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# Microwave-assisted rapid and efficient synthesis of *C*-alkyl imidazoisoquinolinone derivatives

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ABSTRACT

The synthesis of a set of 10-benzyl-2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one and 5-oxo-imidazo[1,2-*b*]isoquinolin-10-yl)-*N*-phenylacetamide derivatives was achieved by exposing the corresponding alkylating agent and imidazoisoquinolinone to microwave irradiation and traditional oil bath heating in the presence of $K_2CO_3$ and DMAP. The microwave technique as well as DMAP as base accelerated the alkylation reaction for 2–6 min giving 79–88% yields.



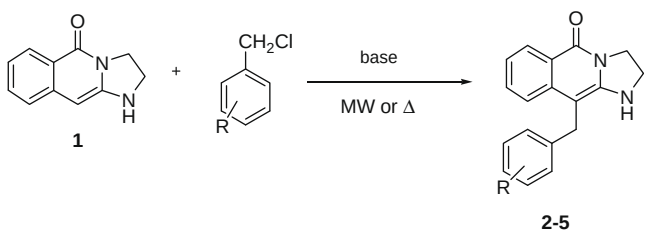
Isoquinolines generally constitute an important branch of heterocyclic compounds and are currently used against parasitic infections.[1] Imidazoisoquinolinones are valuable substrates for the synthesis of potentially biologically active compounds with structural features different from those of existing drugs. In this regard, we have previously synthesized a series of *C*-10 and *N*-1 substituted imidazoisoquinolinones, which possess a planar structure with a tricycle heterocyclic scaffold present in antiprotozoal agents.[2]

In this work, we report an efficient and good yielding method for the synthesis of 10-benzyl-2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one and 5-oxo-imidazo[1,2-*b*]isoquinolin-10-yl)-*N*-phenylacetamide derivatives under microwave irradiation.

The introduction of microwave heating has greatly impacted many aspects of chemical synthesis. There are several reviews and reports on the broad use of microwave irradiation in organic synthesis.[3] It has been demonstrated that the use of microwave heating can dramatically reduce the reaction time, increase the product purity and yields and allow a precise control of the reaction conditions.

To optimize the reaction conditions, the alkylation of 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one (**1**) with 4-chlorobenzyl chloride was selected as a model reaction. A mixture of compound **1**, 3 equiv of 4-chlorobenzyl chloride and 4 equiv of $K_2CO_3$ was exposed to microwave irradiation at 480 W for 10 min (Scheme 1).[4,5] The TLC test indicated that the reaction was incomplete. When increasing the time to 40 min, the process of conversion of **1** was completed, giving 80% of the desired product, 10-(4-chlorobenzyl)-2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one (**3**) (Table 1). Under this condition, another base, 4-dimethylaminopyridine (DMAP), was used to investigate its influence on the alkylation reaction (Table 1). Interestingly, the reaction time was reduced from 40 min to 6 min with a similar yield.

It is accepted that both a thermal effect and a specific microwave effect may induce the acceleration of some reactions. In order to testify whether microwave irradiation speeds up alkylation, the synthesis of compound **2**–**5** was carried out in DMF as solvent, using the same bases, but heating in an oil bath. The time course results of the model reaction are plotted in Figure 1. Microwave-heated reactions produced, along all the processes, a higher conversion of the starting material and a higher yield of the product than when heated in a traditional oil bath. In addition, the best result was obtained using DMAP as a base, using either microwave or conventional heating (Fig. 1, Table 1). The differences were specially significant within




**Scheme 1.**

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**Table 1**

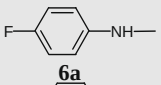
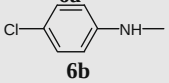
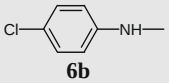
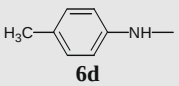
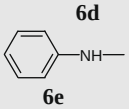
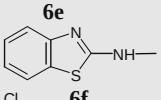
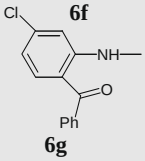
| Product | R | Conventional heating | | | | Microwave irradiation[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DMAP | | $K_2CO_3$ | | DMAP | | $K_2CO_3$ | |
| | | Time (h) | Yield[a] (%) | Time (h) | Yield[a] (%) | Time (min) | Yield[a] (%) | Time (min) | Yield[a] (%) |
| **2** | $-CH_3$ | 48 | 2 | NR | — | 2 | 80 | 40 | 80 |
| **3** | –Cl | 48 | 3 | 168 | 3 | 6 | 88 | 40 | 80 |
| **4** | $-NO_2$ | 24 | 2 | 72 | 2 | 1 | 80 | 15 | 75 |
| **5** | –H | 72 | 2 | 168 | 4 | 3 | 79 | 45 | 87 |

[a] Yields refer to pure products.
[b] Pulsed irradiated at 450 W.

the first 5 min of the reaction: 98% conversions with the microwave technique using DMAP, but only 28% when using $K_2CO_3$ as a base. The completion of the reaction took only 6 min with DMAP and 40 min with $K_2CO_3$. When the reaction was carried out under conventional heating, we encountered longer reaction times (68–168 h) and lower yields (3%) for both bases (Table 1). These results may elucidate that microwave irradiation may play a certain role in alkylation.

To expand the scope of this chemistry to the synthesis of other *C*-alkyl imidazoisoquinolinone derivatives, we selected diverse substrates **6a–g** and exposed each of them and compound **1** (2.7 mmol) to microwave irradiation at 480 W using DMAP (2.7 mmol) and 0.1 mL of DMF as solvent (Scheme 2, Table 2). The desired products **7–13** were isolated and purified in good to excellent yields (63–98%).[6,5] In general, the properties of R displayed an effect on the isolated products. When the aromatic ring (R) was substituted with 4-chloro or 4-fluoro group (entries a and b), we obtained a product with a relatively higher yield than *N*-phenylacetamides and substituted *N*-phenylacetamides containing an electron-donating group (entries c–e).

**Table 2**
Reation times, yields and melting points of compounds **7–13**

| Entry | R′ | Product | Time (min) | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|---|
| **a** |  **6a** | **7** | 2 | 90 | 201–203 |
| **b** |  **6b** | **8** | 2 | 98 | 310–311 |
| **c** |  **6b** | **9** | 3 | 63 | 151–153 |
| **d** |  **6d** | **10** | 4 | 70 | 210–212 |
| **e** |  **6e** | **11** | 2 | 80 | 270–273 |
| **f** |  **6f** | **12** | 2 | 85 | 283–284 |
| **g** |  **6g** | **13** | 4 | 75 | 109–111 |

[a] Yields refer to pure products.

However, when we used alkyl halides (1-bromobutane, 1,4-dibromobutane, (2-chloroethyl)diethylamine, (3-chloropropyl)dimethylamine) in an attempt to obtain *C*-alkyl imidazoisoquinolinone derivatives, the reaction yielded complicated mixtures of carbonaceous compounds and impurities using either microwave or conventional heating.

In conclusion, in the present work, we developed an efficient and novel methodology for the preparation of a series of 10-benzyl-2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one derivatives under microwave irradiation and in the presence of DMAP as the best base.

The reaction time was dramatically reduced from 72 to 24 h (traditional oil bath heating) to 2–6 min using the microwave technique. A diverse range of 5-oxo-imidazo[1,2-*b*]isoquinolin-10-yl)-*N*-phenylacetamide derivatives were synthesized to demonstrate that the reported method provides an opportunity to acquire many other analogues.

Melting points were determined in a capillary with an Electrothermal 9100 SERIES-Digital apparatus and were uncorrected. IR spectra were recorded with an FT Perkin Elmer Spectrum One from KBr discs. UV spectra were measured with a Jasco V-570 UV/vis/NIR spectrophotometer. $^1$H NMR (300 MHz) spectra were obtained with a Bruker spectrometer at room temperature with tetramethylsilane as an internal standard. Chemical shifts ($\delta$) are reported in ppm and coupling constants ($J$) in Hertz. Elemental analysis was carried out in our laboratories with a Coleman Analyser.

The microwave-assisted reaction was carried out in a household microwave oven (BGH-QUICK chef 15240). The apparatus was modified for laboratory application with an external reflux condenser.

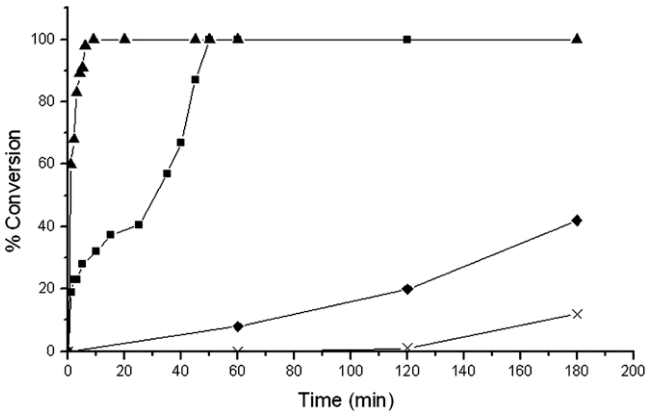
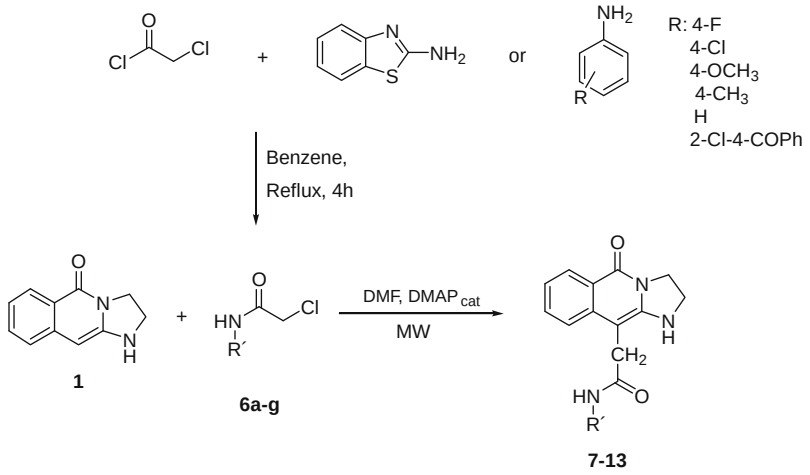



**Figure 1.** Comparison of the effect of microwave irradiation and oil-bath heating on the alkylation reaction in the presence of DMAP or $K_2CO_3$ as bases: Kinetic curves of conversion determined by HPLC at 256 nm. —▲— MW DMAP; —■— MW $K_2CO_3$; —♦— Δ DMAP; —×— Δ $K_2CO_3$.




**Scheme 2.**

## Acknowledgement

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.083.

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4. *Typical procedures for compounds* **2**–**5**: (A) *Conventional heating*: A mixture of compound **1** (0.5 g, 2.7 mmol), the corresponding alkylating agent (7.6 mmol), $K_2CO_3$ or DMAP (10.8 mmol) and DMF (5 mL) was stirred at reflux for 24–168 h (see Table 1). Then, the mixture was allowed to remain at room temperature and the solvent was evaporated under reduced pressure. The oil product was diluted with $CH_2Cl_2$ and washed with water ($3 \times 15$ mL), then the organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was collected and recrystallized with ethanol. (B) *Microwave assistant:* A mixture of compound **1** (0.5 g, 2.7 mmol), 10.8 mmol $K_2CO_3$ or DMAP and the corresponding alkylating agent (7.6 mmol) was introduced into a bottom flask and subjected to microwave irradiation at 480 W for 2–45 min (Table 2). The reaction was monitored by thin layer chromatography. After complete conversion, the product was recrystallized with ethanol.
5. See Supplementary data.
6. *Typical procedure for compounds* **7**–**13**: A mixture of compound **1** (0.5 g, 2.7 mmol), DMAP (0.6 g, 2.7 mmol), the corresponding *N*-phenylchloroacetamide and 0.1 mL DMF was introduced into a bottom flask and subjected to microwave irradiation at 480 W for 2–4 min. The reaction mixture was diluted with $CH_2Cl_2$ ($3 \times 15$ mL) and washed with water ($3 \times 10$ mL) and brine (10 mL). It was then dried with anhyd $MgSO_4$ and concentrated under reduced pressure to give a solid product, and was recrystallized with water–ethanol.