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Pictet–Spengler heterocyclizations via microwave-assisted degradation of DMSO

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Abstract—For the first time the ability of DMSO to decompose rapidly under microwaves was explored in order to perform heterocyclizations in good conditions. This modified Pictet–Spengler reaction allowed, in this case, the synthesis of rigidified melatonin analogues.

Microwave-assisted reactions are now well established and have gained popularity as indicated by the large number of papers, reviews and books published recently on this topic.[1] Using microwave heating offers the possibility of reducing reaction time from hours to minutes and improving product yield. Key advantages of modern scientific microwave apparatus is the ability to control reaction conditions precisely, monitoring temperature, pressure and reaction times.[2] The variability of chemical reactions pushed a lot of chemistry groups to develop several methods, performing reactions in solvent free conditions or by adsorbing reactants onto various supports. If a reaction is carried out in a solvent, the medium or reactants need to have high dielectric constant (ε) in order to benefit from microwave heating. Due to this, most of the work in this area was performed using 1-methyl-2-pyrrolidinone (NMP, $\varepsilon = 32.2$), DMF ($\varepsilon = 36.7$) and DMSO ($\varepsilon = 46.7$). Among these solvents, DMSO appears to be quite stable thermally but upon prolonged reflux it does decompose slightly to dimethylsulfide, dimethyldisulfide, bismethylthiomethane, water and formaldehyde (Fig. 1). Formation of these compounds was suggested via various intermediates such as hemithioformal,[3] methyl methanesulfenate[4] or methyl dimethylsulfenate.[5] The decomposition of dimethyl sulfoxide is aided by acids and retarded by many bases.[5–9] Thus, heating this solvent in the presence of various catalysts such as NBS,[6] PPA,[7] TMSCl,[8] $POCl_3$ and $SOCl_2$[9] is now an efficient alternative for the use of formaldehyde in organic chemistry and it has been used in the transformation of aliphatic diols into cyclic acetals or in the formation of methylene bis-amides from amides. Considering these facts and in connection with our work on the use of microwaves in organic synthesis, we decided to realize a preliminary study of the microwave-assisted decomposition of dimethylsulfoxide and we applied the defined conditions to the synthesis of novel rigidified heterocyclic analogues of melatonine.

The approach described in this letter is an interesting alternative to the Pictet–Spengler reaction,[10] a heterocyclization that usually involves formaldehyde. Our goal was to establish its feasibility and to identify standard experimental conditions, which could be transposed to various starting molecules.

Working on benzothiophenic derivatives of melatonin[11–13] we observed that microwave-assisted heating (140 W) of the benzothiophene **1** (prepared as described in Ref. 13) in large excess of DMSO (35 mL), at reflux for 3 h, afforded a new cyclized molecule **2** (Scheme 1)

Keywords: Microwave-assisted reactions; Dimethyl sulfoxide; Formaldehyde; Pictet–Spengler heterocyclization.

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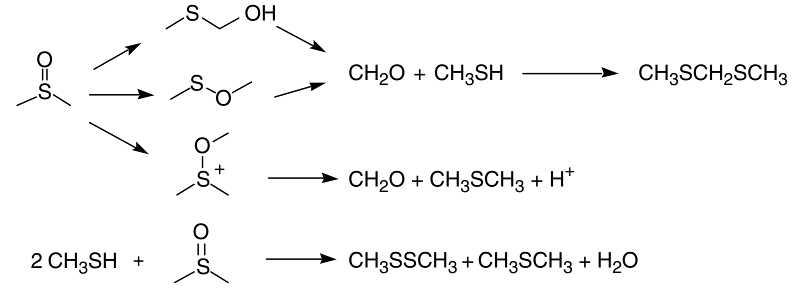
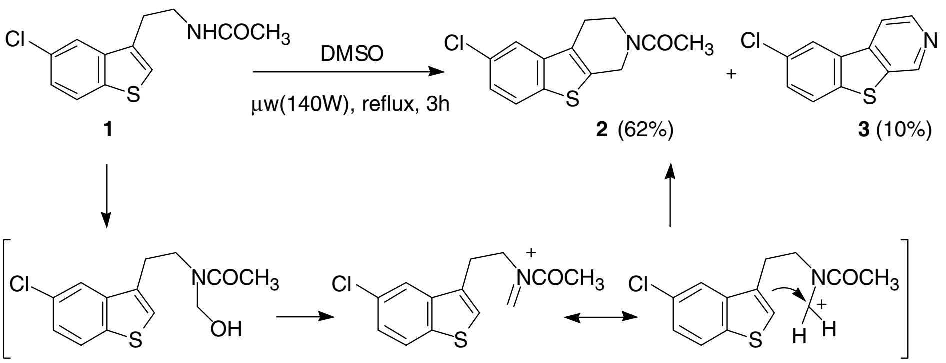


Figure 1. Products mainly described in DMSO decomposition by heating.[2–6]



Scheme 1. Proposed mechanism of formation of compound **2**.

in a good yield (62%), accompanied by a small amount of the aromatized analogue **3** (yield: 10%).

The mechanism involved (Scheme 1) suggests a modified Pictet–Spengler reaction in which the formaldehyde was provided by the thermal decomposition of DMSO. The aldehyde formed in situ reacted with the starting *N*-2-(5-chloro-benzo[*b*]thiophen-3-yl)ethylacetamide (**1**) to form a carbinolamide. This intermediate may rearrange to form an *N*-acylium ion which cyclized by electrophilic substitution affording the final 1-(6-chloro-1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridin-2-yl)ethanone (**2**). This hypothesis was confirmed during the reaction by the presence of a white precipitate of paraformaldehyde on the glassware. The same reaction was also performed with deuterated DMSO (DMSO-d_6). Comparison between the ^{1}H NMR spectra of **2** and its deuterated homologue demonstrated univocally that the methylene bridge (4.8 ppm) of the final product was effectively furnished by DMSO.

The preceding hypothesis was definitively confirmed by the synthesis of **2** by conventional heating of the starting benzothiophene **1** with formaldehyde in the presence of *para*-toluenesulfonic acid (*p*-TSA, 1.5 equiv), following a process previously described by Venkov and Lukanov[14] for the preparation of *N*-acyltetrahydroisoquinolines. In our conditions (DMSO, microwaves), addition of *p*-TSA was experimented in the hope of favouring formation of the intermediate *N*-acylium ion or, more probably, to accelerate the decomposition of DMSO into formaldehyde and then, to allow cyclization. After experimental design, we observed that a similar yield (65%) of product **2** was more rapidly obtained (20 min instead of 3 h), confirming the crucial role of *p*-TSA in the mechanism of the reaction, as previously de-

Table 1. Microwave-assisted experiments for the synthesis of **2**, **5** and **8**[a]

Method[b]	Starting material[c] (2 mmol)	DMSO (mL)	*p*-TSA (equiv)	Product	Microwave irradiation	
					Reaction time (min)	Yield (%)
A	**1**	35	—	**2**	360	62[d]
B	**1**	35	1.5	**2**	20	65[e]
C	**1**	7	1.5	**2**	10	69
C	**4**	7	1.5	**5**	10	40
C	**7**	7	1.5	**8**	10	65

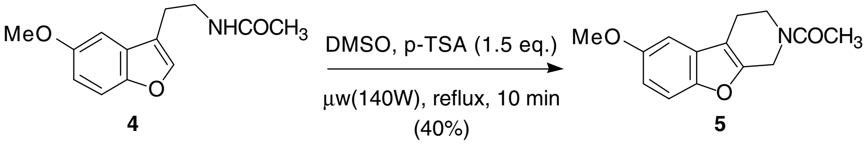
[a] All compounds were fully characterized by spectroscopic and elemental analysis (see Ref. 17).

[b] See Refs. 15 and 16 for description of the procedures.

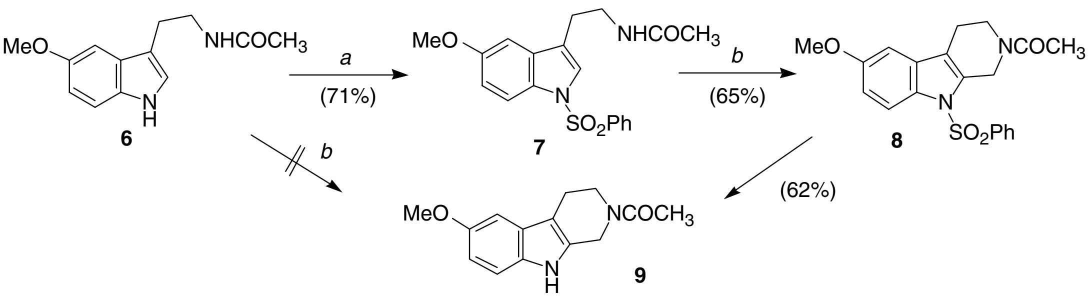
[c] Compounds **1**, **4** and **7** were prepared as described, respectively, in Refs. 13,18,19.

[d] Conventional heating: reaction time: 15 h; yield: 52%.

[e] Conventional heating: reaction time: 70–80 min; yield: 57%.



Scheme 2.



Scheme 3. Reagents and conditions: (a) (i) NaOH, $(Bu)_4N^+I^-$, 0 °C, 15 min; (ii) $PhSO_2Cl$, rt, 3.5 h; (b) DMSO, *p*-TSA (1.5 equiv), µw (140 W), reflux, 10 min; (c) Mg, NH_4Cl, CH_3OH, rt, 2 h.

scribed by Venkov for isoquinolines. In the same conditions of reactants, a similar ratio in the reduction of reaction time was also observed with conventional heating (70–80 min instead of 15 h, see Table 1).

The influence of the quantity of DMSO on yields of **2** and reaction times were also studied. Various experiments were performed with the same quantity of starting material and we observed that changing the volume of DMSO (between 7 mL and 70 mL) did not really affect the good yield of the reaction. The shorter reaction time was observed with 7 mL of DMSO (see Table 1, method C) allowing the use of concentrated mixtures and extension of the process to 1 g of the starting molecules.

Extension of such a reaction to various heterocyclic rings (e.g., benzofurane and indole) was studied according to the conditions described above for the benzothiophenic derivative. The benzofuranic analogue of melatonin (**4**)[18] gave the expected product (**5**) in a 40% yield (Scheme 2).

Transformation of melatonin (**6**) itself was also explored. Since degradation of the starting material **6** was rapidly observed, protection of the nitrogen atom in the indole ring was performed as previously described.[19] The heterocyclization of the *N*-protected product **7** was successfully realized in good yield (65%), affording the tricyclic compound **8** which was easily deprotected applying a known method[19] to give the 1,3,4,9-tetrahydro-β-carboline **9** in a good yield (62%) (Scheme 3).

In conclusion, we described for the first time the rapid microwave-assisted decomposition of DMSO in order to perform rapid Pictet–Spengler heterocyclization and to allow, in this case, the synthesis of novel rigidified melatonin analogues. The results described in this note may be compared with data previously published by Alterman and Hallberg, where DMF was degraded under microwaves.[20] This work confirms that working under focused microwave irradiation needs special attention. Even controlling the ratio between the quantity of the material and the solvent is very important (e.g., for scale up experiments). The stability of the reactants (e.g., the solvent) should be carefully checked, especially for a solvent, like DMSO, which is commonly used in microwave experiments, because of its interesting property to be rapidly heated. The experimental microwave conditions described in this letter are now well established and controlled and can be safely and beneficially reproduced. The preparation and the biological evaluation of various analogues are under development and will be described later.

Acknowledgements

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15. Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM Discover$^{\mathrm{TM}}$). The instrument consists of a continuous focused microwave power output from 0 W to 300 W. Reactions were performed in a glass vessel prolonged by a condenser; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar, tubes of 10 mL, sealed with a septum) if necessary (warning: the use of decomposing solvent in sealed vessel may be dangerous even with pressure and temperature control). The temperature content of a vessel is monitored using calibrated infrared sensor mounted under the vessel. All the experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature of 190 °C (DMSO bp: 189 °C) was selected together with a power of 140 W. The target temperature was reached with a ramp of 2 min and the microwave power stay constant to hold the mixture at this temperature. The time of the reaction does not include the ramp period.
16. *Typical microwave procedures for the synthesis of compound* **2**: Method A, is the same procedure as in method C without *p*-TSA and with a longer reaction time (6 h). Method B, is the same process as in Method C in 35 mL of DMSO with a longer reaction time (20 min). Method C: a solution of *N*-[2-(5-chloro-benzo[*b*]thiophen-3-yl)ethyl]-acetamide **1** (1 g, 4 mmol)and *p*-toluenesulfonic acid monohydrate (*p*-TSA, 1.14 g, 6 mmol) in DMSO (7 mL) was irradiated at reflux (power input 140 W) for 10 min. (completion of the reaction monitored by TLC). After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization from toluene–cyclohexane afforded the expected product.
17. *Data for new compounds* **2**, **3**, **5**, **8** *and* **9**.
    1-(6-Chloro-1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridin-2-yl)ethanone (**2**): white solid; mp 120–122 °C (toluene–cyclohexane, 2/1); IR (KBr) ν 1646 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10, 2.14 (s, s, 3H); 2.77, 2.89 (m, m, 2H); 3.79 (m, 2H); 4.77, 4.81 (s, s, 2H); 7.35 (d, $J = 8.6$ Hz, 1H); 7.73 (d, $J = 1.9$ Hz, 1H); 7.97, 7.99 (d, d, $J = 8.6$ Hz, 1H); ^{1}H NMR (300 MHz, DMSO-d_6, 75 °C) δ 2.14 (s, 3H); 2.89 (m, 2H); 3.82 (m, 2H); 4.79 (s, 2H); 7.35 (dd, $J = 8.6$ and 1.9 Hz, 1H); 7.73 (d, $J = 1.9$ Hz, 1H); 7.95 (d, d, $J = 8.6$ Hz, 1H); MS (EI) $m/z = 267$ (^{37}Cl–M$^+$); 265 (^{35}Cl–M$^+$). Found: C, 58.73; H, 4.55; N, 5.27. $C_{13}H_{12}ClNOS$ requires: C, 58.75; H, 4.55; N, 5.27.
    6-Chlorobenzo[4,5]thieno[2,3-*c*]pyridine (**3**): white solid; mp 138–142 °C (column chromatography (silica gel), with ethyl acetate–petroleum ether, 3/7 as eluant); IR (KBr) ν 2921 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, $J = 8.4$ and 1.9 Hz, 1H); 7.87 (d, $J = 8.4$ Hz, 2H); 7.98 (dd, $J = 5.5$, 1.1 Hz, 1H); 8.22 (d, $J = 1.9$ Hz, 1H); 8.68 (d, $J = 5.5$ Hz, 1H); 9.18 (m, 1H); MS (EI) $m/z = 221$ (^{37}Cl–M$^+$); 219 (^{35}Cl–M$^+$).
    1-(6-Methoxy-1,2,3,4-tetrahydro-benzo[4,5]furo[2,3,*c*]pyridin-2-yl)-ethanone (**5**): white solid; mp 128–131 °C (column chromatography (silica gel), with ethyl acetate–petroleum ether, 4/6 as eluant); IR (KBr) ν 1636 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 75 °C) δ 2.14 (s, 3H); 2.72 (m, 2H); 3.79 (t, $J = 5.6$ Hz, 2H); 3.81 (s, 3H); 4.65 (s, 2H); 6.86 (dd, $J = 8.4$ and 2.6 Hz, 1H); 7.05 (d, $J = 2.6$ Hz, 1H); 7.41 (d, $J = 8.4$ Hz, 1H). MS (EI) $m/z = 245$ (M$^+$). Found: C, 68.33; H, 6.21; N, 5.66. $C_{14}H_{15}NO_3$ requires: C, 68.56; H, 6.16; N, 5.71. 1-(9-Benzenesulfonyl-6-methoxy-1,2,3,4-tetrahydrobenzo[4,5]pyrro[2,3-*c*]pyridin-2-yl) ethanone (**8**): white solid; mp 187–190 °C (toluene–cyclohexane, 2/1); IR (KBr) ν 1644 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 75 °C) δ 2.13 (s, 3H); 2.70 (m, 2H); 3.76 (t, $J = 5.9$ Hz, 2H); 3.79 (s, 3H); 4.93 (s, 2H); 6.93 (dd, $J = 9.0$ and 2.2 Hz, 1H); 6.97 (d, $J = 2.2$ Hz, 1H); 7.53–7.83 (m, 5H); 7.88 (d, $J = 9.0$ Hz, 1H). MS (EI) $m/z = 384$ (M$^+$). Found: C, 62.01; H, 5.23; N, 7.29. $C_{20}H_{20}N_2O_4S$ requires: C, 62.48; H, 5.24; N, 7.29.
    1-(6-Methoxy-1,3,4,9-tetrahydro-β-carbolin-2-yl)ethanone (**9**): white solid; mp 188–192 °C (toluene–cyclohexane, 2/1); IR (KBr) ν 3283, 1629 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 75 °C) δ 2.12 (s, 3H); 2.73 (m, 2H); 3.71–3.81 (m, 5H); 4.65 (s, 2H); 6.70 (dd, $J = 8.8$ and 2.4 Hz, 1H); 6.90 (d, $J = 2.4$ Hz, 1H); 7.20 (d, $J = 8.8$ Hz, 1H); 10.44 (br s, 1H). MS (EI) $m/z = 244$ (M$^+$). Found: C, 68.43; H, 6.57; N, 11.10. $C_{14}H_{16}N_2O_2$ requires: C, 68.83; H, 6.60; N, 11.47.

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