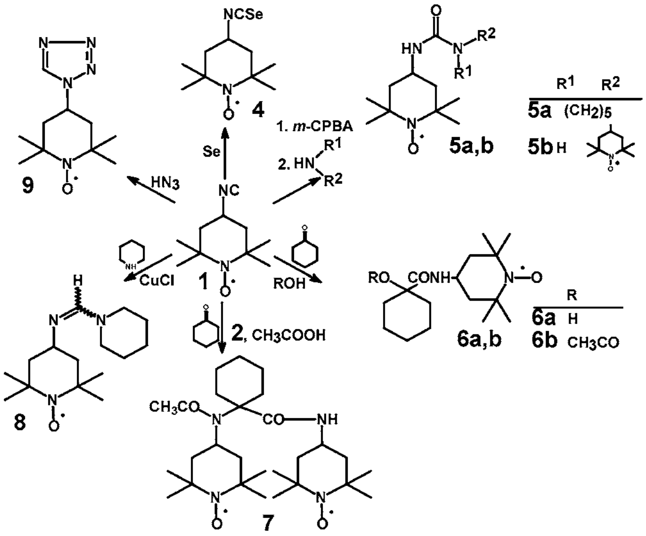
in MCR reactions and/or hetrocycles built from isonitriles by the spin-labeling technique.

The carbenoid character attributed to the isonitrile group [$R-N^{+}\equiv C^{-} \leftrightarrow R-N{=}C$:] may potentially be incompatible with the unpaired electron of the nitroxyl moiety. The ability of isonitriles bearing a nitroxyl moiety to react in a characteristic manner, is not apparent. Hence, in this work we wish to present the application of 4-isocyano-2,2,6,6-tetramethylpiperidin-1-oxyl **1** in some typical reactions of isonitriles.

**Products.** The reactions of isocyanide **1** are shown in Scheme 2.

**Scheme 2.** Reactions of **1**



The reaction of isocyanide **1** with selenium yielded isoselenocyanate **4**, an example of a nitroxide containing a selenium atom.[6]

Isonitriles cannot be oxidized directly by oxygen unless in the presence of a catalyst.[7] To obtain the corresponding isocyanate, isocyanide **1** was oxidized with several oxidizing systems. The use of DMSO/$p$-$CH_3C_6H_4SO_3H$[8] and DMSO/$Br_2$[9] as oxidizers was unsuccessful. The oxidation with $m$-CPBA ($m$-$ClC_6H_4CO_3H$) resulted in the formation of the corresponding isocyanate, which was trapped with piperidine or **2** as amines. The resulting urea derivatives **5a** and **5b**, respectively, were isolated, **5b** being a dinitroxide.

The reaction of isocyanide **1** and cyclohexanone with acidic components, water or acetic acid, leads to products of a Passerini reaction **6a** or **6b**, respectively, whereas acetic acid together with the amine **2** results in the product of an Ugi reaction **7**. When 2,2,6,6-tetramethyl-4-piperidinon-1-oxyl was used as the ketone component instead of cyclohexanone, both Passerini and Ugi reactions failed, probably due to the instability of 2,2,6,6-tetramethyl-4-piperidinon-1-oxyl. Both 2,6-dimethyl-6-nitrosohept-2-en-4-one[10] and phorone (2,6-dimethylhepta-2,5-dien-4-one) were recognized as products. Additionally, slow hydrolysis of **1** to **3** was also observed.

The ability of isocyanide **1** to insert into the N−H bond in the presence of cuprous chloride[11] was demonstrated for piperidine as a typical amine. As a result, the compound **8** was obtained.

The reaction of **1** with hydrazoic acid[12] caused 1,3-dipolar cycloaddition leading to the tetrazole derivative **9**. This demonstrates the ability of **1** to undergo a cyclization.

Procedures for the synthesis of **4**−**9** are available in the Supporting Information. Yields, melting points, and $R_f$ data of **4**−**9** are presented in Table 1.

**Table 1.** Yields, Melting Points, and $R_f$ Data for **4**−**9**

| product | yield (%) | mp (°C) | $R_f$[b] |
|---|---|---|---|
| **4** | 38 | 156−158 | 0.75 |
| **5a** | 54 | 85−87 | 0.32 |
| **5b** | 16 | 118−120[a] | 0.18 |
| **6a** | 86 | 139−142 | 0.21 |
| **6b** | 85 | 119−122 | 0.28 |
| **7** | 49 | oil | 0.20 |
| **8** | 57 | 89−92 | 0.35[b] |
| **9** | 33 | 157−159 | 0.23 |

[a] Melting point literature data for **5b**: 116−118 °C (EtOAc/pentane),[13] 145 °C (benzene),[14] 198−199 °C (hexane).[15] [b] On silica (**8** on alumina), benzene/methanol 9:1.

**EPR Spectra of Dinitroxides 5b and 7.** The EPR spectra for both **5b** and **7** (Figure 1) exhibit the biradical nature of the compounds.[16−19] The presence of five or more lines in the EPR spectrum results from the hyperfine interaction

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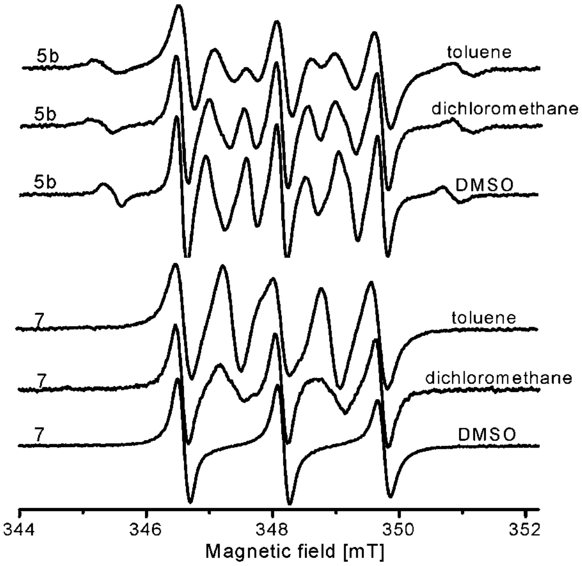

**Figure 1.** EPR spectra of biradicals **5b** and **7** in different solvents at room temperature.

(measured by $a_N$ parameter) between nitroxide nitrogen nuclei and biradical unpaired electrons efficiently coupled by the exchange interaction. The exchange interaction (measured by $J$ integral) leads to the triplet ($S = 1$) and singlet ($S = 0$) states for the case when $J/a_N > 0$.

For **7**, the spectra recorded in toluene, dichloromethane, and DMSO significantly differ from each other. A similar dependence of the spectral feature on the solvent was described for 2,2′-di(R$^\bullet$)biphenyl[16] and for $^\bullet$R$-$R$^\bullet$ (R$^\bullet$ = 2,2,6,6-tetramethyl-4-piperidyl-1-oxyl).[17] The spectra of **7**, however, differ substantially from those observed by us in this work and those previously observed for biradical **5b** in the same solvents.[14,18,20]

The EPR spectra of biradical **5b** exhibit seven lines due to the "triplet" –"triplet" (T) resonances and two much lower intensity lines due to the "singlet" –"triplet" (S) resonances. The hyperfine coupling constants $a_N$ (measured between $T$ resonances for the hypothetical case when $J/a_N \approx 0$) are weakly dependent on the solvent polarity. The value of $a_N$ changes from 1.53 mT in toluene to 1.57 in dichloromethane and 1.58 in DMSO and is in agreement with the results reported in.[20] The spectral feature is similar to that observed previously for **5b** which was assigned to $J/a_N \sim 1.1$.[17]

The EPR spectra of **7** shown in Figure 1 are strongly dependent on the solvent. The spectrum of **7** in toluene consists of five lines separated by 0.77 mT which is approximately a half of the $a_N$ determined for **5b**. The intensity ratio between the spectral lines is close to 1:1:1:1:1. Assuming a static mechanism of exchange interaction between unpaired electrons of the radical, the spectrum of **7** in toluene quite closely resembles the spectrum calculated theoretically, for $J/a_N \sim 10$.[17,19] In toluene solution the molecular structure of **7** may be treated as basic since it is weakly affected by the nonpolar solvent. However, the dissolution of biradical **7** in the polar solvent, DMSO, substantially changes the spectral properties leading to the three EPR lines separated by 1.58 mT. This fact, together with a strong static exchange between unpaired electrons of **7** (consistent with $J/a_N \sim 10$ for toluene solution), indicates the presence of a dynamic exchange between the radical conformers. A stabilization of different radical conformations by solvents seems to be more probable for **7**, due to its unsymmetrical structure, than for **5b**. The exchange between the conformations modulates the isotropic hyperfine interaction with nitroxide nitrogen nuclei, and the spectral lines located between the basic triplet are broadened according to the mechanism postulated for other biradicals.[17] This mechanism for **7** in toluene leads to the smallest change of the spectral lines, in dichloromethane to the characteristic line broadening, and finally in DMSO, due to the slowest exchange between the molecular conformations, to the appearance of a three line spectrum. It has been shown theoretically[19] that the spectra change from the 1:2:3:2:1 quintet (for the highest speed of exchange between the conformers) to the 1:1:1 triplet (for the lowest speed) in the case when $J = 33a_N$ which supports our supposition that the spectra observed by us for **7** correspond to $J/a_N$ value smaller than 33 and greater than 1. The spectral analysis reveals only a small change of $g_{iso}$ parameter value upon the solvent. In toluene, dichloromethane and DMSO solutions $g_{iso}$ = 2.00619, 2.00608, 2.00606 for **5b** and 2.00619, 2.00608, 2.00604 for **7**, respectively.

In conclusion, 4-isocyano-2,2,6,6-teramethylpiperidin-1-oxyl (**1**) was successfully used as an isonitrile bearing a nitroxyl moiety in some typical reactions of isonitriles. The expected compounds were obtained: isoselenocyanate, amides (products of Passerini and Ugi reactions), and tetrazole derivative. The yields varied from medium to good. Significantly, the application of **1** in MCR reactions would allow the design of combinatorial libraries which may contain a nitroxide fragment useful for spin-label measurements.

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**Supporting Information Available:** Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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