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Syntheses of New Spirocarbocyclic Nucleoside Analogs Using Iminonitroso Diels-Alder Reactions

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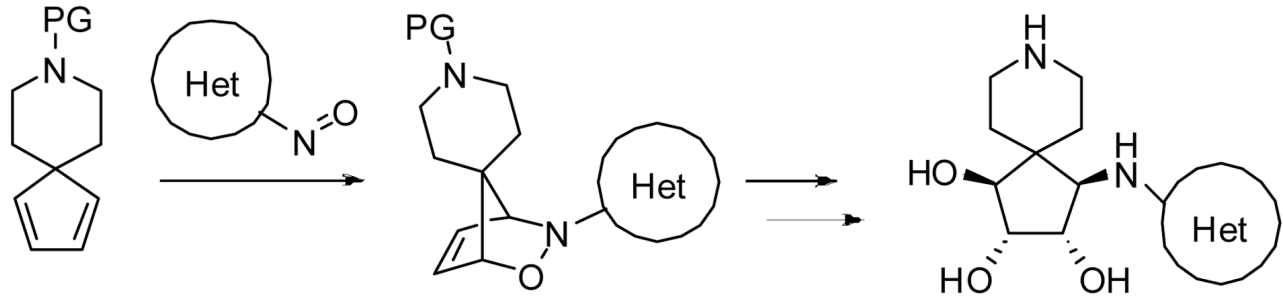
Abstract



PG = Cbz, Boc

N-Cbz and Boc protected spirocyclic dienes were prepared by dialkylation of cyclopentadiene. These dienes coupled efficiently in a series of iminonitroso Diels-Alder reactions to produce a series of new spirocyclic adducts. Hydrogenolysis of these adducts afforded new spirocycles that contain multiple handles for further functionalization. Furthermore, stereo-controlled dihydroxylation and reductive cleavage of the spirocyclic adducts generated versatile scaffolds for the syntheses and derivatization of novel spirocyclic carbocyclic nucleoside analogs.

Nitroso containing compounds have been studied from the very early days of organic chemistry.[1] Many different types of nitroso agents, including acylnitroso,[2] iminonitroso,[3] arylnitroso,[4] α chloronitroso moieties,[5] *C*-nitroso sugar derivatives,[6] and vinylnitroso agents,[7] have been used in a number of reactions, including ene and hetero Diels-Alder reactions. In 1947, Wichterle and Arbuzov reported the first nitroso Diels-Alder (NDA) reaction between nitroso benzene and cyclohexadiene to demonstrate its utility as a one-step 1,4-aminohydroxylation process.[8] Since the discovery of this reaction, many groups have continued to develop and apply nitroso Diels-Alder reactions in syntheses,[9] including elaboration of diastereoselective and enantioselective protocols with and without catalyst.[10] Cycloadducts obtained from nitroso Diels-Alder reactions have been used as versatile building blocks for the syntheses of natural products and biologically active molecules, including carbocyclic nucleoside analogs.[11]

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Supporting Information Available: General methods and procedures for compounds **3**, **6b-k**, **6n-p**, **7a**, **8b**, and **10a-b**, ^{1}H and ^{13}C NMR spectra for **2**, **3**, **6a-p**, **7a-b**, **8a-b**, **9**, **10a-b**. This material is available free of charge via the Internet at http://pubs.acs.org.

Carbocyclic nucleosides, in which the furanose oxygen is replaced with a methylene unit, have attracted much attention in the development of novel antitumor and antiviral therapeutic agents. The absence of a glycosidic linkage within the ring of the carbocyclic nucleoside confers stability toward cleavage by nucleoside phosphorylases or hydrolases.[12] However, the relative lack of conformational rigidity induced by the methylene function may result in reduced activity compared to the natural furanose ring.[13] Thus, novel structural modifications of carbocyclic nucleosides, including conformationally restricted analogs are of interest. Several research groups have successfully prepared different types of nucleoside analogs that address conformational and other concerns.[14]

Syntheses of interesting biologically relevant molecules using versatile chemical methodologies is of growing interest for our research group.[15] We have successfully used nitroso Diels-Alder reactions to obtain cycloadducts as versatile building blocks for a variety of synthetic applications,[16] including preparation of carbocylic nucleoside analogs. [11f-h] To further explore this area, we designed the novel spirocyclic dienes **3a** and **3b** as key components for the preparation of new spirocyclic scaffolds and novel spirocarbocyclic nucleosides that incorporate an amine handle for further diversification.

The synthesis of spirocyclic dienes **3a** and **3b** is shown in Scheme 1. Dialkylation of cyclopentadiene with *N*-protected *bis*-2-chloroethylamine was the key step required for construction of the spirocycle. Commercially available *bis*-(2-chloro ethyl)amine hydrochloride **1** was converted to the corresponding *N*-Cbz and *N*-Boc protected derivatives **2a** and **2b** in quantitative yields.[17] Of numerous different conditions attempted to form spirocyclic dienes **3a** and **3b**, the dimsyl anion initiated substitution of compound **2** with cyclopentadiene was found to be the most effective.[18] Spirocyclic dienes **3a** and **3b** were thus prepared in 79% and 68% yields, respectively, on a 20 mmol scale. Dienes **3a** and **3b** can be stored at room temperature without problematic dimerization.

A series of iminonitroso compounds **5** were prepared in moderate yield from aminoheterocyclic derivatives **4** in a two-step sequence (*N*,*N*-dimethylsulfilimine derivative formation, followed by the oxidation using *m* CPBA).[19] Most of the iminonitroso compounds could be stored for several months at -20 °C, except for compounds **5l-o**, which were prepared and used immediately without purification. The nitroso Diels-Alder reaction between spirocylic dienes **3** and iminonitroso species **5** usually was complete within 2 h at room temperature (Scheme 2). The corresponding racemic spirocycloadducts **6a-j** were obtained in good to excellent yields after column chromatography. The instability of compounds **5k-o** required *in situ* trapping with diene **3a** or **3b** to give spirocycloadducts **6k-o** in moderate yields except for compound **6m**, which could be only detected in trace amounts in the crude reaction mixture due to competitive sulfur oxidation of the intermediate sulfilimine.[20]

We next elaborated the spriocyclic adducts **6a** and **6b** to demonstrate their utility. Hydrogenation of compounds **6a** and **6b** at atmospheric pressure using 10% Pd-C afforded three desirable transformations in a single flask: N-O bond cleavage, alkene reduction, and Cbz deprotection. Thus, products **7a** and **7b** were provided from **6a** and **6b**, respectively, in excellent yield. Though some partial reduction products were occasionally observed from the reaction mixtures, additional portions of palladium catalyst and extended reaction times allowed completion of the full cleavage-reduction process (Scheme 3).

Spriocycles such as **6a** and **6b** also lend themselves to more selective, stepwise modification that is useful for the preparation of nucleoside analogs (Scheme 4). Thus, dihydroxylation of cycloadducts **6a** and **6b** using *N*-methylmorpholine oxide (NMO) and a catalytic amount of osmium tetroxide[21] gave diol derivatives **8a** and **8b** with high diastereoselectivity (*de* > 95%) based on the ^{13}C NMR spectra of the crude reaction mixtures. The facial selectivity of the

dihydroxylation was clarified using a 2D ROSEY study of the acetonide derivative **9** (see supporting information) Interestingly, the newly introduced hydroxyl groups were found to be on the opposite face of the five membered ring (exo) relative to the aminohydroxyl group incorporated during the iminonitroso Diels-Alder reaction and thus, appeared to be delivered to the same face occupied by the spirocyclic component. This stereochemistry is favorable for preparing nucleoside mimetics.

Hydrogenolytic deprotection of **8a** and **8b** gave novel conformationally restricted spirocarbocyclic nucleoside analogs **10a** and **10b** in 94% and 92% yields, respectively (Scheme 5).

In conclusion, we have prepared novel spirocyclic dienes and showed them to efficiently participate in several hetero Diels-Alder reactions. The resulting spirocyclic adducts can be easily manipulated to provide novel amino alcohols and spriocyclic carbocyclic nucleoside analogs. Additional development of this chemistry and the results of biological testing of the products will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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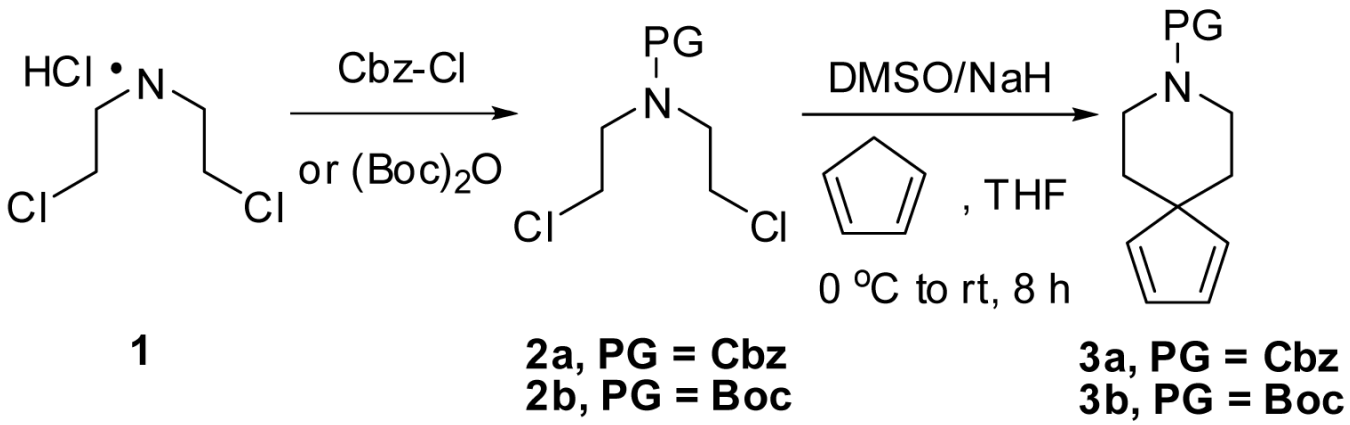
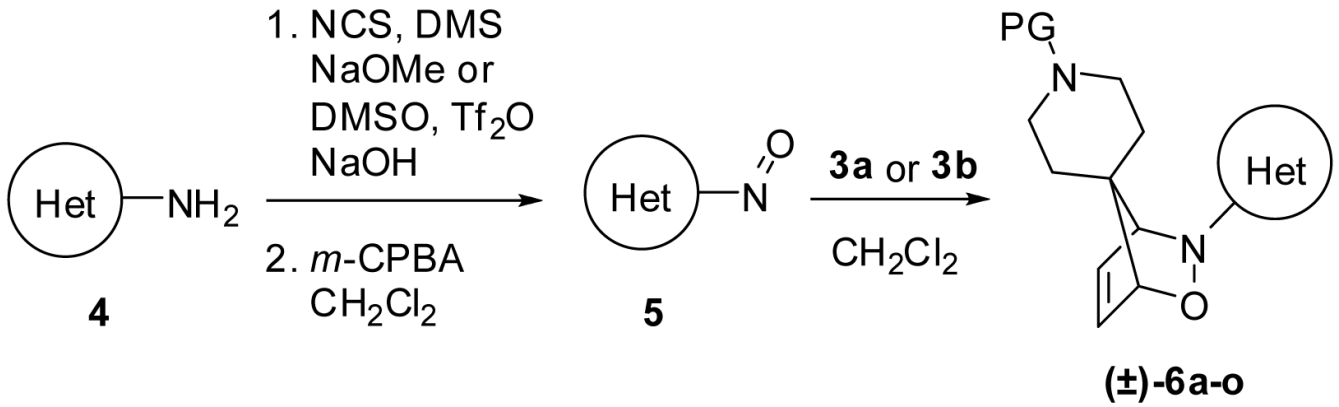


Scheme 1.



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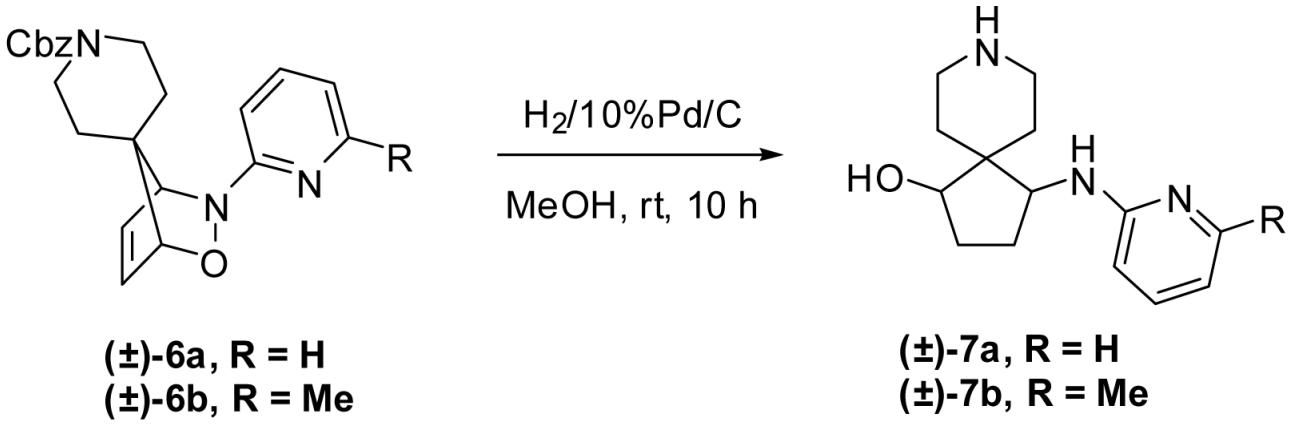
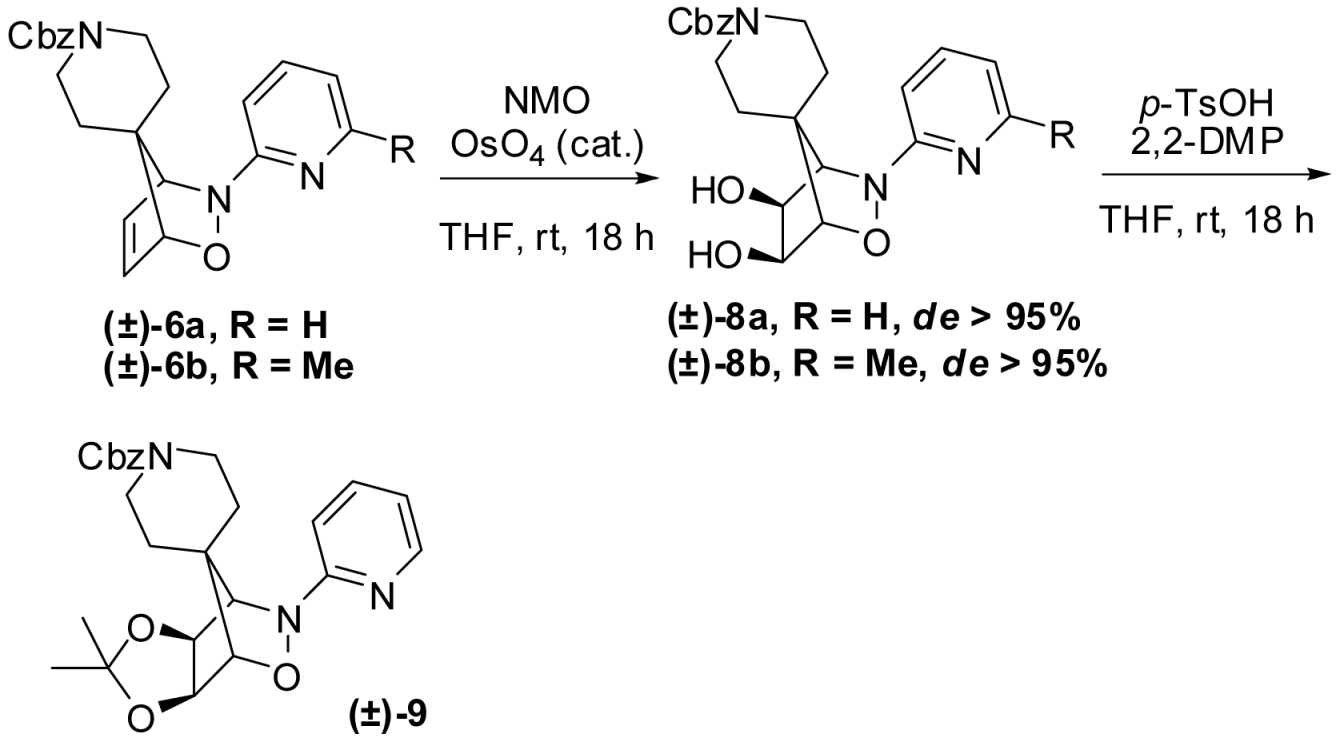


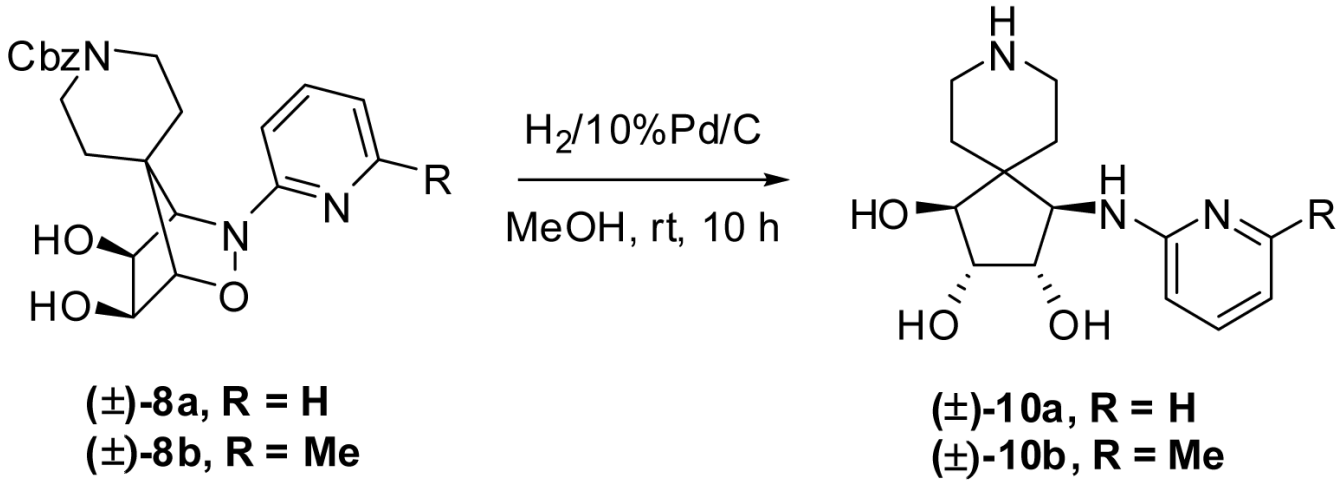
(±)-6a, R = H
(±)-6b, R = Me

(±)-7a, R = H
(±)-7b, R = Me

Scheme 3.



Scheme 4.



(±)-8a, R = H
(±)-8b, R = Me

(±)-10a, R = H
(±)-10b, R = Me

Scheme 5.

Table 1

Iminonitroso Diels- Alder Reactions on Protected Spirocyclic Dienes

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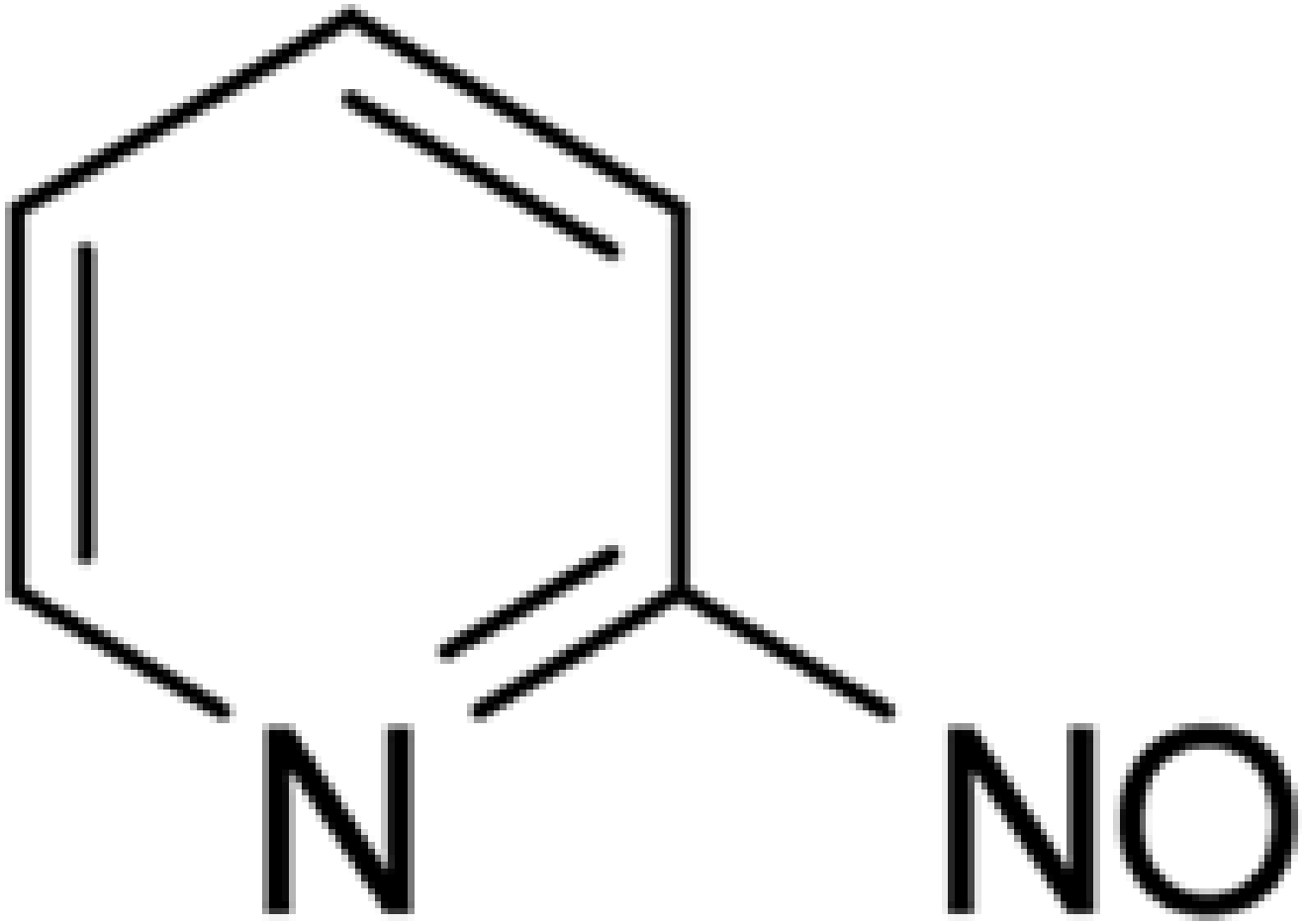
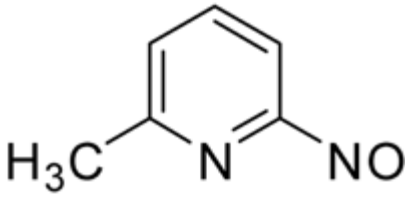
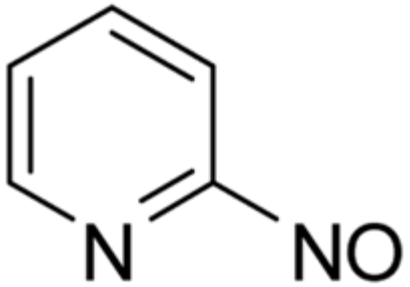
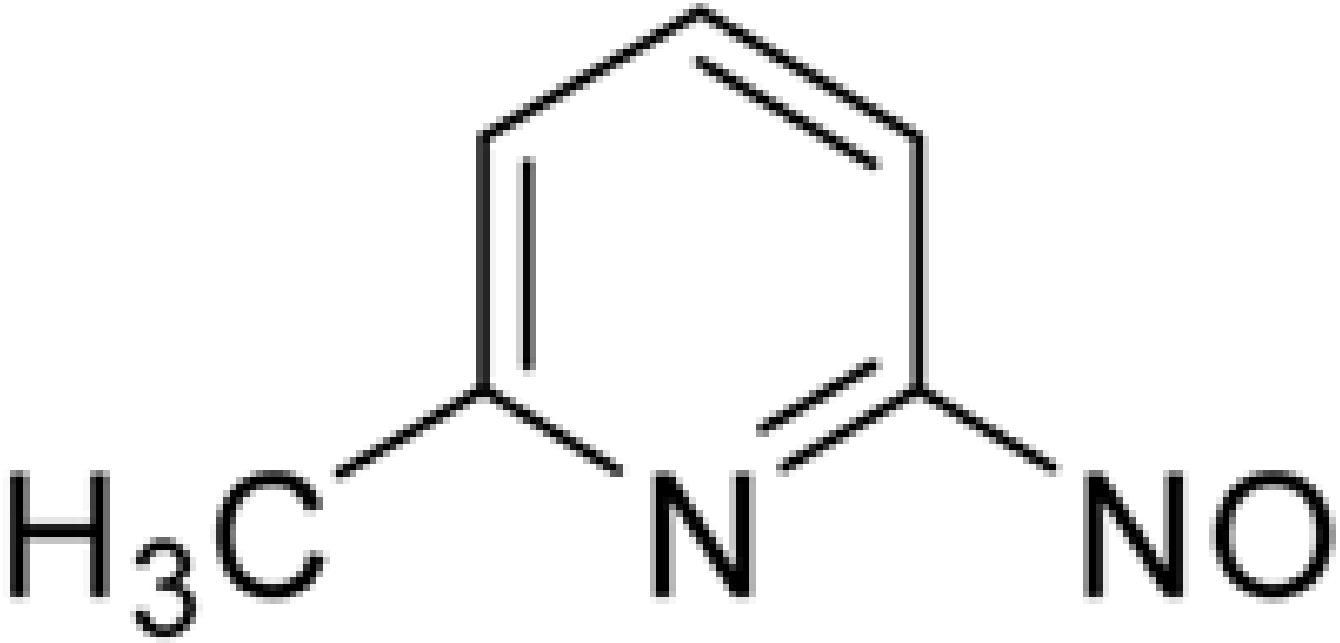
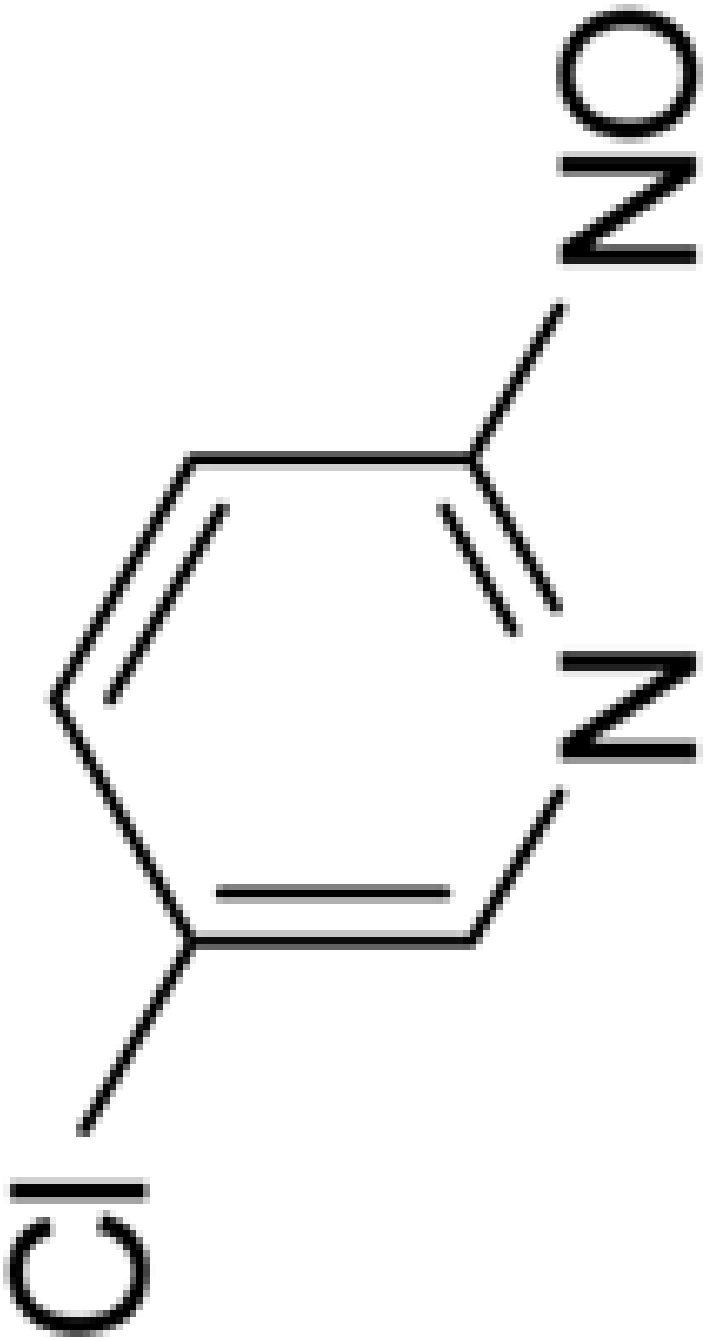
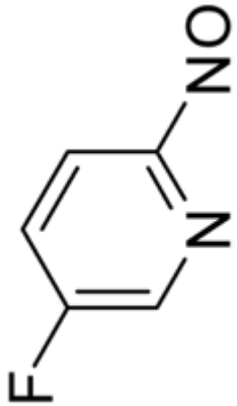
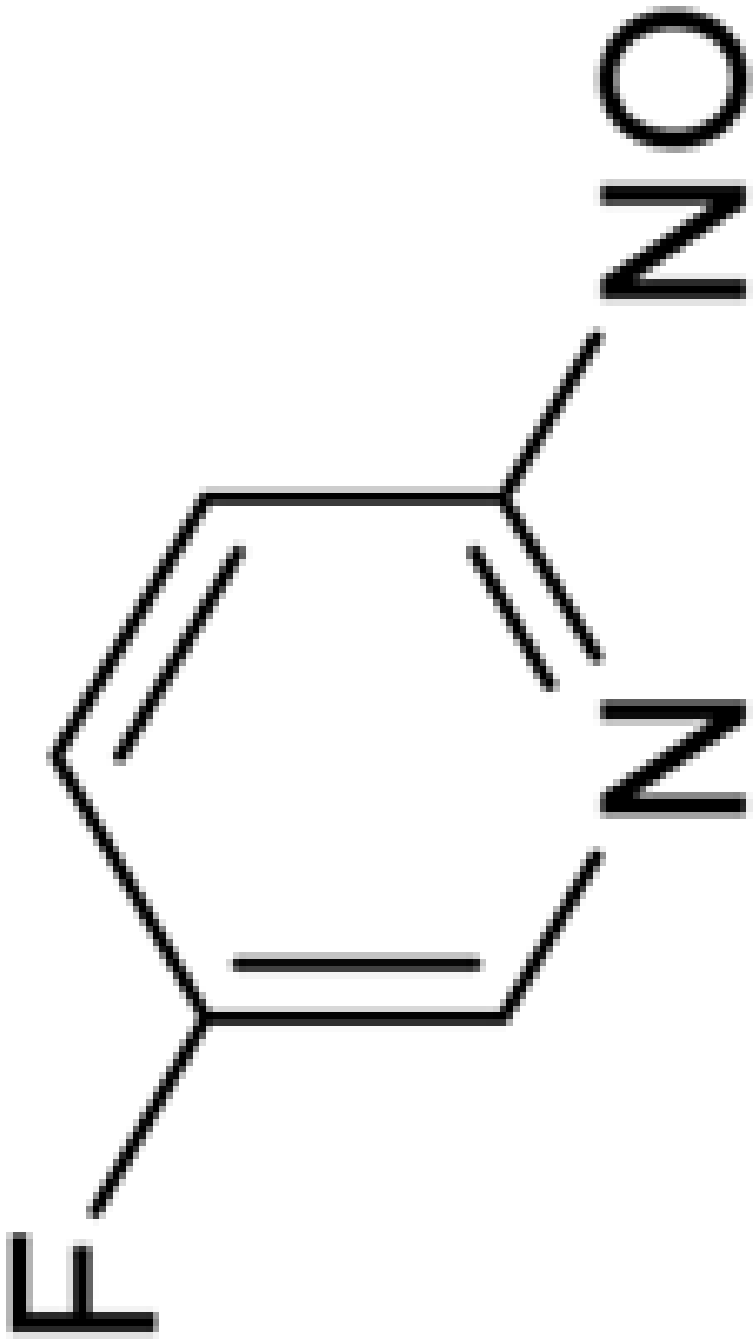
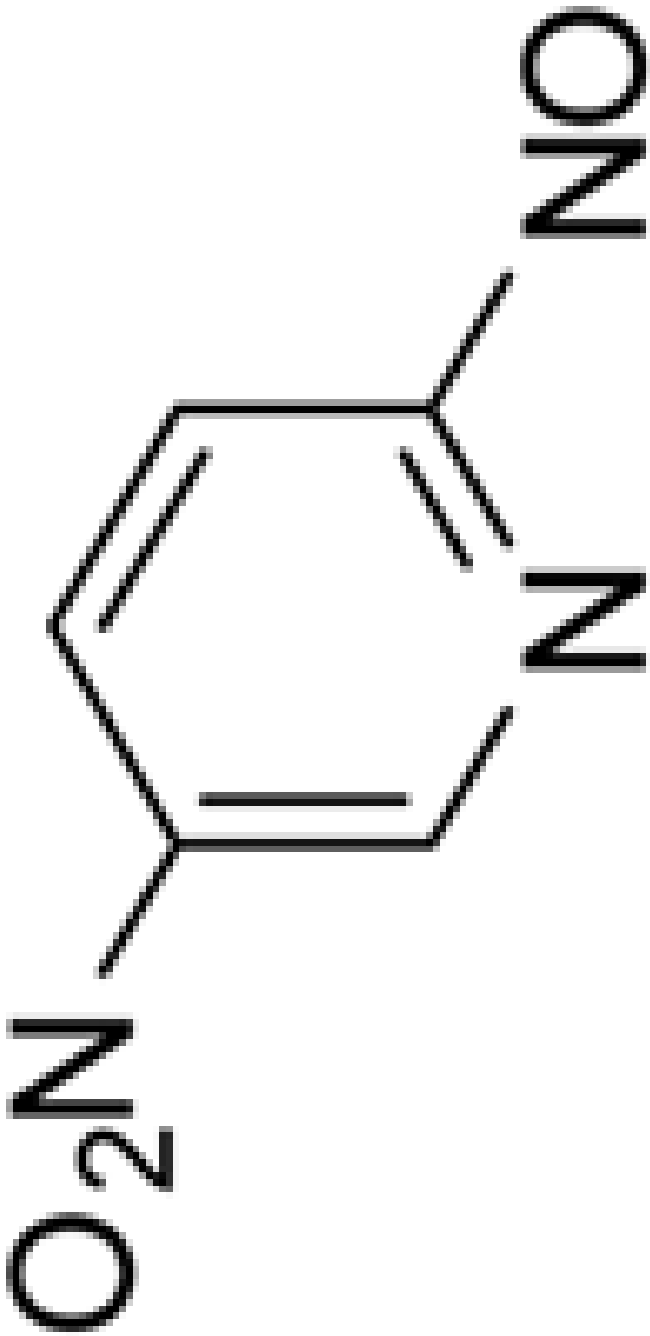
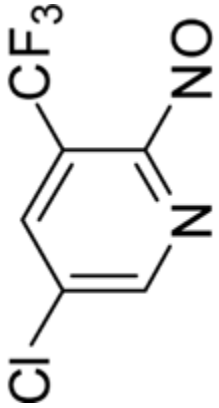
a)		Cbz	88%

	nitrosos 5	PG	yield
b)		Cbz	85%
c)		Boc	83%
d)		Boc	89%

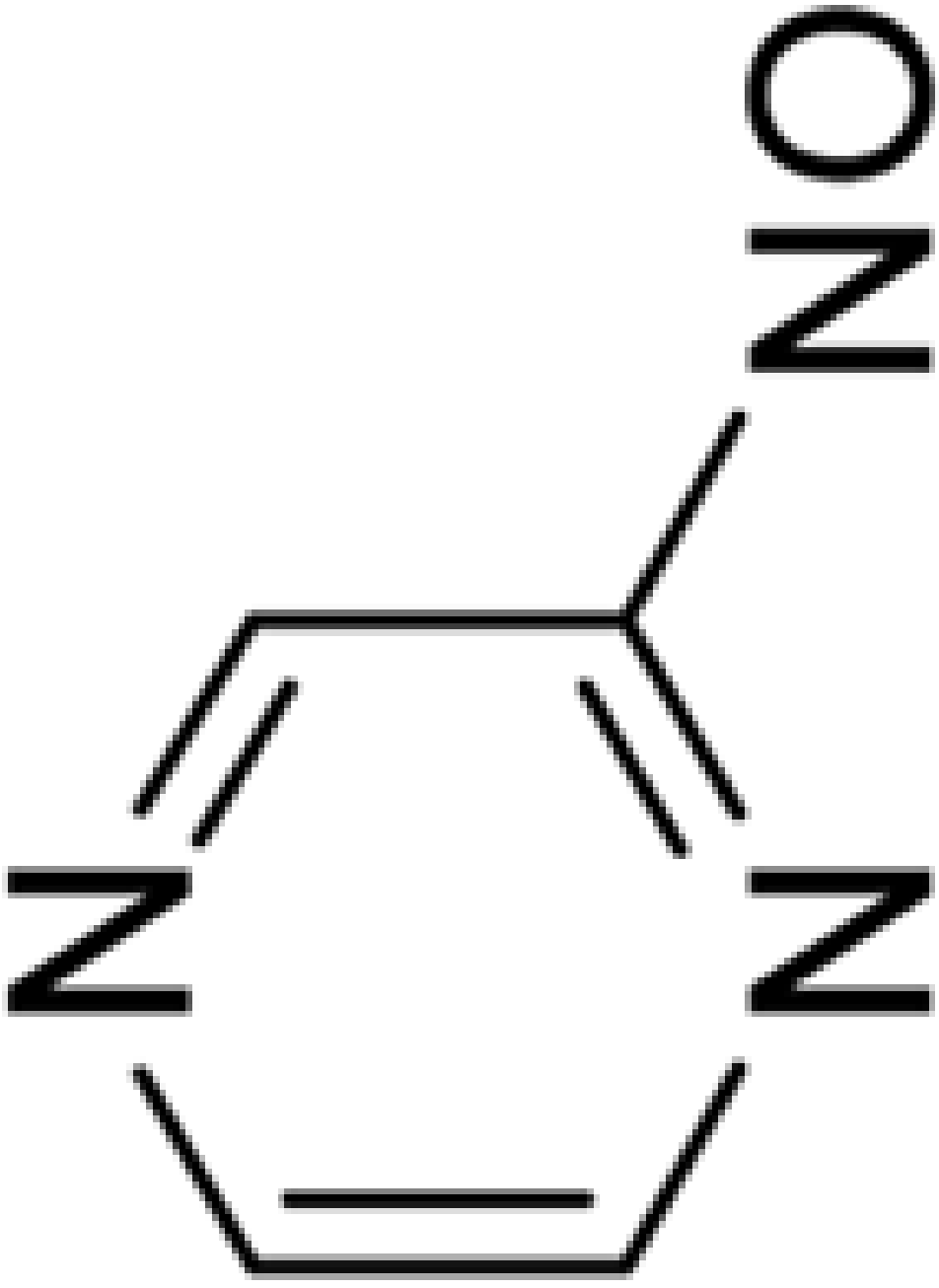
	nitrosos 5	PG	yield
e)		Cbz	82%
f)		Cbz	80%

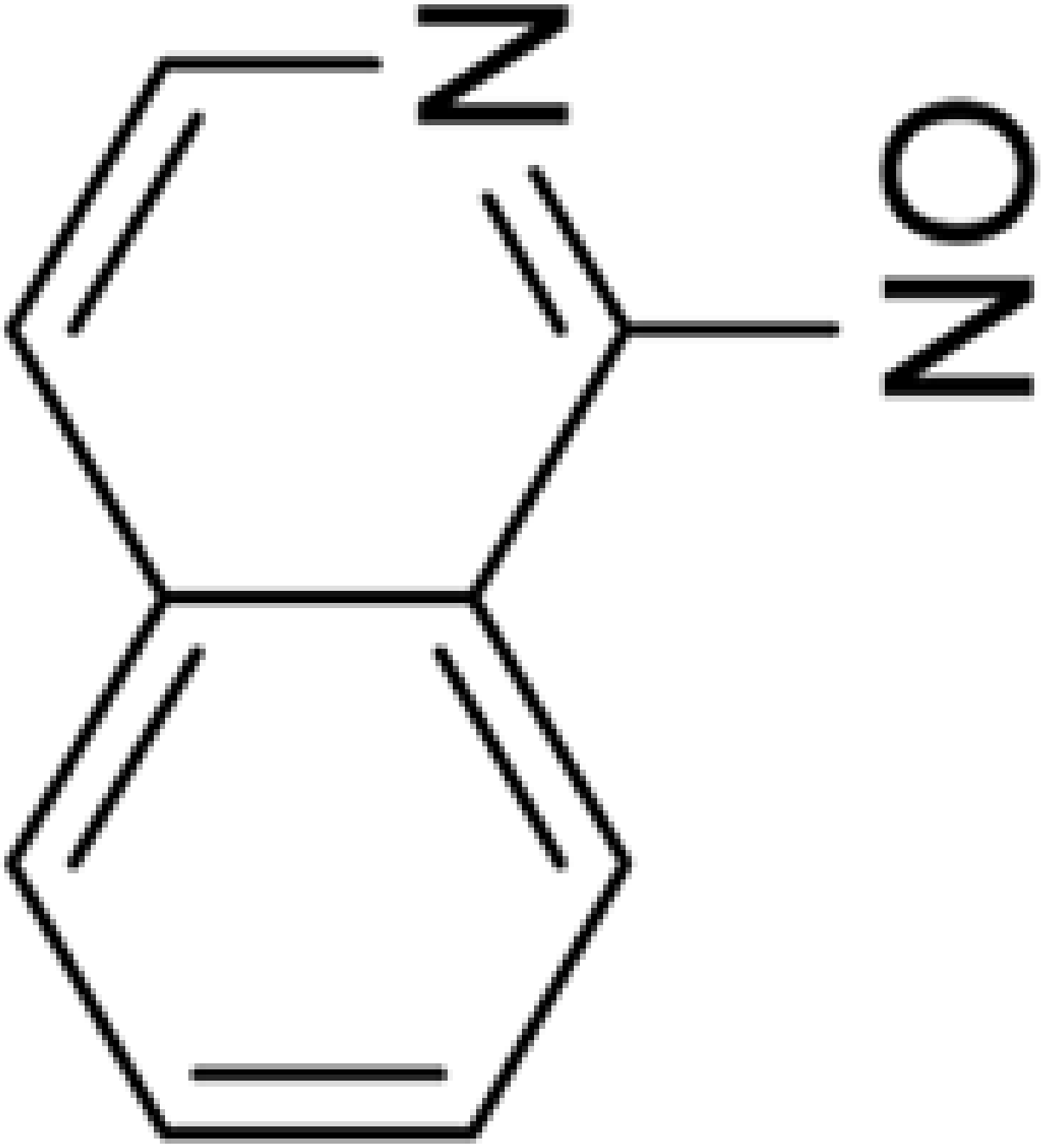
nitrosos 5	PG	yield
	Boc	83%

g)

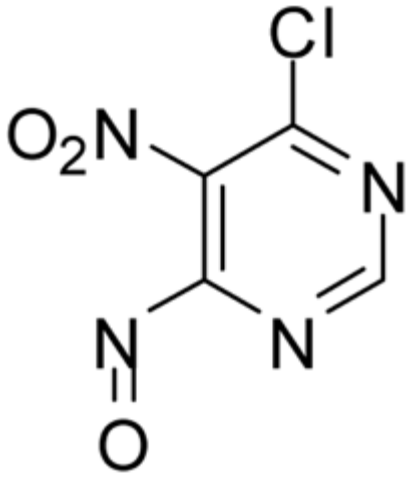
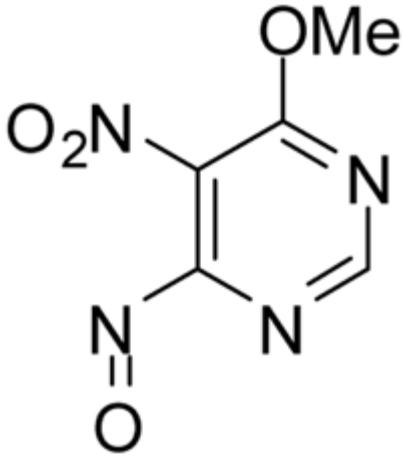
	nitrosos 5	PG	yield
h)		Cbz	80%
i)		Boc	94%

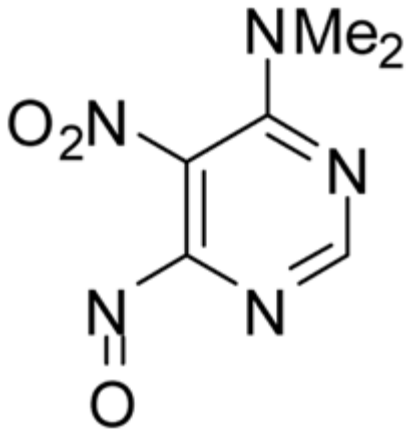
	nitrosos 5	PG	yield
j)		Cbz	85%

nitrosos 5	PG	yield
	Cbz	55%
k)[a]		

nitrosos 5	PG	yield
	Cbz	45%

[a]

	nitrosos 5	PG	yield
m)[a, b]		Boc	trace
n)[a,b]		Boc	60%

	nitrosos 5	PG	yield
o)[a,b]		Boc	51%

[a] *in situ* trapping required.

[b] sulfoximine derivatives separated form the reaction mixture.