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Tetrahedron Letters 44 (2003) 8697–8700

TETRAHEDRON LETTERS

Environmentally friendly and efficient: iron-mediated reduction of 3-methyl-5-aryl-1,2,4-oxadiazoles to benzamidines

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Received 21 August 2003; accepted 17 September 2003

Abstract—A new synthetic method is described for the mild and selective reduction of 3-methyl-5-aryl-1,2,4-oxadiazoles to amidines employing iron powder in aqueous medium. Its application is demonstrated in the synthesis of **1**, a potent and selective urokinase-type plasminogen activator (uPA) inhibitor.

Trypsin-like serine proteases, which include trypsin, tryptase, factor Xa, factor VIIa, thrombin, urokinase-type plasminogen activator (uPA), and tissue-type plasminogen activator (tPA), are involved or implicated in disease states. Most known inhibitors of these enzymes bear an amidino group as a basic group, which helps to produce high binding affinity with the proteases due to its interaction with Asp189 in the S1 specificity pocket.[1]

As part of a program to develop highly potent and selective uPA inhibitors, we have prepared a variety of novel benzamidine-based inhibitors.[2] A number of different methods for the preparation of amidines are reported.[3]

Existing routes to benzamidines from benzonitriles include conversion via amination of imidates (Pinner reaction)[4] or thioimidates,[5] addition of aluminium amide to nitriles,[6] reduction of amidoximes,[7] and reduction of 1,2,4-oxadiazoles.[8]

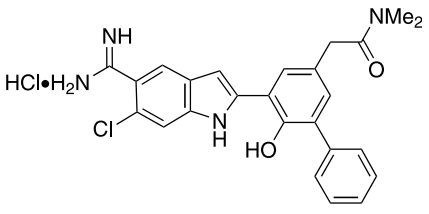

Figure 1. Selective uPA-inhibitor **1**.

We required that a suitable masked amidino group was introduced early in the synthetic sequence in order to provide the most efficient entry to a variety of differently functionalized analogues.[9] The 3-methyl-1,2,4-oxadiazole was chosen for the protection of the amidino group.

3-Methyl-5-aryl-1,2,4-oxadiazoles are stable to a variety of reaction conditions and can easily be isolated and purified by crystallization or silica gel chromatography. Their use as masked protected amidines is diminished somewhat by difficulties involved in unmasking the amidine. Reduction using Raney-Ni or Pd/C under H_2 atmosphere has been described in the literature.[7a] While these methods are very effective and efficient, they suffer from the disadvantage of involving reagents that are highly reactive, toxic, or expensive, and do not tolerate many other functionalities such as chlorine or benzyl protecting groups.

Amidine **1** is a highly potent and selective uPA-inhibitor identified at Celera (Fig. 1).[2b] The corresponding *des*-chloro analogue retains its potency but loses its selectivity.[10] In the process of synthesizing larger amounts of **1** (>5 g), reduction of the oxadiazole was carried out initially using Raney-Ni or Pd/C. This led to a high level of dechlorination and resulted in a significant amount of the nonselective uPA inhibitor (6% and 4%, respectively). Its removal—as well as the removal of Ni^{2+}-ions—and purification of **1** required several recrystallization steps, causing further loss of material.

In this report we describe our studies in the mild and chemoselective reduction of 3-methyl-5-aryl-1,2,4-oxa-

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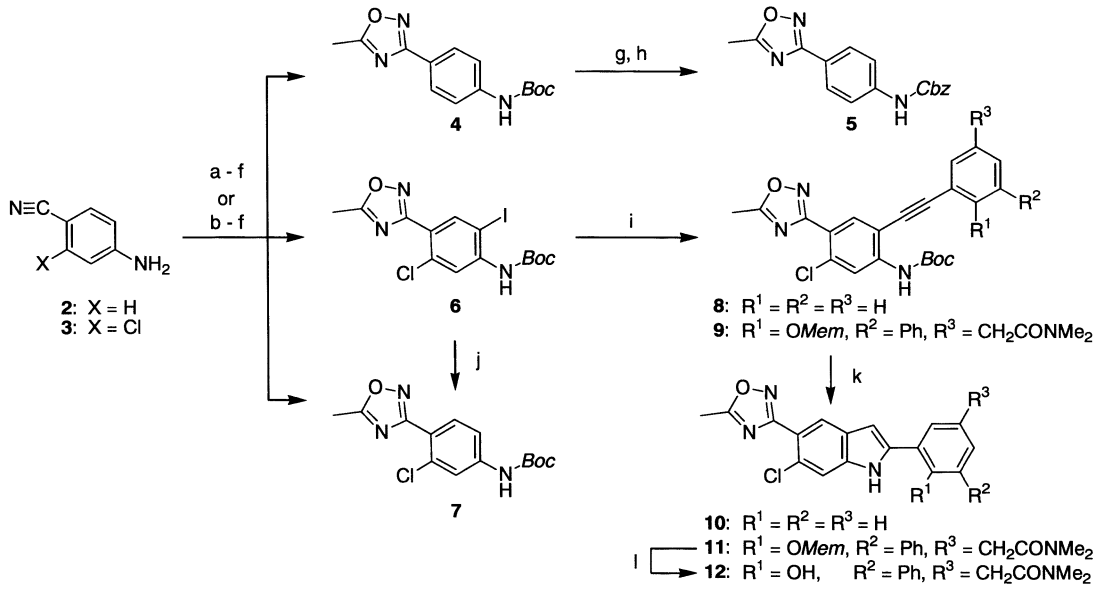
0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.09.139



Scheme 1. *Reagents and conditions*: (a) 1 equiv. NIS, AcOH, 48%; (b) 2.2 equiv. Boc_2O, cat. DMAP, THF; (c) 50 wt% aq. NaOH, THF/EtOH (1/1), 90% over 2 steps; (d) 50 wt% aq. NH_2OH, EtOH, reflux, 1.5 h; (e) AcCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C; (f) Bu_4NF, THF; >95% over 3 steps; (g) TFA, 95%; (h) CbzCl, THF, NEt_3, 83%; (i) cat. $Pd(PPh_3)_2Cl_2$, H-≡-Ar, NEt_3, cat. $Cu^{(I)}I$, DMF, 72%; (j) 20 equiv. Zn, AcOH, quant.; (k) 40 wt% aq. Bu_4NOH, THF, reflux, 89%; (l) for **11**: 4 M HCl/dioxane, MeOH, quant.

diazoles to benzamidines using iron powder in aqueous solution and its application to the preparation of uPA-inhibitor **1**.[11]

Scheme 1 outlines the chemistry employed to prepare the oxadiazoles **4**, **5**, **7**, **8**, **10**, and **12**. Amino benzonitriles **2** and **3** were mono-Boc protected via their bis-Boc intermediates through treatment with Boc-anhydride followed by sodium hydroxide solution. Conversion of the nitrile to the oxadiazole was achieved using reported procedures providing **4** and **7**.[12] Similarly, oxadiazole **6** was prepared from benzonitrile **2** after initial iodination with *N*-iodosuccinimide. Biaryl compounds **8** and **9** were synthesized through Sonogashira coupling of Boc-aniline **6** with the appropriate arylacetylenes.[13,14] Following treatment of these with aqueous tetrabutylammonium hydroxide solution, cyclisation and concomitant Boc-deprotection provided indoles **10** and **11**. Oxadiazole **12**, the direct precursor of the uPA-inhibitor **1**, was obtained by Mem-deprotection of **11** with 2M HCl in dioxane/methanol.

In initial experiments, oxadiazole **7** was chosen as a test system. Table 1 summarizes the reaction conditions we examined for the reductive transformation of oxadiazole **7** to 2-chloro-benzamidine **7a**. We found that the reduction with iron powder[15] takes place in acetic acid (entry 1). Dilution with water reduces the reaction time but also lowers the solubility of the oxadiazole in acetic acid (entry 2). Addition of methanol homogenized the reaction solution but slowed the reaction noticeably (entries 3 and 4). Reaction times were significantly reduced when the amount of reducing reagent was increased (entry 9). The same effect was observed by increasing the reaction temperature from room temperature to 40°C (entry 8). Further temperature increase led to a partial loss of the acid labile Boc-group. Both acetic acid and formic acid can be used as proton source (entries 10 to 12). Des-chloro-**7a** could not be detected in any of the reactions. A variety of different solvents were investigated (entries 13 to 23). It should be noted that the addition of a homogenizing solvent is essential for the reduction of oxadiazoles with limited solubility such as **8**, **10**, and **12** (Table 2). Alcohols such as methanol, ethanol, and *iso*-propanol in two-phase systems worked as good as chlorinated solvents such as dichloromethane and chloroform in three-phase systems (entries 19 and 20).

To extend the utility of the iron-mediated reduction, additional oxadiazoles bearing functional groups sensitive to hydrogenation were also investigated. Thus, **5** was prepared from **3** via a protecting group switch from Boc to Cbz. The reactions were carried out with 10–20 equivalents of iron powder in methanol: acetic acid: water (1:1:~1) at 40 to 50°C. A closed apparatus with pressure equalization was used to avoid air-oxidation of generated Fe^{2+} to Fe^{3+}, which can complicate the isolation of the product by forming $Fe^{2+/3+}$-hydrates. Progression of the reactions was monitored with analytical HPLC. The products were isolated by filtration over C_{18} or by crystallization. Table 2 shows that yields of >89% were obtained and that a number of functional groups tolerated the reductive conditions, including: aryl chlorides, acetylene and the Cbz-group.

General procedure: Oxadiazole **12** (4.87 g 10 mmol) was suspended in MeOH/AcOH/H_2O (90 mL/90 mL/90 mL). Iron powder (5.58 g, 100 mmol) was added and the reaction mixture was vigorously stirred and heated at 50°C for 5 h giving a clear light yellow solution.[16] The reaction was cooled to room temperature and the

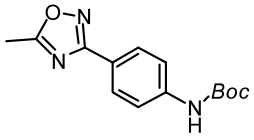
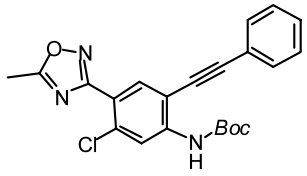
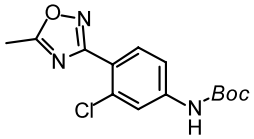
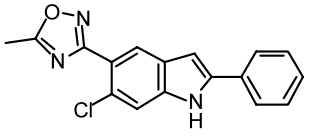
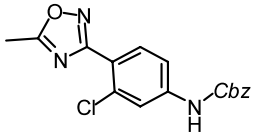
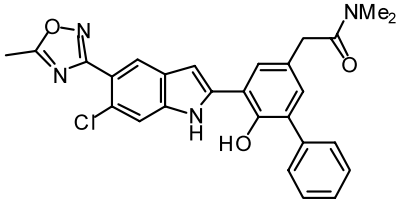
Table 1. Optimization conditions for the iron-mediated reduction of **7** to **7a**[a]

Entry	Conditions					Conversion (%)[b]	
	Fe (equiv.)	Acid (1 mL)	H_2O (mL)	Solvent	Temp.	5 h	20 h
1	20	AcOH	0	–	rt	13	81
2	20	AcOH	1	–	rt	48	100
3	20	AcOH	0	1 mL MeOH	rt	16	59
4	20	AcOH	1	0.5 mL MeOH	rt	41	100
5	20	AcOH	1	1 mL MeOH	rt	31	88
6	20	AcOH	1	2 mL MeOH	rt	32	83
7	10	AcOH	1	1 mL MeOH	rt	14	67
8	10	AcOH	1	1 mL MeOH	40°C	100	[c]
9	30	AcOH	1	1 mL MeOH	rt	47	100
10	20	HCOOH	1	1 mL MeOH	rt	42	84
11	20	HCOOH	1	1 mL CH_2Cl_2	rt	55	100
12	20	HCOOH	1	–	rt	55	89
13	20	AcOH	1	1 mL EtOH	rt	21	87
14	20	AcOH	1	1 mL *i*-PrOH	rt	27	72
15	20	AcOH	1	1 mL acetone	rt	24	84
16	20	AcOH	1	1 mL EtOAc	rt	19	79
17	20	AcOH	1	1 mL THF	rt	14	46
18	20	AcOH	1	1 mL dioxane	rt	14	48
19	20	AcOH	1	1 mL CH_2Cl_2	rt	35	100
20	20	AcOH	1	1 mL $CHCl_3$	rt	24	81
21	20	AcOH	1	1 mL AcCN	rt	28	79
22	20	AcOH	1	1 mL DMSO	rt	14	51
23	20	AcOH	1	1 mL DMF	rt	20	52

[a] The reactions were carried out in a 0.2 mmol scale.
[b] Determined by analytical HPLC.
[c] Partial loss of Boc-group.

elemental iron was removed. 1 M HCl (~100 mL) was added until the solution became light yellow. The solution was extracted with diethylether (5×) giving a white precipitate in the aqueous layer. The aqueous phase was concentrated to half of its volume and the precipitate was filtered and washed with 1 M HCl. The white solid was dissolved in a minimum amount of hot ethanol and precipitated by the slow addition of 1 M HCl

Table 2. Examples for iron-mediated reduction

	Oxadiazole	Amidine[a]	Isolated yield		Oxadiazole	Amidine[a]	Isolated yield
4		**4a**	90%	**8**		**8a**	89%
7		**7a**	96%	**10**		**10a**	93%
5		**5a**	92%	**12**		**1**	92%[b]

[a] Isolated as its HCl salt.
[b] Isolated by recrystallization.

and cooling to room temperature. The precipitate was filtered and the dissolving–precipitation process repeated. The solid was dried in vacuo to afford the hydrochloride salt of **1** (4.46 g, 9.23 mmol, 92%)[17] as a white solid with a purity of >99%. The iron content was determined to be 33 ppm (Robertson Microlit Laboratories, Inc.). Alternatively, the aqueous layer was lyophilized, dissolved in a small amount of acetonitrile/1 M HCl, filtered through a short plug of C_{18} to remove iron salts and re-lyophilized to provide pure amidine hydrochloride salt.

In conclusion, we have described a new synthetic method for the chemoselective reduction of 5-aryl-1,2,4-oxadiazoles to benzamidines employing iron powder in acidic aqueous solution. The conditions are sufficiently mild to be compatible with functional groups such as chlorine, benzyl ether, and alkynes. The method was successfully applied in the synthesis of the potent and selective uPA-inhibitor **1**.

Acknowledgements

We would like to thank Dr R. L. Mackman for helpful discussions and Dr. K. E. Wesson for the review of this manuscript.

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14. (a) The alkyne, which is required for the synthesis of **11**, with $R^1 = OMem$, $R^2 = Ph$, $R^3 = CH_2CONMe_2$ was prepared from methyl *p*-hydroxyphenyl acetate in 7 steps; (b) See also: Young. W. B.; Kolesnikov, A.; Rai, R.; Sprengeler, P. A.; Leahy, E. M.; Shrader, W. D.; Sanalang, J.; Burgess-Henry, J.; Spencer, J. R.; Elrod, K.; Cregar, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2253–2256.
15. Iron, powder, −325 mesh, 97%; commercially available from Acros Organics.
16. Heating the reaction mixture for 3 days at 50–55°C does not initiate the formation of byproducts.
17. **12**: ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.68 (s, 1H), 7.57–7.33 (m, 7H), 7.11 (d, 1H, $J = 2.0$ Hz), 7.04 (d, 1H, $J = 0.7$ Hz), 3.71 (s, 2H), 3.06 (s, 3H), 2.84 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (68 MHz, DMSO-d_6) δ 176.2, 170.4, 149.2, 138.3, 138.1, 137.6, 131.6, 131.3, 129.3, 128.3, 127.1, 127.0, 124.1, 123.2, 121.5, 116.4, 113.0, 101.8, 37.2, 35.0, 11.9; MS ESI (m/z) 487 (MH^+). HPLC (Polaris 5μ 50×2.0 mm; 2–95% in 5 min with 1 mL/min, MeCN/H_2O, 0.05% TFA), retention time: 3.97 min, purity >99%. **1**: ^{1}H NMR (270 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.34 (s, 2H), 9.21 (s, 2H), 8.94 (s, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 7.58 (s, 1H), 7.53–7.32 (m, 5H), 7.07 (s, 2H), 3.68 (s, 2H), 3.04 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (68 MHz, DMSO-d_6) δ 185.0, 153.6, 136.9, 126.2, 125.9, 125.5, 119.4, 119.1, 116.9, 116.1, 116.0, 114.8, 114.1, 109.8, 109.4, 108.9, 107.8, 100.0, 89.39, 24.87, 22.69. MS ESI (m/z) 447 (MH^+). HPLC (Polaris 5μ 50×2.0 mm; 2–95% in 5 min with 1 mL/min, MeCN/H_2O, 0.05% TFA), retention time: 3.02 min, purity >99%. Anal. ($C_{25}H_{23}ClN_4O_2$–HCl), C, H, N, Cl. Fe detection (Robertson Microlit Laboratories, Inc.) = 33 ppm.