

Note

# Organotin mediated nitration in heteroaromatic series using tetranitromethane or dinitrogen tetroxide

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## Abstract

2-Trimethylstannylated benzo[*b*]furan, benzo[*b*]thiophene, N-substituted indoles and pyridine afford the corresponding nitro derivatives in regioselective fashion upon treatment with tetranitromethane (using sun-lamp irradiation in the case of N-containing heterocycles) or with dinitrogen tetroxide. © 2000 Elsevier Science S.A. All rights reserved.

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## 1. Introduction

The nitration reaction in heteroaromatic series using conventional electrophilic conditions is highly disfavored due to the presence of the heteroatom which interacts with the electrophile to give onium species (poorly reactive in terms of electrophilic substitution) [1].

For instance in the case of pyridine, under very hard experimental conditions (HNO<sub>3</sub>–H<sub>2</sub>SO<sub>4</sub>, 300°C), only very poor yields (< 3%) of 3-nitropyridine are usually obtained [2,3] and acceptable yields in 3-nitroderivatives have been obtained only in the presence of electron withdrawing groups on the other positions, as exemplified by the nitration of 2,6-dichloropyridine [4] or by using N<sub>2</sub>O<sub>5</sub> in liquid sulfur dioxide [3,5]. When 4-nitropyridine is desired, the electrophilic nitration reaction must be performed on pyridine *N*-oxide [6] and when the target is 2-nitropyridine, the strategy must be completely modified using generally an amina-

tion/oxidation sequence [7]. In the case of indole, similar problems were encountered and 2-nitroindole has only been described recently in a reaction scheme where the five membered ring bearing the nitro group is constructed in the last step [8].

Taking these trends into account, two major points have to be considered:

1. the acidic medium required for usual electrophilic aromatic nitration must be avoided in these series;
2. the approaches using lithiated heterocycles must also be considered selectively since the destruction of the aromatic ring can be observed in diazines series [9].

On the basis of these considerations, a reasonable proposal might be a nitration under nearly neutral conditions (free radical reactions or single electron transfer reactions). For this purpose, we consider that stannyl substituted heterocycles might be good candidates since these compounds are readily obtainable by quenching the corresponding lithium reagents with organotin halides [9–11] or by reacting heteroaryl halides with stannyl anionoids [12]. Furthermore, when neutral conditions are required to obtain the stannyl precursors, the palladium promoted cross-coupling of

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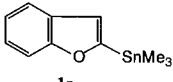
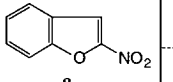
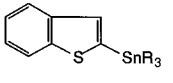
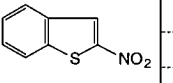
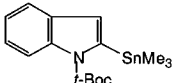
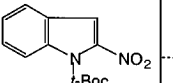
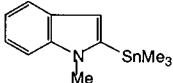
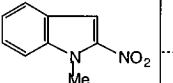
heteroaryl halides with hexaorganoditins is also possible [11,13].

Such a strategy is not completely unprecedented since Corey has described the conversion of vinyltins into nitro-olefins [14]. More recently, Einhorn has obtained 2-nitrobenzo[*b*]furans by the reaction of the corresponding organotin precursors with tetranitromethane [15]. However, in both cases, no consideration of the involved mechanism has been published.

In order to extend this strategy to our problem, we decided to use Einhorn's experimental conditions (tetranitromethane–DMSO: A) for other types of stannylated heterocycles, especially in the case of those containing nitrogen. The results obtained are reported in Tables 1 and 2.

As previously described, 2-trimethylstannylbenzo[*b*]furan (**1a**) affords **8** in good yield [15], and this nitration can be extended successfully to 2-trimethylstannylbenzo[*b*]thiophene (**2a**) to give **9**. However, the reaction suffers from limitations since, under these experimental conditions, only moderate to low yields were obtained with the trimethylstannylated heterocycles (**3a–7a**). Furthermore, an important decrease in the yields was observed when tributylstannyl derivatives are involved as exemplified by the reactivity of 2-tributylstannylbenzo[*b*]thiophene (**2b**) or of 2-tributylstannylpyridine (**5a**).

Table 1  
Nitration of 2-stannylated five membered heterocycles with tetranitromethane (TNM) [22–24]

Stannylated Heterocycles	Experimental Conditions <sup>a</sup>	2-Nitroheterocycles <sup>b</sup>	Yield
 <b>1a</b>	A	 <b>8</b>	86%
	B		84%
 <b>2a</b> (R = Me), <b>2b</b> (R = Bu)	A	 <b>9</b>	70%
	B		73%
	A		10% <sup>c</sup>
 <b>3a</b>	A	 <b>10</b>	30% <sup>c</sup>
	B		48% <sup>c</sup>
 <b>4a</b>	A	 <b>11</b>	36% <sup>c</sup>
	B		41% <sup>c</sup>

<sup>a</sup>Experimental conditions:


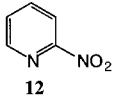
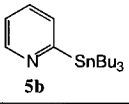
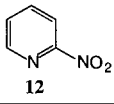
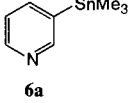
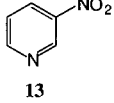
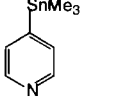
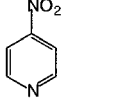
A: organotin precursor (2 mmol), TNM (1.1 eq.), DMSO (4 ml), 3 h.  
 B: organotin precursor (2 mmol), TNM (1.1 eq.), DMSO/CCl<sub>4</sub> (2/3; 4 ml), sun lamp (100 W) [22].

<sup>b</sup>Compounds **8–11** were fully identified on the basis of previous reports [8,23,24].

<sup>c</sup>Benzo[*b*]thiophene or *N*-substituted indoles (substitution of SnR<sub>3</sub> by H) were also observed in these cases in 10–20% yield.

Table 2

Nitration of triorganostannylpyridines with tetranitromethane or dinitrogen tetroxide

Stannylpyridines	Experimental Conditions <sup>a</sup>	Nitropyridines <sup>b</sup>	Yield
 <b>5a</b>	TNM, A	 <b>12</b>	5%
	TNM, B <sup>d</sup>		43% <sup>e</sup>
	N <sub>2</sub> O <sub>4</sub> , C <sup>d</sup>		44%
 <b>5b</b>	TNM, A	 <b>12</b>	2% <sup>c</sup>
	TNM, B		15% <sup>c</sup>
	N <sub>2</sub> O <sub>4</sub> , C		22% <sup>c</sup>
 <b>6a</b>	TNM, B	 <b>13</b>	2%
	N <sub>2</sub> O <sub>4</sub> , C		2%
 <b>7a</b>	TNM, B	 <b>14</b>	0%
	N <sub>2</sub> O <sub>4</sub> , C		0%

<sup>a</sup>Experimental conditions for reactions performed from 2 mmol of organotin precursor:

A: TNM (2 eq.), DMSO (4 ml), 2h30.

B: TNM (2 eq.), DMSO/CCl<sub>4</sub> (2/3; 4 ml), sun lamp (1000 W) with AgCl filter, 5 h [22].

C: N<sub>2</sub>O<sub>4</sub> (2 eq.), DMSO/CCl<sub>4</sub> (2/3; 4 ml), dark, room temperature, 16 h [22].

<sup>b</sup>Authentic samples of compounds **12–14** were prepared according to previously described methods [2–7].

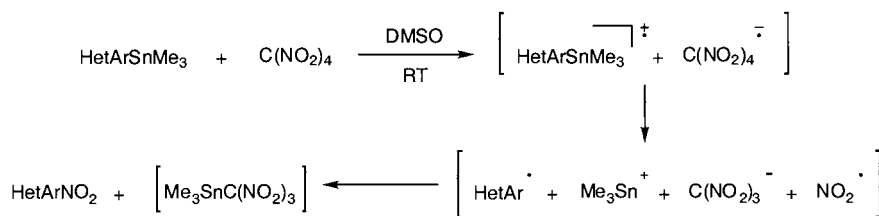
<sup>c</sup>Pyridine was obtained as a by product.

<sup>d</sup>In these experimental conditions, **5a** was almost completely consumed (>95%) to give a mixture of trimethyltin derivatives containing trimethylstannyl nitrite on the basis of MS spectra (*m/z* = 211 for <sup>120</sup>Sn in EI mode and *m/z* = 212 for <sup>120</sup>Sn in CI mode using NH<sub>3</sub> as reacting gas).

<sup>e</sup>In this case, the reaction was partially inhibited by addition of 1,3,5-trinitrobenzene (5% conversion rate against 43% yield).

Considering the fact that obtaining nitroderivatives is probably due to a monoelectronic transfer followed by a fragmentation of the radical cation (Scheme 1), depending on the structure of the heterocycle, the initial electronic transfer can be easy or difficult and the fragmentation of the radical cation is expected to be easier with an increased stability of the heteroaromatic radical.

Furthermore, it is known that light can induce this type of reaction [16] and interestingly, when the reaction mixture was submitted to light in a Pyrex reactor (sun lamp or UV lamp with a filter at 400 nm in order to avoid undesired destruction of tetranitromethane), noticeable improvements were observed when the Sn–C linkage is on the  $\alpha$ -position relative to the heteroatom. While no significant improvement was brought about by irradiation when high yields have been obtained previously without light (reactions involving **1a** and **2a**), interesting increase in the yields was observed starting



Scheme 1.

from 2-trimethylstannylindoles (**3a** and **4a**) allowing access to the corresponding 2-nitroindoles (**10** and **11**) in 48 and 41% isolated yields (cf. Table 1). In the case of stannylpyridines (**5–7**), under irradiation, meaningful yields were obtained with the orthostannylpyridines (**5a** or **5b**) while *meta* and *para* isomers remained nearly unreactive [17]. For compounds **2–5**, hydrogen abstraction by heteroaryl radicals has also been observed, this hydrogen abstraction being a limiting factor for the use of tributylstannyl derivatives due to the possible abstraction of the  $\beta$ -hydrogens related to tin [18]. However, even in the case of low yields, it is worth noticing that the stannylated precursors (**1–5**) afford the expected nitroderivatives in a perfect regioselective fashion (cf. Tables 1 and 2) and with a good tolerance for sensitive functions as in **3a**.

In the trimethylstannylpyridine series, attempts of nitration with dinitrogen tetroxide, which is known to dissociate into nitro radicals above room temperature [19], allow observation of similar trends and yields when performed in the dark. The use of sun lamp irradiation in this case allows no improvement: nitropyridine (**12**) was obtained in 22% yield only without special control of the temperature. This result might be due to a partial evaporation of nitrogen tetroxide due to the warming effect of the lamp, and this assumption was confirmed by the fact that a 37% yield was obtained when the reactor was cooled by blowing a cold nitrogen flow (0°C) during the irradiation. In these reactions, 2-nitropyridine was obtained unpolluted with 2-nitrosopyridine suggesting an homolytic mechanism involving nitro radicals. For comparison, it is worth noticing that the reaction of 1,3-bis(triethylplumbyl)-2,4,6,8-tetranitrocubane with dinitrogen tetroxide, performed at  $-15^\circ\text{C}$  in methylene chloride, affords a mixture of nitro and nitrosoderivatives indicating the occurrence, at least, of two reaction mechanisms [20], which can be understood as an homolytic pathway and an ionic pathway. Finally, even limited to 2-trimethylstannylpyridine, this method allows the obtaining of 2-nitropyridine in mild experimental conditions and can be fairly easily scaled-up compared to the reaction of dinitrogen tetroxide with aryl or heteroaryllithiums, which requires very low temperatures and very sharp experimental conditions [21].

Even if requiring further studies in order to have a better understanding of the observed results, the present study opens new prospects in the field of the synthesis of nitro hetero-aromatics under nearly neutral experimental conditions, and we can reasonably hope further improvements in terms of yields through a more accurate knowledge of the reaction mechanism. Work is in progress in this direction.

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