A Convenient Synthesis of Highly Substituted Furans by Microwave Irradiation of Ring-Fused Alkylidenecyclopropanes

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Abstract: Microwave irradiation of ring-fused alkylidenecyclopropanes under solvent-free conditions afforded highly substituted furans in good yields.

Key words: microwave reaction, solvent-free, substituted furan, ring-fused alkylidenecyclopropane, bicyclo[4.1.0]heptane derivative

Furans can be found in many naturally occurring compounds.¹ Polysubstituted furans are present as a key structural unit in many natural products and pharmaceuticals.^{1b,2} Substituted furans are important intermediates and building blocks in organic synthesis. There are many strategies developed for the preparation of a multi-substituted furan ring.^{3,4} One of the simplest involves starting with either furan itself or a mono-substituted furan followed by the introduction of functional groups at various positions around the furan ring. The introduction of functional groups into the 3- and 4-positions is, however, sometimes difficult since the direct lithiation of furan rings followed by the reaction with electrophiles preferentially occurs at the 2- or 5-position. Many synthetic methods for the preparation of substituted furans⁵ and one mechanistic study on thermolysis of 1-cyclopropylidene-2-propanone to give 2,4-dimethylfuran⁶ have been reported. However, further synthetic development on thermolysis of methylenecyclopropanes and solvent-free approaches using microwave irradiation affording highly substituted furans still remain unknown. Microwave-assisted organic syntheses have attracted chemists recently⁷ because chemical transformations can be accelerated both in solution and in solid phases. High yields of highly pure products are reached within a short time. There is an increasing interest in the use of environmentally benign conditions, particularly solvent-free procedures.⁸ Avoiding organic solvents during the reaction in organic synthesis provides a clean, efficient and economical procedure, and easy workup process. In addition, methylene- and alkylidenecyclopropanes are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.^{9–13} They have also been widely used for the syntheses of various heterocycles.¹⁴ Recently, we reported a facile method for the preparation of

SYNLETT 2004, No. 11, pp 1933–1936 Advanced online publication: 28.07.2004 DOI: 10.1055/s-2004-830857; Art ID: U11704ST © Georg Thieme Verlag Stuttgart · New York ring-fused alkylidenecyclopropanes (bicyclo[n.1.0] alkylidene derivatives)¹⁵ and their transformation to various useful compounds.¹⁶ We also reported a stereoselective preparation of 7-*exo*-amino-7-*endo*-substituted bicyclo[4.1.0]heptanes.¹⁷ In this study, we attempted to prepare highly substituted ring-fused furans **2** and **4** by microwave irradiation of either ring-fused alkylidenecyclopropanes **1**, **3** or 7-*exo*-morpholino-7-*endo*-substituted bicyclo[4.1.0]heptanes **5** under solvent-free conditions (Scheme 1).





The results of the transformations of 1a into furan 2a under various conditions, including microwave irradiation, are summarized in Table 1. Conventional heating of 1a in o-xylene for five hours gave furan 2a only in 33% yield, and 60% of 1a was recovered (entry 1). On the other hand, ten minutes microwave irradiation of 1a in o-xylene resulted in a quantitative recovery of 1a (entry 2), while a similar microwave reaction in DMSO instead of o-xylene gave 2a in 20% yield, along with 75% of 1a (entry 3). We next tried to use a solid support such as acidic alumina,¹⁸ silica gel¹⁹ or bentonite.²⁰ Microwave irradiation of **1a** impregnated onto the solid support for five minutes yielded no products and most of the substrate 1a was recovered (entries 4-6). Next, we carried out microwave irradiation of the substrate 1a under a solvent-free condition for three minutes at 200 °C and surprisingly obtained the furan derivative 2a in 60% isolated yield along with 35% recovery of 1a (entry 7). When the irradiation time was increased to five minutes at the same temperature, 2a was isolated in 78% yield and a trace of 1a was observed (entry 8). However, upon further increase of irradiation time to six minutes at the same temperature, there remained no substrate 1a but the product yield was lower (75%), presumably due to the decomposition of 2a (entry 9). On the other hand, conventional heating of 1a at 200 °C under solventfree conditions resulted in a quantitative recovery of 1a(entry 10). These results indicate that five minutes microwave irradiation of 1a under solvent-free conditions was required to obtain the maximum product yield. Therefore, we decided to carry out the microwave irradiation of all ring-fused alkylidenecyclopropanes (bicyclo[n.1.0]alkylidene derivatives) 1 and 3 for five minutes under solventfree conditions.²¹

 Table 1
 Optimization of Reaction Conditions under Microwave Irradiation^a

Entry	Condition	Reaction time (min)	Yield of 2a (%) ^b	Recovery of 1a (%)
1	o-Xylene ^c	300	33	60
2	o-Xylene ^d	10	_	100
3	DMSO ^d	10	20	75
4	Acidic alumina ^e	5	_	95
5	Silica gel ^e	5	_	98
6	Bentonite ^e	5	_	94
7	Solvent-free ^f	3	60	35
8	Solvent-free ^f	5	78	Trace
9	Solvent-free ^f	6	75	_
10	Solvent-free ^g	300	0	100

^a Compound **1a** (300 mg) was used in all the reactions. The general experimental procedure is given in ref.²¹

^b Isolated yields.

^c Solvent (5 mL) was used and heated under reflux temperature using an oil bath.

^d Solvent (5 mL) was used and irradiated under microwave at reflux temperature.

^e Solid support (100 mg), **1** (300 mg) and CH_2Cl_2 (5 mL) was stirred for few minutes at r.t. and then evaporated the solvent thoroughly in vacuo prior to microwave irradiation.

^f Irradiated at 200 °C.

^g Heated at 200 °C without microwave irradiation.

Microwave irradiation of bicyclo[4.1.0]heptylidene derivatives **1** under solvent-free conditions for five minutes afforded ring-fused furans **2** in good yields. The results are summarized in Table 2.

Methyl- and phenyl ketones **1a** and **1b** under microwave irradiation at 200 °C for five minutes afforded 2-methyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**2a**) and 2phenyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**2b**) in 78% and 61% isolated yields, respectively (entries 1 and 2). Similarly, **1c** and **1d** afforded 2,3-dimethyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**2c**) and 3-methyl-2-phe

 CH_3

 CH_3

3

4

1c

1d

5 **1e** Η p-Br-C₆H₄ 2e (63) ^a Compound 1 (300 mg) was used in all the reactions. General experiment is given in ref.²¹ ^b Isolated yields are shown in parentheses. ^c Irradiation was carried out at 200 °C. nyl-5, 6, 7, 8-tetrahydro-4*H*-cyclohepta[*b*]furan (2d) in 63% and 80% isolated yields, respectively (entries 3, 4). We also succeeded to prepare 2-(p-bromophenyl)-5,6,7,8tetrahydro-4H-cyclohepta[b]furan (2e) in good isolated yield (entry 5). When **1a** or **1b** was irradiated under microwave without temperature control, the yield of 2a or 2b

CH₃

C₆H₅

2c (63)

2d (80)

crowave without temperature control, the yield of **2a** or **2b** was decreased, probably due to the decomposition of the product. Microwave irradiation of alkylidenecyclopropanes **1c–e** required no temperature control to obtain the products **2c–e**.

We also carried out the microwave irradiation of bicyclo[5.1.0]octylidene derivatives **3** in a similar fashion and isolated ring-fused furans **4** in good yields. The results are summarized in Table 3. Irradiation of **3a** and **3b** at 200 °C for five minutes afforded 2-methyl-4,5,6,7,8,9-hexahydrocycloocta[*b*]furan (**4a**) and 2-phenyl-4,5,6,7,8,9hexahydrocycloocta[*b*]furan (**4b**) in 55% and 59% isolated yields, respectively (entries 1, 2). Similarly, **3c** and **3d** afforded 2,3-dimethyl-4,5,6,7,8,9-hexahydrocycloocta[*b*]furan (**4c**) and 3-methyl-2-phenyl-4,5,6,7,8,9hexahydrocycloocta[*b*]furan (**4d**) in 61% and 73% isolated yields, respectively (entries 3 and 4).

Irradiation of **3e** also afforded 2-(*p*-bromophenyl)-4,5,6,7,8,9-hexahydrocycloocta[*b*]furan (**4e**) in good isolated yield (entry 5). Microwave irradiation of alkylidenecyclopropanes **3c**–**e** required no temperature control to obtain the furan derivatives **4c**–**e**.

We were also able to prepare furans by using 7-*exo*-morpholino-7-*endo*-substituted bicyclo[4.1.0]heptanes **5**. Alkylidenecyclopropanes were formed as an intermediate products during the synthesis of 7-*exo*-amino-7-*endo*-substituted bicyclo[4.1.0]heptanes **5**.^{15,17} Therefore, under microwave irradiation, 7-*exo*-morpholino-7-*endo*-substituted bicyclo[4.1.0]heptanes **5** also gave ring-fused furans

Table 3 Microwave Irradiation of Bicyclo[5.1.0]octylidene Derivatives



^a Compound $\mathbf{3}$ (300 mg) was used in all the reactions. The general experimental procedure is given in ref.²¹

^b Isolated yields are shown in parentheses.

° Irradiation was carried out at 200 °C.

in good yields (Scheme 2). Conventional heating of both 1-(7-morpholinobicyclo[4.1.0]hept-7-yl)-2-propanone (5a) and 2-(7-morpholinobicyclo[4.1.0]hept-7-yl)acetophenone (5b) required 12 hours reflux in o-xylene to give 2a and 2b in 35% and 37% yields, respectively. Whereas microwave irradiation of solid substrates 5a and **5b** under solvent-free conditions required only nine minutes to obtain 2a and 2b in 65% and 70% isolated yields, respectively. 7-exo-Morpholino-7-endo-substituted bicyclo[4.1.0]heptanes 5 required a little longer irradiation time (nine minutes) compared to that of alkylidenecyclopropanes 1, 3 (five minutes) because in this case, 5 first converted to alkylidenecyclopropanes by the elimination of free morpholine and then formed furans. The elimination of morpholine is proven by the ¹H NMR spectrum of the irradiated crude reaction mixture, which shows two peaks at $\delta = 2.88$ ppm (t, J = 4.62 Hz, 4 H) and $\delta = 3.85$ ppm (t, J = 4.62 Hz, 4 H), indicating the liberation of free morpholine from 5.

The structure of the furan derivatives 2 and 4 obtained by microwave irradiation were confirmed by comparison with an authentic sample 2a which was prepared in 10% yield by using an independent route²² as shown in Scheme 3. Enamine 6 was reacted with mono-bromoacetone 7 in refluxing toluene to give 8. Acidification with 10% H_2SO_4 and heating afforded furan 2a. NMR spectra of authentic 2a were identical with that obtained by microwave irradiation.

Microwave irradiation of ring-fused alkylidenecyclopropane A causes rupture of the cyclopropane ring due to its inherent strain to give allyl type radical **B** which is resonance stabilized to C. Cyclization of C gives ring-fused furan derivatives **D** which aromatized to furnish **E**. On the other hand, 7-exo-morpholino-7-endo-substituted bicyc-



Scheme 2



Scheme 3

lo[4.1.0]heptanes F under microwave irradiation eliminates morpholine to give A which follows the same pathways to furnish E (Scheme 4).

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Scheme 4

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