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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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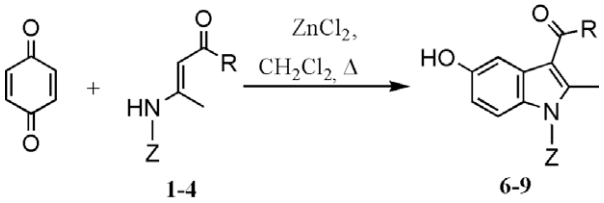
ABSTRACT

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.

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.

* 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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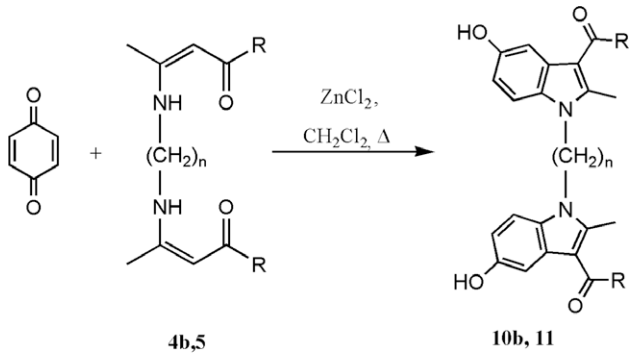


4,10b n = 2, R = OEt;
5,11a n = 6, R = Me;
5,11b n = 6, R = OEt;
5,11c n = 6, R = Ph.

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

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

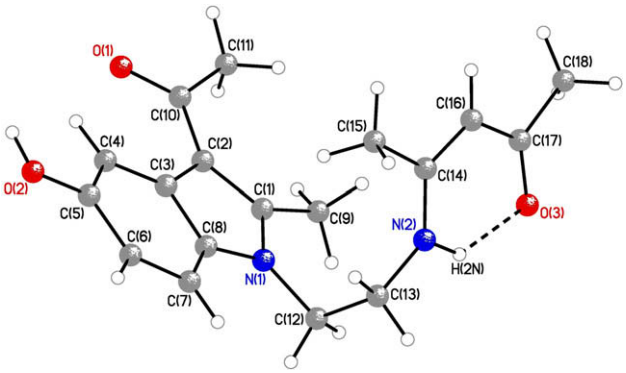


Figure 1. The general view of **9a**, atoms represented by thermal ellipsoids at 50% probability level.

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.

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

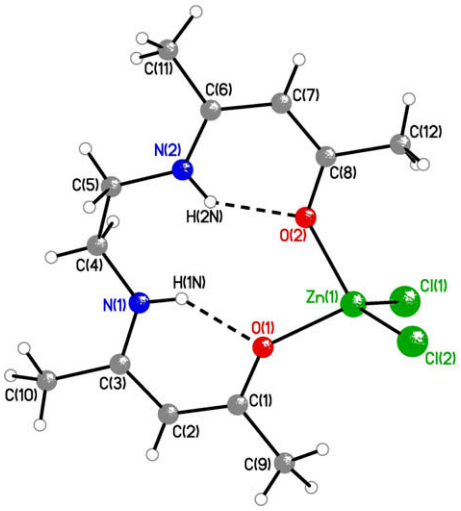
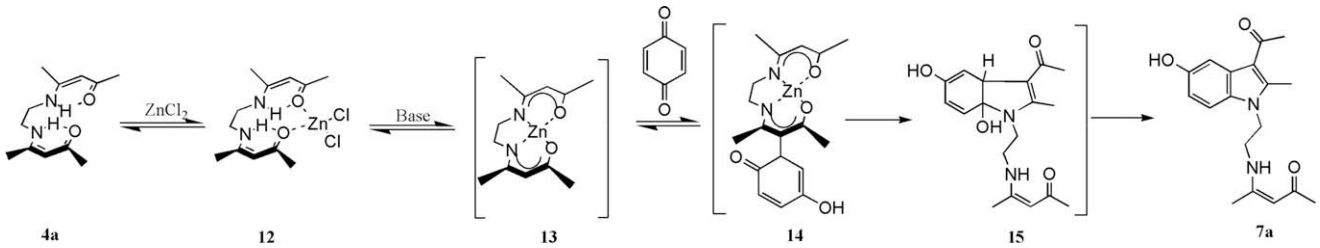


Figure 2. The general view of **12**, atoms represented by thermal ellipsoids at 50% probability level.



Scheme 3.

summarized in Tables 1 and 2. High yields of indoles **7** could be achieved when a catalytic amount of $ZnC1_2$ was employed (Tables 1 and 2).

The yields of indoles **7a** and **8a** obtained in the presence of the more azaphilic Lewis acids ($ZnC1_2$ or ZnI_2) exceeded those achieved in the presence of oxophilic $AlCl_3$. We tried to test whether the origin of the catalytic effect was due to enamine activation, in accordance with a hypothesis involving an enamine-Michael reaction, that is, the nucleophilic addition of a coordinated enamine complex (prepared from a β-diketone and an amino acid derivative) to methyl vinyl ketone.[13,14] This hypothesis prompted us to examine whether indole **9a** could result from a diketodienamine-$ZnC1_2$ complex and, if so, whether it depended on the presence or absence of a base. Recently, Lectka et al. successfully used bifunctional catalyst systems, in which cinchona alkaloid derivatives worked best when paired with Lewis acids based on, in particular, Zn(II) salts.[15] An enaminone-$ZnCl_2$ complex was reported earlier.[16] We observed that treatment of the diketodienamine **4a** with one equivalent of anhydrous $ZnCl_2$ in THF or CH_2Cl_2 generated a complex **12** (Scheme 3) in which, according to X-ray diffraction data, ligand **4a** coordinated to Zn(II) via two oxygen atoms (Fig. 2).[17] The complex alone failed to react with PBQ, but a high level of acceleration for formation of indole **9a** was achieved in the presence of triethylamine as a base (>four-fold reduction in reaction time). Thus, a deprotonated enaminone-$ZnC1_2$. complex turned out to be an intermediate in the Nenitzescu reaction with diketodienamine **4a** and probably with the other enaminones as well. Our findings confirmed that **4a** was activated via precomplexation with $ZnC1_2$ followed by deprotonation with a base.

On the basis of the results obtained and the literature precedents for the Lewis acid-catalyzed enamine-Michael reaction,[13,14,18] a plausible mechanism for the novel modification of the Lewis acid-catalyzed Nenitzescu reaction is proposed in Scheme 3.

The route involves in situ formation of a coordination complex **12** followed by its rearrangement into a complex with even more acidic NH proton(s). When the latter is generated, however, it is rapidly deprotonated by a base such as the enaminone component itself or an additional base, to a highly nucleophilic complex **13**. Then, the first C–C bond is formed via an enamine-Michael reaction between nucleophilic complex **13** and PBQ. The complex formation is likely to prevent the reversion of this addition due to increasing the rate of direct reaction through a shift of the equilibrium. It is noted that a large or even stoichiometric amount of a Lewis acid is necessary to promote the enamine-Michael reaction with methyl vinyl ketone.[18] The high nucleophilicity of complex **13** can also facilitate the formation of cyclic intermediate **15** through a ring closure step. A non-redox mechanism seems to occur on account of a high rate for the cyclization step. An excess of PBQ proved not to give rise to oxidative side products as the reaction took place under conditions related to a redox mechanism.[8,10,11] Our explanation also underlines why Zn(II) works so efficiently as compared to other Lewis acids, Al(III), in particular. This result is almost certainly due to the preferential binding of the more azaphilic Zn(II) to the enaminone nitrogens; Zn(II) is known to have a high affinity for amines.[15] Furthermore, Lewis acid catalysts can promote the reactions of both *N*-alkyl functionalized enaminones and simple ones with PBQ and other quinones through type **12–14** catalyst—enaminone complexes.

In summary, we have developed an efficient and versatile method to obtain 5-hydroxyindoles containing a range of substituents at the N-1 and C-3 positions as well as 5,5′-dihydroxydiindoles bearing a linker between the ring nitrogens. The method requires the use of 10–100 mol % of a Lewis acid. The amount of the catalyst employed depends on the nature of the enamine component. We showed that the catalytic effect occurs due to enamine component activation through a diketodienamine-$ZnC1_2$ complex, in particular, followed by its deprotonation. The structure of a similar deprotonated ethylenediamine-based complex with Zn–N bonds was reported recently.[19] Further studies on the utility of this reaction are in progress and will be reported in due course.

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11. *3-Acetyl-5-hydroxy-2-methyl-1-(N-tosyl-2-aminoethyl)-indole* (**7a**). To a solution of 1,4-benzoquinone (0.33 g, 3.00 mmol) in CH_2Cl_2 (6 ml) was added $ZnCl_2$ (0.04 g, 0.30 mmol). The resulting mixture was heated to reflux and then a solution of enamine **2a** (0.98 g, 3.30 mmol) in CH_2Cl_2 (10 ml) was added drop by drop with stirring over 5–10 min. The mixture was stirred at reflux for an additional 25 min and cooled to 0–5 °C for 2–3 h. The precipitated crystals were filtered off and washed with CH_2Cl_2 (2 × 1 ml) and acetone (2 × 1 ml) to afford 1.02 g (88%) of **7a**. IR (KBr): ν_{max} 3262 (NH), 1603 (C=O) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 2.36 (3H, s, CH_3 (Ts)), 2.48 (3H, s, C(O)CH_3), 2.65 (3H, s, 2-CH_3), 2.98 (2H, q, J = 6.2 Hz, NH–CH_2), 4.16 (2H, t, J = 6.2 Hz, N–CH_2), 6.62 (1H, dd, J = 8.6 Hz, 2.3 Hz, H^6), 7.18 (1H, d, J = 8.6 Hz, H^7), 7.29, 7.55 (4H, 2d, J = 8.1 Hz, $H^{2,3}$ (SO_2-*p*-Tol)), 7.34 (1H, d, J = 2.3 Hz, H^4), 7.77 (1H, t, J = 6.2 Hz, NH), 8.96 (1H, s, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 13.11, 21.41, 31.70, 42.09, 43.17, 106.00, 110.88, 111.73, 113.79, 126.86, 127.67, 130.10, 130.36, 137.64, 143.27, 145.10, 153.43, 193.27; MS *m*/*z* 386. Anal. Calcd for $C_{20}H_{22}N_2O_4S$: C, 62.16; N, 7.25; H, 5.74. Found: C, 62.07; N, 7.19; H, 5.81.
12. Crystallographic data for **9a** ($C_{18}H_{22}N_2O_3$ ½(C_3H_6O), M = 343.42): crystals are monoclinic, space group *C*2/*c*, at 120 K: a = 20.817(3), b = 10.6378(13), c = 16.799(2) Å, β = 98.608(5)°, V = 3678.1(8) Å^3, Z = 8, d_{calc} = 1.240 g cm^{-3},

μ(Mo Kα) = 0.85 cm^{-1}, F(000) = 1472. The refinement of **9a** using 4864 independent reflections ($2\theta < 58°$) is converged to $wR_2 = 0.1650$, GOF = 1.005 and $R_1 = 0.0622$ (for 3001 observed reflections with $I > 2\sigma(I)$). Further details are available from CCDC 694501.

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17. Crystallographic data for **12** ($C_{12}H_{20}Cl_2N_2O_2Zn$, $M = 360.57$): crystals are monoclinic, space group $P2_1/n$, at 100 K: $a = 8.1250(2)$, $b = 18.9964(5)$, $c = 10.3853(3)$ Å, $\beta = 101.3350(10)°$, $V = 1571.66(7)$ Å^3, $Z = 4$, $d_{calc} = 1.524$ g cm^{-3}, μ(Mo Kα) = 19.01 cm^{-1}, F(000) = 744. The refinement of A using 4999 independent reflections ($2\theta < 62°$, $R_{int} = 0.0359$) is converged to $wR_2 = 0.0505$, GOF = 1.042 and $R_1 = 0.0191$ (for 4720 observed reflections with $I > 2\sigma(I)$). Further details are available from CCDC 694502.
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