Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7957–7959

TETRAHEDRON LETTERS

An efficient and rapid synthesis of β-carboxamide derivatives using 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones by microwave irradiation☆

Bruhaspathy Miriyala and John S. Williamson*

Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, MS 38677 USA

Received 16 July 2003; revised 29 August 2003; accepted 29 August 2003

Abstract—A general, efficient and rapid method for the synthesis of various β-carboxamide derivatives using microwave irradiation is described. Excellent isolated yields were obtained in very short reaction times when conventional heating was replaced by microwave irradiation.

The efficient and rapid synthesis of β-carboxamide derivatives is of significant importance due to their presence in various nitrogen containing heterocycle systems that have extensive application in medicinal chemistry.[1–3] It is also used as yellow-dye forming image couplers in photographic systems.[4]

β-Carboxamide derivatives were originally prepared by heating the reaction of methyl or ethyl ketocarboxylates with amines in high boiling solvents like xylene for prolonged time periods.[5] More recent approaches have focused on the use of 2,2-dimethyl dioxin-4-ones in lieu of the less reactive β-ketocarboxylates.[6–8] However, the yields of the reaction, as well as the reaction durations, are generally unsatisfactory, especially when 5- or 6-monosubstituted or 5,6-disubstituted dioxinones are involved. Such inefficient syntheses necessitate the need to develop more rapid reaction conditions.

In recent years, owing to its ability to couple directly with the reacting molecules and bypassing thermal conductivity leading to rapid rise in temperature, microwave irradiation has been used to improve many organic syntheses, leading to shorter reaction times, higher yields, cleaner reaction products and easier work-up than classical heating. In this respect, we have focused our attention on replacing conventional heating with microwave irradiation, and we now report a very fast, simple and efficient procedure for the synthesis of β-ketocarboxamides starting from β-diketones and primary or secondary amines.

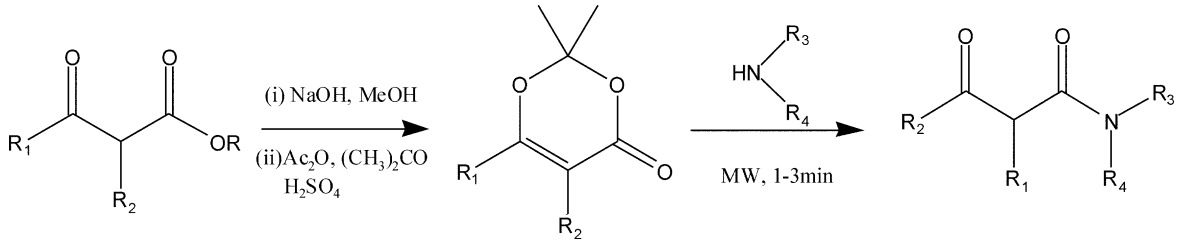
Substituted 2,2-dimethyldioxin-4-ones were initially synthesized from β-ketoesters after base hydrolysis followed by the acid catalyzed cyclic adduct formation with acetone according to established procedures.[9] Subsequent formation of the β-ketocarboxamides was accomplished by microwave irradiation of 2,2-dimethyldioxin-4-ones with an amine in a commercially available multimode microwave reactor dedicated for organic synthesis. The microwave irradiated reaction proceeds through the initial formation of a highly reactive α-oxoketene intermediate via pseudopericyclic reaction pathways.[10] The subsequent addition of the nucleophile (in this case, the amine) then captures the ketene which results in the formation of the corresponding β-ketocarboxamide.

Table 1. Standardization of MW irradiation time for the synthesis of *N*-benzyl-3-oxo butyramide produced via Scheme 1

E	Time (min)	Yield (%)
1	1.0	40
2	2.0	72
3	4.0	88
4	8.0	91

☆ Financial support for this project was provided in part by grants from the Center for Disease Control (CDC U50-CCU418839 and CDC UR3-CCU418652).
* Corresponding author. Tel.: 1-662-915-7142; fax: 1-662-915-5638; e-mail: mcjsw@olemiss.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.08.118



Scheme 1.

The experimental procedure for the formation of β-carboxamides was very simple: the 2,2-dimethyldioxin-4-one derivatives (1 mmol) was mixed with the amine (2–3 mmol) in a closed glass container and subjected to microwave irradiation for a specific time with stirring. The resulting amide product was taken in ethyl acetate and washed sequentially with water and aqueous HCl to remove excess amine. The organic layer was separated, dried over magnesium sulfate, concentrated, and purified chromatographically over silica gel to yield the required β-ketocarboxamide.

For an initial evaluation of the method, 2,2,6-trimethyl dioxin-4-one was selected as a suitable representative example. The diketone was mixed with benzylamine in 1,2-dichlorobenzene and irradiated. Based on a similar procedure for the synthesis of β-enaminoketones,[11] microwave power was set at 200 watts and the temperature was controlled by selecting a maximum of 178°C. As evident from Table 1, 2,2,6-trimethyl dioxin-4-one reacts rapidly with benzylamine. Optimum results were obtained when the reaction mixture was irradiated for 4 min. A cursory examination of solvent effects suggested that the absence of non-reactive solvent appears to hasten the completion of the reaction as is indicated in Table 2. This was somewhat surprising given that 1,2-dichlorobenzene is the most commonly used solvent for microwave-assisted chemical reactions due to its high dielectric loss tangent (tan δ), chemical stability and boiling point.[12] All subsequent reactions were performed using 2–3 equivalents of amine as solvent, except in the case of low boiling amines such as diisopropylamine where a 1:1 mixture of 1,2-dichlorobenzene and amine was used.

Since a wide range of β-ketoesters are either commercially available or easily accessible as substrates for this reaction, we have divided our validation methodology into three groups: the simple alkyls (methyl), the alicyclics (cyclohexyl), and the aromatics (phenyl). The 2,2-dimethyldioxin-4-one derivatives in each of the three groups were successfully reacted with a variety of primary and secondary amines, as shown in Tables 3–5, resulting in good yield of the desired β-ketocarboxamide in all cases.

Table 2. Effect of solvent for the synthesis of *N*-benzyl-3-oxo butyramide by MW irradiation

E	Time (min)	Solvent	Yield (%)
1	10	1,2-Dichloroethane	62
2	5	Xylene	75
3	3	1,2-Dichlorobenzene	88
4	1	Neat	95

Table 3. Synthesis of β-carboxamide derivatives from 2,2,6-trimethyl-[1,3]dioxin-4-one

Entry	Time (min)	R_3	R_4	Yield (%)
1	3	H	C_6H_5	79
2	1	H	$-(CH_2)-C_6H_5$	95
3	2	H	$-(CH_2)_2-C_6H_5$	89
4	2	$-(CH_2)_2-O-(CH_2)_2-$		90
5	2	$-(CH_2)_4-$		87
6	3	$-CH(CH_3)_2$	$-CH(CH_3)_2$	85

Table 4. Synthesis of β-carboxamide derivatives from 2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one

Entry	Time (min)	R_3	R_4	Yield (%)
1	3	H	C_6H_5	82
2	1	H	$-(CH_2)-C_6H_5$	96
3	2	H	$-(CH_2)_2-C_6H_5$	88
4	2	$-(CH_2)_2-O-(CH_2)_2-$		90
5	2	$-(CH_2)_4-$		88
6	3	$-CH(CH_3)_2$	$-CH(CH_3)_2$	85

Table 5. Synthesis of β-carboxamide derivatives from 2,2-dimethyl-5,6,7,8-tetrahydro-benzo[1,3]dioxin-4-one

Entry	Time (min)	R_3	R_4	Yield (%)
1	3	H	C_6H_5	78
2	1	H	$-(CH_2)-C_6H_5$	92
3	2	H	$-(CH_2)_2-C_6H_5$	88
4	2	$-(CH_2)_2-O-(CH_2)_2-$		90
5	2	$-(CH_2)_4-$		85
6	3	$-CH(CH_3)_2$	$-CH(CH_3)_2$	80

The presence of substitution at position 5 or alicyclic substitution at position 5 and 6 of 2,2-dimethyldioxin-4-one did not influence its reactivity to either primary or secondary amines. Aniline, the least nucleophilic of the amines, produced slightly low yields as compared to other amines. The reactivity of various 2,2-dimethyl

dioxi-4-ones was rapid with benzylamine, morpholine and pyrrolidine. Even though the yields obtained using diisopropylamine and phenethylamine were satisfactory, the reaction times were longer owing to their low reactivity. Steric factors associated with amines appeared to have little effect on the nature of the reaction.

In conclusion, microwave irradiation offers an efficient and rapid methodology for the formation of a considerable range of β-ketocarboxamide derivatives using substituted 2,2-dimethyl dioxin-4-ones, which are prepared from commercially available β-diketones and a variety of primary and secondary amines. Presently, efforts to extend the scope of this procedure to other nucleophilic groups is underway.

References

1. Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951–1960.
2. Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961–1970.
3. Gordeev, F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett*. **1996**, *37*, 4643–4646.
4. Hanisch, G.; Gahler, I.; Richter, J.; Ebisch, R.; Bruggraf, R. Ger. (East), 1990, DD 276684 A1 19900307.
5. Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc*. **1998**, *120*, 2493–2500.
6. Carroll, M. F.; Bader, A. R. *J. Am. Chem. Soc*. **1953**, *75*, 5400.
7. Sato, M.; Ogasawar, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull*. **1984**, *32*, 3848–3855.
8. Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull*. **1989**, *37*, 2952–2960.
9. Sato, M.; Ogasawara, H.; Oi, H.; Kato, T. *Chem. Pharm. Bull*. **1983**, *31*, 1896–1901.
10. Birney, D. M.; Xu, X.; Ham, S.; Huang, H. *J. Org. Chem*. **1997**, *62*, 7114–7120.
11. Strohmeier, G. A.; Kappe, C. O. *J. Comb. Chem*. **2002**, *4*, 154–161.
12. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev*. **1998**, *27*, 213–223.