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Microwave-assisted synthesis of 4-keto-4,5,6,7-tetrahydrobenzofurans

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ABSTRACT

The use of TMSCl in methanol under microwave irradiation allows the facile intramolecular condensation of a large panel of triketones, giving rise to 4-keto-4,5,6,7-tetrahydrobenzofurans in good to excellent yields.

The core structure of 6,7-dihydrobenzofuran-4(5*H*)-one **1**, or more commonly referred to as 4-keto-4,5,6,7-tetrahydrobenzofuran, is an important intermediate in the preparation of a wide range of synthetic compounds with diverse biological applications (Fig. 1).[1] Indeed, Hayakawa demonstrated recently that tetrahydrobenzofuran derivatives (**1**) represent an interesting alternative scaffold to benzofuran, for the generation of new heterocyclic libraries.[2] Interestingly, higher oxidized analogues of **1**, such as Stemofuran B **2**, are isolated from natural plants.[3] In addition, such molecules **1** (R = alkyl) have also been used as useful building blocks for the total synthesis of other natural products like the angular furanocoumarin oroselone **3**.[4]

To date, several synthetic methods have been reported for the synthesis of 4-keto-4,5,6,7-tetrahydrobenzofuran derivatives of **1**.

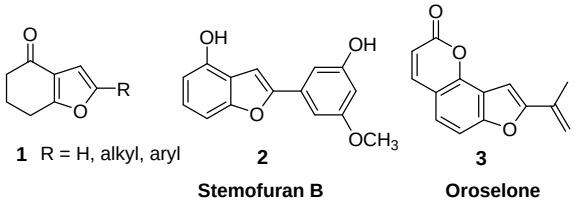
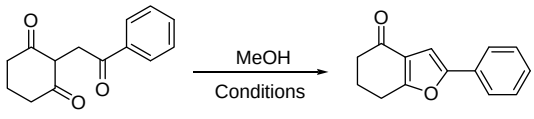


Figure 1. Structures of **1** and natural compounds **2** and **3**.

Among them, the thermal [3+2]-cycloaddition of copper or rhodium stabilized carbenoids with acetylenes or alkenes has been widely applied with more or less success.[5,6] Pekel and Kim have described the addition of α-carbon radicals of 1,3-cyclohexandione on alkynes affording tetrahydrobenzofuran derivatives.[7] A photochemical approach that involves phenyliodonium dimedonide with phenylacetylene has also been reported as another alternative for the preparation of **1**.[8] Finally, the last methods reported so far for the synthesis of scaffold **1** are based on the intramolecular cyclization of triketones or the cycloisomerization of alkynyl-1,3-cyclohexanediones using protic acid, the Lawesson's reagent or

Table 1
Optimization conditions for the cyclization of **4**



4 **5**

Entry	Promoter	Time (h)	Temperature	Yield[a] (%)
1	H_2SO_4[b]	0.5	rt	/
2	HCl (4 equiv)	14	rt	31
3	AcCl (4 equiv)	14	rt	61
4	TMSCl (4 equiv)	14	rt	90
5	TMSCl (1.6 equiv)	14	rt	65
6	TMSCl (4 equiv)	0.13	90 °C[c]	100

[a] Isolated yields.
[b] Reaction performed in pure 96% H_2SO_4.
[c] Reaction performed under microwave irradiation.

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mercuric triflate as promoter, respectively.[9–11] In the course of our study toward the synthesis of natural products, we were interested in the intramolecular cyclization of triketones substrates such as compound **4** for the preparation of the 4-keto-4,5,6,7-tetrahydrobenzofuran derivative **5** (Table 1). However, reported methods starting from triketones which use conventional chemical techniques are plagued with some limitations such as drastic reaction conditions, limited scope of application, or the use of highly toxic Lewis acid.[9d,11] As a consequence, the need of an efficient general synthesis of this important class of compounds **1,** starting from triketone substrates, is still of great interest. Herein, we report a new and expedient procedure for the intramolecular condensation of triketones, promoted by TMSCl in MeOH under microwave irradiation, leading to 4-keto-4,5,6,7 tetrahydrofurans in high yields.

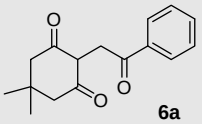
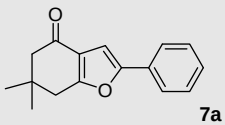
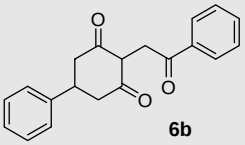
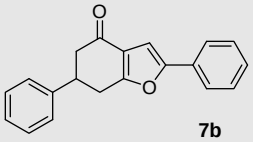
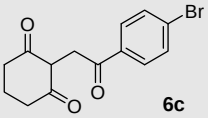
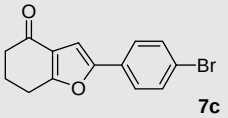
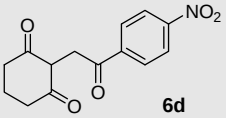
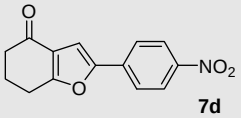
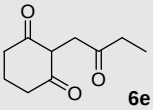
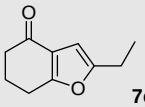
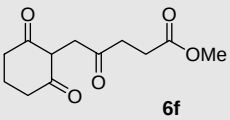
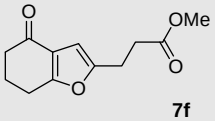
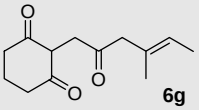
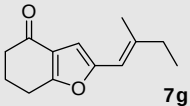
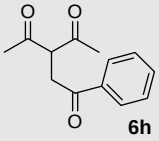
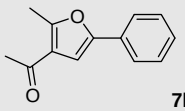
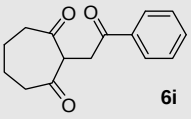
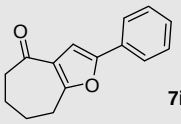
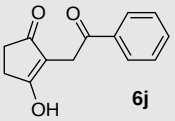
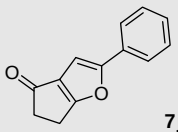
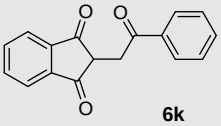
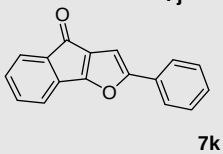
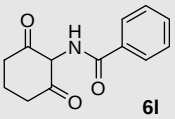
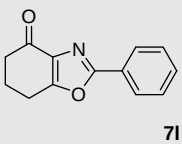
We initially tested sulfuric acid, which is known to promote the cyclization efficiently.[9d] However, the reaction performed in the reported conditions with substrate **4** failed in providing the desired cyclized product **5** (Table 1, entry 1). Complete degradation of the starting material was observed instead, without traces of **5**. In contrast, when **4** is treated with an excess (4 equiv) of aqueous HCl in methanol at rt, product **5** is obtained with an isolated yield of 31% (Table 1, entry 2). Interestingly, the use of in situ generated dry HCl, by adding 4 equiv of AcCl in methanol, yielded 61% of the cyclized condensation compound (Table 1, entry 3). The reaction performed in the presence of 4 equiv of TMSCl in MeOH, as another source of anhydrous HCl, afforded the desired substrate with a gratifiying yield of 90% (Table 1, entry 4). Attempts to decrease the amount of TMSCl were not satisfactory, and **5** was always obtained with lower isolated yields (Table 1, entry 5). With the aim to get a quantitative yield while shortening the reaction time, we decided to exploit the benefit of microwave irradiation. The treatment of **4** with 4 equiv of TMSCl in MeOH and under microwave irradiations in a sealed tube for 8 min at 90 °C, gave **5** in a quantitative yield (Table 1, entry 6).

In this optimized conditions, we next investigated the scope of the reaction with a panel of different triketone substrates. Several triketone derivatives were prepared from commercially available 1,3-cyclohexandiones, according to known procedures.[12] In general, most of the microwave-assisted reactions[13] proceeded smoothly and without complications. The expected cyclized products were obtained in excellent to good yields (Table 2). Indeed, triketones **6a** and **6b**, having 5-dimethyl- or 5-phenyl-substituted 1,3-cyclohexandiones moiety, behaved similarly to **4** and gave the condensation products **7a**[9d] and **7b**[6b] in 100% and 99% yields, respectively (Table 2, entries 1 and 2). In the case of aromatic triketones **6c** and **6d**, bearing a *p*-electronwithdrawing substituent (–Br and $-NO_2$) on the exocyclic ketone counterpart, the cyclized compounds **7c**[14] and **7d** were obtained in 99% and 71% yields (Table 2, entries 3 and 4).

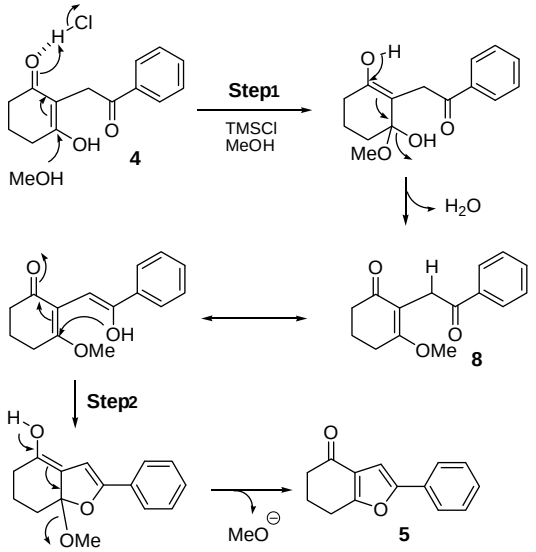
Alkyl triketones **6e**, **6f**, and **6g** were also well tolerated and the corresponding 4-keto-4,5,6,7-tetrahydrobenzofurans **7e**,[15] **7f**, and **7g** were isolated with high yields, ranging from 81% to 100% (Table 2, entries 5–7).

It is noteworthy to mention that the cyclized product **7g** is accompanied with the complete isomerization of the olefinic double bond. We next extended our methodology to acyclic triketone **6h,** and triketone **6i** bearing a 1,3-seven-membered diketone moiety. In both cases, the cyclized products, 2,3,5-trisubstituted furan **7h**[6a] and 5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan-4-one **7i**, were obtained in excellent isolated yields, 100% and 90%, respectively (Table 2, entries 8 and 9). In sharp contrast, C5-membered triketones **6j** and **6k** were completely unreactive in the same conditions, the starting material was recovered unchanged (Table 2, entries 10 and 11). This intriguing lack of reactivity might be ascribed to the cyclic strain, precluding 1,4-addition of MeOH (Scheme 1, step 1). Further experiments by using 1,3-dicarbonyl

Table 2
MW-assisted cyclization for the synthesis of 4,5,6,7-tetrahydrobenzofuran and other heterocycles[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **6a**	 **7a**	100
2	 **6b**	 **7b**	99
3	 **6c**	 **7c**	99
4	 **6d**	 **7d**	71
5	 **6e**	 **7e**	86
6	 **6f**	 **7f**	81
7	 **6g**	 **7g**	100
8	 **6h**	 **7h**	100
9	 **6i**	 **7i**	90
10	 **6j**	 **7j**	/[c]
11	 **6k**	 **7k**	/[c]
12	 **6l**	 **7l**	56

[a] All reactions were carried out in the following conditions: 0.5 mmol of substrate, TMSCl (2 mmol), MeOH (2.3 mL), MW, 8 min at 90 °C.
[b] Isolated yields of pure compounds.
[c] Starting material recovered.



Scheme 1. Proposed mechanism for the formation of **5**.

substrate having an amide function allowed the preparation of other heterocycles such as oxazoles **7l**[16] in an acceptable yield of 56% (Table 2, entry 12).

In a mechanistical point of view, it is envisioned that the reaction proceeds through the intermediate **8** (Scheme 1). Evidences supporting the proposed mechanism came from the isolation of **8** when the reaction was stopped after 12 h at rt without MW irradiations. Furthermore, the treatment of **8** with TMSCl in MeOH under MW furnished quantitatively the expected cyclized product **5**.

In summary, we report herein the first synthesis of 4-keto-4,5,6,7-benzofuran derivatives under microwave-assisted cyclocondensation. Under these optimal conditions (TMSCl/MeOH/MW/8 min/90 °C), a series of 4-keto-4,5,6,7-tetrahydrobenzofurans were synthesized, as well as of other heterocycles, in good to excellent yields.

Acknowledgments

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13. *Typical experimental procedure*: Experiments were carried out in a Biotage microwave reactor in a sealed vial.
In a 5 mL reaction vial, trimethylsilylchloride (2 mmol) was added to a solution of triketones (0.5 mmol) in methanol (2.3 mL). The vial was capped and the mixture was irradiated for 8 min at a maximum power of 250 W and 90 °C. The reaction mixture was then allowed to cool to room temperature and methanol was removed under reduced pressure. The residue was taken up into water (5 mL) and diethyl ether (5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the product. Compounds were then purified by column chromatography on silica and characterized by ^1H, ^{13}C, IR, and MS analysis.
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