Expedient Microwave-Assisted Synthesis of Novel 6-Substituted 5-Alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones

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Abstract: Novel 6-substituted 5-alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones have been prepared in good yields and very short reaction times by intramolecular cyclization of α-hydroxyhydrazonates in the presence of sodium ethoxide under microwave irradiation.

Key words: hydrazonates, nitrogen heterocycles, cyclization, microwave-assisted synthesis, ring closure

Due to the development of highly productive screening systems for drug targets the time-efficient construction and modification of biologically active heterocyclic compounds is becoming very important in drug discovery. Microwave irradiation has been applied to a large number of chemical modifications in recent years, and there are now very few areas of synthetic organic chemistry that have not been shown to be enhanced using microwave-assisted synthesis.[1–4] In particular, this method of energy transfer to a reaction mixture can grant access to synthetic transformations, which may be prohibitively long or low yielding using conventional reaction conditions.[1–4]

The esters of hydrazonoic acids, namely hydrazonates, are important building blocks in heterocyclic chemistry and have been utilized for the synthesis of numerous five-, six- and seven-membered heterocycles as well as fused derivatives thereof.[5–8] Moreover, hydrazonates have continued to attract great attention of the scientific community, particularly because of their presence in various biologically active compounds. Hydrazonates offer a wide range of interesting biological activities including anthelmintic, antifungal, and anti-inflammatory properties.[9] In addition, the hydrazonate moiety has been identified as pharmacophore in bactericides and herbicides.[10] Very recently, we found that α-hydroxyhydrazonates of type **4** display excellent antiplasmodial activity.[11]

As part of our ongoing research directed to biological active heterocyclic compounds we became interested in the synthesis of 6-substituted 5-alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **5**, which can be considered as semicyclic hydrazonate derivatives and rigid analogues of the α-hydroxyhydrazonates **4** (Figure 1). We here describe a simple and convenient microwave-assisted synthesis of compounds **5a–j** by intramolecular cyclization of α-hydroxyhydrazonates **4**.

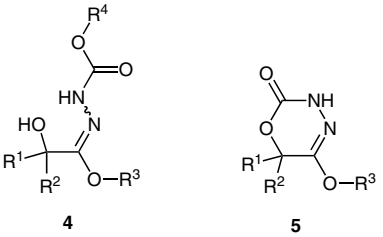

Figure 1 Antiplasmodial active α-hydroxyhydrazonates **4** and targeted heterocyclic analogues **5**

The α-hydroxyhydrazonates **4** have been prepared according to our recently disclosed three-step protocol starting from literature-known cyanohydrins **1**,[11] which upon a Pinner reaction[12] delivered α-hydroxyimidatehydrochlorides **2**. Unfortunately, the reaction of **2** with carbazates provided amidrazones **6** as byproducts (see Supporting Information) and the desired α-hydroxyhydrazonates **4a–d** were obtained in only moderate yields of 36–41%. Consequently, we developed a more efficient synthesis for the key intermediates **4**. Treatment of **2** with a saturated solution of hydrogen sulfide in dry dichloromethane–pyridine[13] afforded the α-hydroxythiocarboxylic-*O*-esters **3** in 82–88% yield, which upon reaction with carbazates furnished smoothly the desired α-hydroxyhydrazonates **4e–j** in 73–81% yield as mixtures of *E*- and *Z*-isomers (Scheme 1, Table 1).

Next, we investigated the ring-closing reaction of the α-hydroxyhydrazonates by refluxing a solution of **4a–c** in ethanol in the presence of one equivalent of sodium ethoxide. Followed by a simple workup procedure the desired heterocycles **5a–c** were obtained in 74–80% yield. However, relatively long reaction times were required (2–8 h). Therefore, we repeated the synthesis of **5** by means of microwave irradiation. The reaction conditions were optimized regarding to temperature and power to increase the yields and shorten the reaction times. In all cases completion of the reaction was monitored by IR spectroscopy as well as TLC. Best results were achieved using T_{max} = 100 °C and P_{max} = 200 W. Under these conditions the targeted 6-substituted 5-alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **5a–j** were isolated in 78–87% yield within only 5–10 minutes (Scheme 2, Table 2, see Supporting Information). Heterocycles **5** dis-

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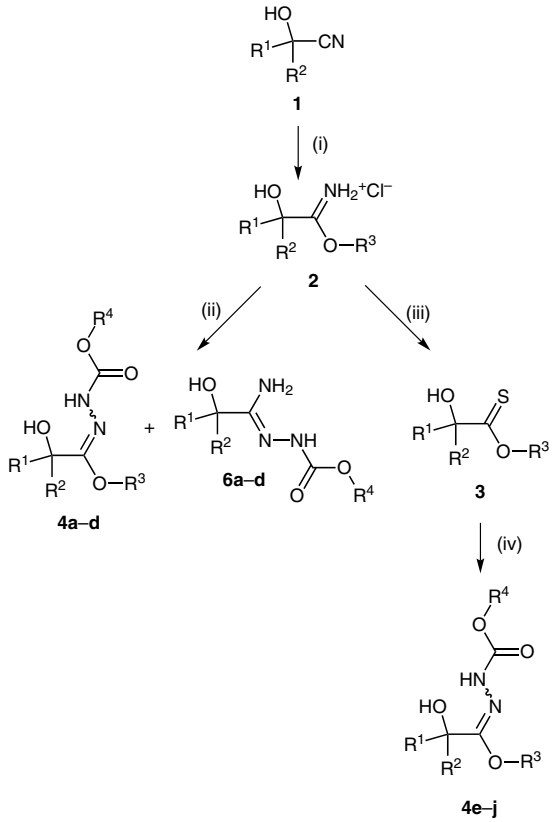


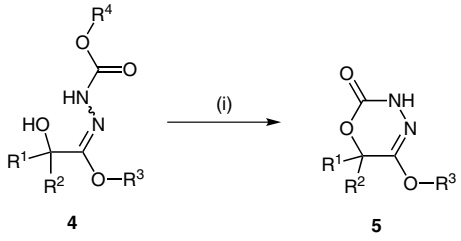
Scheme 1 Synthesis of α-hydroxyhydrazonates **4**. *Reagents and conditions*: (i) HCl (g), R^3OH, Et_2O, 0 °C; (ii) $H_2NNHCO_2R^4$, EtOH, r.t.; (iii) H_2S, pyridine, CH_2Cl_2, 5 °C, r.t.; (iv) $H_2NNHCO_2R^4$, EtOAc, r.t.

Table 1 Prepared α-Hydroxyhydrazonates **4a–j**

Entry	Compound **4**	R^1	R^2	R^3	R^4	Yield (%)
1	**4a**	*c*-Pr	Me	Et	Et	41
2	**4b**	2-Naphthyl	Me	Et	Me	36
3	**4c**	Ph	Et	Et	Et	38
4	**4d**	Ph	H	Et	Et	39
5	**4e**	4-MeC_6H_4	Me	Et	Et	81
6	**4f**	4-ClC_6H_4	Me	Et	Et	76
7	**4g**	3,4-$Me_2C_6H_3$	Me	Et	Et	81
8	**4h**	3,4-$Cl_2C_6H_3$	Me	Me	Et	73
9	**4i**	2-Naphthyl	Me	Me	Et	80
10	**4j**	Me	Me	Bn	Et	78

play sharp IR C=O absorption bands at 1703–1726 cm^{-1} and C=N absorption bands at 1655–1667 cm^{-1}.

Structure determination of all synthesized compounds is based on IR, ^1H NMR, ^{13}C NMR spectroscopic data and elemental analysis. In addition, X-ray analysis of **5e** proved unambiguously its structure as 5-ethoxy-6-methyl-6-(4-methylphenyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one **5e** (Figure 2).[14]



Scheme 2 Synthesis of 6-substituted 5-alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **5**. *Reagents and conditions*: (i) NaOEt, EtOH, microwave.

Table 2 Microwave Synthesis of 6-Substituted 5-Alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **5**[a]

Entry	Compound **5**	R^1	R^2	R^3	Hold time (min)	Yield (%)
1	**5a**	*c*-Pr	Me	Et	10	80
2	**5b**	2-Naphthyl	Me	Et	5	87
3	**5c**	Ph	Et	Et	10	86
4	**5d**	Ph	H	Et	10	84
5	**5e**	4-MeC_6H_4	Me	Et	5	86
6	**5f**	4-ClC_6H_4	Me	Et	10	81
7	**5g**	3,4-$Me_2C_6H_3$	Me	Et	5	80
8	**5h**	3,4-$Cl_2C_6H_3$	Me	Me	10	84
9	**5i**	2-Naphthyl	Me	Me	10	85
10	**5j**	Me	Me	Bn	10	78

[a] Microwave-assisted synthesis of compounds **5** was carried out using a CEM Corporation Focused Microwave System, Model Discover. Parameters for compounds **5**: discover mode; power: 200 W; ramp time: 0.5 min; temp: 100 °C; pressure: 10 bar; PowerMax cooling.

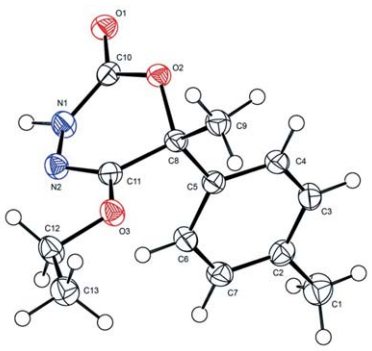


Figure 2 X-ray crystal structure of compound **5e**

In summary, we have developed a rapid and convenient synthesis of hitherto unknown 5-alkoxy(benzyloxy)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **5** under microwave

irradiation. The described microwave-assisted procedure offers a considerable advantage over conventional reaction conditions with regard to reaction times.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References

(1) (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325. (b) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903.
(2) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
(3) Wathey, B.; Tiemey, J.; Lidström, P.; Westman, J. *Drug Discov. Today* **2002**, *7*, 373.
(4) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(5) (a) Ikizler, A.; Demirbas, N.; Ikizler, A. A. *J. Heterocycl. Chem.* **1996**, *33*, 1765. (b) Ikizler, A. A.; Yildirim, N. *J. Heterocycl. Chem.* **1998**, *35*, 377.
(6) Malbec, F.; Milcent, R.; Barbier, G. *J. Heterocycl. Chem.* **1984**, *21*, 1689.
(7) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Synth. Commun.* **1989**, *19*, 2321.
(8) For an excellent review, see: Shawali, A. S.; Sherif, S. M. *Curr. Org. Chem.* **2007**, *11*, 773.
(9) (a) Wing, K. D. EP 361645, **1990**; *Chem. Abstr.* **1990**, *113*, 151998. (b) Ishida, S.; Koike, K. JP 48028421, **1973**; *Chem. Abstr.* **1973**, *79*, 65812. (c) Nesvadba, H. DE 2659528, **1977**; *Chem. Abstr.* **1977**, *87*, 117863.
(10) (a) Yoshimoto, T.; Hosono, A.; Miki, J.; Oda, K.; Ura, M.; Sato, N.; Toyama, T.; Tachibana, H.; Enomoto, Y.; Funakoshi, Y.; Fujita, T.; Hojo, Y. DE 2944783, **1980**; *Chem. Abstr.* **1980**, *93*, 167904. (b) Gy, E. T. GB 1382781, **1975**; *Chem. Abstr.* **1975**, *83*, 43386.
(11) Khankischpur, M.; Hansen, F. K.; Meurer, R.; Mauz, T.; Bergmann, B.; Walter, R. D.; Geffken, D. *Arch. Pharm. Life Sci.* **2011**, *344*, 755.
(12) Pinner, A. *Die Imidoäther und ihre Derivate;* Oppenheim: Berlin, **1892**.
(13) Kurz, T.; Khankischpur, M.; Widyan, K. *Tetrahedron Lett.* **2006**, *47*, 4241.
(14) CCDC 845877 contains the supplementary crystallographic data for the deposited structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

