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# Microwave-assisted synthesis of tetrahydroindoles

Leonarda Piras [a], Chiara Ghiron [b], Giacomo Minetto [a,b], Maurizio Taddei [a,*]

[a] *Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via A. Moro 2, 53100 Siena, Italy*
[b] *Siena Biotech SpA, Via Fiorentina 1, 53100 Siena, Italy*

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**Abstract**

An efficient synthesis of tetrahydroindoles with different substituents in position 1 is described. Microwave-assisted aminolysis of 4-oxo-4,5,6,7-tetrahydrobenzofuran with different primary amines gives the corresponding tetrahydroindoles in few minutes. All attempts to use microwave dielectric heating to reduce the time required for preparation of 4-oxo-4,5,6,7-tetrahydrobenzofuran, starting from 1,3-cyclohexandione were on the other hand unsuccessful, demonstrating that in some cases, long time conventional heating may be superior to microwaves.


*Keywords:* Microwaves; Cyclocondensation; Benzofuran; Indol

Many libraries designed for hit discovery are based on a central core scaffold carrying different functional groups for further decoration. The scaffold establishes the nature of the library and often affects the biological activity of the library components. Amongst the broad range of possible templates, heterocyclic molecules represent the most utilised scaffold for discovery of new synthetic entities.[1]

Tetrahydroindolones have been reported to present several interesting biological activities as selective Kv1.5 blockers,[2] antiproliferative and cytotoxic agents,[3] as GABAA-α5 receptor ligands for enhancing cognition[4] or as molecules useful in treating psychotic disorders.[5] Although the synthesis of some tetrahydroindoles has been reported based on cycloadditions or organometallic chemistry,[6] an analysis of the older literature suggests the direct ammonolysis of benzofuran (or partially reduced benzofurane) as the most practical route to 4-oxo-4,5,6,7-tetrahydroindoles.[7] These compounds are important intermediates for the preparation of a wide variety of other indole derivatives through modification of the oxo functional group.[8] The starting benzofuran derivative can be obtained through the Stetter cyclocondensation from cyclohexandione and bromopyruvic acid ester, followed by a ring opening–closure reaction, which leads to the final pyrrole ring system.[9] Both reactions are carried out at high temperature and for a long time. In particular, the second step has been described to occur with a large excess of the amine (generally ammonia or benzylamine) in EtOH in a sealed tube at 150 °C for 12–24 h, thus preventing an extensive application to the synthesis of more complex molecules.[10]

Following our interest in the field,[11] we decided to investigate the possibility to perform the Stetter synthesis of tetrahydrobenzofuran and the further transformation into indoles under MW dielectric heating to find milder reaction conditions and prepare a larger array of compounds (Scheme 1).

The Stetter cyclocondensation has been described to proceed by refluxing 1,3-cyclohexanedione **1** with ethyl bromopyruvate in the presence of EtOH/KOH for 12 h. Further acidification and heating for 30 min gives directly carboxylic acid **2** as a white solid.[9] Following this procedure we obtained compound **2** in 75% overall yield. With the idea of improving on this first step, we investigated different reaction conditions under microwave irradiation. In

* Corresponding author. Tel.: +39 0577234280; fax: +39 0577234275.
*E-mail address:* taddei.m@unisi.it (M. Taddei).

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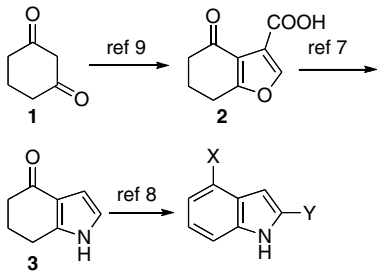
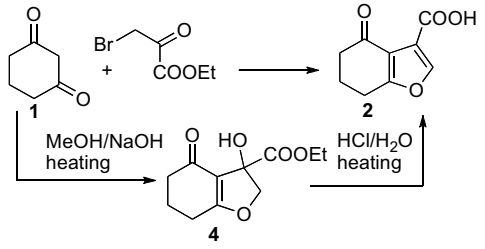



Scheme 1. General scheme for the synthesis of substituted indoles through the Stetter cyclocondensation.

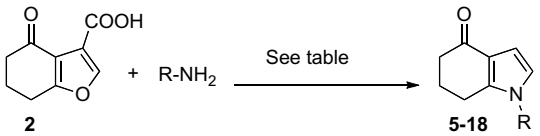
the first experiment, we modified the reported conditions, and heated a mixture of **1** and ethyl bromopyruvate in EtOH in the presence of NaOH in an open flask located inside the microwave cavity of a Discover apparatus (CEM). After 20 min of heating, the mixture was acidified to pH 3 with HCl and heated additional 10 min using the same microwave oven. No trace of **2** was found in the reaction mixture. Then, we tried different conditions, changing solvent, base, time of heating and mode of the reaction. However, as reported in Table 1, all the attempts gave compound **2** in much lower yield and purity with respect to the standard procedure.

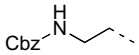
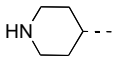
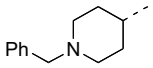
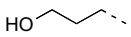
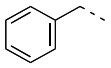
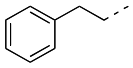
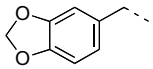
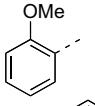
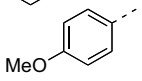
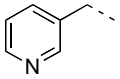
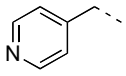
Table 1
Exploration of reaction conditions for microwave-assisted synthesis of **2**




| Entry | Conditions | Yield of **2** (%) |
|---|---|---|
| 1 | (1) NaOH–EtOH (100 °C, open flask, 20 min)<br>(2) HCl/$H_2O$ (110 °C, open flask, 20 min) | 0 |
| 2 | (1) NaOH EtOH/$H_2O$ 1/1 (100 °C, open flask, 20 min)<br>(2) HCl (110 °C, open flask, 20 min) | 10 |
| 3 | (1) NaOH EtOH/$H_2O$ 1/1 (140 °C, sealed vial, 30 min)<br>(2) HCl (110 °C, sealed vial, 20 min) | >10 |
| 4 | (1) NaOH $H_2O$ (110 °C, open flask, 20 min)<br>(2) HCl (110 °C, open flask, 20 min) | 10 |
| 5 | (1) NaOH $H_2O$ (180 °C, sealed vial, 20 min)<br>(2) HCl (110 °C, open flask, 20 min) | 0 |
| 6 | (1) KO*t*-Bu/*t*-BuOH (130 °C, sealed vial, 20 min)<br>(2) HCl (110 °C, open flask, 20 min) | 5 |
| 7 | (1) KO*t*-Bu/DMF (130 °C, sealed vial, 20 min)<br>(2) HCl (110 °C, open flask, 20 min) | >10 |

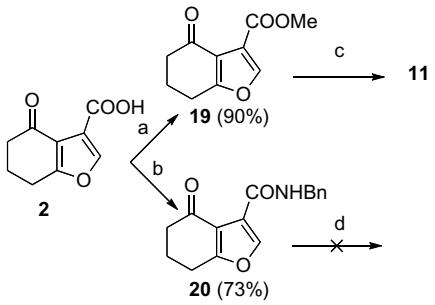
Table 2
Transformation of **2** into 4oxo-4,5,6,7-tetrahydroindolones




| Entry | R–$NH_2$ | Product[a] | Power, internal temperature, max internal pressure, time | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  | **5**[c] | 250 W, 120 °C, 200 psi, 10 min | 85 |
| 2 |  | **6**[c] | 250 W, 120 °C, 200 psi, 10 min | 84 |
| 3 |  | **7** | 250 W, 120 °C, 200 psi, 10 min | 70 |
| 4 |  | **8** | 250 W, 120 °C, 200 psi, 10 min | 91 |
| 5 |  | **9** | 250 W, 120 °C, 200 psi, 10 min | 70 |
| 6 |  | **10** | 250 W, 120 °C, 200 psi, 5 min | 91 |
| 7 |  | **11**[d] | 250 W, 120 °C, 200 psi, 10 min | 92 |
| 8 |  | **12** | 250 W, 120 °C, 200 psi, 10 min | 86 |
| 9 |  | **13** | 250 W, 120 °C, 200 psi, 10 min | 74 |
| 10 |  | **14**[c] | 250 W, 120 °C, 200 psi, 20 min | 75 |
| 11 |  | **15** | 250 W, 120 °C, 200 psi, 3 × 10 min | 35 |
| 12 |  | **16**[e] | 250 W, 120 °C, 200 psi, 3 × 10 min | 76 |
| 13 |  | **17** | 250 W, 120 °C, 200 psi, 10 min | 79 |
| 14 |  | **18** | 250 W, 120 °C, 200 psi, 10 min | 76 |

[a] Except for compounds **6**, **12** and **17**, all the products are new and have been fully characterised.
[b] Isolated yields.
[c] See Ref. 3a.
[d] See Ref. 10.
[e] See Ref. 6a.

Thus, we isolated the reaction intermediate **4**[12] and monitored its formation during microwave heating. After 1 h of heating (MeOH/NaOH), compound **4** was present




Scheme 2. Reagents and conditions: (a) $MeOH/SOCl_2$, rt, 12 h; (b) $BnNH_2$, MTMM, NMM, THF, rt, 12 h; (c) $BnNH_2$, $EtOH/H_2O$, MW, 120 °C, 200 psi, 30 min; (d) $Me_2CHCH_2NH_2$, $EtOH/H_2O$ MW, 150 °C, 200 psi, 40 min.

in less than 5%, suggesting that its formation may be the rate determining step. Although a complete kinetic study was not done, we think that the temperature has a scarce influence on the formation rate of **4**, thus vanishing the effect of the more efficient microwave heating.

The transformation of carboxylic acid **2** into the corresponding substituted tetrahydroindoles **5**–**18** (see Table 2) however, occurred rapidly under microwave dielectric heating using $H_2O/EtOH$ 5/1 as the solvent in a sealed vial at 120 °C for 10–30 min.[13] The products were recovered simply by extraction with an organic solvent in an acceptable degree of purity ($^1H$ NMR). Different amines, some of which carrying groups suitable for further functionalisation, were employed, giving always the required indolones in good yields. An hydroxy group and a secondary amine can be present in the reagent without the need for protection (Table 2, entries 4–6). Only in the case of a less nucleophilic and hindered *o*-substituted aniline, 30 min of heating were required and product **15** was isolated in lower yields compared to the other examples. To compare results obtained with microwave and conventional thermal heating, the sealed vial containing the reaction mixture employed to prepare **11** was immersed in an oil bath previously heated at 130 ° and stirred for 20 min, but in this case only 40% conversion to compound **11** was observed.

Unfortunately, in all cases explored, the carboxylic group in position 3 of the starting furane was lost. Trying to keep it intact by reducing the reaction temperature produced a mixture of the indolone and some starting material (**2**) still carrying the COOH group. With the target of maintaining the carboxylic function in position 3 of the heterocycle, we tried to protect the carboxylic acid as the methyl ester **19,** obtained in good yields under standard conditions (Scheme 2). However, when **19** was submitted to aminolysis with benzyl amine under our conditions, the decarboxylated compound **11** (50%) was obtained exclusively after heating at 120° for 30 min.

To strengthen the group in position 3 with respect to solvolysis, amide **20** was prepared by reaction of **2** with 2-methylpropan-1-amine in the presence of DMTMM as the coupling agent.[14] Unfortunately, any attempt to transform **20** into the corresponding indolone in the presence of benzyl amine was unsuccessful. Even at 150 °C for more than 40 min, unreacted starting material was recovered.

This result suggests that probably the furane ring opening-pyrrole ring closing reaction is not a simple aminolysis but the mechanism involves the carboxylic (or the carboxylate) function.

In conclusion we have demonstrated that the overall transformation of 1,3-cyclohexanedione **1** into indolones **5**–**18** can be accelerated by microwave irradiation of the second step, whereas the Stetter cyclocondensation resulted unaffected by exposure to microwave heating. Moreover, we observed that the presence of the free COOH in position 3 is indispensable for effective cyclisation.

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11. For our last application of microwave in heterocycle synthesis see: Ferrini, S.; Ponticelli, F.; Taddei, M. *Org. Lett.* **2007**, *9*, 69–72; See also: Rodriquez, M.; Taddei, M. *Top. Heterocycl. Chem.* **2006**, *1*, 213–265.
12. The presence of compound **4** in the reaction mixture was determined by HPLC–MSESI analysis of the reaction mixture after 12 h of reaction. This was the main component of the crude as **2** starts to form after the addition of HCl.

13. *Synthesis of 6,7-dihydro-1-phenethyl-1H-indol-4(5H)-one* (**13**). *General procedure*. To a solution of 4,5,6,7-tetrahydro-4-oxobenzofuran-3-carboxylic acid (200 mg, 1.11 mmol) in 2 ml of a mixture $H_2O$/EtOH (5:1), 2-phenylethanamine (400 mg, 3.33 mmol) was added. The reaction mixture was heated under microwave irradiation (250 W) at 110 °C for 10 min; the ethanol was evaporated at reduced pressure, the aqueous solution was acidified with HCl 1 N and extracted with ethyl acetate. The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure, the crude obtained was purified by flash chromatography ($SiO_2$ petroleum ether/ethyl acetate 1:1) to give 226 mg of 6,7-dihydro-1-phenethyl-1H-indol-4(5H)-one (**13**) (yield = 86%) and $^1$H NMR (200 MHz, chloroform-*d*): $\delta$ $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.17–6.93 (3H, m), 6.89–6.83 (2H, m), 6.47 (2H, s), 3.94 (t, 2H, $J = 6.5$ Hz), 2.87 (t, 2H, $J = 6.5$ Hz), 2.31–2.15 (4H, m), 1.82 (2H, m). $^{13}$C NMR (400 MHz, chloroform-*d*): 193.46, 143.30, 137.17, 128.19, 127.96, 127.58, 126.23, 121.23, 119.69, 105.06, 76.99, 47.61, 37.02, 36.98, 22.99, 20.75. MS (EI, 70 eV), 240 $[M+H]^+$, 262 $[M+Na]^+$.

14. DMTMM: 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride. See: Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 277–279.