Conversion of α-Anilino Alkenenitriles to Amides by Chemoselective Palladium-Catalyzed Arylations

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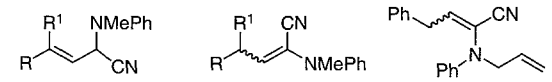
The reactions of α-anilino alkenenitriles with iodobenzene catalyzed by palladium gave amides and benzonitrile. A general mechanism is proposed to explain the chemoselective arylation at the cyano group.

Introduction

The Heck reaction[1] is one of the powerful methods for carbon-carbon bond formation. The palladium-catalyzed reactions of aryl or vinyl halide with olefin in inter- and intramolecular manner were widely used in organic synthesis. We demonstrated in a previous paper[2] that intramolecular palladium-catalyzed arylation at cyano group is feasible. Using this method, a series of α-(*o*-bromoanilino)alkenenitriles is converted to 2-(*N*-methylamino)benzonitrile and varied γ-carbolines. The organopalladium complex undergoes intramolecular cyclizations chemoselectively by attacking the cycano group but not the olefinic double bonds. α-Amino alkenenitriles are versatile in organic synthesis, they can function as Michael acceptors,[3] induce carbonyl umpolungs[4] and are precursors of α-amino acids.[5] Conjugated α-amino alkenenitriles are generally hydrolyzed by an acid catalyst to afford the corresponding acids.[6] In this paper we report the conversion of α-anilino alkenenitriles **1** and **2** to the corresponding amides **5** and **6** by intermolecular chemoselective palladium-catalyzed arylation.

Results and Discussion

The requisite starting materials **1** and **2** were prepared according to the literature methods.[7] α,β-Unsaturated aldehydes were condensed with KCN and anilines (the Strecker reaction)[8] to give high yields of α-anilino β-alkenenitriles **1a–e**. Treatment of **1a–e** with a strong base *t*-BuOK in *t*-BuOH–THF at 0 °C for 2 h gave the more stable conjugated α-anilino alkenenitriles **2a–e**.[7] The (*Z*)-isomers exhibited the H-3 and C-3 signals at lower fields than those of the (*E*)-isomers due to the deshielding effect of the cyano group.[9] 2-(*N*-Methylanilino)but-2-enenitrile **2f** was prepared from 2-(*N*-methylanilino)butanenitrile by consecutive sulfenylation and dehydrosulfenylation.[10] 2-(*N*-Allylanilino)-4-phenylbut-2-enenitrile **2g** was prepared from the Strecker reaction of cinnamaldehyde followed by the double bond migration.[11]



1a R = Me, R¹ = H
1b R = Et, R¹ = H
1c R = Pr, R¹ = H
1d R = R¹ = Me
1e R = Ph, R¹ = H

2a R = Me, R¹ = H
2b R = Et, R¹ = H
2c R = Pr, R¹ = H
2d R = R¹ = Me
2e R = Ph, R¹ = H
2f R = R¹ = H

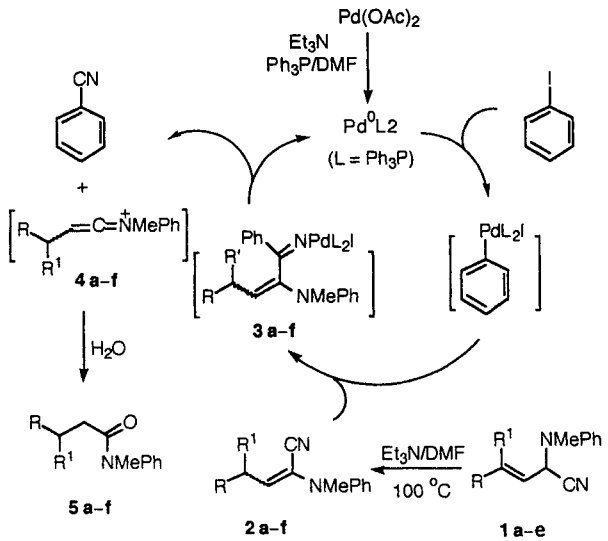
2g

Table 1 lists the results of the palladium-catalyzed reactions of **1** and **2** with iodobenzene. In a typical procedure, the α-anilino alkenenitrile **1a** was treated with PhI (3 equiv), $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv) and Et_3N (1.2 equiv) in DMF at 100 °C for 24 h under an argon atmosphere.[12] The reaction mixture was worked up and separated by silica gel chromatography using EtOAc/hexane as eluent to give *N*-methyl-*N*-phenylbutanamide **5a**[13] and benzonitrile in 63% and 58% yields, respectively. Amides **5b–f** were also obtained in 50-86% yields from the reactions of **1b–e** and **2a–f** by the palladium-catalyzed arylations.

Table 1. Conversion of α-anilino alkenitriles (1 or 2) to amides (5 or 6) via palladim-catalyzed arylations[a]

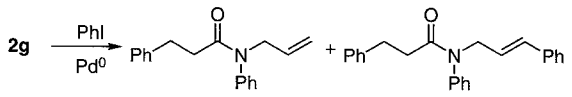
Entry	Substrate	Products (yield %)[b] Amides + Benzonitrile **7**
1	**1a**	**5a** (63) + **7** (52)
2	**2a*E***	**5a** (85) + **7** (68)
3	**2aZ**	**5a** (80) + **7** (72)
4	**1b**	**5b** (60) + **7** (48)
5	**2b*E***	**5b** (86) + **7** (78)
6	**2bZ**	**5b** (82) + **7** (75)
7	**1c**	**5c** (50) + **7** (38)
8	**2c*E***	**5c** (72) + **7** (63)
9	**2cZ**	**5c** (52) + **7** (35)
10	**1d**	**5d** (62) + **7** (47)
11	**2d*E***	**5d** (85) + **7** (75)
12	**2dZ**	**5d** (80) + **7** (70)
13	**1e**	**5e** (60) + **7** (42)
14	**2e*E***	**5e** (82) + **7** (70)
15	**2eZ**	**5e** (75) + **7** (68)
16	**2f*E***	**5f** (77) + **7** (70)
17	**2fZ**	**5f** (70) + **7** (58)
18[c]	**2g**	**5g** (35) + **6** (22) + **7** (45)

[a]The reactions were carried out under an argon atmophere with anilinoalkenenitrile(**1** or **2**), PhI (3 equiv), Et_3N (1.2 equv), Ph_3P (20 mol%), and $Pd(OAc)_2$ (10 mol%) in DMF at 100 °C for 24 h to give amides (**5** or **6**) and benzonitrile. [b]Isolated yields of amides and benzonitrile. [c]When the reaction time was increased to 40 h, amides **5g** and **6** were obtained in 25% and 30% yields, respectively.



Scheme 1

A proposed mechanism of the palladium-catalyzed arylations is shown in Scheme 1. The reaction was presumably initiated by an oxidative insertion of Pd^0 to iodobenzene. The phenylpalladium added at the cyano group of 2-amino-2-alkenenitriles **2**, but not at the olefinic double bond. Owing to the effect of the α-amino group, the iminopalladium intermediate **3** ruptured readily to give benzonitrile and the iminium ion **4**, which was subsequently hydrolysed to give the amides **5**. Both the *E*- and *Z*-isomers of **2** reacted similarly. In the presence of Et_3N, 2-anilino-3-alkenenitriles **1** might isomerize to the thermodynamically favored conjugated α-anilino alkenenitriles **2** at high temperature.



5g **6**

(Eq 1)

For *N*-allyl-4,*N*-diphenyl-2-butanenitrile **2g**, the palladium-catalyzed reaction (Eq 1) was similarly carried out to give the desired amide **5g** (35%) and a further phenylated product **6** (22%), *N*-cinnamyl-4,*N*-diphenylpropanamide. The yield of **6** increased as the reaction time increased. From these results, arylation at the cyano group appeared to be kinetically favored over the arylation at the olefinic double bond, although the intramolecular mode has been found.[2b]

In summary, this study demonstrates the preference of palladium-catalyzed phenylation at the cyano group over the olefinic double bond. This is the first report of conversion of α-amino alkenenitriles to their corresponding amides. In the mean time, iodobenzene is transformed into benzonitrile via cyanation of the phenylpalladium intermediate.

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(13) Analytical data for amides **5a–5g** and **6**:

***N*-Methyl-*N*-phenylbutanamide (5a).** Oil; TLC (EtOAc/hexane (15:85)) R_f = 0.125; IR (neat) 2950, 1640 (CO), 1590, 1490, 1380, 765, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.77 (3 H, t, *J* = 7 Hz), 1.54 (2 H, qt, *J* = 7, 7 Hz), 2.00 (2 H, t, *J* = 7 Hz), 3.21 (3 H, s), 7.10–7.14 (2 H, m), 7.27–7.40 (3 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6 (q), 18.7 (t), 35.8 (t), 37.1 (q), 127.1 (2 C, d), 127.5 (d), 129.5 (2 C, d), 144.1 (s), 172.9 (s, CO); MS, *m/z* (rel intensity) 178 (29, $[M+1]^+$), 177 (53, M^+), 107 (100), 93 (29), 77 (62); HRMS calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1154; Anal. Calcd for $C_{11}H_{15}NO$: C, 74.53; H, 8.54; N, 7.91. Found C, 74.89; H, 8.61; N, 7.76.

***N*-Methyl-*N*-phenylpentanamide (5b).** Oil; TLC (EtOAc/hexane (20:80)) R_f = 0.19; IR (neat) 2960, 1650 (CO), 1590, 1490, 770, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.72 (3 H, t, *J* = 7 Hz), 1.13 (2 H, qt, *J* = 7, 7 Hz), 1.48 (2 H, tt, *J* = 7, 7 Hz), 2.00 (2 H, t, *J* = 7 Hz), 3.18 (3 H, s), 7.07–7.12 (2 H, m), 7.24–7.37 (3 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5 (q), 22.1 (t), 27.4 (t), 35.5 (t), 37.1 (q), 127.1 (2 C, d), 127.4 (d), 129.5 (2 C, d), 144.1 (s), 173.0 (s, CO); MS, *m/z* (rel intensity) 191 (18, M^+), 149 (65), 134 (12), 107 (100), 92 (23), 77 (71); HRMS calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1310; Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found C, 74.99; H, 8.90; N, 7.17.

***N*-Methyl-*N*-phenylhexanamide (5c).** Oil; TLC (EtOAc/hexane (10:90)) R_f = 0.11; IR (neat) 2940, 1640 (CO), 1590, 1490, 770, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.78 (3 H, t, *J* = 7 Hz), 1.11-1.21 (4 H, m), 1.45-1.60 (2 H, m), 2.02 (2 H, t, *J* = 7 Hz), 3.22 (3 H, s), 7.13 (2 H, dd, *J* = 8, 1 Hz), 7.28–7.41 (3 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7 (q), 22.2 (t), 25.1 (t), 31.3 (t), 33.9 (t), 37.1 (q), 127.1 (2 C, d), 127.5 (d), 129.5 (2 C, d), 144.1 (s), 173.2 (s, CO); MS, *m/z* (rel intensity) 205 (16, M^+), 133 (12), 107 (100), 92 (23), 77 (69); HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1468; Anal. Calcd for $C_{13}H_{19}NO$: C, 76.04; H, 9.33; N, 6.83. Found C, 75.87; H, 9.12; N, 6.65.

3,*N*-Dimethyl-*N*-phenylbutanamide (5d). Oil; TLC (EtOAc/hexane (20:80)) R_f = 0.20; IR (neat) 2950, 1640 (CO), 1590, 1490, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.76 (6 H, d, *J* = 6.6 Hz), 1.89 (2 H, d, *J* = 6.8 Hz), 1.95–2.10 (1 H, m), 3.19 (3 H, s), 7.06–7.11 (2 H, m), 7.25–7.39 (3 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.4 (2 C, q), 25.8 (d),37.2 (q), 42.7 (t), 127.4 (2 C, d), 127.5 (d), 129.6 (2 C, d), 144.3 (s), 172.5 (s, CO); MS, *m/z* (rel intensity) 192 (18, $[M+1]^+$), 191 (46, M^+), 149 (36), 134 (32), 107 (100), 92 (24), 77 (82); HRMS calcd for $C_{12}H_{17}NO$ 1191.1310, found 191.1310; Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found C, 74.90; H, 8.53; N, 7.25.

***N*-Methyl-3,*N*-diphenylpropanamide (5e).** Oil; TLC (EtOAc/hexane (20:80)) R_f = 0.18; IR (neat) 3020, 2930, 1650 (CO), 1590, 1490, 770, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (2 H, t, *J* = 7.5 Hz), 2.90 (2 H, t, *J* = 7.5 Hz), 3.23 (3 H, s), 7.02 (4 H, dd, *J* = 8, 8 Hz), 7.16 (2 H, dd, *J* = 8, 8 Hz), 7.23–7.39 (4 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.7 (t), 35.9 (t), 37.3 (q), 122.3 (d), 125.9 (2 C, d), 127.7 (d), 128.2 (2 C, d), 128.3 (2 C, d), 129.6 (2 C, d), 141.1 (s), 143.9 (s), 172.1 (s, CO); MS, *m/z* (rel intensity)

239 (36, M^+), 149 (65), 107 (100), 91 (50), 77 (45); HRMS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1304; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.29; H, 7.16; N, 5.86. Found C, 79.97; H, 7.87; N, 5.61.

***N*-Methyl-*N*-phenylpropanamide (5f).** Oil; TLC (EtOAc/hexane (20:80)) $R_f = 0.16$; IR (neat) 2950, 1640 (CO), 1590, 1490, 1385, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (3 H, t, $J = 7.5$ Hz), 2.02 (2 H, q, $J = 7.5$ Hz), 3.22 (3 H, s), 7.13 (2 H, dd, $J = 8$, 1 Hz), 7.28–7.37 (3 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.52 (q), 27.3 (t), 37.2 (q), 127.1 (2 C, d), 127.5 (d), 129.5 (2 C, d), 144.1 (s), 173.8 (s, CO); MS, *m/z* (rel intensity) 164 (87, $[M+1]^+$), 163 (95, M^+), 135 (70), 107 (100), 106 (100), 77 (91); HRMS calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0999.

***N*-Allyl-3,*N*-diphenylpropanamide (5g).** Oil; TLC (EtOAc/hexane (10:90)) $R_f = 0.11$; IR (neat) 3050, 1640 (CO), 1590, 1490, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.34 (2 H, t, $J = 8$ Hz), 2.90 (2 H, t, $J = 8$ Hz), 4.26 (2 H, dd, $J = 6$, 1 Hz), 5.00 (1 H, dd, $J = 17$, 1 Hz), 5.07 (1 H, dd, $J = 10$, 1 Hz), 5.72–5.89 (1 H, m), 6.97–7.33 (10 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.6 (t), 36.0 (t), 52.1 (t), 117.6 (t), 125.9 (d), 126.3 (s), 127.8 (d), 128.2 (4 C, d), 128.3 (3 C, d), 129.4 (d), 133.0 (d), 141.0 (s), 171.6 (s, CO); MS, *m/z* (rel intensity) 265 (49, M^+), 133 (100), 132 (34), 105 (40), 91 (65), 77 (35); HRMS calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1463; Anal. Calcd for $C_{18}H_{19}NO$: C, 81.46; H, 7.22; N, 5.28. Found C, 81.13; H, 7.38; N, 5.11.

***N*-Cinnamyl-3,*N*-diphenylpropanamide (6).** Oil; TLC (EtOAc/hexane (10:90)) $R_f = 0.10$; IR (neat) 3020, 1640 (CO), 1590, 1490, 960, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (2 H, t, $J = 8$ Hz), 2.93 (2 H, t, $J = 8$ Hz), 4.41 (2 H, d, $J = 6$ Hz), 6.21 (1 H, dt, $J = 16$, 6 Hz), 6.35 (1 H, d, $J = 16$ Hz), 7.00–7.33 (15 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.6 (t), 36.0 (t), 51.6 (t), 124.3 (d), 125.9 (d), 126.3 (2 C, d), 127.5 (d), 127.9 (d), 128.2 (3 C, d), 128.3 (5 C, d), 129.4 (2 C, d), 133.1 (d), 136.6 (s), 141.0 (s), 142.2 (s), 171.7 (s, CO); MS, *m/z* (rel intensity) 341 (21, M^+), 161 (72), 132 (100), (117 (63), 106 (61), 91 (73), 77 (77); HRMS calcd for $C_{24}H_{23}NO$ 341.1780, found 341.1781; Anal. Calcd for $C_{24}H_{23}NO$: C, 84.41; H, 6.79; N, 4.10. Found C, 83.98; H, 7.02; N, 3.98.