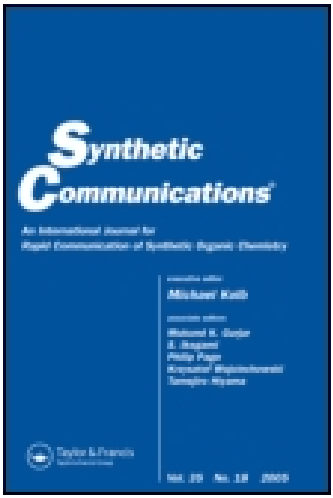

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Solvent-Free Microwave-Assisted Organic Reactions Preparation of β-Keto Esters

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Published online: 04 Dec 2007.

To cite this article: Massimo Gianotti, Giorgio Martelli, Giuseppe Spunta, Eileen Campana, Mauro Panunzio & Monica Mendozza (2000) Solvent-Free Microwave-Assisted Organic Reactions Preparation of β-Keto Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:10, 1725-1730, DOI: 10.1080/00397910008087215

To link to this article: http://dx.doi.org/10.1080/00397910008087215

SYNTHETIC COMMUNICATIONS, 30(10), 1725–1730 (2000)

SOLVENT-FREE MICROWAVE-ASSISTED ORGANIC REACTIONS PREPARATION OF β-KETO ESTERS

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Abstract: Microwave technique has been utilised in the preparation of β-keto esters. Two different procedures are described: transesterification of β-keto esters and ring opening of 2,2,6-trimethyl-1,3-dioxin-4-one.

We recently needed to prepare a series of differentially esterified azetidin-2-ones **1** from the corresponding 4-acetoxy-derivative and the silyl-enolether acetals, according the well established Merck procedure.[1] Despite several attempts, using different reaction conditions, very poor yields were obtained in the preparation of **1**, except for the methyl and ethyl esters. Following our recent work on the use of microwave technique for the synthesis of highly functionalized compounds,[2] we explored the applicability of this technique to the above reported problem by means of a transesterification reaction of the ethyl alkoxy group in the intermediate **1a**.[3] The main advantages of microwave-assisted organic synthesis are shorter reaction times, minimum waste and generally higher yields.[4]

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We have found that reacting azetidinone **1a**, in chlorobenzene, with alcohols **2**, *in the absence of acidic or basic catalyst* in a normal domestic microwave oven as a safe and convenient laboratory device without alteration, the desired azetidinones **1(b-f)** were obtained in fairly good yields (Scheme 1, Table 1).[5]

Either deprotection of the TBDMS group neither diastereomeric mixture formation, arising from racemization of the starting alcohols (see Table 1 entries 3 and 5) have been observed. Transesterification of the ethoxy group takes place even in the absence of any solvent. Unfortunately, due in our opinion to the shortage of homogeneity of the reaction mixture, poorer yields, in the range of 25-40%, were obtained.

Scheme 1

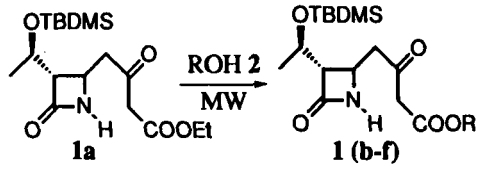
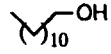
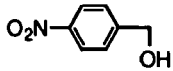
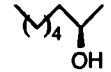
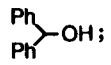
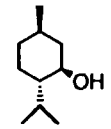


Table 1: Transesterificazion of Azetidinone **1a**

Entry	ROH 2	W	t (min)[a]	Y%	Prod.	Ref.
1		650	20+20	>95	**1b**	
2		650	10+10+10	89	**1c**	[6]
3		650	10+10+10	92	**1d**	
4		650	10+10+10	81	**1e**	
5		650	10+10+10	93	**1f**	

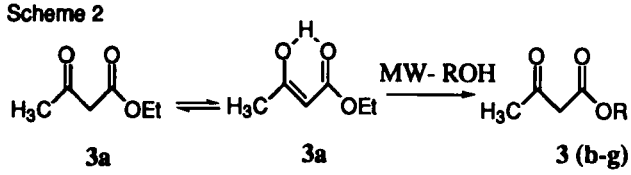
a: To avoid burst-temperature the reaction was stopped at the given time, cooled and re-ovened.

In order to explore the scope and limitations of this new microwave-induced transesterification of β-ketoesters[7], a range of acetoacetic esters were prepared starting from ethyl acetoacetate **3a**, *in absence of solvents and catalysts*. As a matter

of fact one of the most interesting advantage of the microwave technique is the possibility of carrying out solvent free reactions.[8] The results are reported in Scheme 2 and Table 2.

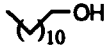
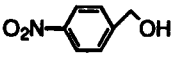
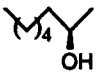
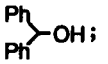
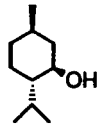
It is worthy mentioning that only enolizable β-keto esters gave rise to the transesterification reaction in absence of acid catalyst.[9] A blank experiment in toluene at reflux after 12 hr gave the same results with poorer yields. We feel that the reactive species is the enolic form of the β-keto esters with the attack of the nucleophilic alcohol on the carboethoxy moiety according the scheme 2. The role of microwaves in enhancing the reaction efficiency is not yet fully clarified. Work is in progress to light this point.

Scheme 2



3a 3a 3 (b-g)

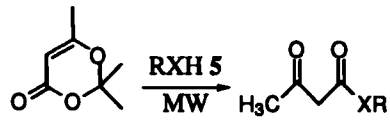
Table 2: Transesterificazione of Ethyl Acetoacetate 3a

Entry	ROH 2	W	t (min)	Y%	Prod.	Ref
1		650	10+10	>95	3b	[10]
2		750	20	82	3c	[2]
3		650	10+10	>95	3d	[11]
4		750	20+10	62	3e	[12]
5		650	20+5	92	3f	[13]
6	TBDMSiOH	650	20	60	3g	

A further application of this technique has been found out with the preparation of the β-keto ester 3 itself. Among the methods reported in literature for the preparation of acetoacetic esters, one of the most useful is represented by the

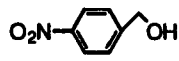
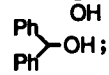
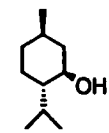
reaction of an alcohol with diketene or its synthetic equivalent 2,2,6-trimethyl-1,3-dioxin-4-one **4**.[10] Once again our microwave-based technique proved to be very useful since the corresponding β-keto-esters were obtained in fairly good yields (Scheme 3, Table 3). From the results obtained it is evident that the protocols described, based on microwave-assisted solvent-free organic reaction, are very efficient. Yields are at least equivalent, or better than those reported in literature, *even on 100 mmoles scale* (Table 3 entry 1a) and experimental conditions are exceptionally mild.

Scheme 3



4 **3**

Table 3: Synthesis of β-ketoesters **3** from **4**

Entry	RXH 2	W	t (min)	Y%	Prod.	Ref
1		650	3+3	98	**3b**	[11]
1a		650	1	98[a]	**3b**	[11]
2		500	3	94	**3c**	[2]
3		650	3+3	98	**3d**	[11]
4		500	2+1	92	**3e**	[12]
5		500	4	98	**3f**	[13]
6	TBDMSiOH	650	4+4+4	87	**3g**	
7	TPhSiOH	500	3+3	93	**3h**	
8	*tert*-BuOH	500	3+3	70	**3i**	[14]
9	*tert*-BuSH	650	3	83	**3k**	[15b]

a: 100 mmoles scale

The procedure avoids solvents and reactions are complete in very short time under safe conditions. Extension of this work to more challenging cases is currently in progress in our laboratories.

EXPERIMENTAL

General procedure for the synthesis of azetidinones **1(b-f)**: *Synthesis of* **1f**

The azetidinone **1a** (0.357g, 1mmol) was placed in an Erlenmeyer flask with the (*S*)-(-)-menthol (0.156g, 1mmol) in chlorobenzene (5ml). The mixture was irradiated during three times period of 10 min (keeping the volume of solvent constant in order to avoid burst-temperature) at 650 Watt until t.l.c. showed the absence of starting material. After removing the solvent, the reaction mixture was subjected as such to a flash chromatography to give **1f** (93%, $[\alpha]_D^{20}$=-14.7 (c=1.34 $CHCl_3$)). By the same procedure and under the MW power and reaction time reported in Table 1, azetidinones **1b-e** were obtained in the yields reported in Table 1.

Procedure for the synthesis of acetoacetates **6(b-g)**: *Synthesis of* **6f.**

Ethyl acetoacetate **6a** (0.260g, 2mmol) and (*S*)-(-)-menthol (0.312, 2mmol) were placed in an Erlenmeyer flask. The mixture was irradiated during two times period of 20 and 5 min (in order to avoid burst-temperature) at 650 Watt The reaction mixture was subjected as such to a short flash chromatography to give **6f** (92%).$[\alpha]_D^{20}$=-69.3 (c=10 benzene), lit[13] $[\alpha]_D^{20}$=-69.32 (c=10 benzene). By the same procedure β-keto esters **6b-g** were obtained in the yields reported in Table 2.

General procedure for the synthesis of acetoacetate from 2,2,6-trimethyl-1,3-dioxin-4-one: Synthesis of **6d.**

2,2,6-Trimethyl-1,3-dioxin-4-one **7** (0.142g, 1mmol) and (*S*)-(+)-octan-2-ol (0.13g, 1mmol) were placed in an Erlenmeyer flask. The mixture was irradiated during two times period of 3 min at 500 Watt. until t.l.c. spot-test showed the absence of starting material. The reaction mixture was subjected as such to a short flash chromatography to give **6d** (98%, $[\alpha]_D^{20}$=+5.8 (c=2.2 $CHCl_3$)). By the same procedure and following the MW power and reaction time reported in Table 3, β-keto esters **6b-i** were obtained in the yields reported in Table 3.

Acknowledgements: We wish to thank "Progetto Strategico sulle Applicazioni Industriali della Tecnologia a Microonde" CNR-Rome, for financial support.

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Accepted 8/1/99