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Microwave-induced solid-supported Fischer indolization, a key step in the total synthesis of the sempervirine type methoxy analogues☆

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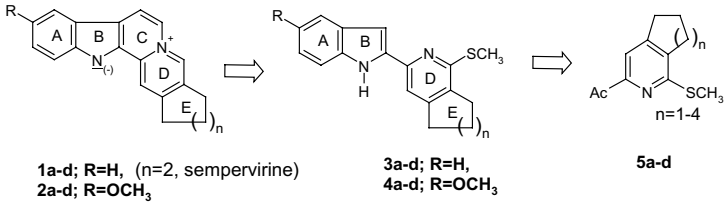
Abstract—A general protocol for the synthesis of 2-heteroaryl-5-methoxyindoles has been developed utilizing a microwave-induced solid-supported Fischer indolization under controlled conditions This route uses 2-acetylpyridine as a model and 3-acetyl derivatives of cycloalkeno[*c*]fused pyridines as the synthetic building blocks towards new 9-methoxyindolo[2,3-*a*]quinolizine alkaloids.

The indolo[2,3-*a*]quinolizine ring system is the main structural moiety of sempervirine **1a** and some related alkaloids, which exhibit cytostatic, anti-HIV, immunostimulant and sedative activities.[1] This type of alkaloid can exist as either cations or inner salts (zwitterions), depending on pH.[2] This balance is of great importance for biological systems where it is responsible for transport into cells as well as for interactions with DNA.[3] These unique structural and biological characteristics have promoted interest in the synthesis of sempervirine[2,4,5a] and its analogues.[5b] However, no synthetic approach to derivatives bearing a methoxy group on the phenyl ring has as yet been reported. Some methoxy-substituted indole alkaloids exhibit strong effects on the nervous system.[6]

We have recently reported the preparation of 3-acetyl derivatives of cycloalkeno[*c*]fused pyridines **5a–d** as valuable intermediates in the synthesis of sempervirine **1a** (R = H, *n* = 2)[5a] and related systems **1b–d**[5b] via the route outlined in Scheme 1.

The present paper describes microwave-induced solid-supported Fischer indolization as the key step in the preparation of the model compound 9-methoxyindolo[2,3-*a*]quinolizine **9b** from 2-acetylpyridine **6** (Scheme 2), and in the total synthesis of new sempervirine methoxy analogues **2a–d** from ketones **5a–d** (see Schemes 1 and 3).

The methods reported for Fischer synthesis of 2-(2-pyridinyl)indoles **7a** involve heating phenylhydrazones in polyphosphoric acid at 180 °C,[7] or in zinc chloride–methylnaphthalene at over 200 °C.[8] These drastic conditions are not suitable for obtaining 5-methoxyindoles, which can be synthesized only in a weak acid medium



Scheme 1.

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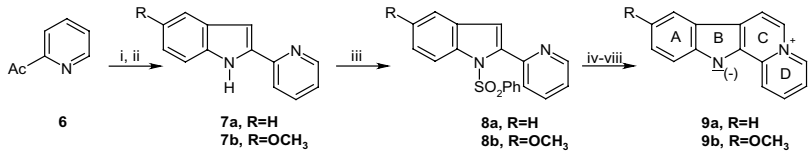
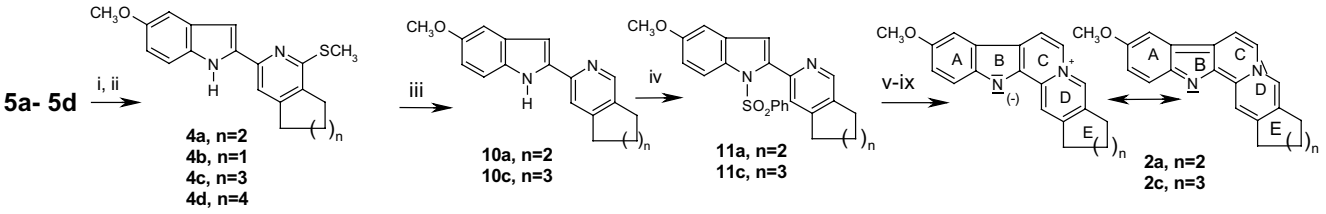


Scheme 2. Reagents and conditions: (i) $PhNHNH_2$·HCl for **7a** or *p*-$CH_3OC_6H_4NHNH_2$·HCl for **7b**, reflux EtOH; (ii) MK10/$ZnCl_2$, MW; (iii) NaH, THF, $PhSO_2Cl$, 0 °C to rt; (iv) THF, *n*-BuLi, −70 °C, $BrCH_2CHO$; (v) AcOH, −78 °C to 0 °C, NH_4Cl (aq), AcOEt; (vi) $CHCl_3$, rt 2 h; (vii) MeOH, 10% NaOH, Δ; (viii) 10% NaOH/$CHCl_3$.



Scheme 3. Reagents and conditions: (i) *p*-$CH_3OC_6H_4$ $NHNH_2$·HCl, reflux EtOH, 20 min; (ii) MK10/$ZnCl_2$, MW; (iii) Ni-R, EtOH, 0–5 °C; (iv) NaH, THF, $PhSO_2Cl$, 0 °C to rt; (v) THF, *n*-BuLi, −70 °C, $BrCH_2CHO$; (vi) AcOH, −78 °C to 0 °C, NH_4Cl (aq), AcOEt; (vii) $CHCl_3$, rt 2 h; (viii) MeOH, 10% NaOH, Δ; (ix) 10% NaOH/$CHCl_3$.

due to cleavage of the methoxy group.[9] Until now only simple Fischer indole syntheses have been performed on solid support under microwave irradiation.[10] To develop conditions for obtaining 2-heteroaryl-5-methoxyindoles **4a**–**d**, first we investigated the synthesis of 5-methoxy-2-(2-pyridyl)indole **7b** (Scheme 2) as a model by using the Fischer indole synthesis on an acidic solid support under microwave irradiation.[11]

We used a single-mode microwave reactor, with feedback temperature control (IR detector). Firstly, the activity of the fresh solid support, montmorillonite K 10 modified with zinc chloride (MK10/$ZnCl_2$) was examined by performing the synthesis of **7a**[12] (Scheme 2). Then, we developed the conditions (temperature and time) for the Fischer synthesis of 5-methoxy-2-(2-pyridinyl)indole (**7b**) from 2-acetylpyridine and *p*-methoxyphenylhydrazine with (MK10/$ZnCl_2$), but without solvent.[13] The temperature diagram of the ongoing Fischer reaction towards **7b** is shown in Figure 1a. We arrived at a reasonable yield of 40–45% when we stopped irradiation after 2.5 min from the moment the temperature started to increase rapidly (about 100 °C) due to the initiation of the microwave-induced Fischer reaction. We found that over a short period of time, the transformation of the substrate was not complete, while over longer periods the yield of product **7b**[14a] decreased, because degradation processes set in. Next, the following steps were undertaken: the reaction leading to *N*-protected methoxyindole **8b** (60%) and a one-pot procedure for C ring construction, were performed under the conditions developed previously.[5b,15] The final product **9b**[16a] was obtained as an inner salt.

Our preliminary investigations thus suggested that the syntheses of **2a**–**d**, that is, the new methoxy analogues of sempervirine could be successfully conducted.

The starting compounds were the acetyl derivatives of condensed pyridines **5a**–**d** which were obtained from 3-(methylthio)-1,2,4-triazine[17] via a three-step synthesis, which included an aza-Diels–Alder reaction with cyclic enamines.[5,18] These ketones were transformed into the appropriate *p*-methoxyphenylhydrazones (see Scheme 3), mixed with the support (MK10/$ZnCl_2$) and irradiated (after evaporation of ethanol) in a microwave reac-

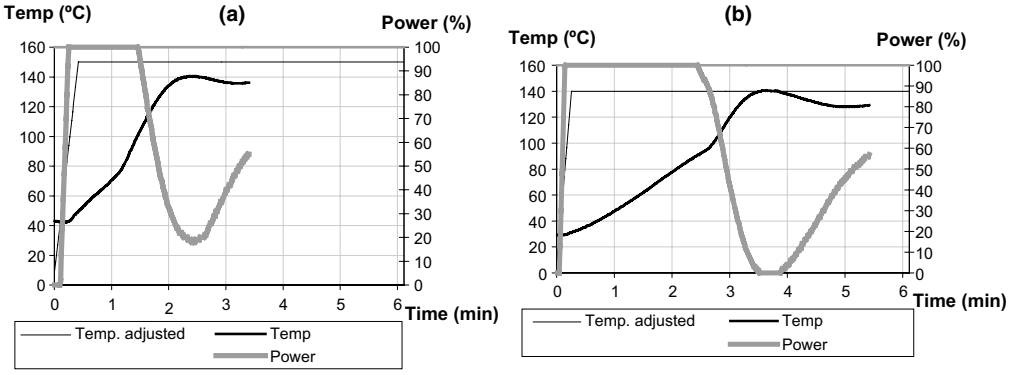


Figure 1. Temperature and power of the ongoing microwave-induced Fischer reactions on the solid support MK10/$ZnCl_2$ (monomode microwave reactor Synthewave 402, 300 W, Prolabo). (a) Synthesis of **7b** (b) synthesis of **4c**.

Table 1. Yields and properties of indole **7b** and **4a–d** obtained from the solid-supported Fischer synthesis under microwave irradiation[13]

Entry	Substrate	*n*	Product	R_f[a]	Yield[b] (%)	Mp (°C)
1	**6**		**7b**[14a]	0.33	43	128–129
2	**5a**	2	**4a**	0.65	35	177–178
3	**5b**	1	**4b**	0.62	45	193–194
4	**5c**	3	**4c**[14b]	0.68	40	182–183
5	**5d**	4	**4d**	0.70	38	141–142

[a] TLC plates (silica gel 60 F_{254} on aluminium roll, Merck) were developed in chloroform-acetone 50:1 system.
[b] Product isolated by column chromatography.

tor at the programmed temperature up to 150 °C.[13] The temperature diagram observed in the course of the microwave-assisted Fischer synthesis of **4c**[14b] is shown in Figure 1b. A similar temperature increase was observed during the synthesis of indoles **4a**, **4b** and **4d**. The yields and the physical properties of the products **4a–d** and **7b** are reported in Table 1. We performed pilot rearrangements of **4a** and **4c** into the new sempervirine methoxy analogues **2a** and **2c** as shown in Scheme 3. The desulfurization of **4a** and **4c** resulted in compounds **10a** and **10c** (45–55%). After *N*-protection, intermediates **11a** and **11c** were isolated by preparative thin layer chromatography (silica gel plates) in 35–45% yields. We used the Gribble method[15] for the final construction of the C ring. The final sempervirine analogues **2a**[16b] and **2c**[16c] were obtained as neutral (inner) compounds (zwitterions are not the sole forms, see Scheme 1) by extraction with chloroform from a strong alkaline medium.

The structures of all the new intermediates: **7b**,[14a] **8b**, **4a**,**b**, **4c**,[14b] **4d**, **10a**,**c** and **11a**,**c** and the final synthetic alkaloids: **9b**,[16a] **2a**[16b] and **2c**[16c] were determined by spectroscopic methods: IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS-ESI(+). The presence of the methoxy group was verified by the ^{1}H NMR spectra of these compounds, appearing as a singlet at ~3.95 ppm and by a simplification of the aromatic proton signals in comparison to the spectra of the corresponding analogues not possessing the CH_3O group, as obtained earlier.[5] In the ^{13}C NMR spectra the MeO signals appeared at ~56 ppm.

In conclusion, we have determined conditions for the microwave-induced solid-supported Fischer synthesis of 5-methoxy-2-(2-pyridyl)indole **(7b)** and four new 5-methoxy-2-(cycloalka[*c*]pyridin-3-yl)indoles **(4a–d)** as the key intermediates in the preparation of 9-methoxy-indolo[2,3-*a*]quinolizine alkaloids. After testing the synthesis of tetracyclic molecule **9b**, we performed two pilot syntheses towards the methoxy analogues of sempervirine with six- and seven-membered E rings (**2a** and **2c)**. Currently, research is being carried out to expand the scope of this synthesis and to investigate the physico-chemical and pharmacological properties of these compounds.

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13. *General experimental procedure for Fischer synthesis on solid-support under microwave irradiation*: To a refluxing mixture of *p*-methoxyphenylhydrazine hydrochloride (3.3 mmol) in ethanol (15 mL) was added a solution of acetyl pyridine **6** or **5a–d** (3 mmol) in ethanol (10 mL). After 25 min of refluxing, the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure to half the original volume (for removal of water) and the solid support, MK10/$ZnCl_2$[5b] (1 g, 0.36 mmol $ZnCl_2$) was added. After mixing manually, the solvent was evaporated under reduced pressure. The resulting supported substrate was placed into four identical Pyrex vials, which were fitted in turn into a Pyrex cylindrical vessel and irradiated in a Synthewave 402 microwave reactor (Prolabo, 300 W, open system). The temperature setpoint was programmed at 140 °C or 150 °C (Fig. 1: temp adjusted). Irradiation was stopped after 2–2.5 min from the moment the temperature began rapidly increasing. The solids from the vials were cooled and extracted several times with diethyl ether (100 mL) and diethylamine (2 mL). The residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (Merck, 100–200 mesh) to afford the pure products: **7b** (eluted with chloroform) or **4a–d** (eluted with chloroform–hexane 2:1). The yields and physical properties of products **7b** and **4a–d** are shown in Table 1.
14. Selected data for compounds **7b** and **4c**. (a) 5-Methoxy-2-(2-pyridyl)indole **7b**: IR (KBr, cm^{-1}) 3190, 3050, 2990, 2950, 2830, 1620, 1595, 1545, 1450, 1260, 1220, 1150, 1120,

1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H, H_3CO), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 6.95 (d, J = 1.8 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.14–7.17 (m, 1H), 7.26, (d, J = 8.8 Hz, 1H), 7.68–7.72 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 8.57 (d, J = 4.8 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.78 (OCH_3), 100.34, 102.35, 112.13, 113.83, 119.77, 121.83, 129.45, 131.96, 136.59, 137.27, 149.04, 150.44, 154.39; MS-EI *m/z* (%): 224 (M^+, 100), 209 (75), 181 (68); Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%; Found: C, 74.81; H, 5.33; N, 12.39%; (b) 6,7,8,9-Tetrahydro-3-(5-methoxyindol-2-yl)-1-(methylsulfanyl)-5*H*-cyclohepta[*c*]pyridine **4c**: IR (KBr, cm^{-1}): 3405, 3100, 3060, 2995, 2925, 2850, 1620, 1580, 1540, 1490, 1435, 1410, 1345, 1295, 1215, 1190, 1155, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.66 (m, 4H), 1.82–1.86 (m, 2H), 2.67 (s, 3H), 2.78–2.81 (m, 2H), 2.87–2.81 (m, 2H), 3.87 (s, 3H, H_3CO), 6.87 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.26 (s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 14.31, 26.91, 27.54, 30.02, 32.84, 36.24, 55.95 (OCH_3), 99.64, 102.47, 12.18, 113.51, 116.45, 129.87, 131.60, 134.72, 137.98, 147.34, 152.51, 154.54, 156.33; MS-EI *m/z* (%): 338 (M^+, 100), 323 (46), 305 (58), 295 (15); HRMS EI: found 338.1466, calcd for $C_{20}H_{22}ON_2S$: 338.1453.

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