On the Mechanism of Pd\textsuperscript{0}-Initiated Coupling–Cyclization of γ-Aminoalkynes

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Received August 11, 2000

Introduction

Recently, we have been investigating the synthetic utility of alkyne acids of general structure 1, which are useful precursors to a variety of natural product skeletons (Scheme 1).\textsuperscript{1} The versatility of these species derives partly from their bifunctional structure, which incorporates both a nucleophilic and an electrophilic component in the same synthon. In addition, acids of type 1 can frequently be prepared in enantiomerically pure form.\textsuperscript{1c,d} A particularly useful transformation of 1 involves 5-exo-dig cyclization, which we employed in a two-step synthesis of cyclic enamides 2 [Pd\textsuperscript{II}]-induced cyclization followed by aminolysis\textsuperscript{2b} or amidation followed by F\textsuperscript{−}-catalyzed ring closure\textsuperscript{1b}. Enamides 2 are important building blocks for the synthesis of hydroporphyrins,\textsuperscript{3a} employing the Eschenmoser sulfide contraction methodology.\textsuperscript{3b} Also, we have developed an iterative synthesis of dipyrrin derivatives that takes advantage of the ready availability of imidoyl chlorides 3\textsuperscript{a} and triflates 4, each derived in two steps from 2.\textsuperscript{1b} For example, semicorrins 7a, b were prepared by Pd\textsuperscript{0}-initiated coupling–cyclization of imidoyl chloride 3a with the alkyne amide/imide derivatives 1a or 5b, depending upon the meso-substitution pattern at C\textsubscript{5} (85–89% yields).\textsuperscript{1b,c} In similar fashion, Pd\textsuperscript{0}-initiated coupling-cyclization of triflate 4a with the alkyne amines 6a–c afforded good-excellent yields of the (H\textsubscript{2})\textsubscript{6}-dipyrrins 8a–c.\textsuperscript{1d} Interestingly, steric hindrance was not a problem in these transformations, even though the reactive C–X bond is adjacent to a quaternary center. In fact, in some cases this proved to be beneficial (vide infra). Finally, it is worth noting that imidoyl chlorides 3 were much more reactive than triflates 4 in Pd\textsuperscript{0}-initiated coupling–cyclizations with alkyne acids 1.\textsuperscript{1b,c,e} Conversely, imidoyl triflates 4 were better substrates for coupling–cyclization with alkyne amines 6.\textsuperscript{1d} These observations are discussed further below.

Results and Discussion

Semicorrins 7 and (H\textsubscript{2})\textsubscript{6}-dipyrrins 8 are suitably constituted for preparing corrins of type 9 (Figure 1), and the methodology for accomplishing this transformation is well established.\textsuperscript{3b,c} However, most naturally occurring hydroporphyrins have a substitution pattern related to that found in cobyric acid (10), in which the quaternary carbons are located at C\textsubscript{2}, C\textsubscript{7}, C\textsubscript{12}, and C\textsubscript{17} (i.e., regioisomeric to 9).\textsuperscript{3b} In principle, the “natural” corrin regiochemistry can be obtained by altering the substitution pattern of the starting imidoyl chlorides/triflates 3, 4 and alkyne acids/amines 1, 6. This worked well for a number of semicorrin derivatives 11, beginning with acids 1.\textsuperscript{1c} For example, the ring-A,B precursor 11d was readily derived from the imidoyl chloride 3d and the alkyne acid 1d by a two-step sequence involving Pd\textsuperscript{0}-initiated coupling–cyclization, followed by aminolysis of the resultant enol lactone (Figure 1).

In contrast, the construction of ring-C,D dipyrrins 12 incorporating the “natural” regiochemistry was not so straightforward (Scheme 2). This synthesis was based upon the Pd\textsuperscript{0}-initiated coupling–cyclization of alkyne amines 6 with imidoyl triflate 4d, a seemingly minor variation to our syntheses of dipyrrins 8 (cf. Scheme 1). However, with 4d the geminal methyl groups are well removed from the C–OTf bond and provide little steric shielding. Consequently, nucleophilic displacement by the amino group competes effectively with the Pd\textsuperscript{0}-initiated process, a pathway that was not observed with imidoyl triflate 4a. In the most favorable case, coupling of 4d with the alkyne amine 6a gave a 52% yield of the meso-substituted (H\textsubscript{2})\textsubscript{6}-dipyrrin 12a (A = H; B, R = Me), accompanied by 37% of amidine 13a, the product of amine displacement. In analogous fashion, the more sterically hindered alkyne 6d afforded only 31% of the desired (H\textsubscript{2})\textsubscript{6}-dipyrrin 12d (A = Me; B, R = H), and 62% of amidine 13d. Finally, alkyne amine 6e, which contains the most shielded triple bond (A, R = Me) and the least...
hindered amine (B = H), gave amidine 13e as the exclusive product (70% yield). Once again, imidoyl chloride 3d was relatively unreactive toward both coupling and direct displacement with alkyne amines 6.1d Clearly, different mechanisms operate in the Pd 0-initiated coupling—cyclization of alkyne amines 6 and alkyne acids 1. The reactivity pattern of acids 1 is best explained on the basis of the relative Pd(II) ligand bond strengths of Cl −, TfO −, and RCO2 −. This is illustrated in Scheme 3, employing imidoyl chloride 3d (X) and imidoyl triflate 4d (X) as substrates. In both examples, Pd0-initiated coupling reactions were carried out under weakly alkaline conditions, in which the alkyne acid 1 is completely ionized (B = NEt3).

Beginning with 4d, syn-oxidative addition leads initially to the square-planar Pd(II) complex 14, which is likely in equilibrium with the cationic species 16.4 However, a dissociative mechanism is not required. As pointed out by Arcadi et al.,5a carboxylate anions readily displace the labile triflate ligand from Pd(II) complexes. The resultant π-Pd(II)-carboxylate complex 17 is then effectively removed from the catalytic cycle, and little or no enol lactone (E)-21 is formed. In contrast, under identical conditions the imidoyl chloride 3d efficiently produces the desired lactones 21. This change in reaction pathway is most likely due to the greater stability of the Pd–Cl bond in 15,4a which is inert to both heterolytic cleavage (15 → 16) and direct anionic substitution (15 → 17). Instead, π-complexation takes place by dissociation of a neutral ligand L to form the alkyne complex 18.4,5 Ligand substitution is then followed by nucleophilic capture, affording the π-vinylpalladium intermediate 20 either by direct displacement (18 → 20)5a,b or via an anionic, associative process (18 → 19 → 20).6 In either case, π-bond formation is facilitated by the high nucleophilicity of the participating carboxylate anion. Finally, cis-reductive elimination leads initially to the E-enol lactone 21,5 which undergoes rapid equilibration to the observed E,Z mixture (some bond isomerizations have been omitted for clarity).

A similar analysis applies to the Pd0-initiated coupling—cyclization of alkyne amines 6, which is sluggish when effected with imidoyl chloride 3d, but rapid with triflate 4d (Scheme 4, below). This is the opposite chemoselectivity to that exhibited with alkyne acids 1, and presumably reflects the greatly reduced nucleophilicity of the alkyne amine:π-complex 22, as compared to the alkyne carboxylate:π-complex 18 (cf. Scheme 3). Thus, the amino alkyne group in 22 is slow to substitute Cl − by either direct displacement (22 → 24) or by an associative process (22 → 23 → 24).

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Notes


Last, we consider the coupling of imidoyl triflate 4d and alkyne amines 6, which is important for the synthesis of (H₆)-dipyrrins 12 (Scheme 4). As described above, this transformation was much faster than that observed with chloride 3d and afforded mixtures of dipyrrins 12 and amidines 13.²¹ We briefly explored the possibility that amidines 13 were derived by a Pd⁰-catalyzed process. However, control experiments demonstrated that TFO₂⁻ substitution occurred by direct nucleophilic displacement and was not catalyzed by Pd⁰ when L = PPh₃. The more favorable Pd⁰-initiated coupling of trialkyl 4d and alkyne amines 6 is consistent with a mechanism in which syn-nucleophilic addition of Pd⁰ affords the square planar complex 14, followed by dissociation of the labile TFO²⁻ ligand to give cation 16. An identical sequence was postulated for steps 1–2 in the attempted coupling-cyclization of alkyne acids 1 and imidoyl triflate 4d (cf. Scheme 3). At this point, however, the reaction pathways diverge. With carboxylic acids 1, ion-pair bonding with cation 16 affords the neutral Pd(II)-₀-complex 17, a favorable, albeit nonproductive step (Scheme 3).²⁵ In contrast, primary alkyne amines 6 are less likely to undergo Pd(II)-₀-bond formation. This type of association typically requires concomitant deprotonation by strong base (LiNR₂, NaOR, etc.) or additional activating functionality (SnNR₂).²⁷–²⁹ In the present case, σ-complexation of 6 with 16 is more favorable (Scheme 4) and affords the cationic species 25 which is highly activated toward nucleophilic capture (25 → 24). The resultant α-vinyl palladium complex 24 then undergoes cis-reductive elimination, followed by E,Z equilibration, to give the (H₆)-dipyrrins 12.

A number of observations support the mechanistic pathway(s) outlined in Scheme 4. The most important of these pertain to the effect of ligands L on the course of the Pd⁰-initiated coupling-cyclization. With imidoyl chloride 3d, the nature of L had only a marginal impact on the rate of formation of dipyrrins 12. Low reactivity was observed across a wide range of experimental conditions (Table 1). Employing alkyne amine 6a, the best results were obtained with L = tri(2-furyl)phosphine (TFP), which afforded 30% of dipyrrin 12a and 70% of recovered 3d after 3 h at 75 °C (entry 1). Unfortunately, however, the yield of 12a showed no improvement with increasing time, which instead led to extensive decomposition of 3d (entry 2). Also, little or no dipyrrin 12a was formed employing electron-rich and/or bulky phosphine ligands (entries 3 and 4; PCY₃ = tricyclohexylphosphine; f-Bu₂PO-Ø = 2-[di-tert-butylphosphino]bi-phenyl), or under “ligand-free” conditions (entry 5; dba = dibenzylideneacetone). These data are in agreement with a rate-determining step involving Pd-₀-bond formation (22 → 24), as opposed to substitution of L (15 → 22). Interestingly, at temperatures <80 °C we could detect no trace of amidines 13, the product of noncatalyzed nucleophilic displacement. Rouden et al. have recently noted a similar lack of reactivity of primary amines with heteroaryl imidoyl chlorides.³¹ Finally, we obtained closely related results with other alkyne amines 6.

The reactivity pattern of imidoyl triflate 4d is more complex, owing to the exceptional leaving group ability of TFO⁻. In this case, amidine formation competes effectively with the Pd⁰-initiated coupling-cyclization. We devoted considerable effort to differentiating these...
pathways and, in particular, to adjusting the reactivity of cation 16 (cf. Scheme 4). If sufficiently activated, we believed that ð-complexation of 16 with alkyne amine 6 might be accelerated (16 → 25), thereby favoring the cyclization process. Several experiments designed to probe this possibility are summarized in Table 2 for the reaction of triflate 4d and alkyne amine 6a. Our original conditions employed TFP as ligand, which gave a 52% yield of dipyrrin 12a together with 37% of amidine 13a (entry 1). In this case, electron-rich and/or sterically hindered ligands had a deleterious effect on dipyrrin formation, since cation 16 is stabilized by such groups (cf. Scheme 4). Typically, we observed either increased decomposition (entry 2) or higher proportions of amidines 13 (entry 3). In contrast, the ratio of 12a:13a improved significantly employing "ligand-free" Pd0 (Pd2dba3). This was especially true with weakly coordinating solvents, which afforded ratios of 12a:13a on the order of 8:1 (entries 4–6). However, in DMF this selectivity was reversed, affording only 18% of 12a and 72% of amidine 13a (entry 7). In this case, electron-rich PdL4 afforded ratios of 12a:13a ranging from 31:62 (THF, entry 1) to 18:70 (MeCN, entry 3). These results improved greatly using TFP as ligand, which afforded 48% of dipyrrin 12a and 15% of amidine 13a. However, we obtained none of the desired 12a employing "ligand-free" Pd0 (entry 5), our most effective catalyst system with the internal alkyne amine 6e (Scheme 5; see also Scheme 4). This experiment points toward a different rate determining step in the formation of 12a, as compared to that with dipyrrins 12a (Table 2) and 12e (Table 3). The reasons for this change are not clear. Steric hindrance is not likely to be a factor, since ð-complex 25a is less crowded than the case with internal alkyne 6e (Scheme 5; see also Scheme 4). Also, it is doubtful that the cyclization of 25a to 24a would be significantly slower than with 6e.
with Ph₃P as ligand, which facilitates reductive elimination. Both of these processes should be favorable downfield from Me₄Si as an internal standard. 11 NMR were recorded at 300 MHz and are expressed as ppm from TMS.

**Experimental Section**

Melting points were determined on a Fisher-Johns microscope melting point apparatus and are not corrected. 1H NMR and 13C NMR were recorded at 300 MHz and are expressed as ppm downfield from MeSi as an internal standard.

2-(4,4-Dimethylpyrrolidin-2-yldiene)ethyl)-4,4,5-trimethyl-1-pyrrole-5-carbonitrile (12a). A solution of 35 mg (0.12 mmol) of imidoyl triflate 4d, 20 mg (0.15 mmol) of alkyne amine 6a, and 0.18 mL (1.2 mmol) of NEt 3 in 10 mL of MeCN was degassed with argon for 5 min and was then treated with 26 mg (0.024 mmol) of Pd₂(dba)₃ followed by trans-metalation. In the case of alkyne amine 6d this affords the Pd—ο-alkyne complex 26d, which can produce the desired alkyne amine 12d by either of two pathways: Reductive elimination to the alkyne amine 27d, followed by 5-εo-dig cyclization; or alternatively, initial cyclization of 26d to 24d, followed by reductive elimination. Both of these processes should be favorable with Ph₃P as ligand, which facilitates reductive elimination. At present we cannot conclusively differentiate these pathways, although we have some evidence for the transient formation of alkyne amine 27d.

Currently we are extending this methodology to the synthesis of meso-substituted corrins of type 10, as well as to chlorins and bacteriochlorins of potential use in photodynamic therapy (PDT). The results of these studies will be reported in future papers.

(Scheme 4). Most likely this rate difference derives from the reductive elimination step (24d → 12d), a process that is well-known to be strongly influenced by ligands L. 7

In any event, this difficulty was circumvented using a relatively minor modification. Thus, with PPh₃/Cul/NET₃ as co-reactants (entry 6), we obtained dipyrin 12d as the exclusive product under conditions otherwise identical to those employed in entry 1. This transformation is a variant of a Sonogashira coupling, 9 which is initiated by the Pd/NET₃-catalyzed production of Cu-acetylides, followed by trans-metalation. In the case of alkyne amine 6d this affords the Pd—ο-alkyne complex 26d, which can produce the desired alkyne amine 12d by either of two pathways: Reductive elimination to the alkyne amine 27d, followed by 5-εo-dig cyclization; or alternatively, initial cyclization of 26d to 24d, followed by reductive elimination. Both of these processes should be favorable with Ph₃P as ligand, which facilitates reductive elimination. At present we cannot conclusively differentiate these pathways, although we have some evidence for the transient formation of alkyne amine 27d.

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(11) Copies of NMR spectra for compounds 12a, d and 13a, e are available in the Supporting Information for ref 1d.
stirred at room temperature for a period of 16 h. The reaction mixture was then concentrated to dryness. The residue was diluted with 100 mL of CH₂Cl₂, washed with saturated NaHCO₃ and saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give 59 mg (97%) of 13d as a colorless oil: Rf 0.10 (25% EtOAc/hexane); IR (neat) 3295, 3213, 3037, 2966, 2226, 2108, 1602 (vs), 1472, 1449, 1367; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (s, 3H), 1.26 (s, 6H), 1.32 (s, 3H), 1.49 (s, 3H), 1.69 (t, J = 6.0 Hz, 2H), 2.15 (s, 1H), 2.22/2.28/2.55/2.61 (AB, J = 18.0 Hz, 2H), 3.47 (br m, 2H), 4.59 (br s, 1H); MS (EI) m/z 246 (M⁺ + H, 14), 219 (M⁺ – CN, 100); HRMS (EI) calcd for C₁₅H₂₄N₃ (M⁺ + H) 246.1970, found 246.1964.

Acknowledgment. Financial support of this work by the National Institutes of Health, NIGMS Grant No. GM38913 is gratefully acknowledged.