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Novel Nitroxyl Radical Synthesis

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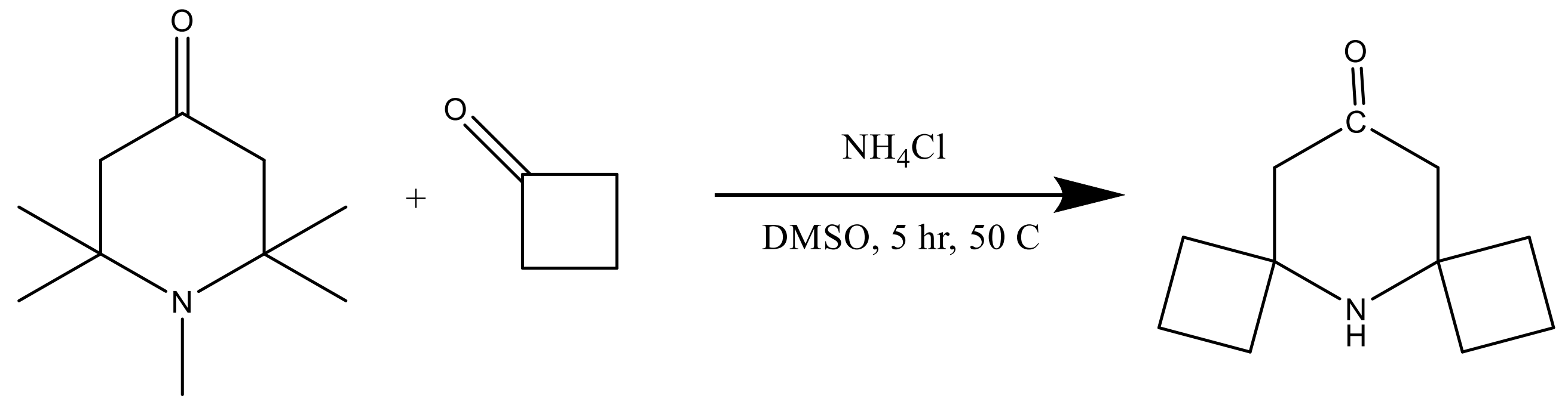
Background

Cyclic nitroxyl radicals have many applications, from preventing radiation-induced alopecia to polymerization agents [3]. 2,2,5,5-tetrasubstitued pyrrolidine and 3-pyrroline 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 pyrrolidine 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-pyrroline 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-penatamethyl-piperidine-4-one (A) with ketone (B) and NH_4Cl in DMSO at 55^{O}C for 5 hrs (RXN 1). Multiple trials using different equivalents of ketones and NH_4Cl, temperatures, and dilutions were attempted.

Reaction



A + B → P

RXN 1

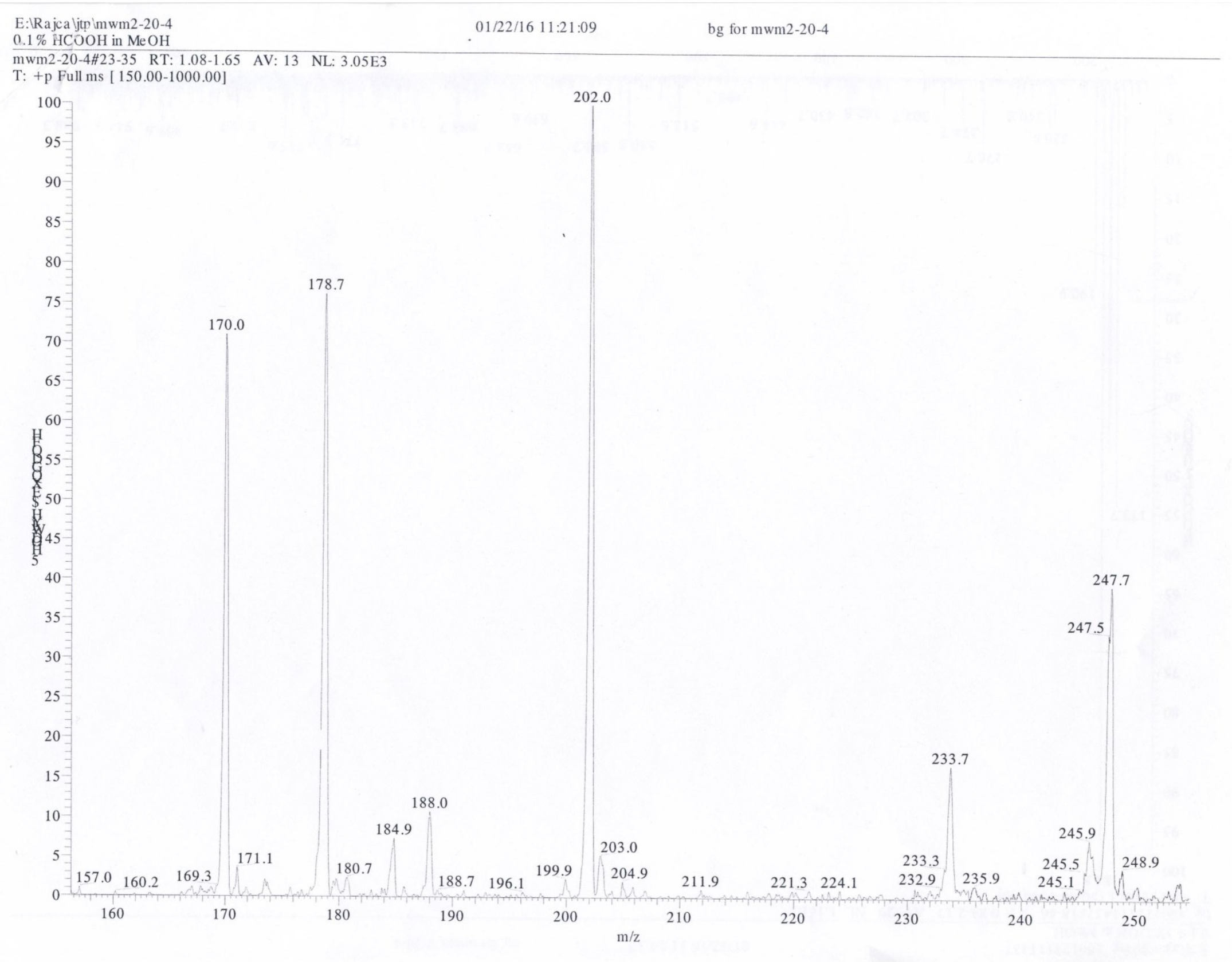


Figure 1: ESI following acid workup, 0.1% HCOOH in MeOH.

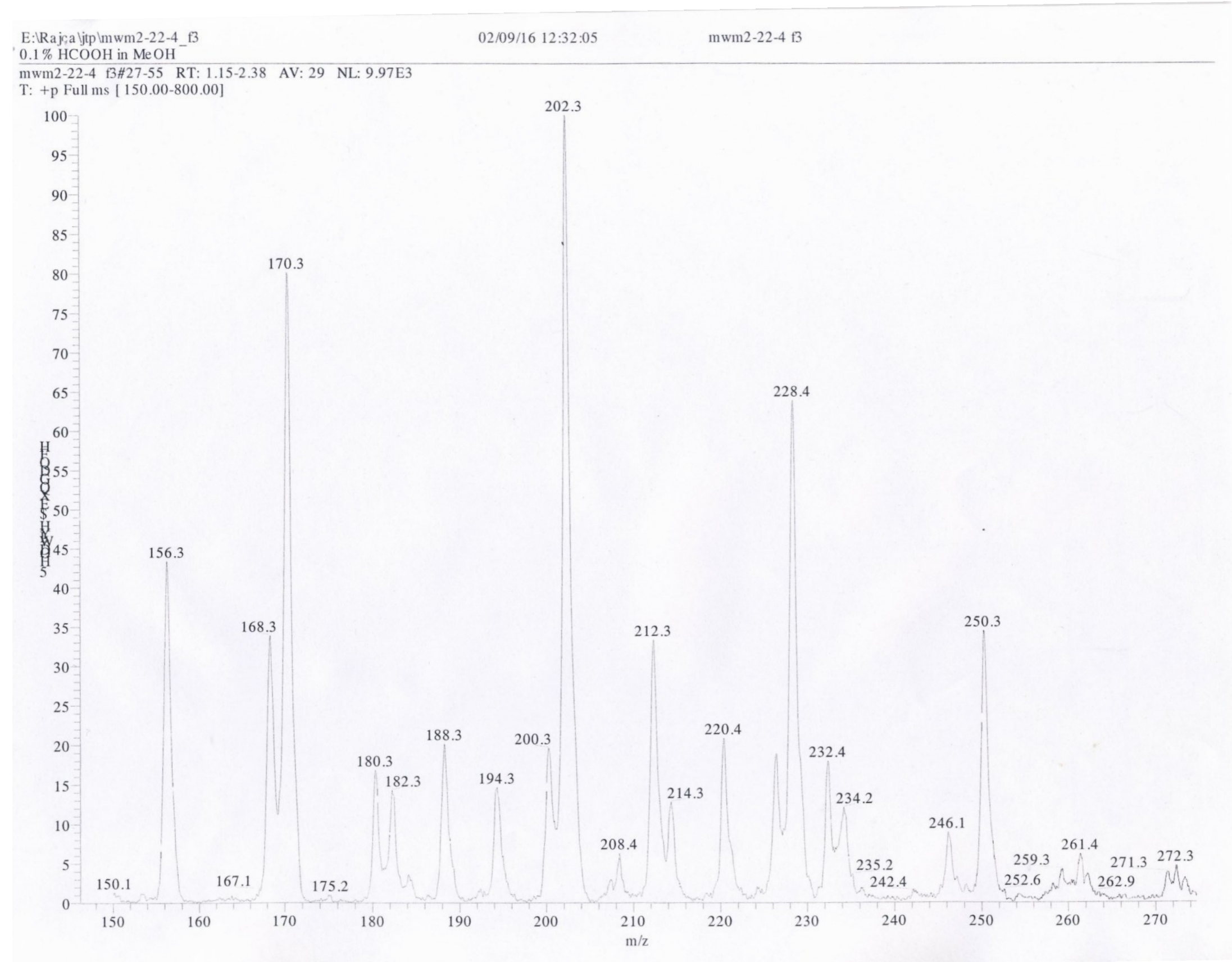


Figure 2: ESI of PTLC fraction, 0.1% HCOOH in MeOH.

Separation

Separation of the product (P) from the starting pentamethyl piperidine (A) is difficult due to the similarity in molecular mass (169 vs. 179), moieties, and structure. The product solution is first diluted with water and HCl, extracted with ether to remove non-alkaloid products, neutralized with K_2CO_3, and then extracted with ethyl acetate, all at 0^{O}C. ESI of the this fraction shows starting material (A+H, 170), product (P, 179), and sodium conjugated product (P+Na, 202). Separation was attempted using plate, thin layer chromatography. ESI of resulting fractions yielded promising results (Fig. 2). In all trials, following plate separation, no 179 product was seen; however, 202 became more prominent.

Results

Detection of the product was attempted using nuclear magnetic resonance (NMR) and electro spray ionization (ESI) spectroscopies. 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 NH_4Cl, 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.

Purpose

The purpose of this research is to synthesize a novel compound, 2,2,6,6-dispirocyclobutyl-piperidine-4-one (P), for use as an oxidation reactant to form the corresponding nitroxyl radical. This is to be conducted using a reliable method for a variety of 2,2,6,6-tetrasubstituted piperidine-4-one compounds as detailed by Sakai et al. [3]. Sakai uses a variety of 6-member cyclic ketones, which are quite stable. It was attempted to use 4-member cyclic ketones to research the effectiveness of 2,6-substitution using a less-stable carbonyl compound. Cyclobutanone and 3-oxycetanone were used as candidates for this reaction. Both are delicate, expensive ketones.

Citations

[1] Paletta, Joseph T., Maren Pink, Bridget Foley, Suchada Rajca, and Andrzej Rajca. "Synthesis and Reduction Kinetics of Sterically Shielded Pyrrolidine Nitroxides." Org. Lett. Organic Letters 14.20 (2012): 5322-325. Web.

[2] Rajca, Andrzej, Ying Wang, Michael Boska, Joseph T. Paletta, Arnon Olankitwanit, Michael A. Swanson, Deborah G. Mitchell, Sandra S. Eaton, Gareth R. Eaton, and Suchada Rajca. "Organic Radical Contrast Agents for Magnetic Resonance Imaging." J. Am. Chem. Soc. Journal of the American Chemical Society 134.38 (2012): 15724-5727. Web.

[3] Sakai, Kiyoshi, Ken-Ichi Yamada, Toshihide Yamasaki, Yuichi Kinoshita, Fumiya Mito, and Hideo Utsumi. "Effective 2,6-substitution of Piperidine Nitroxyl Radical by Carbonyl Compound." Tetrahedron 66.13 (2010): 2311-315. Web.

[4] Wang, Ying, Joseph T. Paletta, Kathleen Berg, Erin Reinhart, Suchada Rajca, and Andrzej Rajca. "Synthesis of Unnatural Amino Acids Functionalized with Sterically Shielded Pyrroline Nitroxides." Org. Lett. Organic Letters 16.20 (2014): 5298-300. Web.

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