Novel Nitroxyl Radical Synthesis

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Cyclic nitroxyl radicals have many applications, from preventing radiation-induced alopecia to polymerization agents [3]. 2,2,5,5-tetrasubstituted pyrrolidine and 3-pyrrrole radicals are of particular interest because of the relatively long lifespans in biological environments before being reduced. Magnetic resonance imaging (MRI) typically relies on organometallic contrast agents. These have been shown to cause fibrosis in patients with renal issues. Dispirocyclohexyl substituted pyrroline nitroxyl radicals have been incorporated into poly(ethylene glycol) polyproylenimine dendrimer complexes for use as organic radical contrast agents [2]. 2,2,5,5-tetraethyl and -dispirocyclohexyl substituted 3-pyroline nitroxyl radicals have been effectively incorporated into amino acids for use as spin labels to study protein synthesis [4]. The kinetics of reduction of variously substituted pyrrolidine nitroxyl radicals has been studied using electron paramagnetic resonance (EPR) and the rates vary widely based on the protecting groups substituted to the 2,2,5,5 positions [1]. The synthesis of the various five-membered-cyclic nitroxyl radicals begins with the corresponding 2,2,6,6-tetrasubstituted-piperidine-4-one compound. The synthesis of novel compounds in this class is of interest because the corresponding nitroxyl radicals have potentially different properties from those previously synthesized, which may be utilized in the aforementioned medical research.

**Description**

Reaction of 1,2,2,6,6-pentamethyl-piperidine-4-one (A) with ketone (B) and NH₄Cl in DMSO at 55°C for 5 hrs (RXN 1). Multiple trials using different equivalents of ketones and NH₄Cl, temperatures, and dilutions were attempted.

**Reaction**

\[ A + B \rightarrow P \] RXN 1

**Background**

Detection of the product was attempted using nuclear magnetic resonance (NMR) and electro spray ionization (ESI) spectrosopies. Detection of the product molecule using NMR is difficult due to its similarity in structure to the starting molecule. Good conditions for RXN 1 were found to be 6.4 mmol B, 5.4 mmol NH₄Cl, and 16 mL DMSO per mmol A. The key to the reaction is dilution to prevent side-reactions of the unstable 4-member rings with one another. Trials attempting to react 3-oxycetanone with A proved unsuccessful. Future work includes oxidation of the product into the corresponding nitroxyl radical using MCPBA in DCM followed by spin measurement using EPR spectroscopy.

**Results**

**Citations**


**Purpose**

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