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Microwave-assisted synthesis of 1-aryl-3-acetyl-1,4,5,6-tetrahydrobenzimidazo[1,2-*d*][1,2,4]triazine: first example of a novel ring system

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Abstract—Novel highly functionalized benzimidazoles were synthesized in two steps by microwave irradiation: construction of the benzimidazole ring followed by ring closure to the new tricyclic system.

Microwave-assisted organic syntheses often result in dramatic increases in yields of chemical transformations.[1–5] Furthermore, microwave-assisted reactions under solvent-less conditions provide access to work with open vessels and to scale up reactions.[6]

Various benzimidazole derivatives are of interest for their diverse pharmaceutical uses[7] and they play a vital role in the synthesis of fused heterocyclic systems.[8] Recently, we have demonstrated that the nitrile imines **2** display electrophilic and nucleophilic reactivity which upon reaction with 4-deoxy-4-amino-2,3-anhydropyranosides afforded the corresponding chiral triazines fused to pyranose sugars.[9] Extending the potentials of these nitrile imines, we planned to exploit the reaction with 2-chloromethylbenzimidazole (**3**).

Chloromethyl-1*H*-benzimidazole (**3**)was prepared from *o*-phenylenediamine according to Ref. 10. The 1,3-dipole-like nitrile imines **2a**–**g** were generated in situ from the reaction of triethylamine with the hydrazonyl chlorides **1a**–**g**.[11] Treatment of **3** with the nitrile imines **2a**–**g** using microwave irradiation was explored under solvent-free conditions using silica gel as a solid support. The reactants were impregnated on the support and then irradiated at 900 W for 4 min using a domestic microwave apparatus (Frigidaire/China) to give the new tricyclic benzimidazole derivatives **4a**–**g** in 81–88% yields (Scheme 1).

The highest yield was achieved by irradiating the reactants for 4 min (Table 1). Extending the heating time results in a dramatic decrease of the yield (Table 1, entries 1–5). For comparison, a classical method for the preparation of the new benzimidazoles was also investigated by refluxing **3** with the nitrile imine **2a** in ethanol or DMF for 6 h. It was very obvious that the classical approach for the synthesis of this novel system is a tedious method affording a low yield of **4a** (26–32%) in addition to other by products, difficult to separate. Compounds **4b**–**g** were synthesized under the same conditions (Table 1: entries 6–11).

For **4a**: 2-chloromethylbenzimidazole (**3**; 2.4 mmol), hydrazonyl chloride (**1a**; 2 mmol), triethylamine (8 mmol) and silica gel (1 g) were mixed and introduced in an open Erlenmeyer flask. The reaction mixture was irradiated in a domestic microwave oven for 4 min (the temperature inside 220–250 °C). After cooling to room temperature, methanol was added (30 mL) and the

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Keywords: Microwave-assisted synthesis; Triazines; Benzimidazoles.

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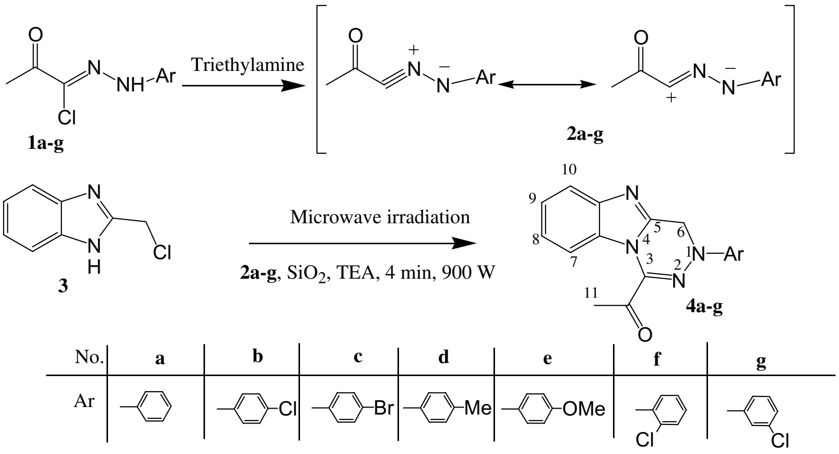

Scheme 1.

Table 1. Reaction conditions and yields of **4a**–**e**

Entry	Product	Conditions	Yield (%)
1	**4a**	SiO_2 (1 g), TEA (4 equiv), **1a** (1 equiv), **3** (1.2 equiv), 2 min	52 ± 2
2	**4a**	SiO_2 (1 g), TEA (4 equiv), **1a** (1 equiv), **3** (1.2 equiv), 4 min	79 ± 2
3	**4a**	SiO_2 (5 g), TEA (4 equiv), **1a** (1 equiv), **3** (1.2 equiv), 4 min	85 ± 2
4	**4a**	SiO_2 (5 g), TEA (4 equiv), **1a** (1 equiv), **3** (1.2 equiv), 6 min	63 ± 2
5	**4a**	SiO_2 (5 g), TEA (4 equiv), **1a** (2 equiv), **3** (1.2 equiv), 4 min	81 ± 2
6	**4b**	SiO_2 (1 g), TEA (4 equiv), **1b** (1 equiv), **3** (1.2 equiv), 4 min	88
7	**4c**	SiO_2 (1 g), TEA (4 equiv), **1c** (1 equiv), **3** (1.2 equiv), 4 min	84
8	**4d**	SiO_2 (1 g), TEA (4 equiv), **1d** (1 equiv), **3** (1.2 equiv), 4 min	82
9	**4e**	SiO_2 (1 g), TEA (4 equiv), **1e** (1 equiv), **3** (1.2 equiv), 4 min	82
10	**4f**	SiO_2 (1 g), TEA (4 equiv), **1f** (1 equiv), **3** (1.2 equiv), 4 min	84
11	**4g**	SiO_2 (1 g), TEA (4 equiv), **1g** (1 equiv), **3** (1.2 equiv), 4 min	80

reaction mixture filtered. The filtrate was evaporated to dryness and subjected to column chromatography (10% hexane/dichloromethane) to afford **4a** in 85% yield. The ^{13}C NMR[12] spectra exhibit a quaternary carbon resonance at about 152 ppm, indicative for the imine bond (C═N). C-6 and C-11 resonate at 44–45 and 25–26 ppm, respectively, and the carbonyl signals arise at 190–193 ppm. The ^{1}H NMR spectra show methylene signals at 5.0–5.2 ppm and methyl resonances at 2.72–2.74 ppm.[13]

In summary, the synthesis of the new tricyclic benzimidazole system have been accomplished under solvent-free microwave irradiation. The new benzimidazole derivatives with potential biological activities are under active investigations.

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13. *Selected data for compound* **4a**: white prisms, mp 155–156 °C (ethanol); EI-MS: *m/z* 290; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 2.72 (s, 3H, $COCH_3$), 5.09 (s, 2H, NCH_2), 7.16–7.80 (m, 9H, phenyl, *H-7, H-8, H-9, H-10*); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 25.9 (C-11), 44.8 (C-6), 151.2 (C═N), 115.2, 115.9, 119.8, 124.1, 124.2, 124.3, 129.6, 144.7, 144. 8, 144.9 (phenyl, C-7, C-8, C-9, C-10), 189.9 (C═O).