Tetrahedron Letters 56 (2015) 573–576

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formation of 1,3,4-oxadiazolines and 1,3,4-oxadiazepines through acetylation of salicylic hydrazones

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ARTICLE INFO

Article history:
Received 23 May 2014
Revised 25 November 2014
Accepted 9 December 2014
Available online 15 December 2014

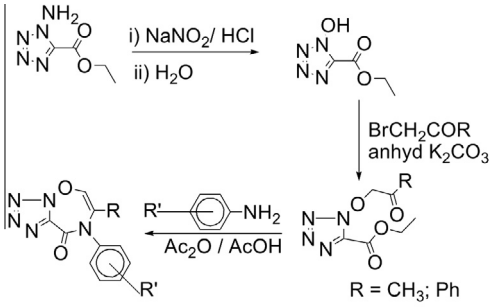
Keywords:
1,3,4-Oxadiazoline
1,3,4-Oxadiazepine
Acetylation
Acid catalyzed

ABSTRACT

A new series of 1,3,4-oxadiazolines and 1,3,4-oxadiazepines are prepared in a one-step reaction through cyclization of various *N*-benzylidene-2-hydroxybenzohydrazides. Cyclization in acetic anhydride yielded 1,3,4-oxadiazolines, while the reaction carried out in acetic anhydride–acetic acid gave 1,3,4-oxadiazepines, in some cases.

Oxadiazolines and oxadiazepines are important compounds for both chemical and biological purposes.[1,2] They have been used extensively as synthons in various organic syntheses such as for the preparation of spiro-fused β-lactam oxadiazolines[3] and of fused oxadiazepines used as gamma secretase modulators for the treatment of Alzheimer's disease.[4] In addition, oxadiazolines and oxadiazepines have been reported to exhibit diverse pharmacological properties,[5] which include antimicrobial,[6] cytotoxic,[7] antifungal, and anticancer activities.[8] Various aldehyde and ketone acyl hydrazones have been cyclized to give 3-acyl-1,3,4-oxadiazolines under acylating conditions.[9,10] However, there are only three reports on acylhydrazones with a hydroxyl group at the *ortho* position of the benzene ring being cyclized to give 3-acyl-1,3,4-oxadiazolines.[11] In the case of oxadiazepines, several methods have been reported for their synthesis, all of which are multi-step in nature.[6,12–14] For example, El Badry and Taha[2] reported that the diazotization of ethyl 1-aminotetrazole-5-carboxylate in the presence of water resulted in the formation of ethyl 1-hydroxytetrazole-5-carboxylate. (Scheme 1).

Condensation of ethyl 1-hydroxytetrazole-5-carboxylate with bromoacetone and/or phenacyl bromide in absolute ethanol in the presence of anhydrous potassium carbonate provided acetyloxy and 2-oxyacetophenone compounds, which were then reacted



a, R = CH_3; R' = H
b, R = CH_3; R' = 4-CH_3
c, R = CH_3; R' = 4-OCH_3
d, R = CH_3; R' = 4-NH_2
e, R = CH_3; R' = 4-Cl
f, R = CH_3; R' = 4-NO_2
g, R = Ph; R' = H
h, R = Ph; R' = 4-CH_3
i, R = Ph; R' = 4-OCH_3
j, R = Ph; R' = 4-NH_2
k, R = Ph; R' = 4-Cl
l, R = Ph; R' = 4-NO_2

Scheme 1. El Badry and Taha's work.[2]

with various 4-substituted anilines in the presence of acetic anhydride/acetic acid to give 7-methyl(phenyl)-8-aryltetrazolo[1,5-*b*]-1,2,5-oxadiazepin-9-ones in three steps.[6] Herein, we report a novel, one-step intramolecular oxidative cyclization of a variety of substituted benzaldehyde acylhydrazones **1**[15] with a free hydroxyl group at the *ortho* position to give the oxadiazolines **2**, which

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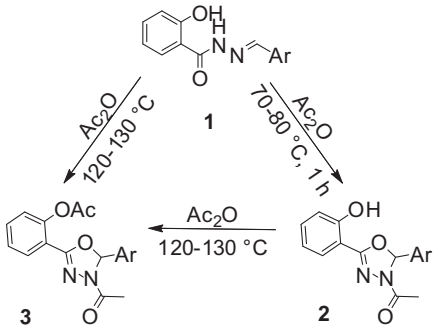
http://dx.doi.org/10.1016/j.tetlet.2014.12.037
0040-4039/



Scheme 2. Synthesis of 1,3,4-oxadiazoline derivatives **3**.

were isolated and characterized. Acetylation of the oxadiazoline **2** led to the formation of 1,3,4-oxadiazoline derivatives **3**[16–18] as shown in Scheme 2. Thus, reactions of substituted benzaldehyde acylhydrazones **1** in acetic anhydride at 120–130 °C resulted in the cyclized products **3** (Scheme 2). The reactions proceeded smoothly with no side products being observed under these conditions.[15,19]

Under these acylation conditions, compounds **1a–i**, possessing either electron-donating or electron-withdrawing substituents on the aryl ring cyclized to give 1,3,4-oxadiazolines **3a–i**[16–18,20] in 58–85% yields[18] (Table 1). The presence of an electron-withdrawing substituent on the phenyl ring tended to give better yields with the best yield being obtained with a nitro substituent, and the lowest with a *tert*-butyl substituent.[17,18] This is to be expected since a strong electron-withdrawing group such as NO_2 on the aryl ring would enhance the electrophilicity of the iminium carbon, while an electron-donating group would decrease the electrophilicity.[18]

In some cases, when the cyclization reactions of **1** were carried out at 50–60 °C in acetic anhydride/acetic acid solution, 1,3,4-oxadiazepines **4** were obtained instead of 1,3,4-oxadiazolines **3** (Scheme 3).[18,20,21]

Table 2 summarizes the products of the cyclization reactions of compound **1** using the Ac_2O–AcOH conditions. Presumably, the acidic conditions influenced the reaction to form the seven-membered oxadiazepines.[18,20,21]

We have proposed two pathways leading to the formation of oxadiazolines **3** (Scheme 4). One pathway involves acetylation of the free hydroxyl group on the benzene ring to form **5**, which then undergoes intramolecular oxidative cyclization to form **3** (Pathway A). An alternative pathway involves intramolecular oxidative cyclization of **1** to first produce **2a** and **2b**, followed by acylation of the phenol to form **3** (Pathway B).

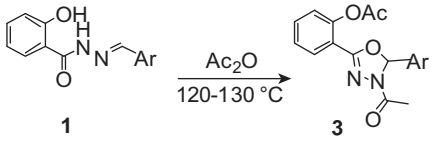
However, since we isolated only the oxadiazolines **2a** and **2b** with a free *ortho* phenolic group and no product **5** from this reaction, we concluded that the cyclization occurred through pathway B. Compounds **2a** and **2b** (Scheme 4), then underwent acetylation to produce **3a** and **3b**.

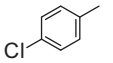
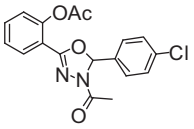
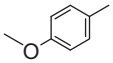
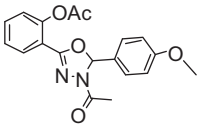
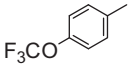
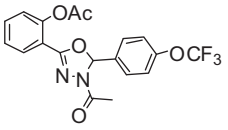
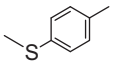
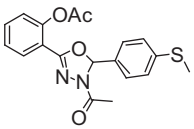
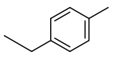
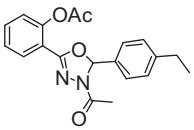
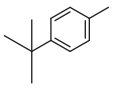
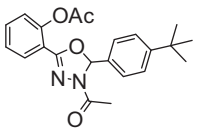
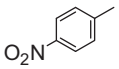
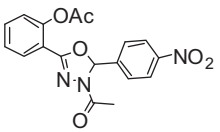
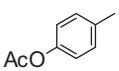
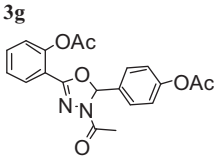
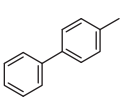
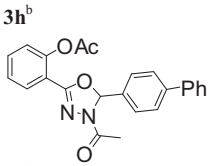
It has been well established that compound **1** can undergo keto–enol tautomerisation as shown in Scheme 5.

We propose that the mechanism for the oxidative cyclization reactions leading to **2a** and **2b** involves attack of the enolic oxygen of the enol tautomer on the azomethine imine moiety as shown in Scheme 6.

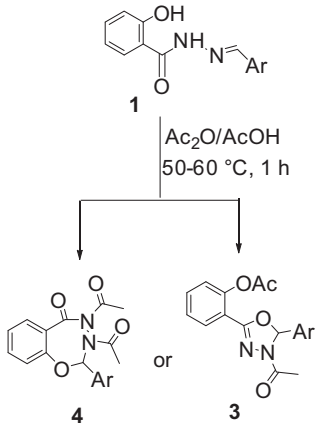
In the case of the seven-membered oxadiazepines, we propose that the reaction occurs via nucleophilic attack of the phenolic oxygen on the iminium carbon as shown in Scheme 7. Here, the iminium carbon acts as a carbonyl analogue and participates in an intramolecular nucleophilic addition reaction[19,22] with the *ortho* phenolic group. Subsequently, the oxadiazepine underwent acetylation to give only the diacetylated product **4** (Scheme 7).

Table 1
Structures and yields of synthesized compounds **3a–i**



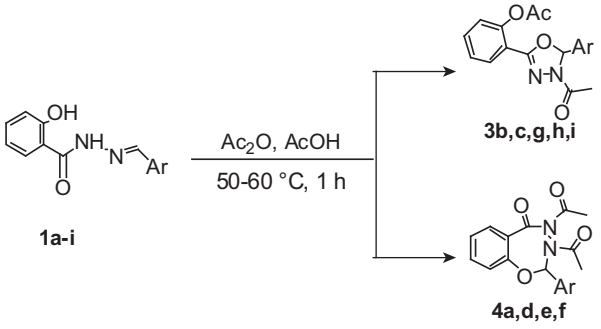
Entry	Ar	Product[a]	Yield[c] (%)
1		 **3a**	78
2		 **3b**	70
3		 **3c**[b]	70
4		 **3d**	65
5		 **3e**	60
6		 **3f**	58
7		 **3g**	85
8		 **3h**[b]	70
9		 **3i**[d]	75

[b] Structure was confirmed by X-ray crystallography.
[d] This compound was previously reported in Ref. 11 along with a crystal structure, but without any data.
[a] All products were identified by ATIR, NMR, and EI-HRMS analyses.
[c] Isolated yield after recrystallization.



Scheme 3. Synthesis of 1,3,4-oxadiazepines **4** and 1,3,4-oxadiazolines **3**.

Table 2
Structures and yields of compounds **4a**,**d**,**e**,**f** and **3b**,**c**,**g**,**h**, **i**



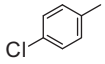
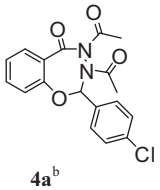
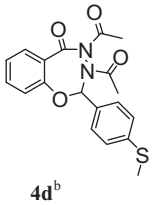
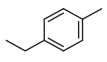
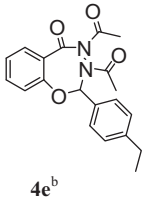
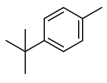
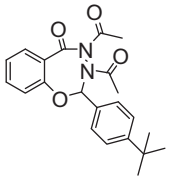
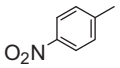
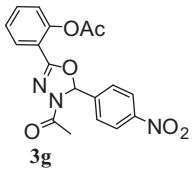
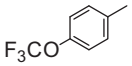
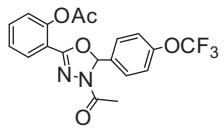
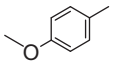
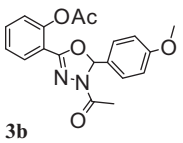
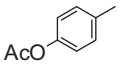
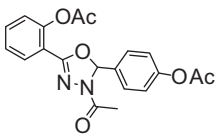
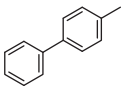
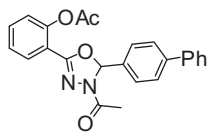
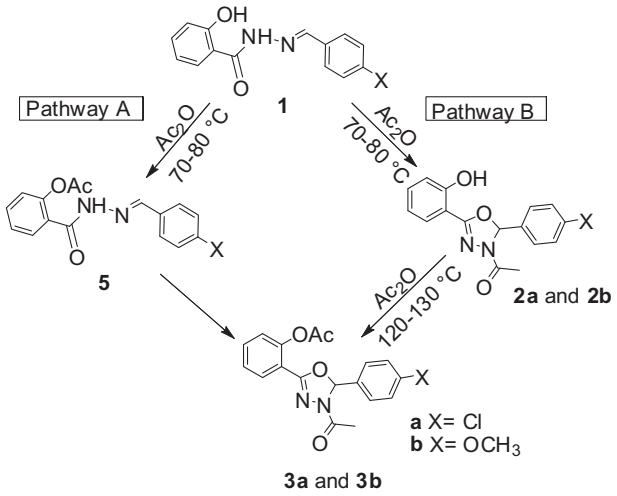
Entry	Ar	Product[a]	Yield[c] (%)
1		 **4a**[b]	63
2		 **4d**[b]	75
3		 **4e**[b]	66
4		 **4f**	55

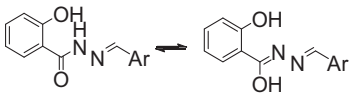
Table 2 (*continued*)

Entry	Ar	Product[a]	Yield[c] (%)
5		 **3g**	70
6		 **3c**	65
7		 **3b**	65
8		 **3h**	63
9		 **3i**	70

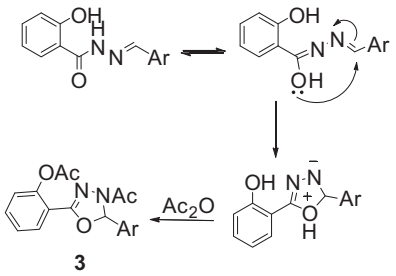
[b] Structure was confirmed by X-ray crystallography.
[a] All products were identified by ATIR, NMR, and EI-HRMS analyses.
[c] Isolated yield after recrystallization.



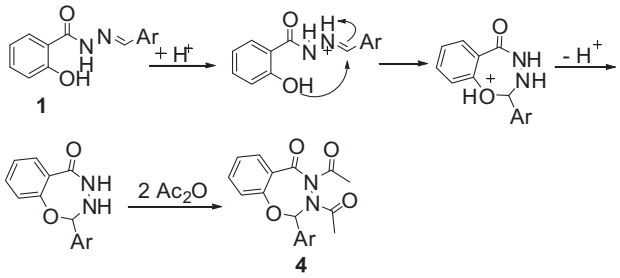
Scheme 4. Proposed pathways for the cyclization of **1**.



Scheme 5. Tautomerisation of compound **1**.



Scheme 6. A plausible mechanism for the formation of compounds **3a–i**.



Scheme 7. A plausible mechanism for the formation of compounds **4**.

In summary, 1,3,4-oxadiazolines containing an acetoxy group at the *ortho* position of the benzene ring were prepared in one-step, via intramolecular oxidative cyclization of acylhydrazones in acetic anhydride, which serves both as a reactant and the solvent. However, 1,3,4-oxadiazolines or 1,3,4-oxadiazepines were obtained in some cases, when the reactions were carried out under acid-catalyzed conditions.

Acknowledgments

The authors acknowledge support from the University of Malaya under the UMRG: RG056/11BIO and UMRG program RP002/2012.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.037.

References and notes

1. Yang, J.-F.; Cao, H.; Liu, H.; Li, B.-Q.; Ma, Y.-M. *J. Chin. Chem. Soc.* **2011**, *58*, 369–375.
2. El Badry, S. M.; Taha, M. A. *J. Korean Chem. Soc.* **2011**, *55*, 974–977.
3. Zoghbi, M.; Warkentin, J. *Can. J. Chem.* **1993**, *71*, 912–918.
4. Li, H.; Qin, J.; Dhondi, P.; Zhou, W.; Vicarel, M.; Bara, T.; Cole, D.; Josien, H.; Pissarnitski, D.; Zhu, Z.; Palani, A.; Aslanian, R.; Clader, J.; Czarniecki, M.; Greenlee, W.; Cohen-Williams, M.; Hyde, L.; Song, L.; Zhang, L.; Chu, I.; Huang, X. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 466–471.
5. Ke, S.; Liu, F.; Wang, N.; Yang, Q.; Qian, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 332–335.
6. Fuloria, N. K.; Singh, V.; Shaharyar, M.; Ali, M. *Molecules* **2009**, *14*, 1898–1903.
7. Manojkumar, P.; Ravi, T. K.; Subbuchettiar, G. *Acta Pharm.* **2009**, *59*, 159–170.
8. (a) Daeniker, H. U.; Druey, J. *Helv. Chim. Acta* **1957**, *40*, 918–932; (b) Autio, K.; Pyysalo, H. *J. Agric. Food Chem.* **1983**, *31*, 568–571; (c) Ishiwata, S.; Shiokawa, Y. *Chem. Pharm. Bull.* **1970**, *18*, 1245–1248.
9. Somogyi, L. *J. Heterocycl. Chem.* **2007**, *44*, 1235–1246.
10. Arora, P.; Mittal, A.; Kaur, G.; Chauhan, A. *Int. J. Pharm. Sci. Res.* **2013**, *4*, 419–424.
11. Yehye, W. A.; Ariffin, A.; Rahman, N. A.; Ng, S. W. *Acta Crystallogr., Sect. E.* **2010**, *66*, 0878.
12. Oe, K.; Tashiro, M.; Tsuge, O. *J. Org. Chem.* **1977**, *42*, 1496–1499.
13. Oe, K.; Tashiro, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3281–3287.
14. Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett.* **2007**, *48*, 2617–2620.
15. General procedure for the synthesis of hydrazones **1a–i**: 2-Hydroxybenzohydrazide (0.30 g, 2 mmol) and different *para*-substituted benzaldehyde derivatives (0.2 g, 2 mmol) were refluxed in EtOH (20 ml) for 5 h. The solvent was removed by evaporation and the resulting products were obtained as white solids (**1a**,**c–i**) or as a yellow solid (**1b**).
16. General procedure for synthesis of oxadiazoline analogs (Table 1): A mixture of hydrazone **1a–i** (1.58 mmol) in Ac_2O (6 ml) was refluxed for 2 h under vigorous stirring. The solution was cooled and then poured onto crushed ice and stirred vigorously. A precipitate formed which was washed with distilled H_2O to remove the Ac_2O. The obtained solid was further purified by crystallization from an appropriate solvent.
17. Most products were found to be homogeneous by TLC and 400 MHz NMR analyses, but when necessary, heterogeneous products were readily purified by silica gel column chromatography using hexane/$CHCl_3$ as the eluent.
18. See Supplementary data for complete experimental details.
19. Jiang, L.; Chen, Y.-C. *Catal. Sci. Tech.* **2011**, *1*, 354–365.
20. Crystallographic data for compounds **3c**, **3h**, **4a**, **4d** and **4e** have been deposited at the Cambridge Crystallographic Data Centre, with the deposition numbers 963045, 963044, 963041, 963043 and 963042, respectively.
21. General procedure for the synthesis of oxadiazepine derivatives (Table 2): Compounds **4a**,**f**,**e**,**d** were obtained from the reaction of Ac_2O (6 ml) with hydrazones **1a**,**f**,**e**,**d** (2 mmol) in the presence of AcOH (6 ml), and the resulting solution was stirred vigorously for 1 h at 50–60 °C. A precipitate formed which was washed with distilled H_2O to remove the Ac_2O. The obtained solid was further purified by crystallization from an appropriate solvent.
22. Dewick, P. M. *Essentials of Organic Chemistry: For Students of Pharmacy, Medicinal Chemistry and Biological Chemistry*; Wiley: Chichester, 2006; pp 369–370.