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Regioselective cleavage of *O*-benzyl-*N*-arylamidoximes: synthesis of *N*-aryl amidines and amidoximes

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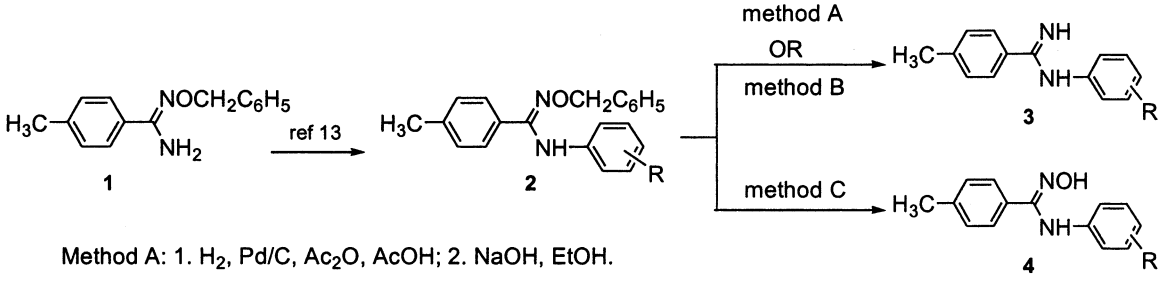
Abstract—*O*-Benzyl-*N*-arylamidoximes have been regioselectively deprotected to provide either *N*-aryl amidines or amidoximes. As a result, the targeted compounds can now be prepared using palladium-catalyzed *N*-arylation chemistry.

The amidine functional group is found in a wide range of biologically active molecules, including various serine protease[1] inhibitors (e.g. thrombin inhibitors) and nitric oxide synthase (NOS)[2] inhibitors. In addition, several classes of diamidines structurally related to pentamidine exhibit broad spectrum antimicrobial activity.[3] Amidoximes are also of biological interest, as they serve as prodrugs for amidines,[4] and certain acyl derivatives are highly active against cytomegalovirus (HCMV).[5] As an important class of *N*-substituted derivatives, *N*-aryl amidines possess potent activity as well against NOS[2] and various microbial diseases.[6] Considering this, the corresponding *N*-aryl amidoximes are of interest as potential prodrugs.

N-Aryl amidines are typically prepared from anilines, either by direct reaction with a thioimidate[2,7] or, under more forcing conditions, with a nitrile.[8] *N*-Aryl amidoximes are also prepared from anilines, either by reaction with an *N*-hydroxybenzimidoyl chloride[9] or nitrile oxide.[10] While there are other more tedious routes to these compounds,[6,11] there has been no report thus far of the direct (or indirect) *N*-arylation of amidines or amidoximes. Such chemistry, which has now been applied to many other nitrogen-containing functional groups,[12] would greatly facilitate the synthesis of the *N*-aryl derivatives for drug discovery by not only allowing for the straight-forward *N*-arylation of the functional groups, but also allowing for the introduc-



Scheme 1.

Keywords: *O*-benzylamidoximes; amidines; amidoximes; Pd/C/EtOH; HBr/HOAc.

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tion of an amidine or amidoxime directly into a parent molecule by substitution of an appropriate halogen or triflate.

Recently, we reported the Pd-catalyzed *N*-arylation of the alkyl-protected *O*-methylamidoximes.[13] Unfortunately, the arylation of the corresponding amidines and amidoximes using the same chemistry does not proceed. Our attention has thus turned to the selective deprotection of the *O*-alkyl *N*-arylamidoximes, which would allow for an indirect *N*-arylation route to the targeted compounds. As a result of our efforts, we now wish to report that the *O*-benzyl *N*-arylamidoximes can be selectively cleaved in good yield, depending on reaction conditions, to either the *N*-aryl amidines or amidoximes.

Initially, we explored the selective cleavage of the *O*-methyl *N*-arylamidoximes to either the amidines or amidoximes. Unfortunately, both attempted N–O cleavage to the amidine via catalytic hydrogenation (Pd/C in EtOH or in Ac_2O/AcOH), as well as O–C cleavage to the amidoxime by heating with HBr/AcOH, resulted in little to no reaction. We thus turned to the *O*-benzylamidoximes, which were readily prepared using the same *N*-arylation chemistry as previously described for synthesis of the *O*-methyl derivatives[13] (Scheme 1).

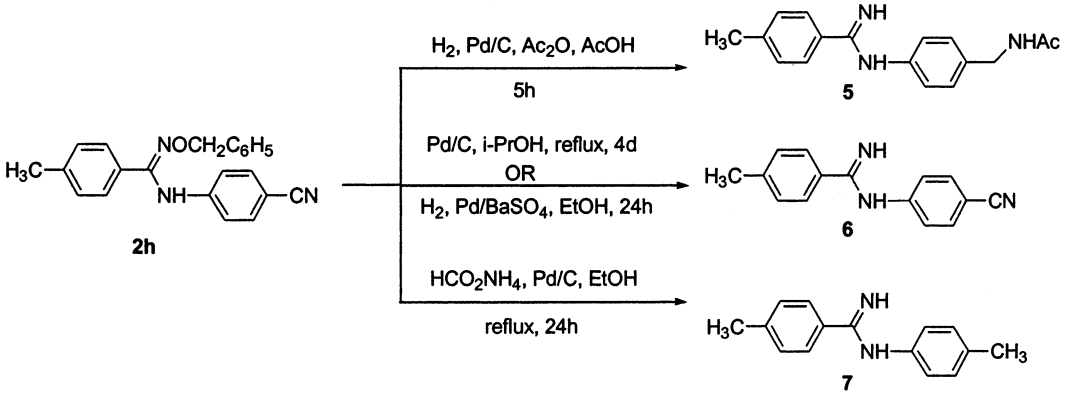
In contrast to the *O*-methyl derivatives, standard catalytic hydrogenation (Pd/C, EtOH, rt) of the *O*-benzylamidoximes resulted in a significant amount of reduction, although we were routinely left with mixtures of amidine and debenzylated amidoxime once hydrogen uptake subsided. In an attempt to activate the intermediate amidoxime toward reduction by acetylation,[14] we turned to acetic acid/acetic anhydride as a solvent mixture. With this change, we observed complete reduction after about 4 h, albeit to the *N*-acetylated amidines which required hydrolysis to the amidines. Although somewhat cumbersome, this approach nonetheless provided a number of amidines in fair to good isolated yields as noted in Table 1 (Method A). In the case of the cyano-substituted derivative **2h** (Scheme 2), reduction to the acetylated benzylamine **5**[15] (64% yield) was observed. On the other hand, by using $Pd/BaSO_4$ as catalyst we were able to selectively reduce the amidoxime to give **6** (60% yield), keeping the nitrile intact.

To eliminate the need for the hydrolysis step, as well as for hydrogen gas, we next explored the use of transfer hydrogenation[16] for reduction to the amidine. Ammonium formate (AF)[17] with Pd/C (EtOH, reflux) (Method B), which to our knowledge has not been used for the reduction of amidoximes, was found to be an excellent alternative to the catalytic hydrogenation method. With most examples (Table 1), the AF/Pd/C reduction method gave the *N*-aryl amidines in good to excellent isolated yields without the need for hydrolysis. As an exception to this, attempted cleavage of a biphenyl derivative (entry 5) resulted in partial reduction of one of the biphenyl rings,[18] leaving an inseparable mixture. In contrast, ring reduction was not observed with the catalytic hydrogenation method. With compound **2h** (Scheme 2), the AF/Pd/C method converted the cyano group to a methyl to give **7** (30% yield), a transformation that has been previously described.[19] However, a milder (and much slower) transfer hydrogenation method using 2-propanol as

Table 1. Synthesis of *N*-aryl amidines **3**[20,21]

Entry	R	Method A yield (%)[a]	Reaction time (h)	Method B yield (%)[a]	Reaction time (h)
1	H	64	4	69	6
2	4-CF_3	84	4	65	5
3	3-CH_3	69	4	70	6
4	3-OCH_3	31	4	95	3
5	4-C_6H_5	70	4	Mixture	16

[a] Yields represent analytically pure material.



Scheme 2.

Table 2. Synthesis of *N*-aryl amidoximes **4**[22]

Entry	R	Reaction time (h)	Yield (%)[a]
1	H	6	61
2	4-CF_3	4	68
3	3-CH_3	4	70
4	4-Cl	6	75
5	4-C_6H_5	6	72
6	4-NO_2	6	65
7	4-CN	4	Mixture

[a] Yields represent analytically pure material.

hydrogen donor (Pd/C as catalyst, reflux 4 days) left the nitrile untouched, giving compound **6** in 52% yield with a small amount of starting material (about 10%) also being recovered (Scheme 2).

With methods in hand for cleavage of the *O*-benzylamidoximes to the amidines, we next examined selective conversion of these compounds to the amidoximes. While heating with BF_3 in CH_2Cl_2 or aqueous HBr (48%) led to no *O*-debenzylation, reaction with HBr/AcOH (30% by wt) at 65°C for about 6 h provided good isolated yields of the amidoximes (Scheme 1, Table 2). Not surprisingly, the nitrile group of **2h** was sensitive to these acidic conditions, and an inseparable mixture was obtained in this case (Table 2, entry 7).

In summary, we have described methods for selective conversion of *O*-benzyl-*N*-arylamidoximes to the corresponding amidines or amidoximes. These regioselective methods of deprotection provide convenient methodology for synthesis of these biologically important compounds by way of Pd-catalyzed *N*-arylation chemistry.

Acknowledgements

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15. **Spectral data for benzylamine derivative**: δ ^{1}H NMR (300 MHz, DMSO-d_6): 1.82 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 4.15 (d, 2H, J=4.5 Hz, NCH_2); 6.09 (br, 2H, NH); 6.73 (d, 2H, J=6.0 Hz, Ar); 7.13 (d, 2H, J=6.0 Hz, Ar); 7.17 (d, 2H, J=6.0 Hz, Ar); 7.80 (d, 2H, J=5.4 Hz, Ar). δ ^{13}C NMR (DMSO-d_6): 21.7, 23.2, 42.8, 122.8, 127.8, 129.3, 129.8, 133.2, 133.8, 141.3, 149.2, 157.1, 171.6. MS (EI) m/z (%): 281.2 (M^+, 64%), 265 (18%), 211.2 (6%), 164.1 (8%), 118.1 (75%), 106.1 (100%), 77.1 (45%).
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20. **Method A** (Table 1, entry 1): An oven-dried 25 mL round-bottomed flask was charged with 316 mg of **1** and 10 mL of glacial acetic acid. To that 0.5 mL of acetic anhydride and 31 mg of Pd/C (10%) was added. The mixture was hydrogenated at 40 psi for 4 h. No starting

material was observed by TLC and the mixture was filtered over Celite rinsing with acetic acid. The filtrate was concentrated under vacuum and the residue was diluted with EtOAc, washed successively with water (3× 25 mL), brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to yield the *N*-acetylated amidine, which was dissolved in ethanol (~5 mL) and stirred with 2N NaOH (~2 mL) overnight at rt. The mixture was diluted with water, extracted with ethyl acetate (3×50 mL), and the combined organic layers were washed twice with water, once with brine, dried and evaporated under vacuum. The crude product was passed through a short column pretreated with 1% triethylamine eluting with 50% ethyl acetate in hexanes to give the pure amidine as an off-white solid. δ ^{1}H NMR (300 MHz, $CDCl_3$): 2.40 (s, 3H, CH_3); 4.80 (br, 2H, NH); 6.97 (d, 2H, $J=7.5$ Hz, Ar); 7.21–7.40 (m, 5H, Ar); 7.75 (d, 2H, $J=7.5$ Hz, Ar). δ ^{13}C NMR ($CDCl_3$): 21.4, 121.7, 122.9, 123.2, 125.0, 125.6, 126.7, 129.2, 129.5, 154.7. MS (EI) *m*/*z* (%): 210.1 (M^+, 100%), 194.1 (55%), 165.1 (6.2%), 135.1 (5%), 118.1 (64%), 93.1 (92%), 77.1 (81%). The HCl salt was prepared for analysis. Anal. calcd for $C_{14}H_{14}N_2{\cdot}HCl{\cdot}0.75H_2O$: C, 64.61; H, 6.39; N, 10.76. Found: C, 64.78; H, 6.10; N, 10.88.

21. **Method B** (Table 1, entry 1): 316 mg (1 mmol) of the *O*-benzylamidoxime was dissolved in 10 mL of absolute ethanol. To that was slowly added 315 mg of ammonium formate (5 mmol) and 316 mg of 10% Pd/C. The mixture was heated at reflux, with progress of the reaction monitored by TLC. After starting material was consumed, the solvent was removed under vacuum and the residue was diluted with ethyl acetate. The solution was filtered through Celite and the filtrate was washed with water (3×50 mL), brine, then dried (Na_2SO_4) and concentrated. The crude product was passed through a short silica gel column as described in method A to yield 145 mg (69%) of the amidine, which was identical spectroscopically to that obtained by method A.
22. **Synthesis of *N*-aryl amidoximes** (Table 2, entry 1): In a 25 mL round-bottom flask, 316 mg (1 mmol) of the *O*-benzylamidoxime and 5 mL of HBr in acetic acid (30% by wt) was stirred at 65°C for 3 h. TLC showed that some starting material remained, and thus an additional 3 mL of HBr in acetic acid was added and stirring was continued at 65°C. After the reaction was over, the mixture was cooled, basified with 2N NaOH, and extracted with EtOAc (3×25 mL). The combined organic layers were washed with water (3×25 mL), brine and dried (Na_2SO_4). The solvent was removed under pressure and the crude product was purified by flash chromatography using 45% ethyl acetate in hexanes to give the amidoxime as a white solid (138 mg, 61%). δ ^{1}H NMR (300 MHz, DMSO-d_6): 2.28 (s, 3H, CH_3); 4.22 (br, 1H, NH); 6.85 (d, 2H, $J=8.0$ Hz, Ar); 7.01 (m, 2H, Ar); 7.11 (m, 3H, Ar); 7.21 (d, 2H, $J=7.9$ Hz, Ar); 10.85 (br, 1H, OH). δ ^{13}C NMR (DMSO-d_6): 21.0, 123.1, 124.8, 125.6, 128.8, 129.2, 129.3, 137.16, 142.0, 156.4. MS (EI) *m*/*z* (%): 226.1 (M^+, 58%), 209.1 (97%), 194.1 (43%), 165.1 (4%), 131 (45), 118.1 (33%), 93.1 (100%). Anal. calcd for $C_{14}H_{14}N_2O{\cdot}HCl{\cdot}0.5H_2O$: C, 61.85; H, 5.93; N, 10.03. Found: C, 61.81; H, 6.17; N, 9.75.