Pergamon

Tetrahedron Letters 39 (1998) 3931–3934

TETRAHEDRON LETTERS

Novel Synthesis of Oxadiazoles *via* Palladium Catalysis

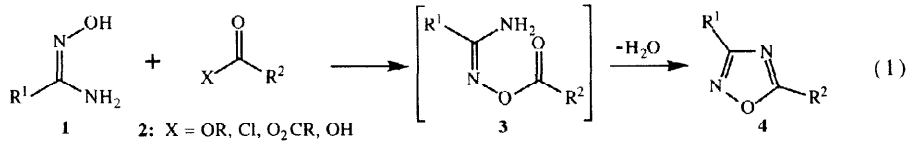
Jonathan R. Young* and Robert J. DeVita

Department of Medicinal Chemistry
Merck Research Laboratories
P.O. Box 2000, Rahway, NJ 07065

Received 27 February 1998; accepted 19 March 1998

Abstract: *Oxadiazoles have been prepared in a one-pot procedure by the palladium-mediated coupling of aryliodides with amidoximes under one atmosphere of carbon monoxide. This reaction proved applicable to both electron-rich and deficient aryliodides.* © 1998 Elsevier Science Ltd. All rights reserved.

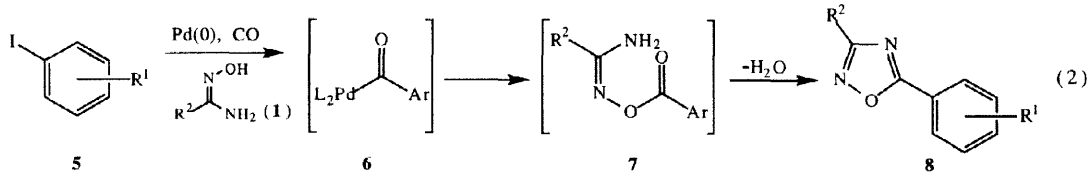
Oxadiazoles have often been described as bioisosteres for amides and esters.[1] Due to the increased hydrolytic[2] and metabolic stability of the oxadiazole ring, improved pharmacokinetic and *in vivo* performance is often observed, which make this heterocycle an important structural motif to the pharmaceutical industry. As a consequence of these characteristics, oxadiazoles have impacted numerous drug discovery programs, including muscarinic agonists,[3a] benzodiazepine receptor partial agonists,[3b] dopamine transporters,[3c] antirhinovirals,[3d] growth hormone secretagogues,[3e] and 5-HT agonists.[3f] Several methods are available for the preparation of oxadiazoles (**4**, eq. 1).[2] In general, amidoxime **1** is reacted with a suitably activated acid derivative **2** (for example, an ester,[3f,4] acid chloride,[5] anhydride,[6] or orthoester[7]) and heated at 90-100 °C, wherein *O*-acylation is accompanied by a rapid intramolecular cyclo-dehydration.[8] More recently, researchers from these laboratories have described the coupling of amidoximes to carboxylic acids mediated by EDC and DMAP.[9] This mild procedure was amenable to acid labile substrates.



1 2: X = OR, Cl, O_2CR, OH 3 4 (1)

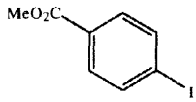
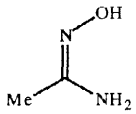
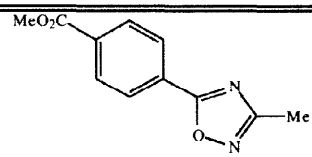
In the course of a recent medicinal chemistry effort, we had prepared numerous benzamide analogs using Heck's aminocarbonylation methodology from the corresponding aryliodides.[10] Although quite potent, this series suffered from a lack of oral absorption and high plasma clearance rates in the rat. This pharmacokinetic profile directed us to consider oxadiazoles as amide replacements. With substantial quantities of the aryl iodide on hand, we sought a direct method to access oxadiazoles from the available materials. We rationalized that an acyl-palladium complex **6** (eq. 2), generated from an aryliodide/Pd(0)/CO (1 atm), would be sufficiently activated to react with **1**. If successful, we anticipated that *O*-acyl complex **7** would undergo cyclodehydration to form **8** under the reaction conditions. This report describes the successful one-pot transformation of aryliodides to oxadiazoles under palladium catalysis.

PII: S0040-4039(98)00719-9



5 6 7 8

Table 1

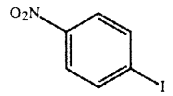
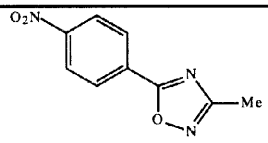
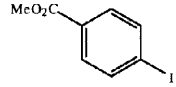
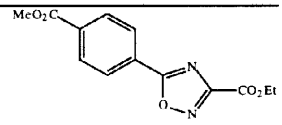
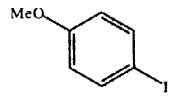
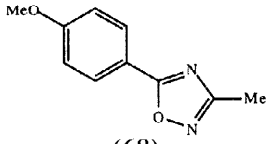
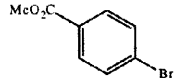
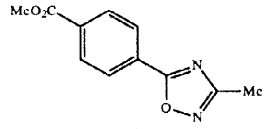
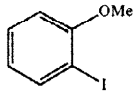
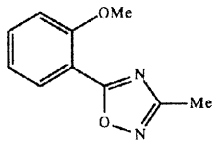
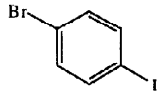
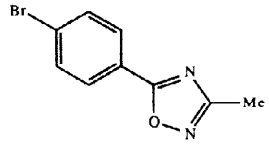
	Arylhalide (**5**)[a]	Amidoxime (**1**)	Palladium Salt[b]	Base/Solvent	Time (hr)/ Temp (°C)	Product (**8**)[c] % Yield
1		 (3.0 equiv)	$Cl_2Pd(Ph_3P)_2$	TEA (2.0 equiv)/ DMF	15/95	 29[d]
2	"	"	"	TEA (2.0 equiv)/ NMP	"	25
3	"	"	"	TEA (2.0 equiv)/ toluene	"	70
4	"	"	"	"	30/95	69
5	"	"	"	"	15/112	71
6	"	(1.5 equiv)	"	"	15/95	70
7	"	(6.0 equiv)	"	"	"	64[e]
8	"	(3.0 equiv)	$(Ph_3P)_4Pd$	"	"	69
9	"	"	$Cl_2Pd(dppf)$	"	"	69
10	"	"	$Cl_2Pd(dppe)$	"	"	8[f]

[a]All reactions were performed on a 1 mmol scale. [b]All reactions used 0.05 equiv of the palladium salt. [c]All products gave satisfactory ^1H NMR and mass spectra. [d]The major product (55% yield) was identified as 4-carbomethoxy-1-*N*,*N*-dimethylbenzamide. [e]A minor constituent (4% yield) was identified as the symmetrical bis-oxadiazole. [f]The balance of material was the starting aryliodide.

We began our investigation by attempting to couple methylamidoxime with methyl 4-iodobenzoate (Table 1, entry 1). Our starting point utilized a protocol similar to the aminocarbonylation reaction.[11] We were pleased to witness that these conditions did in fact provide the oxadiazole, albeit in modest yield. The major product, the corresponding *N*,*N*-dimethylbenzamide, resulted presumably from the capture of the acyl-palladium intermediate with exogenous dimethylamine, formed by the thermal decomposition of DMF. In order to suppress this side reaction, we conducted the above reaction in several alternative solvents. *N*-methylpyrolidinone (NMP) is typically a good alternative to DMF but did not improve the yield (entry 2). A beneficial effect was noted with toluene (70% yield, entry 3), although the balance of material could not be accounted for. We initially speculated that incomplete dehydration of intermediate **7** may have accounted for the remaining mass, yet increased reaction time (entry 4) or temperature (entry 5) yielded the same result. In the case of a valuable amidoxime, it is worth noting that 1.5 equiv of this component was sufficient without

compromising the yield (entry 6). Next, we increased the equivalents of **1** (entry 7) in order to trap the acyl-palladium intermediate **6** with greater efficiency. However, this change led to the consumption of **8** by the thermal reaction between the ester substituent and excess **1**, leading to the symmetrical bis-oxadiazole. We determined that $Pd(Ph_3P)_4$ and $Cl_2Pd(dppf)$ were as effective as $Cl_2Pd(Ph_3P)_2$ (entries 8 and 9, respectively), but the dppe ligand performed poorly (entry 10).

Table II[a]

	Arylhalide (**5**)	Amid-oxime (**1**) R^1	Product (**8**) % Yield		Arylhalide (**3**)	Amid-oxime (**1**) R^1	Product (**8**)[b] (% Yield)
1		Me	 (61)	4		CO_2Et	 (40)
2		Me	 (68)	5		Me	 (0)
3		Me	 (65)	6		Me	 (40)

[a]Arylhalide (1 mmol), amidoxime (3 equiv), and $Cl_2Pd(Ph_3P)_2$ (0.05 equiv) were combined in toluene (4 mL) and triethylamine (2 equiv) and heated to 95 °C under 1 atm CO for 15 hours. [b]All products gave satisfactory ^1H NMR and mass spectra.

The present reaction has been further extended to a broader range of substituted aryliodides and amidoximes (Table 2). Thus, 1-iodo-4-nitrobenzene (entry 1) was subjected to the optimal conditions described in Table 1 (entry 3), which yielded **8** in moderate yield. Methoxy substitution was well tolerated (entries 2 and 3), resulting in yields comparable to that observed for the ester substituent. This indicated that oxidative-addition was not adversely influenced by the electron-releasing substituent. The amidoxime derived from ethyl cyanoformate was found to be a suitable partner, providing the 3-carbethoxy-1,2,4-oxadiazole in moderate yield (entry 4). In contrast to aryliodides, arylbromides were found to be unreactive under these conditions, returning only starting material after prolonged heating (entry 5). This lack of reactivity provided an opportunity to probe whether selective functionalization could be realized. Gratifyingly, 4-iodo-1-bromobenzene did provide the oxadiazole resulting from exclusive oxidative-addition to the aryliodide bond (entry 6).

A novel one-pot method for the formation 3-alkyl-5-aryl-1,2,4-oxadiazoles has been established. Due to the neutral reaction conditions, application to more elaborate substrates should pose no difficulties.[12] Since aryliodides are readily converted to carboxylic acids,[13] the

reaction described herein complements existing literature methods and provides additional synthetic flexibility.

Acknowledgment. The authors would like to kindly thank Amy M. Bernick for mass spectral support.

References

1. (a) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoregh, I. Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112, and references cited therein. (b) Andersen, K.E.; Jorgensen, A.S.; Braestrup, C. *Eur. J. Med. Chem.* **1994**, *29*, 393. For examples of improved in vivo properties, see references 2-5 therein.
2. Clapp, L.B. *Adv. Heterocycl. Chem.* **1976**, 65.
3. (a) Orlek, B.S.; Blaney, F.E.; Brown, F.; Clark, M.S.G.; Hadley, M.S.; Hatcher, J.; Riley, G.J.; Rosenberg, H.E.; Wadsworth, H.J.; Wyman, P.; *J. Med. Chem.* **1991**, *34*, 2726. (b) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C.J.; Wong, E.; Springer, J.P. *J. Med. Chem.* **1989**, *32*, 2282. (c) Carroll, F.I.; Gray, J.L.; Abrahm, P.; Kuzemko, M.A.; Lewin, A.H.; Boja, J.W.; Kuhar, M.J. *J. Med. Chem.* **1993**, *36*, 2886. (d) 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. (e) Ankersen, M.; Peschke, B.; Hansen, B.S.; Hansen, T.K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1293. (f) Chen, C.; Senanayake, C.H.; Bill, T.J.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *J. Org. Chem.* **1994**, *59*, 3738.
4. (a) LaMattina, J.L.; Mularski, C. *J. Org. Chem.* **1984**, *49*, 4800. (b) Steglich, W.; vanRee, T. *Synth. Commun.* **1982**, *12*, 457.
5. (a) Chiou, S.; Shine, H.J. *J. Heterocycl. Chem.* **1989**, *26*, 125. (b) Tiemann, F.; Kruger, P. *Chem. Ber.* **1884**, *17*, 1685.
6. Claisse, J.A.; Foxton, M.W.; Gregory, G.I.; Sheppard, A.H.; Tiley, E.P.; Warburton, W.K.; Wilson, M.J. *J. Chem. Soc. Perkin I* **1973**, 2241.
7. Kim, C-K.; Zielinski, P.A.; Maggiulli, C.A. *J. Org. Chem.* **1984**, *49*, 5247.
8. For a description of the mechanism, see: Ooi, N.S.; Wilson, D.S. *J. Chem. Soc. Perkin II* **1980**, 1792.
9. Liang, G.B.; Feng, D.D. *Tetrahedron Lett.* **1996**, *37*, 6627.
10. Schoenberg, A.; Heck, R.F. *J. Org. Chem.* **1974**, *39*, 3327.
11. In a typical experiment (Table 1, entry 3), methyl 4-iodobenzoate (262 mg, 1 mmol), methylamidoxime (225 mg, 3.0 mmol) and $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol) were taken up in toluene-TEA (4 mL/0.28 mL). The flask, equipped with a carbon monoxide (CO) balloon, was evacuated and purged with CO several times followed by heating to 95 °C for fifteen hours under 1 atm of CO. After cooling, the reaction mixture was filtered through celite and partitioned between ethyl acetate and (1:1) H_2O-brine. After layer separation, the aqueous phase was extracted with ethyl acetate several times and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a gradient elution (5 to 10% EtOAc/hexane) to give 153 mg (70% yield) of the oxadiazole: ^1H NMR (300 MHz, $CDCl_3$) 2.50 (s, 3H), 3.97 (s, 3H), 8.15-8.25 (m, 4H); EIMS *m/z*: 218, 187, 162, 130, 102.
12. An aryliodide, possessing an *N*-BOC protected piperidine, was subjected to the optimized conditions which provided the oxadiazole in 65% yield with no evidence of BOC-deprotection: Young, J.R. unpublished results.
13. Cacchi, S.; Lupi, A. *Tetrahedron Lett.* **1992**, *33*, 3939.