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A New Approach to Difficult Fischer Synthesis: The Use of Zinc Chloride Catalyst in Triethylene Glycol under Controlled Microwave Irradiation

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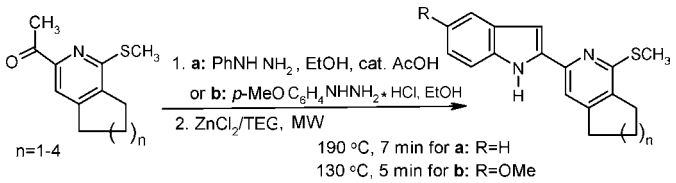
ABSTRACT



Application of triethylene glycol with catalytic quantity of zinc chloride ($ZnCl_2$/TEG) is described as a new and efficient reaction medium for a difficult Fischer synthesis, leading to sensitive indoles. Transformation of the 3-acetyl-1-methylthiocycloalka[*c*]pyridine phenylhydrazones and *p*-methoxyphenylhydrazones into the 2-(2-pyridyl)indoles and 5-methoxy-2-(2-pyridyl)indoles, which are the synthons in our total synthesis of the sempervirine-type alkaloids, is carried out under controlled microwave irradiation in dry zinc chloride solution (0.16 M) in TEG. This protocol produces indoles from acetophenone or cyclohexanone via their phenylhydrazones in excellent yields.

Indoles constitute an important moiety in natural product chemistry and pharmacology.[1] As a consequence, investigations into new methods for the construction of indoles are of considerable interest to many chemists.[2] The Fischer indolization of carbonyl synthons continues to maintain its prominent role as a route to indoles[2,3] and, in this regard, is now used in synthetic combinatorial chemistry.[4]

Transformation of arylhydrazones into indoles is catalyzed and accelerated by protic and Lewis acids.[2,3] The most frequently employed Lewis acid is zinc chloride, either with no solvent or in ethanol or acetic acid. The difficult Fischer indolization of acetophenone[5] and 2-acetylpyridine[6] phenylhydrazones has traditionally been performed via the classic method, with an excess of zinc chloride itself,[5] or together with methylnaphthalene[6] as a high-temperature reaction medium, as an alternative to polyphosphoric acid.[7]

Here, we report that use of zinc chloride in anhydrous triethylene glycol can often give markedly improved product yields in normally difficult Fischer indolization processes such as the Fischer synthesis of the 2-(2-pyridyl)indoles **3a**−**d**[8] and **4a**−**d**.[9] These compounds are key intermediates (Figure 1) in our total synthesis of the modified series of the sempervirine-type alkaloids **1a**−**d** and **2a**−**d** (potential antitumor agents).

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(3) For reviews on mechanism and methodology Fischer synthesis, see: (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley & Sons: New York, 1982. (b) Hughes, D. L. *Org. Prepr. Proced. Int.* **1993**, *25*, 607−647.

(4) (a) Cheng, Y.; Chapman, K. T. *Tetrahedron Lett.* **1997**, *38*, 1497−1500. (b) Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370−372.

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(9) Lipińska, T. *Tetrahedron Lett.* **2004**, *45*, 8831−8834.

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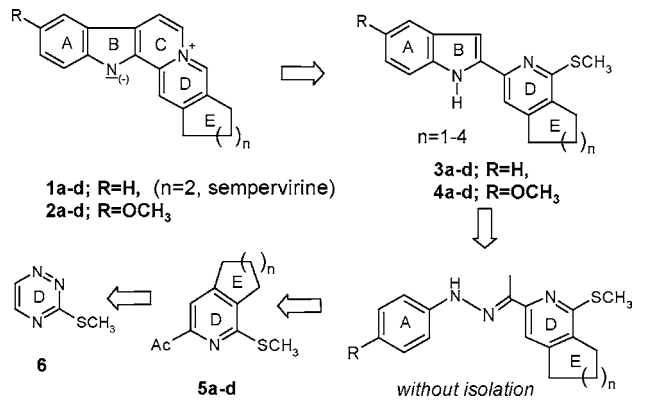


Figure 1. Retrosynthetic analysis.

In our new improved procedure for Fischer indolization, the crude phenylhydrazones of ketone **5a**−**d**[10] were dissolved in triethylene glycol that contained catalytic quantities of zinc chloride. They were then irradiated by microwaves at controlled temperatures. The following experiments have led us to conclude that the zinc chloride functions both as a catalyst and as a heating agent in the new protocol.

First, in the previously described procedure, the microwave-assisted solvent-free Fischer indolization was performed with the phenylhydrazones **5a**−**d** or the corresponding *p*-methoxyphenylhydrazone hydrochlorides of **5a**−**d** adsorbed on the support MK10/$ZnCl_2$ (method 1).[9,11] The programmed and measured parameters in the synthesis of **3a**−**d** are shown in Figure 2. The synthesis of **4a**−**d** by this method was

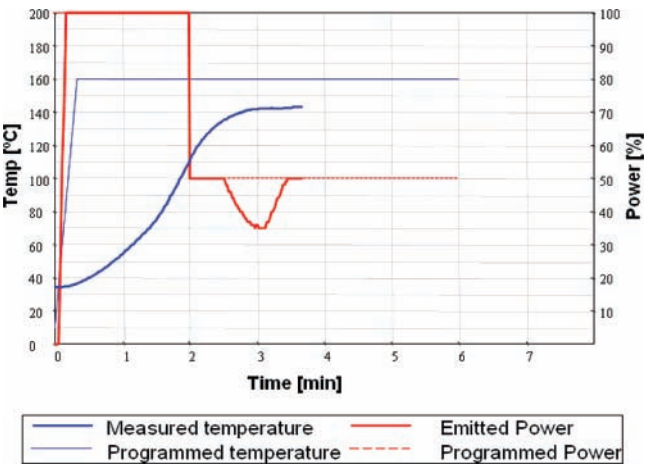
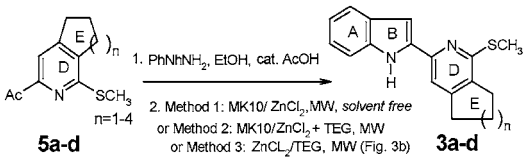


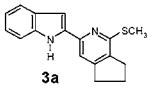
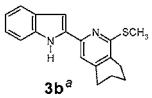
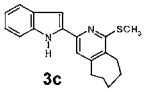
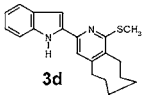
Figure 2. Fischer synthesis of **3a**−**d** via the solvent-free method 1.

described in our earlier paper.[9] Inefficient yields were obtained via this procedure, as a result of degradation of the reactants during their irradiation on the solid support without solvent; *hot spots* emerged which led to a localized temperature that could be much greater than the measured (average).[12]

Second, with a view to eliminating hot spots, we added the anhydrous solvent triethylene glycol to the phenylhydrazones or *p*-methoxyphenylhydrazones adsorbed on the solid support MK10/$ZnCl_2$. Next, we irradiated at the programmed temperature of 190 °C for the synthesis of **3a**−**d** and at 130 °C for the synthesis of **4a**−**d** (method 2)**.** The optimized time whereafter all the substrate had disappeared was 6 min in the first case and 3 min in the second. Better yields were obtained than in method 1 (Tables 1 and 2).

Table 1. Comparison of the Three Microwave-Assisted Fischer Indolization Methods: Yields of **3a**−**d** from Ketones **5a**−**d**



Entry	Subst.	Product	Yield (% isolated product)		
			Met. 1	Met. 2	Met. 3
1	**5a**	 **3a**	29	34	52
2	**5b**	 **3b**[a]	28	33	53
3	**5c**	 **3c**	27	32	51
4	**5d**	 **3d**	26	32	50

[a] Mentioned in ref 8a.

Having obtained these results, we assumed that zinc chloride solution could be applied in anhydrous ethylene glycol for our microwave-assisted Fischer indole synthesis.

We prepared a 0.16 M $ZnCl_2$/TEG solution by heating, until we established a pale-yellow liquid. Initially, we examined the effect of microwave heating of this new reaction medium itself (0.5 cm^3) in a microwave reactor Synthewave 402 (Figure 3a). We then mixed the crude phenylhydrazones or *p*-methoxyphenylhydrazones (0.5 mmol) of ketone **5a**−**d**[10] with this $ZnCl_2$/TEG solution (0.33 mL, 10 mol % of $ZnCl_2$) and irradiated with the parameters as shown in Figure 3b or c (method 3).[13] In the optimized periods, the indoles **3a**−**d** were obtained in yields of 49−53% (Table 1) and the 5-methoxyindoles **4a**−**d** in yields of 59−64% (Table 2).

In Tables 1 and 2, the yields of the Fischer syntheses of **3a**−**d** and **4a**−**d** are shown, obtained via the new method 3 in comparison with our previous methods 1 and 2.

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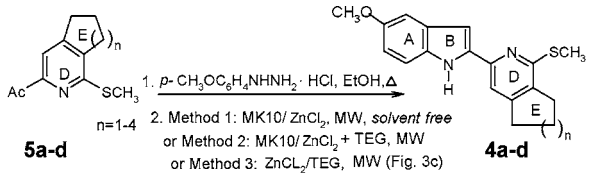
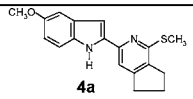
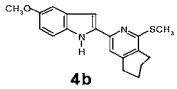
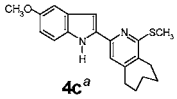
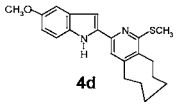
(11) Lipińska, T.; Guibe-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, *29*, 1349−1354.
(12) For reviews on microwave-assisted synthesis, see: (a) Lindström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Loupy, A. *Microwaves in Organic Chemistry*; Wiley-VCH: New York, 2002. (c) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66−76. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.

Table 2. Comparison of the Three Microwave-Assisted Fischer Indolization Methods: Yields of **4a**−**d** from Ketones **5a**−**d**



Entry	Substr.	Product	Yield (% isolated product) Met. 1	Met. 2	Met. 3
1	**5a**	 **4a**	38	53	63
2	**5b**	 **4b**	43	52	62
3	**53**	 **4c**[a]	40	50	61
4	**5d**	 **4d**	38	49	60

[a] Mentioned in ref 9.

Table 3. Testing $ZnCl_2$/TEG Medium Activity in the Fischer Transformation **5a** into **3a** and **4a** and in the Synthesis of 1,2,3,4-Tetrahydrocarbazole **9** from Cyclohexanone **7** and 2-Phenylindole **10** from Acetophenone **8**

entry	subst	conditions:medium energy, T (°C)	time	indole product	yield (%)
1	**5a**	Method 3, MW,180	7 min	**3a**	52
2	**5a**	$ZnCl_2$/TEG, Δ, 180	7 min	**3a**	trace
3	**5a**	$ZnCl_2$/TEG, Δ, 180	3 h	**3a**	12
4	**5a**	Method 3, MW, 180	5 min	**4a**	63
5	**5a**	$ZnCl_2$/TEG, Δ, 130	5 min	**4a**	10
6	**5a**	$ZnCl_2$/TEG, Δ, 130	30 min	**4a**	55
7	**5a**	TEG, MW, 180	7 min	**3a**	trace
8	**5a**	TEG, WM, 180	50 min	**3a**	5
9	**5a**	TEG, MW, 130	5 min	**4a**	15
10	**5a**	TEG, WM, 130	20 min	**4a**	22
11	**7**	Method 3, MW, 100	5 min	**9**	97
12	**7**	AcOH, Δ, reflux	2 h	**9**	76[a]
13	**8**	Method 3, MW,160	6 min	**10**	95
14	**8**	PPA, Δ, 120[a]	10 min	**10**	72−80[a]

[a] Literature[3a] data.

The experiments reported in Tables 1 and 2 show that method 3, which involves our new homogeneous procedure, is more effective in the difficult Fischer synthesis of the sensitive indoles **3a**−**d** and **4a**−**d** than the heterogeneous methods 1 and 2.

We also examined the activity of the $ZnCl_2$/TEG medium in experiments (Table 3) where conventional heating was applied instead of microwave irradiation for the Fischer transformations of the phenylhydrazone of **5a** (entries 2 and 3) and the *p*-methoxyphenylhydrazone hydrochloride of **5a** (entries 5 and 6). These reactions were also tested in TEG itself (without zinc chloride) under microwave irradiation at the same programmed temperatures as in method 3 (entries 7−10). In Table 3, we also report our results from the Fischer indolization of cyclohexanone **7** and acetophenone **8** in $ZnCl_2$/TEG medium under microwave irradiation in comparison to the standard procedures.[3a]

The experiments show that zinc chloride, in a catalytic quantity of 10%, plays a major role in the selectivity and acceleration of our new microwave-assisted Fischer synthesis. It can act both as a Lewis acid catalyst and as a heating agent during microwave irradiation. Triethylene glycol is preferred as it is high-boiling, polar, ethereal, and a protic solvent and as such is capable of dissolving both the substrate and the catalyst.

Our experimental observations are consistent with past mechanistic observations on the Fischer indole synthesis,[3b] wherein cationic transition states exist both before and after the key step, [3.3] rearrangement of the phenylhydrazone. The charge appearance in intermediates is facilitated by

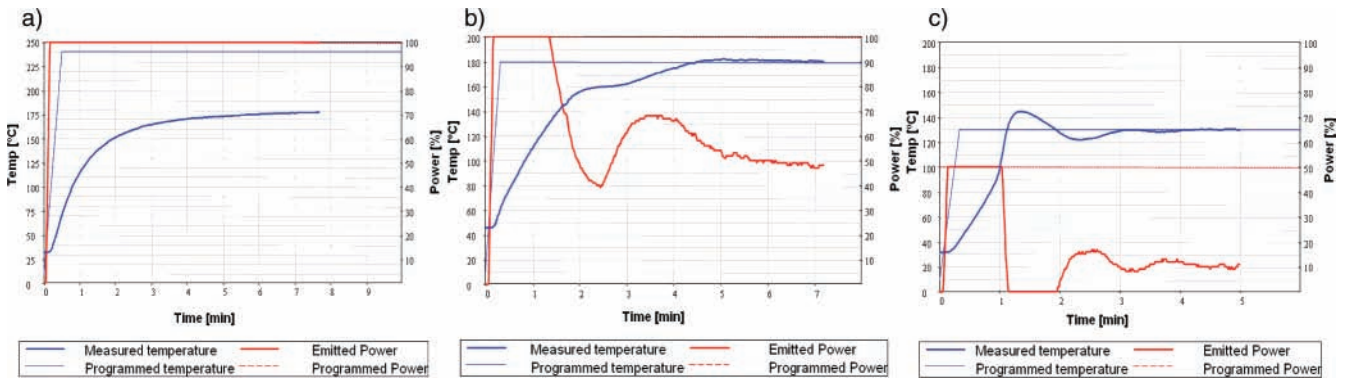


Figure 3. Temperature and power of the ongoing microwave experiments; programmed and measured (monomode reactor Synthewave 402, 300 W, Prolabo): (a) heating during the microwave irradiation of the 0.16 M $ZnCl_2$/TEG solution (0.5 cm^3) itself; (b) synhesis of **3a**−**d** in $ZnCl_2$/TEG medium (method 3 in optimized time); (c) synthesis of **4a**−**d** in $ZnCl_2$/TEG medium (method 3 in optimized time).

microwave irradiation with respect to the dielectric polarization nature of the microwave energy transfer.[12b] This phenomenon has been considered as a mechanism for overall acceleration rate of reactions with charge in transition state which are carried out under microwave irradiation.

Our successful efforts to optimize the Fischer synthesis of the indoles **3a**−**d** and 5-methoxyindoles **4a**−**d** enable us to obtain them in quantities, appropriate for using them as synthons in the preparation of the sempervirine type pentacyclic alkaloids **1a**−**d** and **2a**−**d**.

(13) Typical procedures for synthesis of **3a**−**d** and **4a**−**d** in method 3 performing the Fischer indolization: Ketone **5a** or **5b**−**d** (1 mmol) was refluxed in ethanol with phenylhydrazine (1.1 mmol) and acetic acid (0.2 mmol) or with *p*-methoxyphenylhydrazine hydrochloride (1.1 mmol) for 0.5 h (TLC monitoring). Crude phenylhydrazone or *p*-methoxyphenylhydrazone hydrochloride was obtained (after removing ethanol) and put into two identical Pyrex vessels. Freshly prepared 0.16 M solution of anhydrous zinc chloride in TEG (0.33 mL, 0.05 mmol $ZnCl_2$) was added to each vessel and irradiated in an open system according to the programmed parameters as shown in Figure 3b for phenylhydrazones and in Figure 3c for *p*-methoxyphenylhydrazones. A cooled 0.5 M solution of NaOH (4 mL) was added to both vessels. The precipitate was filtered, washed with cold water, dried, and purified by column chromatography, using silica gel and eluents hexane/CH_2Cl_2 2:1 for **3a**−**d** or hexane/CH_2Cl_2 3:2 for **4a**−**d**. Yields of the products **3a**−**d** are given in Table 1 and **4a**−**d** in Table 2. Full characterization data for all undescribed compounds is given in the Supporting Information.

In summary, we have established an efficient procedure for performing a difficult Fischer synthesis of sensitive indoles. This method involves $ZnCl_2$/TEG-mediated Fischer indolization under controlled microwave irradiation. It is reproductible and simple, does not require isolation of the phenylhydrazone intermediate, and can be used at a wide range of temperatures. In addition, the method utilizes inexpensive and environmentally friendly (biodegradable) solvents (ethanol and TEG) and zinc chloride in catalytic quantity. The aqueous workup of the reaction mixture is important for green technology. We expect that this methodology will find wide application for the Fischer indole synthesis. The $ZnCl_2$/TEG medium can also be used for other reactions with high-temperature and Lewis acid catalyst requirements, which can be performed either under microwave irradiation or with conventional heating.

Supporting Information Available: General experimental data and characterization data for all indoles, including undescribed compounds **3a**,**c**,**d** and **4a**,**b**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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