An efficient route towards the synthesis of monosubstituted *N*-aryl amidines from 4,5-dihydro-1,2,4-oxadiazoles

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Abstract

4,5-Dihydro-1,2,4-oxadiazoles were prepared using 1,3-dipolar cycloaddition of imines with nitrile oxides. Further reductive N-O bond cleavage furnished monosubstituted *N*-aryl amidines in good yield. Thus an efficient route for the synthesis of monosubstituted *N*-aryl amidines has been developed.

Keywords: *N*-aryl amidines, 4,5-dihydro-1,2,4-oxadiazoles, hydrogenolysis, Nitrile oxides, 1,3-dipolar cycloaddition reaction

Introduction

N-Aryl amidines are important synthons for the synthesis of several heterocyclic compounds.¹ These compounds show a wide spectrum of biological activity like antibacterial, antimicrobial, anticancer and antiviral activity.² As substituted amidines have significance in several biologically active compounds, their synthesis has been of interest for several research groups.³ Amongst the reported synthetic strategies, nucleophilic addition of amine to nitrile is one of the important methods. Various Lewis acids like trivalent lanthanide triflates,^{3e} SmI₂,^{3f} CuCl,^{3g} etc. have been used as catalysts. The development of catalytic addition of amines to nitriles is still a challenge in monosubstituted amidine synthesis. Some other methods for the synthesis of monosubstituted amidines are reaction of nitrile and azide catalyzed by Sm^{3h} and reaction of nitrile and azo compound catalyzed by SmI₂.³¹ Considering the need of a good route towards the synthesis of monosubstituted amidines, it was planned to use the N-O bond cleavage reaction of 4,5-dihydro-1,2,4-oxadiazoles for this purpose.

Results and Discussion

1,3-Dipolar cycloaddition reactions have been used in our laboratory for the synthesis of various isoxazolidines⁴ and 2-isoxazolines.⁵ Similarly, preparation of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides and imines has already been reported.⁶ Bolton et al⁷ reported a route to mono-substituted amidines via cleavage of N-O bond of 1,2,4-oxadiazolin-5-ones under catalytic hydrogenation conditions.

Keeping above reported reactions in view, we envisaged that the N-O bond cleavage in 5aryl-4,5-dihydro-1,2,4-oxadiazoles might lead to the formation of either *N*-(hydroxy(aryl)methyl)-*N*-arylbenzamides **27** produced by hydrolysis of a first-formed imine or *N*-aryl amidines (Scheme 1). We herein report the formation of monosubstituted *N*-aryl amidines during the reductive N-O bond cleavage of 4,5-dihydro-1,2,4-oxadiazoles.

The aromatic imines **5-9** were prepared following a reported procedure.⁸ 4,5-Dihydro-1,2,4oxadiazoles were synthesized using 1,3-dipolar cycloaddition reaction. Thus benzaldehyde oxime **1** was converted into the corresponding benzohydroximoyl chloride with NCS. Treatment of the mixture of benzohydroximoyl chloride and imine **5** with triethylamine at 0 °C afforded the expected 4,5-dihydro-1,2,4-oxadiazole **10** in 65% yield. Similarly, other 4,5-dihydro-1,2,4oxadiazoles **11-19** were prepared in good yields (Table 1).

In a model study on the hydrogenolysis, oxadiazole **10** with Raney nickel in methanol at room temperature was exposed to hydrogen gas (balloon pressure) to afford a single product. The product was purified by column chromatography and its structure was assigned as substituted amidine **20** from its NMR spectral data and by analogy with the hydrogenation reaction reported earlier.⁷ The probable mechanism of formation of **20** can be explained by the reductive cleavage of N-O bond to *N*-(hydroxy(aryl)methyl)benzamidine with hydrogenolysis of benzylic alcohol to furnish amidine **20** (Scheme 2).



a. NCS, DCM, r.t., 2 h ; b. NEt₃, DCM, 0°C-r.t., 1 h ; c. Raney nickel, H₂, MeOH, r.t., balloon pressure, 2-3 h

Compound No.	Ar	Ar'	Ar''
1	Ph	-	-
2	4-MeOC ₆ H ₄	-	-
3	$4-ClC_6H_4$	-	-
4	3,4- MeOC ₆ H ₄	-	-
5	Н	Ph	Ph
6	Н	4-MeOC ₆ H ₄	Ph
7	Н	3,4-MeOC ₆ H ₄	Ph
8	Н	$4-NO_2C_6H_4$	Ph
9	Н	$4-NO_2C_6H_4$	$4-MeOC_6H_4$
10	Ph	Ph	Ph
11	Ph	3,4-MeOC ₆ H ₄	Ph
12	Ph	$4-NO_2C_6H_4$	Ph
13	4-MeOC ₆ H ₄	$4-MeOC_6H_4$	Ph
14	4-MeOC ₆ H ₄	$4-NO_2C_6H_4$	Ph
15	$4-C1C_6H_4$	$4-NO_2C_6H_4$	Ph
16	3,4- MeOC ₆ H ₄	$4-NO_2C_6H_4$	Ph
17	$3,4-MeOC_6H_4$	$4-NO_2C_6H_4$	$4-MeOC_6H_4$
18	4-MeOC ₆ H ₄	$4-NO_2C_6H_4$	$4-MeOC_6H_4$
19	$4-ClC_6H_4$	$4-NO_2C_6H_4$	$4-MeOC_6H_4$
20	Ph	-	Ph
21	$4-MeOC_6H_4$	-	Ph
22	3,4- MeOC ₆ H ₄	-	Ph
23	$4-ClC_6H_4$	-	$4-MeOC_6H_4$
24	$4-MeOC_6H_4$	-	$4-MeOC_6H_4$
25	3,4-MeOC ₆ H ₄	-	$4-MeOC_6H_4$
26	$4-ClC_6H_4$	-	Ph

Scheme 1

Oxime	Imine	Oxadiazole	Mp (°C) of Oxadiazole	Yield (%)
1	5	10	76-77 (lit. ⁹ 75-76)	65
1	7	11	64-65 (lit. ¹⁰ 65)	69
1	8	12	149-151(lit. ¹¹ 148-150)	75
2	6	13	115-117	58
2	8	14	132-134	63
3	8	15	114-115	65
4	8	16	150-152	59
4	9	17	177-178	65
1	9	18	Oily liquid	59
3	9	19	130-131	66

Table 1. Synthesis of 1,2,4-oxadiazoles from oxime and imine via 1,3-dipolar cycloaddition

To see the scope and generality of the above reaction, several other 4,5-dihydro-1,2,4oxadiazoles **11-19** were subjected to hydrogenolysis reaction. In all the cases the expected amidines **21-26** were obtained in 74-91% yields (Table 2). Thus, it constitutes a practical and simple method for the synthesis of substituted amidines.



Scheme 2

Table 2. Hydrogenolysis of oxadiazoles to amidines using Raney nickel/hydrogen

Entry	Oxadiazole	Amidine	Mp (°C) of Amidine	Yield (%)
1	10	20	116-118 (lit. ¹² 115-117)	89
2	11	21	137-138 (lit. ¹³ 138-139)	91
3	12	22	137-138 (lit. ¹⁴ 138-140)	85
4	13	23	138-139	88

Entry	Oxadiazole	Amidine	Mp (oC) of Amidine	Yield (%)
5	14	24	148-149 (lit. ¹³ 150)	82
6	15	25	Oily liquid	74
7	16	26	130-131	83

Table 2. Continued

Conclusions

Thus, a new route for the synthesis of monosubstituted amidines, which are otherwise difficult to prepare, has been developed via hydrogenolysis of 4,5-dihydro-1,2,4-oxadiazoles. The present route is straight forward and does not yield any side product. Therefore it is a useful alternative to the existing methodologies for the synthesis of *N*-aryl amidines.

Experimental Section

General. Melting points determined are uncorrected. All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin layer chromatography (TLC) on silica gel (Kieselgel 60 F254, Merck). Column chromatographic purifications were performed using 100-200 mesh silica gel. IR spectra were recorded on Shimadzu 8400 instrument. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on Varian Mercury instrument using TMS as internal standard. ¹H NMR peaks expressed as s, bs, d, t, m correspond to singlet, broad-singlet, doublet, triplet, and multiplet, respectively. Mass spectra were recorded on Shimadzu QP 5050. Elemental analysis was recorded on Flash E. A. 1112 Thermo instrument.

General procedure for the synthesis of 4,5-dihydro-1,2,4-oxadiazoles

In a 100 mL round bottom flask equipped with a guard tube, a solution of benzohydroximoyl chloride (1mmol) in DCM (3 mL) was placed. To this, a solution of triethylamine (1.2mmol) was added dropwise with vigorous stirring. During the addition, the reaction mixture became thick. To this thick reaction mixture, the imine (1mmol) was added. Stirring was continued for 1 h and reaction was monitored by TLC. When the starting material was entirely consumed, water (3 mL) was added to the reaction. The reaction mixture was extracted with DCM. The organic layer was washed with water and dried over sodium sulphate. The crude mixture obtained was purified by column chromatography on silica gel, where hexane-ethyl acetate (9:1) was used as an eluent. **Compound 13.** Yield 58%; mp 115-117 °C; IR(KBr): v 1604, 1231 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.80 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.47 (s, 1H, NCH), 6.81 (m, 4H, ArH), 6.95 (d, J = 8.4 Hz, 2H, ArH), 7.08-7.19 (m, 3H, ArH), 7.51 (m, 4H, ArH); ¹³C NMR (75 MHz,

CDCl₃): δ 55.29, 99.86, 114.02, 114.09, 117.55, 124.17, 125.35, 128.61, 129.07, 129.54, 131.13, 141.19, 149.85, 154.80, 160.63, 161.19; *m*/*z*: 360 (M⁺); Anal. Calcd for C₂₂H₂₀N₂O₃: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.27; H, 5.52; N, 7.73.

Compound 14. Yield 63%; mp 132-134 °C; IR(KBr): v 1602, 1517, 1218, 1346 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.80 (s, 3H, OC<u>H₃</u>), 6.57 (s, 1H, NC<u>H</u>), 6.84 (m, 3H, Ar<u>H</u>), 7.14-7.25 (m, 4H, Ar<u>H</u>), 7.54 (d, *J* = 7.3 Hz, 2H, Ar<u>H</u>), 7.79 (d, *J* = 7.3 Hz, 2H, Ar<u>H</u>), 8.30 (d, *J* = 7.3 Hz, 2H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 55.28, 98.48, 114.47, 116.67, 124.03, 124.21, 124.67, 126.07, 127.96, 128.37, 129.44, 129.61, 141.18, 145.84, 148.62, 155.01, 161.51; *m/z*: 375 (M⁺); Anal. Calcd for C₂₁H₁₇N₃O₄: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.73; H, 6.65; N, 10.19.

Compound 15. Yield 65 %; mp 114-115 °C; IR(KBr): v 1621, 1562, 1349 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.55 (s, 1H, NC<u>H</u>), 6.78 (d, J = 8 Hz, 2H, Ar<u>H</u>), 7.11-7.27 (m, 5H, Ar<u>H</u>), 7.49 (d, J = 8 Hz, 2H, Ar<u>H</u>), 7.73 (d, J = 8 Hz, 2H, Ar<u>H</u>), 8.25 (d, J = 8 Hz, 2H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 98.95, 123.05, 124.00, 124.38, 126.48, 127.96, 129.01, 129.57, 130.38, 136.84, 140.55, 145.29, 148.62, 154.44; m/z: 379 (M⁺), 381 (M+2)⁺ in 3:1 ratio; Anal. Calcd for C₂₀H₁₄ClN₃O₃: C, 63.25; H, 3.72; N, 11.06. Found: C, 63.19; H, 3.77; N, 11.01.

Compound 16. Yield 59 %; mp 150-152 °C; IR(KBr): v 1624, 1559, 1255, 1362 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.78 (s, 3H, OC<u>H₃</u>), 3.86 (s, 3H, OC<u>H₃</u>), 6.88 (s, 1H, NC<u>H</u>), 6.58- 6.88 (m, 3H, Ar<u>H</u>), 7.07-7.28 (m, 5H, Ar<u>H</u>), 7.78-7.81 (m, 2H, Ar<u>H</u>), 8.28-8.31 (m, 2H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 55.76, 55.91, 98.60, 110.40, 110.70, 116.68, 121.46, 123.96, 124.42, 126.19, 127.59, 127.94, 129.04, 141.17, 145.67, 148.81, 151.02, 155.11; *m/z*: 405 (M⁺); Anal. Calcd for C₂₂H₁₉N₃O₅: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.25; H, 4.67; N, 10.33.

Compound 17. Yield 65 %; mp 177-178 °C; IR(KBr): v 1628, 1539, 1267, 1336 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.67 (s, 3H, OC<u>H₃</u>), 3.72 (s, 3H, OC<u>H₃</u>), 3.79 (s, 3H, OC<u>H₃</u>), 6.43 (s, 1H NC<u>H</u>), 6.68-6.71 (m, 3H, Ar<u>H</u>), 6.77-6.81 (m, 2H, Ar<u>H</u>), 6.99-7.01 (m, 1H, Ar<u>H</u>), 7.09 (d, J = 1.9 Hz, 1H, Ar<u>H</u>), 7.71 (d, J = 6.8 Hz, 2H, Ar<u>H</u>), 8.20-8.23 (m, 2H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 55.60, 56.05, 99.57, 110.84, 110.95, 114.99, 117.02, 121.75, 124.19, 127.46, 128.48, 133.95, 145.98, 149.00, 151.15, 156.03, 158.49; *m*/*z*: 435 (M⁺); Anal. Calcd for C₂₃H₂₁N₃O₆: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.38; H, 4.81; N, 9.58.

Compound 18. Yield 59 %; Oily liquid; IR(KBr): v 1625, 1534, 1245, 1323 cm⁻¹; H NMR (300 MHz, CDCl₃): δ 3.74 (s, 3H, OC<u>H₃</u>), 3.77 (s, 3H, OC<u>H₃</u>), 6.44 (s, 1H, NC<u>H</u>), 6.75-6.81 (m, 4H, ArH), 6.91 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 7.02-7.14 (m, 2H, Ar<u>H</u>), 7.46-7.50 (m, 4H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 55.57, 100.10, 114.32, 117.74, 124.39, 125.57, 128.51, 128.80, 129.27, 129.71, 131.26, 141.33, 154.93, 160.76, 161.33; *m/z*: 405 (M⁺); Anal. Calcd for C₁₅H₁₈N₂O₃ requires: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.23; H, 4.69; N, 10.34.

Compound 19. Yield 66 %; mp 130-131 °C; IR(KBr): v 1610, 1597, 1243, 1344 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.74 (s, 3H, OC<u>H</u>₃), 6.48 (s, 1H, NC<u>H</u>), 6.73-6.82 (m, 4H, Ar<u>H</u>), 7.28 (d, *J* = 8.2 Hz, 2H, Ar<u>H</u>), 7.49 (d, *J* = 8.2 Hz, 2H, Ar<u>H</u>), 7.75 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 8.29 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>); ¹³C NMR (75 MHz, CDCl₃): δ 55.36, 99.71, 114.90, 123.11, 124.00, 127.19, 128.22, 128.95, 129.26, 133.03, 136.75, 145.33, 155.19, 158.44; *m/z*: 409 (M⁺), 411 (M+2)⁺ in

3:1 ratio; Anal. Calcd for C₂₁H₁₆ClN₃O₄: C, 61.54; H, 3.94; N, 10.25. Found: C, 61.52 H, 3.89; N, 10.22.

General procedure for the synthesis of N-aryl amidines

To a solution of the 4,5-dihydro-1,2,4-oxadiazole (1mmol) in methanol (5 mL), Raney nickel (10 mol%) was added and the mixture was stirred (2-3 h) under hydrogen atmosphere using balloon at room temperature. The progress of the reaction was followed by TLC. After completion of reaction, the mixture was filtered through celite bed and the filtrate was concentrated on a rotavapor. The crude product was purified by column chromatography using hexane-ethyl acetate (1:1) as an eluent and recrystallized with methanol-water solvent system.

Compound 23. Yield 88 %; mp 138-139 °C; IR (KBr): v 3333, 1613, 1243 cm⁻¹; ¹H NMR (CDCl₃): δ 3.77 (s, 3H, OCH₃), 5.04 (bs, 2H, NH₂), 6.85 (bs, 4H, ArH), 7.33 (d, 2H, J = 8.2 Hz, ArH), 7.71 (d, 2H, J = 8.2 Hz, ArH); ¹³C NMR (75 MHz, CDCl₃, Fig. No. 10b): δ 55.33, 114.74, 122.47, 128.14, 128.48, 133.99, 136.37, 141.64, 154.65, 155.62; *m*/*z* 260 (M⁺), 262 (M⁺ + 2)⁺ in 3:1 ratio; Anal. Calcd for C₁₄H₁₃ClN₂O: C, 64.49; H, 5.03; N, 10.74. Found: C, 64.53; H, 5.07; N, 10.79.

Compound 25. Yield 74 %; Oily liquid; IR (neat): v 3387, 1614 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.16 (bs, 2H, NH₂), 4.02 (s, 9H, 3xOCH₃), 6.67-6.72 (m, 3H, ArH), 7.04 (d, 1H, J = 4.5 Hz, ArH), 7.18-7.29 (m, 3H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 55.29, 114.23, 114.83, 122.64, 128.23, 128.44, 128.76, 155.41, 161.32; m/z 286 (M⁺); Anal. Calcd for C₁₆H₁₈N₂O₃: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.07; H, 6.29; N, 9.83.

Compound 26. Yield 83 %; mp 130-131 °C; IR (neat): v 3308, 1616 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.78 (bs, 2H, NH₂), 6.92-7.01 (m, 3H, ArH), 7.31-7.40 (m, 4H, ArH), 7.91 (bs, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 120.72, 121.56, 127.20, 127.87, 128.43, 133.72, 134.83, 148.95, 153.09; *m*/*z* 230 (M⁺); Anal. Calcd for C₁₃H₁₁ClN₂ requires: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.62; H, 4.75; N, 12.09.

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