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# The role of a Lewis acid in the Nenitzescu indole synthesis

Valeriya S. Velezheva [a,*], Andrey I. Sokolov [b], Albert G. Kornienko [a], Konstantin A. Lyssenko [a], Yulia V. Nelyubina [a], Ivan A. Godovikov [a], Alexander S. Peregudov [a], Andrey F. Mironov [b]

[a] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov Street, 119991 GSP-1 Moscow, Russia
[b] M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 86 Vernadskogo Street, 119571 Moscow, Russia

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ABSTRACT

A highly efficient Lewis acid-catalyzed method for the Nenitzescu synthesis of 5-hydroxyindoles with a range of substituents at N-1 and C-3 and symmetric 5,5′-dihydroxydiindoles has been developed. The amount of the catalyst (10–100 mol %) required depended on the nature of the enaminone component. It has been shown that Lewis acid plays a role in enaminone component activation through an enamine-$ZnC1_2$ complex followed by its deprotonation.

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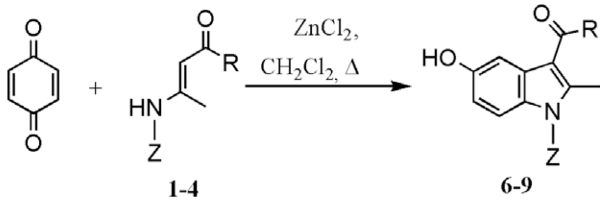
The Nenitzescu reaction has proven to be important in drug discovery for 5-hydroxyindole-based derivatives bearing new additional functions at various positions of the ring system.[1-4] 5-Hydroxyindoles with a high density of functional and pharmacophoric groups are of interest as novel inhibitors for protein targets.[5] However, 3-acyl-5-hydroxyindoles, especially those with *N*-functionalized alkyl tails, and symmetric 5,5′-dihydroxydiindoles bearing a linker between the indole nitrogens, are not easily attainable due to formation of the corresponding 3-acylbenzofurans instead of the target indoles.[6] The use of diketodienamines derived from acetyl acetone and ethylene- or butylenediamines in the Nenitzescu reaction in acetic acid has been reported to afford 3-acetyl-5-hydroxy-2-methyl-benzofuran/naphthofuran, instead of symmetric 5,5′-dihydroxydiindoles.[7] Earlier, Grinev managed to obtain 3-acetyl-5-hydroxy-1-(2-hydroxyethyl)-2-methylindole in very low yield along with 3-acetyl-5-hydroxy-2-methylbenzofuran.[8] We reasoned that employing Lewis acids in the Nenitzescu reaction with enaminones would direct the process to the indolization pathway.[9] The method is simple, rapid, efficient, and allows the preparation of hydroxyindoles from *p*-benzoquinone (PBQ) and simple enaminones in good to excellent yields with the use of low polarity solvents in the presence of weak Lewis acid catalysts (hereafter referred to as ‘standard conditions’). The time required for the indolization decreases by a factor of three or more, compared to the non-catalyzed process, while the formation of 3-acylbenzofurans is supressed. The formation of 5-hydroxyindoles under such mild conditions is explained in terms of a non-redox mechanism. It was noted that the corresponding 5-hydroxybenzofurans were obtained by the condensation of PBQ with acetyl acetone or ethyl acetoacetate in the presence of Lewis acid catalysts.[10]

We chose a series of enaminones **1-5** with the structural unit Z–N–C═C–COR (Z = $(CH_2)_3CH_3$ **1**, $(CH_2)_2NHTs$, **2**, $(CH_2)_2OH$ **3**, $(CH_2)_nNHC(CH_3)$═CHCOR **4** ($n$ = 2), **5** ($n$ = 6); R = Me, OEt, Ph) (Schemes 1 and 2). Under standard conditions (10 mol % $ZnCl_2$/$CH_2Cl_2$ system and PBQ (1 equiv)), the method[9] worked well only with enaminone **2a** of enaminones **1–3a** to give pure indole **7a**[11] in 88% isolated yield (Table 1, entries 1, 5 and 7). Moreover, **2a** reacted with PBQ faster than did the enaminone **3a** and other simple enaminones.[9] Similarly, enaminones **2b,c** reacted smoothly under the same conditions to give indoles **7b,c** in high yields (Table 2).

Poor yields of crude **7a** and **8a** were also obtained, when $AlCl_3$ was employed as the catalyst (Table 1, entries 4 and 6). As expected, enaminones **1–5** reacted poorly with PBQ in the absence



**1,6a** Z = $(CH_2)_3CH_3$, R = Me;
**2,7a** Z = $CH_2CH_2NHTs$, R = Me;
**2,7b** Z = $CH_2CH_2NHTs$, R = OEt;
**2,7c** Z = $CH_2CH_2NHTs$, R = Ph;
**3,8a** Z = $CH_2CH_2OH$, R = Me;
**3,8b** Z = $CH_2CH_2OH$, R = OEt;
**3,8c** Z = $CH_2CH_2OH$, R = Ph;
**4,9a** Z = $(CH_2)_2NH(CH_3)C$=CHCOR, R = Me;
**4,9c** Z = $(CH_2)_2NH(CH_3)C$=CHCOR, R = Ph.

**Scheme 1.**

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[*] Corresponding author. Tel.: +7 499 135 9333; fax: +7 499 135 5085.
*E-mail address:* vel@ineos.ac.ru (V. S. Velezheva).

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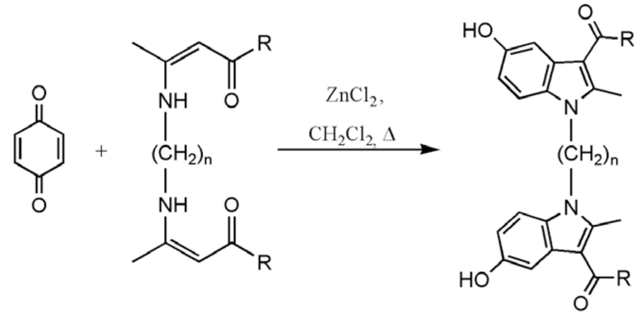

**4b,5**

**10b, 11**

**4,10b** n = 2, R = OEt;
**5,11a** n = 6, R = Me;
**5,11b** n = 6, R = OEt;
**5,11c** n = 6, R = Ph.

**Scheme 2.**

**Table 1**
Yields of indoles **6**–**8a** depending on the type and mol % of catalyst[a]

| Entry | Enaminone | Catalyst (mol %) | Time (min) | Product, isolated yield (%); purity (%) by $^1$H NMR[b] |
|---|---|---|---|---|
| 1 | **1a** | $ZnCl_2$ (10) | 20 | **6a**, 79; <95 |
| 2 | **1a** | $ZnCl_2$ (100) | 20 | **6a**, 60; >95 |
| 3 | **2a** | No catalyst | 210 | **7a**, 23; <95 |
| 4 | **2a** | $AlCl_3$ (10) | 90 | **7a**, 29; <95 |
| 5 | **2a** | $ZnCl_2$ (10) | 30 | **7a**, 88; >95 |
| 6 | **3a** | $AlCl_3$ (10) | 90 | **8a**, 22; <95 |
| 7 | **3a** | $ZnCl_2$ (10) | 90 | **8a**, 37; <95 |
| 8 | **3a** | $ZnCl_2$ (20) | 60 | **8a**, 71; <95 |
| 9 | **3a** | $ZnCl_2$ (50) | 40 | **8a**, 81; <95 |
| 10 | **3a** | $ZnCl_2$ (100) | 20 | **8a**, 56; >95 |
| 11 | **3a** | $ZnI_2$ (100) | 20 | **8a**, 65; >95 |

[a] 1:1.1 PBQ:**1**–**3a**.

[b] Based on 1H NMR analysis (600 MHz, DMSO-$d_6$) of the crude product. Purity of isolated **6**–**8a** determined by integration of the signals corresponding to the main compound and by-product.

of a catalyst (Table 1, entry 3). We observed a reduction of the reaction time and a rise in the yield of **8a** with an increase in the amount of $ZnCl_2$ relative to the standard conditions (Table 1, entries 8–10), 20 mol % of $ZnCl_2$ giving 71% of **8a** after 60 min. If more catalyst was employed (50 mol %), the yield rose to 81% after 40 min. The use of a stoichiometric amount of $ZnCl_2$ gave the purest product after 20 min but in 56% yield. A similar result was achieved when $ZnI_2$ was used as a catalyst (Table 1, entry 11).

The application of 50 mol % of $ZnCl_2$ produced a positive effect relative to catalytic amounts in the reaction of enaminones **3b,c** to afford indoles **8b,c** in high yields (Table 2). As expected, the reaction between diketodien-amines **4**–**5** and PBQ proceeded via the indolization pathway, however, the crude monoindoles **9a**,**c** and diindoles **10b**, **11a–c** were isolated in low yields under the standard conditions. A 50–100% amount of the catalyst appeared to be critical for the efficient synthesis of compounds **8–11**, and under these conditions, **8**–**11** were obtained in good to high isolated yields (Tables 1 and 2). For both diketo- and diethoxycarbonyl diendiamines **5**, the number of intervening methylene groups (6) did not influence the result, since diindoles **11** were obtained as single products (Table 2). Further studies on concentration effects revealed that a three-fold excess of **4a** appears to be optimum to obtain indole **9a** as a pure product in 78% isolated yield (Table 2). Finally, we showed that a stoichiometric amount of $ZnCl_2$ was required to obtain pure (>95%) *N*-butylindole **6a** in good yield (Table 1, entry 2). All reactions were performed in refluxing $CH_2Cl_2$ without exclusion of air or moisture. The results were evaluated through TLC and $^1$H NMR data. The molecular structure of compound **9a** was confirmed by an X-ray analysis (Fig. 1).[12] The structures of compounds **6–11** were deduced from elemental analyses and $^1$H and $^{13}$C NMR data. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values.

**Table 2**
Yields of indoles **7**–**11** depending on reaction conditions

| Entry | Enaminone | Equiv PBQ: **2**–**5b**,**c** (mmol) | $ZnCl_2$, (mol %) | Time (min) | Product | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **2b** | 1:1.1 | 10 | 25 | **7b** | 85 |
| 2 | **2c** | 1:1.1 | 10 | 30 | **7c** | 83 |
| 3 | **3b** | 1:1.1 | 50 | 60 | **8b** | 83 |
| 4 | **3c** | 1:1.1 | 50 | 60 | **8c** | 82 |
| 5 | **4a** | 1:3 | 100 | 20 | **9a** | 78 |
| 6 | **4b** | 2.2:1 | 50 | 30 | **10b** | 80 |
| 7 | **4c** | 1:1.1 | 100 | 30 | **9c** | 77 |
| 8 | **5a** | 2.2:1 | 50 | 30 | **11a** | 78 |
| 9 | **5b** | 2.2:1 | 50 | 25 | **11b** | 75 |
| 10 | **5c** | 2.2:1 | 50 | 30 | **11c** | 82 |

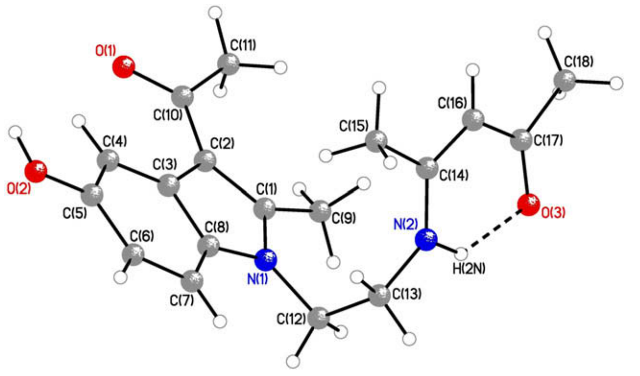

**Figure 1.** The general view of **9a**, atoms represented by thermal ellipsoids at 50% probability level.

As compared with the results under the standard conditions, all the reactions with enaminones **3**–**5** in the presence of 10–100 mol % of $ZnCl_2$ proceeded smoothly and rapidly to give the corresponding indoles in good to high yields as practically pure products. Several examples illustrating this novel method are

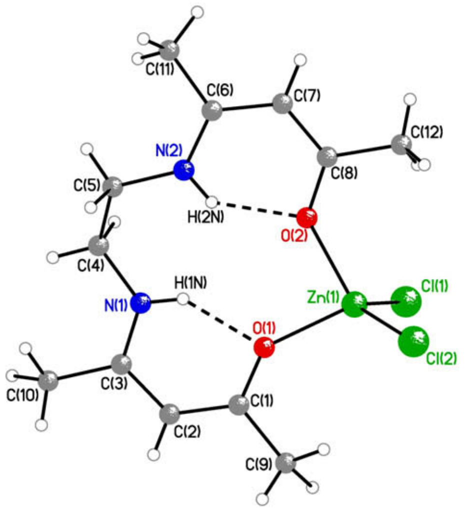

**Figure 2.** The general view of **12**, atoms represented by thermal ellipsoids at 50% probability level.

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