Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2231–2235

A one-pot synthesis of 3-substituted-5-carbonylmethyl-1,2,4-oxadiazoles from β-keto esters and amidoximes under solvent-free conditions

Wu Du,* Quang Truong, Hongbo Qi, Yan Guo, Harry R. Chobanian, William K. Hagmann and Jeffrey J. Hale

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Received 21 December 2006; revised 1 February 2007; accepted 5 February 2007
Available online 7 February 2007

Abstract—Herein we report a high yielding one-pot 'green' synthesis of 3-substituted-5-carbonylmethyl-1,2,4-oxadiazoles from readily available β-keto esters and amidoximes under simple and convenient solvent-free conditions. No additional base is needed. The reaction likely goes through an acyl ketene intermediate.

1,2,4-Oxadiazole is a pharmaceutically important heterocycle. It can be found in many biologically active molecules such as sphingosine-1-phosphate-1 ($S1P_1$) receptor agonist,[1] muscarinic agonist,[2] serotoninergic antagonists,[3] inhibitors of monoamine oxidase,[4] and dopamine ligands.[5] In addition, 1,2,4-oxadiazoles are also often used as bioisosteres of esters and amides for improved physical or biological properties.[6] This includes the development of pseudopeptides by bioisosteric replacement of the amide moiety in peptides,[7] which is currently under intense studies for its important implication in peptide chemistry and peptidomimetics.

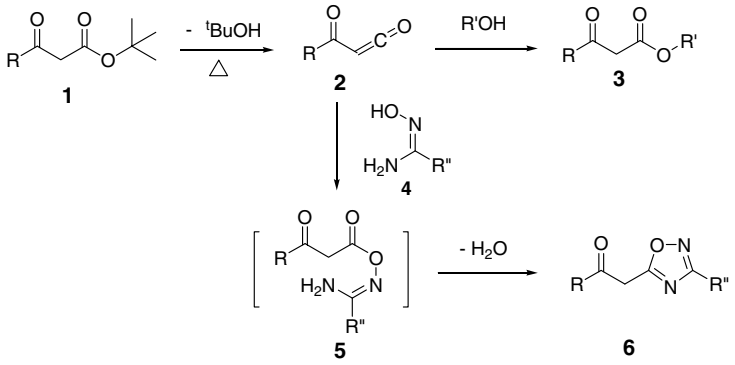
Accordingly, the synthesis of 1,2,4-oxadiazoles has received much attention and has been the subject of intense studies.[8] 1,2,4-Oxadiazoles are often synthesized by 1,3-dipolar cyclization of nitrile oxide and cyano compounds or cyclization/dehydration of *O*-acyl amidoximes. The latter are usually derived from coupling of carboxylic acids and amidoximes.[9] Recently reported TBAF catalyzed cyclization of *O*-acyl amidoximes makes the latter route a popular approach to 1,2,4-oxadiazoles.[10] Further efforts in this area have focused on developing more efficient one-pot synthesis of this ring system. This includes recently published microwave-assisted condensation of aryl amidoxime and aryl aldehyde,[11] condensation of esters with amidoximes promoted by bases such as NaH,[12] NaOMe,[13] K_2CO_3,[14] and condensation of malonic diesters with amidoximes under neutral and solvent-free conditions.[15] We have ongoing interest in efficient synthesis of 1,2,4-oxadiazoles. As an extension of our previous work, we wish to report here an efficient one-pot synthesis of 5-β-keto-1,2,4-oxadiazoles **6** with a broader scope of application.

Beta-keto esters are important building blocks in organic synthesis. The studies on transesterification of β-keto esters revealed that under thermal conditions, a β-keto ester can undergo elimination of a molecule of alcohol to form an α-keto ketene intermediate **2**.[16] Kinetic studies showed that the sterically more hindered alcohol is easier to be eliminated. Thus *tert*-butyl β-keto ester **1** is 15–20 times faster than less hindered methyl β-keto ester in formation of the acyl ketene.[17] Ketenes are a family of highly reactive and versatile intermediate in organic synthesis. Despite the broad application of ketenes in organic synthesis, the application of the α-keto ketenes generated from β-keto esters has only been limited to transesterification to generate other β-keto esters. Amidoxime **4** should react analogously to give transesterification product *O*-acyl amidoxime **5**, which would then yield 5-β-keto-1,2,4-oxadiazole **6** under thermal conditions (Scheme 1).

There is limited literature precedent for the synthesis of 5-β-keto-1,2,4-oxadiazoles. They are typically synthesized

* Corresponding author. Tel.: +1 732 594 2891; fax: +1 732 594 5966; e-mail: wu_du@merck.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.005



Scheme 1.

from 2,2,6-trimethyl[1,3]dioxin-4-one,[18] α-cyanoketone through a multi-step sequence,[19] by TBAF promoted cylization/dehydration of *O*-acyl amidoxime,[10] or by reaction of amidoxime with diketene in the presence of NaOMe.[20] The latter approach yielded 3-acetomethyl-1,2,4-oxadizaoles in one-pot. However, the drawback is that diketene is volatile, difficult to handle, and its scope of application is very limited: only methyl ketone can be made from diketene. The synthesis of 5-acetomethyl-1,2,4-oxadiazoles from ethyl acetoacetate was also minimally explored either in the presence of NaOMe,[21] or under extensive heating in toluene.[22] However, both conditions gave low yields of the oxadiazole products.

Herein we report a convenient, high yielding, and 'green' synthesis of 5-β-keto-1,2,4-oxadiazoles by heating a β-keto ester and an amidoxime under solvent-free conditions. The procedure is very simple: 1 equiv of amidoxime was mixed with 2 equiv of β-keto ester in a vial. The mixture was then heated to 120–140 °C for 2–4 h. After the reaction was complete, the brown reaction mixture was applied to a silica gel column and purified by flash chromatography.[23] When solid reactants were used, the solid melted upon heating to give a homogeneous reaction mixture. The results are summarized in Table 1.

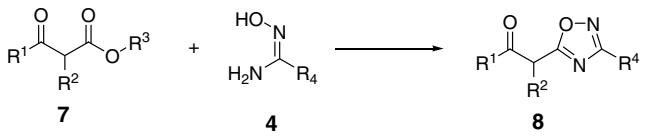
This one-pot procedure works well for a wide range of substrates. Various substituted amidoximes were reacted with *t*-butyl acetoacetate and gave excellent yield of the desired oxadiazole products. As shown in entries 1–3, the electron withdrawing or donating group on the phenyl ring did not affect the reaction. All three reactions gave almost quantitative yields. In entry 4, oxadiazole **8d** containing an electron deficient heterocycle was prepared in 84% yield. In addition, this one-pot procedure is simple and efficient. The reaction conditions are also very mild. As shown in entry 5, the methyl ester in amidoxime **4e** survived the reaction in which only the *t*-butyl ester reacted with **4e** and gave 95% yield of **8e**. Similarly in entry 6, the ethyl ester group of **4f** remained inert in the reaction that gave 88% yield of **8f**. Such chemoselectivity is hard to achieve under previously reported conditions involving bases such as NaH, NaOMe, and K_2CO_3. Amidoximes bearing a simple alkyl group also worked well in this reaction, as shown in entry 7 that **8g** was prepared in 84% yield. Functional groups such as sulfone and benzyl ether were also tolerated under the reaction conditions as shown in entries 8 and 9. The oxadiazole products were prepared in 92% and 84%, respectively.

In addition to substituted amidoximes, various β-keto esters are also good substrates. As shown in entries 10–12, methyl and ethyl β-keto esters worked well in this reaction. Ethyl ester **7b** yielded oxadiazole **8j** in 69% yield while methyl ester **7c** yielded oxadiazole **8k** in 87% yield. These two reactions also showed that substituents at 2 and 3 positions of the β-keto ester are tolerated in this reaction. Selectivity can also be achieved among two esters from the β-keto ester substrate. As shown in entry 12, among the two ester groups of **7d** only the one β to the ketone is reactive in the reaction. Thus the reaction of diester **7d** and phenyl amidoxime yielded oxadiazole mono ester product **8l** in 70% yield. The selective activation of ester group by β-ketone allows a very efficient synthesis of ester containing 1,2,4-oxadiazole products that would otherwise take longer steps to make.

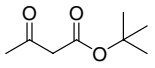
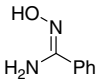
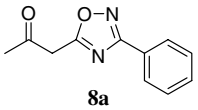
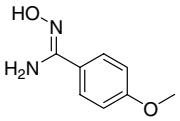
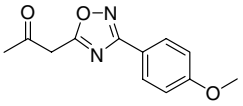
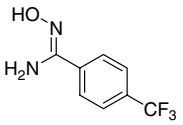
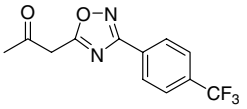
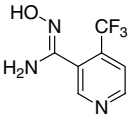
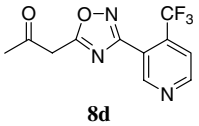
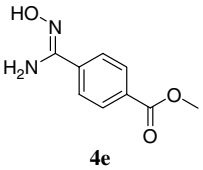
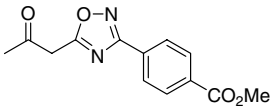
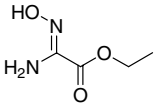
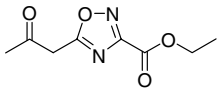
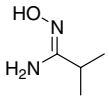
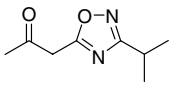
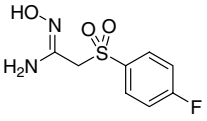
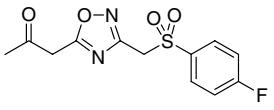
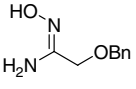
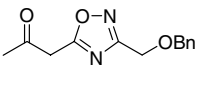
The solvent-free conditions likely contribute to the high efficiency of this reaction in two ways: driving the reaction toward the desired oxadiazole product by removing other volatile products and favored entropy effect by achieving high concentration of amidoxime reactants. In addition to the oxadiazole product, a molecule of alcohol and a molecule of water are also generated according to the proposed mechanism. Removal of these side products becomes easier under the solvent-free conditions, and thus facilitates completion of the reaction. The subsequent addition of an amidoxime to the acyl ketene intermediate is an intermolecular reaction. It is also significantly accelerated by the high concentration of the amidoxime achieved under the solvent-free conditions.

In summary, we report here a high yielding one-pot synthesis of 5-carbonylmethyl-1,2,4-oxadiazoles from readily available β-keto esters and amidoximes under simple and convenient solvent-free conditions. The reaction likely goes through an acyl ketene intermediate. The conditions are mild and a wide range of functional groups can be tolerated. The reaction is also selective:

Table 1.

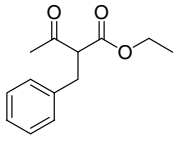
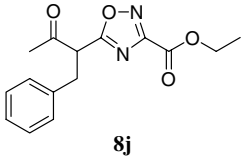
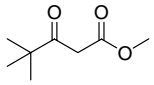
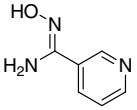
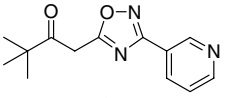
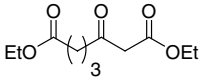
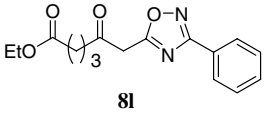


7 **4** **8**

Entry	7	4	8	Yield (%)
1	 **7a**	 **4a**	 **8a**	100
2	**7a**	 **4b**	 **8b**	99
3	**7a**	 **4c**	 **8c**	98
4	**7a**	 **4d**	 **8d**	84
5	**7a**	 **4e**	 **8e**	95
6	**7a**	 **4f**	 **8f**	88
7	**7a**	 **4g**	 **8g**	84
8	**7a**	 **4h**	 **8h**	92
9	**7a**	 **4i**	 **8i**	84

(*continued on next page*)

Table 1 (*continued*)

Entry	7	4	8	Yield (%)
10	 **7b**	**4f**	 **8j**	69
11	 **7c**	 **4j**	 **8k**	87
12	 **7d**	**4a**	 **8l**	70

only the esters that are β to a carbonyl and capable of forming acyl ketene intermediate are reactive. Unlike many 1,2,4-oxadiazole syntheses that require bases, no additional reagents are needed under these conditions. Thus the purification process is much simplified and solvent waste is eliminated, and the reaction is cost efficient and environmentally friendly. Further studies on this topic will be reported in due course.

Acknowledgment

The authors wish to thank Dr. Shrenik K. Shah for helpful discussions and valuable comments on the manuscript.

References and notes

1. Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quackenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. *J. Med. Chem.* **2005**, *48*, 6169.
2. (a) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsorth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726; (b) Suzuki, T.; Uesaka, H.; Hamajima, H.; Ikami, T. *Chem. Pharm. Bull.* **1999**, *47*, 876.
3. Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140.
4. Harfenist, M.; Heuser, D. J.; Joyner, C. T.; Batchelor, J. F.; White, H. L. *J. Med. Chem.* **1996**, *39*, 1857.
5. Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1993**, *36*, 2886.
6. (a) Lima, L. M.; Barreiro, E. J. *Curr. Med. Chem.* **2005**, *12*, 23; (b) Andersen, K. E.; Lundt, B. F.; Joergensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1996**, *31*, 417; (c) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421.
7. Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331.
8. Hemming, K. *J. Chem. Res., Synop.* **2001**, *6*, 209.
9. Liang, G.-B.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627.
10. Gangloff, A. R.; Litvak, J.; Shelton, E. J.; Sperandio, D.; Wang, V. R.; Rice, K. D. *Tetrahedron Lett.* **2001**, *42*, 1441.
11. Adib, M.; Jahromi, A. H.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 2965.
12. (a) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; Macleod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690; (b) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140.
13. Sauerberg, P.; Kindtler, J. W.; Nielsen, L.; Sheardown, M. J.; Honore, T. *J. Med. Chem.* **1991**, *34*, 687.
14. Amarasinghe, K. K. D.; Maier, M. B.; Srivastava, A.; Gray, J. L. *Tetrahedron Lett.* **2006**, *47*, 3629.
15. Du, W.; Hagmann, W. K.; Hale, J. J. *Tetrahedron Lett.* **2006**, *47*, 4271.
16. Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713.
17. Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401.
18. Boehme, T. M.; Augelli-Szafran, C. E.; Hallak, H.; Pugsley, T.; Serpa, K.; Schwarz, R. *J. Med. Chem.* **2002**, *45*, 3094.
19. Cho, S. Y.; Ahn, J. H.; Ha, J. D.; Kang, S. K.; Baek, J. Y.; Han, S. S.; Shin, E. Y.; Kim, S. S.; Kim, K. R.; Cheon, H. G.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1455.
20. Tabei, K.; Kawashima, E.; Takada, T.; Kato, T. *Chem. Pharma. Bull.* **1982**, *30*, 336.
21. Yale, H. L.; Spitzmiller, E. R. *J. Heterocycl. Chem.* **1978**, *15*, 1373.
22. Kocevar, M.; Stanovnik, B.; Tisler, M. *J. Heterocycl. Chem.* **1982**, *19*, 1397.
23. *Experimental procedure*: *t*-Butyl acetoacetate **7a** (160 mg, 1 mmol) and amidoxime **4h** (116 mg, 0.5 mmol) were mixed in a vial. The reaction mixture was then heated in an oil bath at 120 °C for 2 h. TLC showed completion of

the reaction. The brown mixture was then purified by flash chromatography on silica gel to give product **8h** (137 mg) as a white solid in 92% yield. The proton NMR showed that **8h** is a mixture of the ketone form (**8h**) and the enolate form (**8h′**) in a ratio of 4:1 in $CDCl_3$ (Fig. 1). ^1H NMR of the ketone form: ($CDCl_3$, 500 MHz) δ 7.85 (2H, m), 7.22 (2H, m), 4.55 (2H, s), 4.08 (2H, s), 2.29 (3H, s). ^1H NMR of the enolate form: ($CDCl_3$, 500 MHz) δ 7.85 (2H, m), 7.22 (2H, m), 5.49 (1H, s), 4.52 (2H, s), 2.08 (3H, s). ^{13}C NMR of the mixture of both the ketone and the enolate form ($CDCl_3$, 125 MHz) δ 198.3, 176.4, 174.3, 171.7, 167.2, 165.2, 161.4, 158.7, 133.5, 131.65, 131.58, 116.77, 116.59, 83.31, 53.37, 53.1, 41.3, 29.9, 21.4.

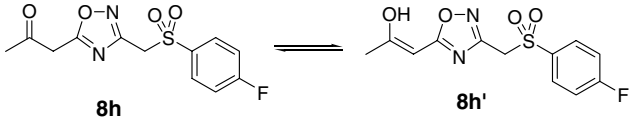


Figure 1.
The spectroscopic data of other oxadiazole products are consistent with their structures.