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Development and Utilization of a Palladium-Catalyzed Dehydration of Primary Amides To Form Nitriles

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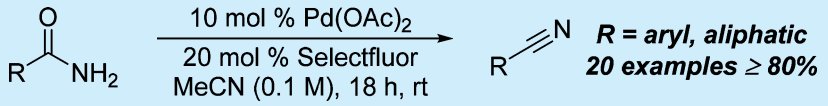
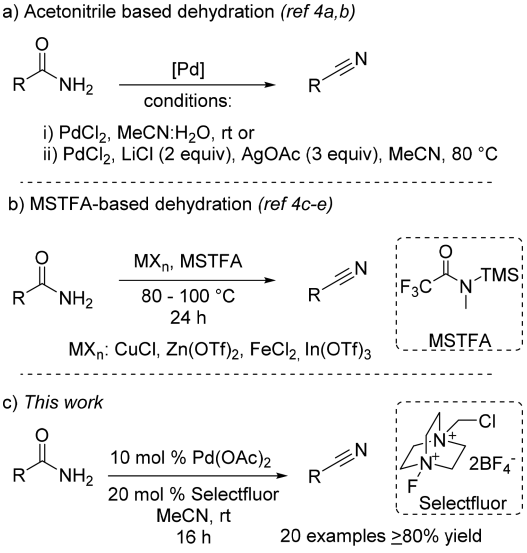
Supporting Information



ABSTRACT: A palladium(II) catalyst, in the presence of Selectfluor, enables the efficient and chemoselective transformation of primary amides into nitriles. The amides can be attached to aromatic rings, heteroaromatic rings, or aliphatic side chains, and the reactions tolerate steric bulk and electronic modification. Dehydration of a peptaibol containing three glutamine groups afforded structure−activity relationships for each glutamine residue. Thus, this dehydration can act similarly to an alanine scan for glutamines via synthetic mutation.

In the area of new reaction design and development, the chemoselective interconversion of functional groups is highly sought after.[1] Two noteworthy examples include (1) the selective methylation of the carboxylic acid of amphotericin B in the presence of seven alkenes, nine secondary alcohols, a hemiacetal, and a primary amine[2] and (2) the C−H oxygenation of a bryostatin analogue with DMDO in the presence of 11 similar C−H bonds, an alkene, an acetal, and three carboxyl groups.[3] The first case represents the conversion of a carboxylic acid to an ester, a relatively simple transformation that modifies reactivity, but the conversion in amphotericin B is complicated by the other functional groups surrounding it. For example, typical Fisher esterification using a strong acid is not compatible with this molecule. Similarly, the dehydration of a primary amide to form a nitrile, which has been previously explored,[4] is often complicated by the presence of other functional groups.[5] Transition metal catalyzed dehydration reactions typically utilize acetonitrile[4a,b] or *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA)[4c−e] as a dehydrating agent (Scheme 1). These reactions generate acetamide as a byproduct from acetonitrile or *N*-methyltrifluoroacetamide and hexamethyldisiloxane from MSTFA. For reactions involving MSTFA, high reaction temperatures and excess amounts of MSTFA are required. Nonaqueous acetonitrile reactions require excess amounts of lithium and silver salts.[4b] On the other hand, reactions involving water as cosolvent can proceed at room temperature,[4a] but are limited to substrates that are stable and soluble under aqueous conditions (Scheme 1a).

Scheme 1. Metal-Catalyzed Methods To Convert Primary Amides into Nitriles



During our studies to semisynthetically improve the activity of natural products, typically by incorporating fluorine into the molecule,[6] we attempted to fluorinate alamethicin F50, a 20-mer peptaibol containing an acetylated N-terminus, a C-

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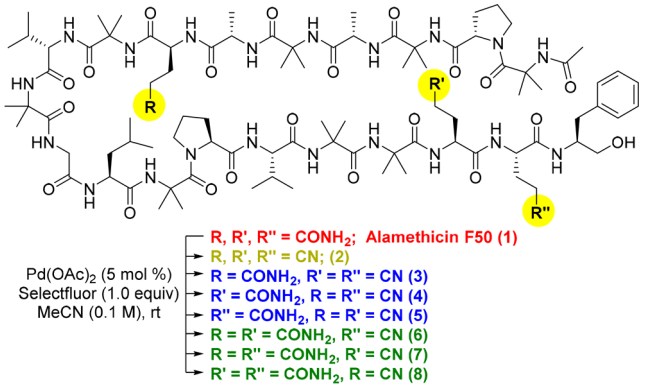
terminal phenylalaninol, and three glutamine (Gln) residues (Gln7, Gln18−19; Scheme 2).[7] Although our fluorination attempts were unsuccessful,[8] it was determined that all three glutamine residues were dehydrated in the presence of $Pd(OAc)_2$ and Selectfluor. This led to the formation of tricyano product **2**, along with semidehydrated analogues (**3**−**8**; *vide infra*). This transformation was efficient and completely chemoselective without modifying the primary alcohol or any of the secondary or tertiary amides. Herein, we describe the further optimization and exploration of this dehydration reaction and utilize the dehydration of alamethicin F50 to illustrate the benefits of this reaction as a quick method to functionalize and determine the biological effects of the glutamine residues in the peptaibol.

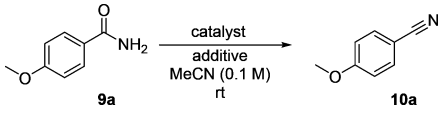
Scheme 2. Identification of a Chemoselective Dehydration



To examine the optimal conditions of the dehydration of primary amides, 4-methoxybenzamide was used as a model substrate in the presence of catalytic amounts of various metal salts and Selectfluor. The reaction gave excellent yields of the nitrile product in the presence of Pd(II) or Pd(0); contrasting results were observed with Zn(II) or Cu(II) catalyzed reactions (Table 1, entries 1−5). Although the $Pd_2(dba)_3$ reaction appears faster than that with $Pd(OAc)_2$, the purification was complicated by the dba (dibenzylideneacetone) ligand. Thus, catalyst loading and Selectfluor stoichiometry were examined using the $Pd(OAc)_2$ catalyst. Using 5 mol % of catalyst, the reaction yielded 71% of the desired nitrile after 16 h (Table 1, entry 6). Increasing the amount of Selectfluor to 40% gave nitrile **10a**, in addition to the fluorinated nitrile derivative (Table 1, entry 8). Reactions performed in the absence of Selectfluor or in the presence of DABCO instead of Selectfluor yielded no nitrile product. Although Selectfluor is a nonhygroscopic reagent, we examined the requirement for water using $Pd(OAc)_2$ in the absence of Selectfluor (Table 1, entries 11−13). Increasing the amount of water in the reaction improved the reaction yield (68% was observed with 2.0 equiv of water). For comparison, the addition of water to the reaction conditions with Selectfluor was not beneficial. A previous report by Maffioli[4a] found that the palladium-catalyzed dehydration requires water. We verified their results in the absence of Selectfluor, which indicates that Selectfluor is modifying the catalytic cycle,[4b] such that water is no longer required. After screening a variety of conditions, it was determined that 10 mol % $Pd(OAc)_2$ and 20 mol % Selectfluor in acetonitrile (entry 1) was optimal.

With the optimal conditions in hand, a series of primary amides were synthesized from their respective carboxylic acids and screened in the dehydration conditions (Scheme 3). The substrate scope is broad, with high yields for both aliphatic and aryl amides to generate aliphatic and aryl nitriles. High yields were observed from reactions involving non-, mono-, and disubstituted benzamides (**10a**−**c** and **10e**−**g**; 80−96% yields). The lower yield for compound **10d** (4-trifluoromethyl-

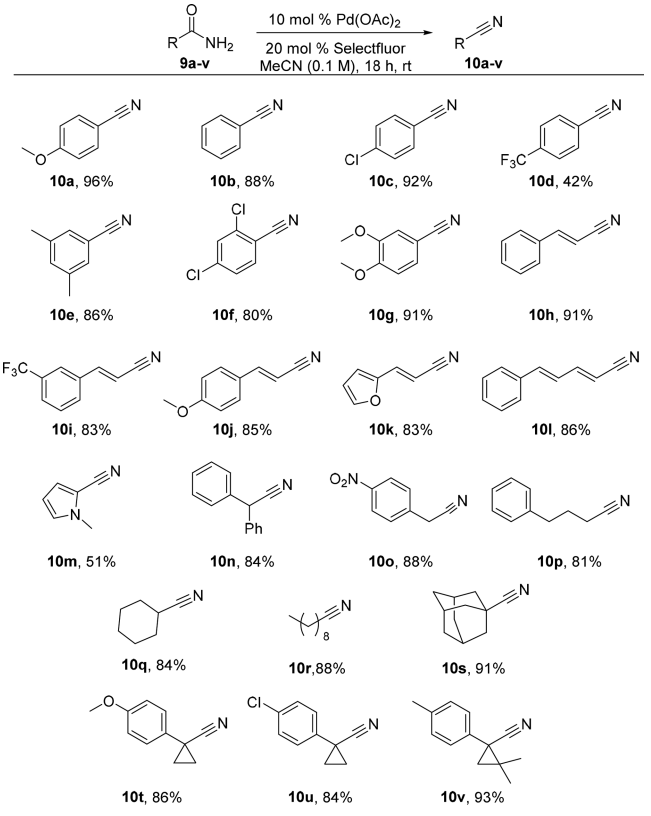
Table 1. Optimization of Palladium-Catalyzed Dehydration with Selectfluor



entry	cat. (mol %)	additive (mol %)	time (h)	yield (%)[a]
1	$Pd(OAc)_2$ (10)	Selectfluor (20)	16	96
2	$PdCl_2$ (10)	Selectfluor (20)	16	82
3	$Pd_2(dba)_3$ (5)	Selectfluor (20)	13	91
4	$ZnBr_2$ (10)	Selectfluor (20)	24	trace
5	$Cu(OTf)_2$ (10)	Selectfluor (20)	24	26
6	$Pd(OAc)_2$ (5)	Selectfluor (20)	16	71
7	$Pd(OAc)_2$ (10)	–	24	trace
8	$Pd(OAc)_2$ (10)	Selectfluor (40)	16	93[b]
9	$Pd(OAc)_2$ (10)	Selectfluor (5)	24	88
10	$Pd(OAc)_2$ (10)	DABCO (20)	24	NR[c]
11	$Pd(OAc)_2$ (10)	H_2O (50)	16	31
12	$Pd(OAc)_2$ (10)	H_2O (100)	16	42
13	$Pd(OAc)_2$ (10)	H_2O (200)	16	68

[a]Isolated yield. [b]7% Fluorinated 4-methoxybenzonitrile was observed. [c]No reaction.

Scheme 3. Various Substrates for Primary Amide Dehydration



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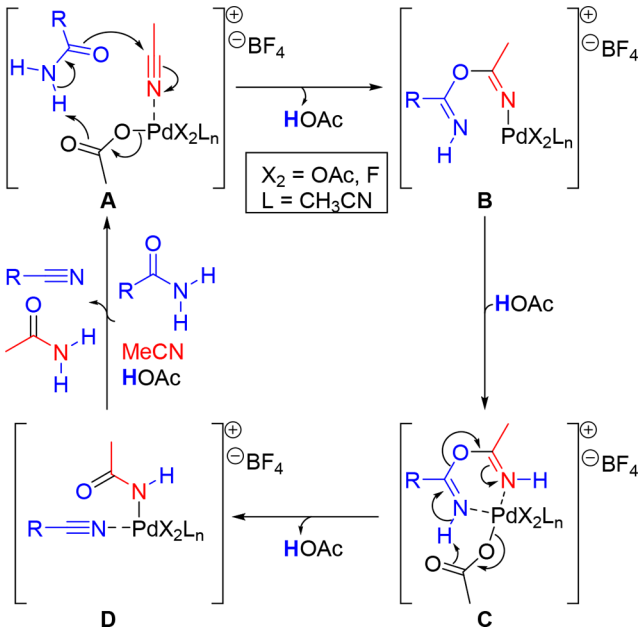
benzamide, 42% yield) was likely due to electronic factors. However, the effect was negligible on cinnamide derivatives (**10h**–**10j**). Several aliphatic amides were also converted to their corresponding primary, secondary, and tertiary nitriles in good yields. Importantly, the cyclopropyl moiety in amides (**9t**–**9v**) has been preserved under the reaction conditions to generate cyclopropyl nitriles (**10t**–**10v**) in excellent yields (86–93%). In total, 22 substrates were screened, and it was determined that this reaction tolerates the presence of alkenes, aromatic rings, heteroaromatic rings, nitro groups, cyclopropanes, and halides. To further test the chemoselectivity of the reaction, we ran the dehydration of **9a** in the presence of either salicylaldehyde or 4-phenylbutyric acid. These reactions gave desired product **10a** (93% and 95% yield, respectively) with quantitative recovery of salicylaldehyde and 4-phenylbutyric acid, illustrating that phenols, aldehydes, and carboxylic acids are also tolerated.

Based on our results and the similarity of conditions to prior reports,[4a] the reaction mechanism (Scheme 4) might involve

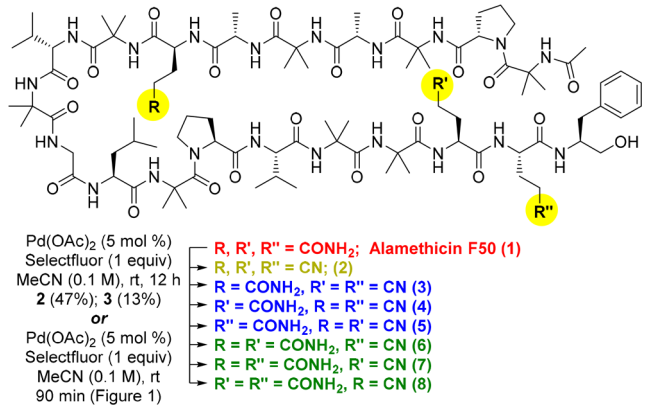
Scheme 4. Postulated Mechanism for Dehydration



the formation of a mixed imidic anhydride (**B**) that undergoes proton transfer and coordination of acetate (**C**) followed by an elimination to yield the desired nitrile and acetamide (**D**), as has been proposed previously.[4b] The role of Selectfluor remains uncertain, but one potential option is that it accelerates the catalytic cycle by formation of a Pd(IV) catalyst, as has been reported by others.[8,9] Additional evidence in support of a Pd(IV) mechanism is the observation of a signal at −181 ppm in the ^{19}F NMR when $Pd(OAc)_2$ is added to Selectfluor (^{19}F NMR signals for SelectFluor are 48 (N–F) and −151 (BF_4) ppm, Supporting Information (SI)). A more resolved mechanism for this reaction is still being examined and will be published in due course.

To further establish the utility of the dehydration, alamethicin F50 was re-examined as a starting material (**1**; Scheme 5), with an approach focused on the exploration of the structure–activity relationship of the different primary amides. The reaction of compound **1** with SelectFluor (1.0 equiv) and $Pd(OAc)_2$ (5 mol %) in MeCN (0.1 M) at room temperature

Scheme 5. Synthesis of Mono-, Di-, and Tricyano Alamethicin F50 Analogues



for 12 h gave the tricyano peptaibol derivative (**2**; 47% yield after purification), along with the dicyano product (**3**) where the glutamines at positions 18 and 19 were dehydrated (13% yield after purification). The structures of compounds **2** and **3** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRESIMS/MS data (SI).

Subsequently, an analysis was carried out to examine the reaction mixture for other variations of dehydration. In order to perform the dehydration of up to three amides of alamethicin F50 (**1**) in a timely manner, peptaibol **1** was reacted with $Pd(OAc)_2$ (5 mol %) using a full equivalent of SelectFluor in MeCN (0.1 M). The reaction was monitored using UPLC-UV-HRESIMS at intervals of 15–20 min for 5 h (see SI for time course of the reaction in three different solvent mixtures). Gratifyingly, UPLC analysis allowed for resolution of all seven products and the starting material (Figure 1).

Scaling up of the reaction with SelectFluor in acetonitrile permitted the isolation, structural characterization, and biological evaluation of dehydrated analogues **2**–**8**. The structures of these analogues were established through analyses of their HRESIMS/MS spectra (SI). Importantly, these seven

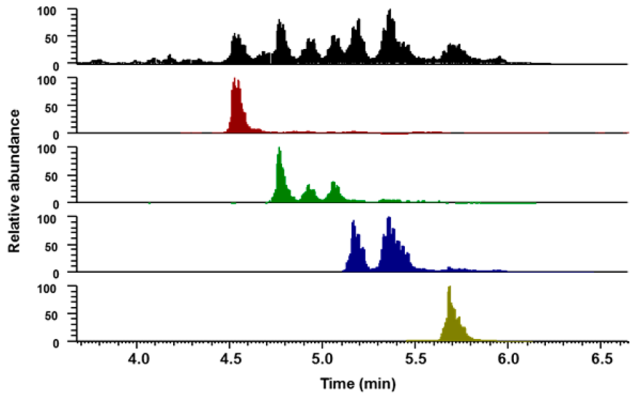


Figure 1. HRESIMS spectra of the reaction of **1** (10 mg, 5.9 μmol) with SelectFluor (2.1 mg, 5.9 μmol) and $Pd(OAc)_2$ (0.011 mg, 0.05 μmol) in MeCN (0.1M) at 25 °C after 90 min. In black is the base peak chromatogram, in maroon the extracted ion chromatogram for the staring material (**1**) at *m*/*z* 1963.0, in green the extracted ion chromatogram at *m*/*z* 1945.0 for the monocyano products (**6**–**8**), in navy the extracted ion chromatogram at *m*/*z* 1927.0 for the dicyano products (**3**–**5**), and in yellow the extracted ion chromatogram at *m*/*z* 1909.0 for the tricyano product (**2**).

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analogues were all accessed by a single reaction using **1** as the starting material instead of designing and developing seven different approaches or through the use of protecting groups.[10] Furthermore, in contrast to the more typically used alanine scan,[11] this method has a minimal change in the overall sterics of the side chain since there is no deletion of carbon over the course of the reaction.

Alamethicin F50 (**1**) is known to be antibacterial, antifungal, anthelmintic, and cytotoxic.[7,12] Based on our groups' attempts to generate anticancer leads,[6a,c,13] we decided to determine the impact of the glutamine residues on the bioactivity in a panel of cancer cell lines (Table 2). The cytotoxicity data indicated

Table 2. Cytotoxicity of Alamethicin F50 and Dehydrated Analogues[a]

compound	MDA-MB-435	MDA-MB-231	OVCAR3
1	4.4	3.7	7.8
2; R,R′,R′′ = CN	>25	>25.0	>25
3; R′,R′′ = CN	2.6	1.2	3.0
4; R,R′′ = CN	3.1	8.7	13.4
5; R,R′ = CN	>25	22.3	>25
6; R′′ = CN	2.2	1.3	4.6
7; R′ = CN	2.8	2.0	3.9
8; R = CN	>25	>25	>25
Taxol	0.0005	0.009	0.002

[a]IC_{50} values in μM in the indicated cell lines were determined as the concentration required to reduce cellular proliferation by 50% relative to the untreated controls following 72 h of continuous exposure.

that the glutamine at position seven was crucial for maintaining the cytotoxic properties of the molecule. This was determined since the analogue dehydrated exclusively at position seven (**8**) was inactive, whereas monocyano **6** and **7** were active. Similarly, dicyano **5** and **4**, both of which had position seven dehydrated, were inactive or much less active, respectively. Dehydration of glutamine 18 and/or 19 led to analogues that had similar activities. These results give unique insight into the impact of each glutamine residue on the cytotoxic properties of **1** and show that position seven is crucial to the observed cytotoxicity.

Several techniques, including X-ray diffraction,[14] NMR,[7,12f,15] CD,[16] Raman, and molecular dynamics,[7,17] have been used to characterize the α-helical conformation of alamethicin F50 (**1**) in both solution and solid states.[7] In an attempt to gain information about the conformational changes induced by the dehydration of the glutamine residues in **1**, the CD spectrum for each analogue was recorded in MeCN (Figure 2). The far UV/CD spectra, 260−180 nm, with absorbances attributed to the peptide bond, is the most extensively used spectroscopic readout to determine the secondary structures of peptides in solution (α-helix, β-pleated sheet, and random coil).[18] The right handed α-helix is reported to give two negative Cotton effects at 222 and 208 nm, while the β-pleated sheet shows one negative and one positive Cotton effect at 217 and 198 nm, respectively.[18] Analysis of the experimental CD data obtained for alamethicin F50 (**1**) and its analogues (**2**−**8**) indicated that the mono- and dicyano compounds (**3**−**8**) predominantly retained the α-helical conformation, with a minor population of 3_{10}-helix, as previously reported by Peggion et al.[19] However, the CD spectrum for tricyano **2** indicated that the conformation was modified, increasing the population of the 3_{10}-helix conformer

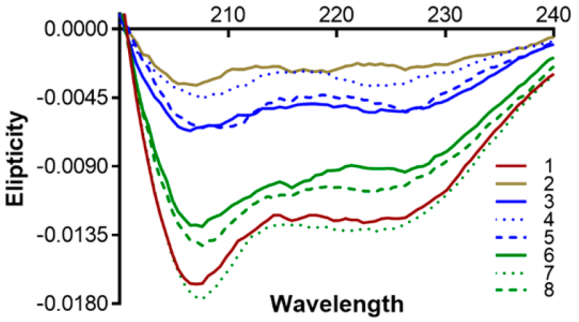

Figure 2. Far UV/CD spectra for alamethicin F50 (**1**) and its dehydrated analogues (**2**−**8**). See SI for full spectra (Figure S19).

(Figure 2 and SI). Surprisingly, the helical nature of the different peptaibol analogues did not have a strong correlation with the cytotoxicity data (compare Figure 2 and Table 2). In Figure 2, the UV/CD spectrum of alamethicin F50 (**1**) is most similar to those of monocyano analogues **6**−**8**, but analogue **8** is inactive. Likewise, there is a grouping in the spectra of dicyano analogues **3**−**5**, but analogue **3** is active, whereas analogue **5** is inactive and compound **4** has decreased activity. These data indicate that the cytotoxicity of alamethicin F50 is dependent on the presence of a glutamine residue at position seven, and that the activity is not simply a stabilization of the α-helix conformation of the peptaibol.

In summary, a Selectfluor-modified palladium catalyst was shown to enable the chemoselective dehydration of primary amides to generate nitriles. The reaction tolerates the presence of primary alcohols, primary amides, secondary amides, aldehydes, carboxylic acids, nitro groups, alkenes, heteroaromatic rings, halides, and cyclopropanes and is efficient with aromatic and aliphatic amides, with little impact by the electronics or sterics of the system. The application of the dehydration method facilitated the synthesis of the seven possible dehydrated analogues of alamethicin F50 (**1**). Importantly, all the peptaibol derivatives were generated in a single reaction in sufficient amounts for purification, characterization, and biological evaluation. The application of this methodology allowed us to generate data that highlight the importance of each individual glutamine residue on the bioactivity and conformation of **1**. We hypothesize that this primary amide dehydration methodology may be used as an alternative to alanine scanning to assess the implications of glutamine and possibly asparagine residues on the activity and 3D structure of peptides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02422.

Experimental information and spectral data for all compounds and cytotoxicity data for compounds **1**−**8** (PDF)

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Notes

The authors declare no competing financial interest.

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