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A NEW PATHWAY FOR THE PREPARATION OF 3-SUBSTITUTED 1,2,4-OXADIAZEPINES BY INTRAMOLECULAR PALLADIUM CATALYZED CYCLIZATION OF (*E*)-O-(2-IODOPHENYLMETHYL) AMIDOXIMES

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ABSTRACT:
A simple synthesis of novel class of heterocyclic compounds - 3-substituted 1,2,4-oxadiazepines from corresponding (*E*)-O-(2-iodophenylmethyl)amidoximes in the system $Pd_2(dba)_3$/ Xantphos / solid Cs_2CO_3 / dioxane has been developed.

Keywords: Palladium catalyst, coupling, amidoximes, *o*-iodobenzyl bromide, phase transfer catalysis, 3-substituted 1,2,4-oxadiazepines

INTRODUCTION

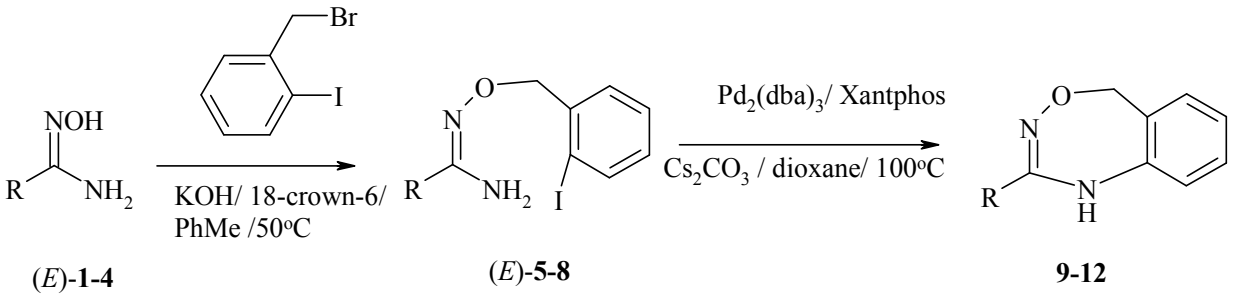
Seven-membered heterocyclic motifs are usually present in the wide range of biologically active molecules [1]. Wide range of recent chemical review literature was dedicated to synthesis and transformation of seven membered rings [2-6]. Among these works two chapters on the chemistry of seven-membered ring with three heteroatoms at the positions 1, 2 and 4 was published [6,7]. There is direct preparation of 3,5,7-trisubstituted 4,7-dihydro-1,2,4-oxadiazepines based on the two step method in the system MeONa / KOH / MeOH starting from enones among the methods described in literature.[8] Beside this intramolecular condensation of methyl 2-chloro-2-(phenylcarbamoylimidoylaminooxycyclopropyl)acetate in the presence of NaH in acetonitrile leading to 9-chloro-6-phenyl-5,7-diaza-4-oxaspiro[2,6]non-5-en-8-one was recently also presented.[9] However, there are no general methods for the synthesis of benzo fused 3-substituted 1,2,4-oxadiazepines.

RESULTS AND DISCUSSION

Herein we report a novel and simple palladium catalyzed method for the preparation of 3-substituted 1,2,4-oxadiazepines from corresponding amidoximes and *o*-iodobenzyl bromide. At first, synthesis of compounds **9-12** were carried out using two step methods. The first step included selective amidoxime **1-4** O-alkylation [10] in the phase transfer catalytic system *o*-iodobenzyl bromide/ solid KOH / 18-crown-6 / PhMe (Scheme 1, see Experimental Section). Unfortunately, that dialkylation of amidoxime **13** with *o*-iodobenzyl bromide in the presence of solid KOH / 18-crown-6 at 50°C leads to desired product **14** in low yield and selectivity. Therefore, solid KOH was substituted for solid K_2CO_3 in this case. O-Alkyl derivatives **5-8** and **14** were isolated by column chromatography in 14-63 % yields.

The second step of reaction step is Pd(0)-catalyzed cyclization of an intermediate (*E)*-O-(2-iodophenylmethyl)amidoximes **5-8**. The high activity of Pd-catalysts in N-arylation of amidoxime O-alkyl derivatives was demonstrated in article [11]. However, palladium catalyzed intramolecular cyclization of oxime O-ethers was not studied till now. Beside this some articles were dedicated to palladium catalyzed N-arylation of amides with aryl halides [12]. Our previously experiments show that catalytic system (*E*)-oxime ether **5-8/** solid dry Cs_2CO_3 / $Pd_2(dba)_3$/ Xantphos in dry dioxane was best for the preparation of oxadiazepines **9-12**. Products **9-12** were isolated in 20-49 % yields (see Experimental Section).

Pyridine derivative **14** readily undergo palladium catalyzed cyclization leading to product **15** isolated in 16 % yield (Scheme 2).

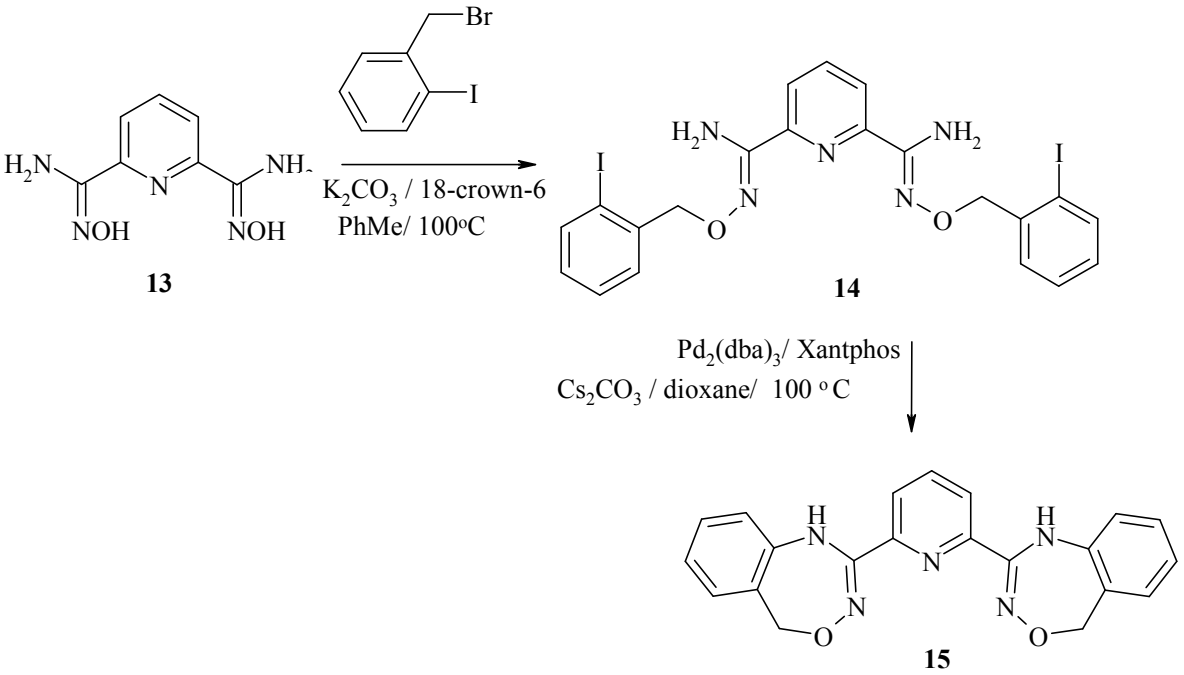


(*E*)-**1-4** (*E*)-**5-8** **9-12**

1, 5, 9 R = $PhCH_2$; **2, 6, 10** (2-benzothiazolyl)$(CH_2)_3$; **3, 7, 11** (2-benzothiazolyl)$(CH_2)_5$;

4, 8, 12 R = $PhSe(CH_2)_3$

Scheme 1



13 **14**

15

Scheme 2

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury BB 400 MHz in $CDCl_3$ using HMDSO as internal standard. LC-MS spectra were recorded on Alliance Waters 2695 instrument and Waters 3100 mass detector. Oximes **1-4, 13** were prepared as described in article [13]. Cs_2CO_3, o-iodobenzyl bromide, $Pd_2(dba)_3$, Xantphos and 18-crown-6 (Acros and Aldrich) were used without additional purification.

Typical procedure for the preparation of (*E*)-O-(2-iodophenylmethyl)oximes 5-8 and oxime ether 14. Solid KOH (0.45 g, 8 mmol) (for the preparation of compound **14** solid K_2CO_3 (6 equivalents) was used; reaction temperature 100^{o}C) was added to solution of oxime **1-4** (2 mmol), 18-crown-6 (0.053g, 0.2 mmol) and (*o*-iodo)benzyl bromide (2 mmol) in dry toluene (8 ml) and the reaction mixture was stirred at 50^{o}C for 12h. Then reaction mixture was filtered and solvent was removed under reduced pressure and crude residue was chromatographed on silica using ethyl acetate: hexane in different mixtures as eluent.

Typical procedure for the preparation 2-substituted 4,5-dihydro-1*H*-benzo[*d*][4,1,3]oxadiazepines 9-12 from oxime ethers 5-8. Mixture of oxime ether **5-8** (0.488 mmol), $Pd_2(dba)_3$ (0.0089g, 0.00976 mmol), Xantphos (0.0056g, 0.00976 mmol), anhydrous Cs_2CO_3 (0.222g, 0.683 mmol) in dry dioxane (2 ml) was heated at 100^{o}C for 12 h in glass reactor under argon. Reaction mixture was diluted with ethyl acetate (30 ml), filtered and solvent was removed under reduced pressure and crude residue was chromatographed on silica using ethyl acetate: hexane in different mixtures as eluent. Compound **15** was prepared from iodide **14** using double amounts of $Pd_2(dba)_3$, Xanthpos and Cs_2CO_3**.** Spectroscopic data of obtained compounds were as followed:

***N*-(2-Iodobenzyloxy)-benzamidine** (**5**). Yield 55 %. LC-MS, 367 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.37 (s, 2H, CH_2), 4.44 (bs, 2H, NH_2), 4.97 (s, 2H, OCH_2), 6.90-6.92, 7.16-7.32 and 7.74-7.76 (all m, 9H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 37.58, 78.67, 97.94, 127.18, 128.03, 128.04, 128.80, 128.80, 129.23, 129.24, 135.85, 139.17, 140.57, 153.26.

4-(Benzothiazol-2-ylsulfanyl)-*N*-(2-iodobenzyloxy)-butyramidine (**6**). Yield 14 %. LC-MS, 484 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.07-2.15 (m, 2H, $CH_2C\underline{H}_2$), 2.33 (t, 2H, J = 7.2 Hz, CCH_2), 3.35 (t, 2H, J = 7.2 Hz, SCH_2), 4.81 (bs, 2H, NH_2), 4.99 (s, 2H, OCH_2), 6.94-6.97, 7.27-7.43 and 7.74-7.85 (all m, 8H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.61, 29.85, 32.39, 78.60, 98.07, 120.97, 131.38, 124.24, 126.03, 128.03, 129.12, 129.33, 135.19, 139.16, 140.61, 153.11, 153.23, 166.79.

6-(Benzothiazol-2-ylsulfanyl)-*N*-(2-iodobenzyloxy)-hexanamidine (**7**). Yield 43 %. LC-MS, 512 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53-1.65 (m, 6H, $CH_2(C\underline{H}_2)_3$), 2.15 (t, 2H, J = 7.2 Hz, CCH_2), 3.31 (t, 2H, J = 7.2 Hz, SCH_2), 4.59 (bs, 2H, NH_2), 4.97 (s, 2H, OCH_2),6.94-6.98, 7.27-7.42 and 7.74-7.87 (all m, 8H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.28, 27.91, 28.80, 31.02, 33.28, 78.52, 97.98, 120.88, 121.42, 124.08, 125.99, 127.98, 129.11, 129.33, 135.14, 139.13, 140.66, 154.00, 155.31, 167.07.

***N*-(2-Iodobenzyloxy)-4-phenylselanyl-butyramidine** (**8**). Yield 63%. LC-MS, 501 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.94 (m, 2H, $CH_2C\underline{H}_2$), 2.45 (t, 2H, J = 7.6 Hz, CCH_2), 2.89 (t, 2H, J = 7.6 Hz, $SeCH_2$), 4.54 (bs, 2H, NH_2), 4.97 (s, 2H, CH_2), 6.94 7.24-7.48 and 7.81 (all m, 9H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.64, 26.28, 30.18, 77.62, 97.11, 125.91, 127.07, 128.12, 128.12, 128.12, 128.93, 131.61, 138.22, 139.66, 152.26.

6-Benzyl-5,9-dihydro-8-oxa-5,7-diazabenzocycloheptene (**9**). Yield 49%. LC-MS, 239 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.59 (s, 2H, CH_2), 4.86 (s, 2H, OCH_2), 5.98 (bs,

1H, NH), 6.48-6.50, 6.75-7.02 and 7.18-7.29 (all m, 9H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 39.84. 77.31, 117.38, 121.37, 127.60, 128.20, 128.85, 128.86, 129.17, 130.00, 133.30, 139.55, 155.70.

6-[3-(Benzothiazol-2-ylsulfanyl)-propyl]-5,9-dihydro-8-oxa-5,7-diazabenzocyclo-heptene (**10**). Yield 20 %. LC-MS, 356 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.27 (m, 2H, $CH_2C\underline{H}_2$), 2.55 (t, 2H, J = 7.2 Hz, CCH_2), 3.50 (t, 2H, J = 6.4 Hz, SCH_2), 4.91 (s, 2H, CH_2), 6.81-7.16, 7.25-7.45 and 7.73-7.78 (all m, 8H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.25, 31.88, 32.30, 77.20, 117.54, 121.04, 121.32, 124.42, 126.16, 127.07, 127.67, 128.29, 130.22, 135.23, 139.81, 152.88, 156.68, 167.14.

6-[5-(Benzothiazol-2-ylsulfanyl)-pentyl]-5,9-dihydro-8-oxa-5,7-diaza-benzocyclo-heptene (**11**). Yield 38 %. LC-MS, 384 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.71-1.90 (m, 6H, $CH_2(C\underline{H}_2)_3$), 2.34 (t, 2H, J = 7.6 Hz, CCH_2), 3.34 (t, 2H, J = 7.3 Hz, SCH_2), 4.90 (s, 2H, CH_2), 6.37 (bs, 1H, NH), 6.74-7.15, 7.25-7.42 and 7.73-7.86 (all m, 8H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.93, 27.80, 28.72, 33.20, 33.58, 77.20, 117.35, 120.95, 121.24, 121.37, 124.18, 126.04, 127.60, 128.25, 130.06, 135.15, 139.78, 153.21, 156.95, 167.06.

6-(3-Phenylselanyl-propyl)-5,9-dihydro-8-oxa-4,7-diazabenzocycloheptene(**12**). Yield 29 %. LC-MS, 345 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.03-2.09 (m, 2H, CH_2), 2.46 (t, 2H, J= 7.6 Hz, CCH_2), 3.02 (t, 2H, J = 7.2 Hz, $SeCH_2$), 4.86 (s, 2H, OCH_2), 6.15 (bs, 1H, NH), 6.65-6.68, 6.85-7.30 and 7.48-7.50 (all m, 9H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.78, 27.57, 33.48, 77.31, 117.35, 121.35, 127.09, 127.63, 128.26, 129.18, 129.50, 130.04, 132.73, 139.56, 156.17.

2,6-{Bis-[*N*-(2-iodo-benzyloxy)amidinyl]}-pyridine (**14**). Yield 55%. LC-MS, 628 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.09 (s, 4H, OCH_2), 5.51 (bs, 2H, NH_2), 6.90-6.92, 7.19-7.53 and 7.74-7.78 (all m, 8H, Ph), 7.58 (t, 1H, J = 7.6 Hz, H-4), 7.89 (d, 2H, J = 7.6 Hz, H-3 and H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 79.49, 98.11, 121.65, 128.12, 129.40, 136.89, 139.22, 140.41, 147.88, 149.91, 171.11.

6-[6-(5,9-Dihydro-8-oxa-5,7-diaza-benzocyclohepten-6-yl)-pyridin-2-yl]-5,9-dihydro-8-oxa-5,7-diaza-benzocycloheptene (**15**). Yield 16%. GC-MS, 374 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.97 (s, 4H, OCH_2), 6.88-7.29 and 7.80-7.90 (both m, 8H, Ph), 7.72-7.74 (m, 1H, H-4), 8.14 (m, 2H, H-3 and H-5), 8.60 (bs, 2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 77.00, 118.26, 122.29, 127.89, 128.31, 128.64, 129.52, 137.79, 139.31, 147.71, 149.50.

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