Tetrahedron Letters, Vol.32, No.2, pp 237-240, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

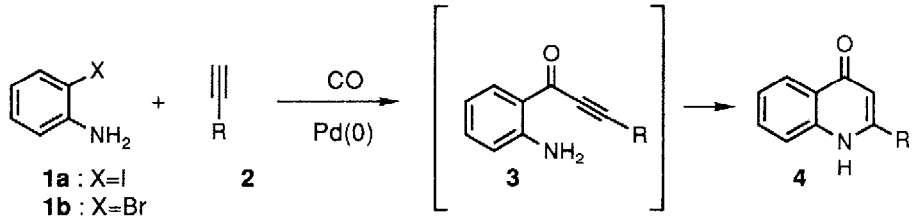
PALLADIUM-CATALYZED CARBONYLATION TO FORM 2-SUBSTITUTED 1,4-DIHYDRO-4-OXO-QUINOLINE

Sigeru TORII,* Hiroshi OKUMOTO, and Long He XU
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima Naka, Okayama 700, JAPAN

Summary; Palladium-catalyzed carbonylation of 2-haloaniline in the presence of terminal acetylenes under proper conditions (20 $Kgcm^{-2}$ of CO at 120 °C) gave a variety of 2-substituted 1,4-dihydro-4-oxo-quinolines in good yields.

Palladium-catalyzed carbonylation has been a powerful tool for the formation of a variety of carbonyl compounds.[1] We have been investigating a carbonylative cyclization of 2-haloaniline derivatives to exploit a straightforward route directed toward quinolinone carboxylic acids.[2] In the course of our research, we have found that the carbonylative coupling reaction of 2-haloaniline or 2-halophenol with terminal acetylenes smoothly occurs, giving rise to 2-substituted 1,4-dihydro-4-oxo-quinoline or flavone analogues, respectively, in good yields. A recent publication[3] in a similar carbonylation of 2-iodophenol leading to flavones prompted us to report our results on the synthesis of the 4-quinolinones, which are the common skeleton of a number of intriguing compounds including the quinolinone antibiotics,[4] an anticancer natural product,[5] and some biologically active substrates.[6]

Our scheme of the convergent construction of such a heterocyclic ring is composed of the carbonylative coupling of 2-haloaniline **1** with terminal acetylenes **2**[7] and ensuing cyclization of **3** as illustrated below.

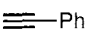
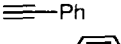
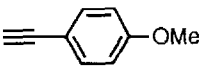
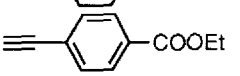
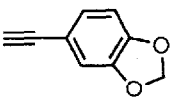
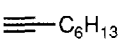
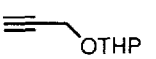
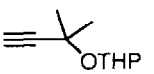
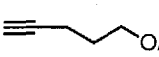


1a : X=I
1b : X=Br
2
3
4

While the reaction took place even at balloon pressure of carbon monoxide, the yield of the product was slightly lower and longer reaction time was required. Pressure of 20 $Kgcm^{-2}$ was enough to complete the carbonylation. The kind of the palladium catalyst showed a little influence on the yield, whereas change of the base and the solvent seriously affected the formation of the desired product. Inspection of the reaction conditions revealed that carbonylation in diethylamine with $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf) as catalyst gave the best

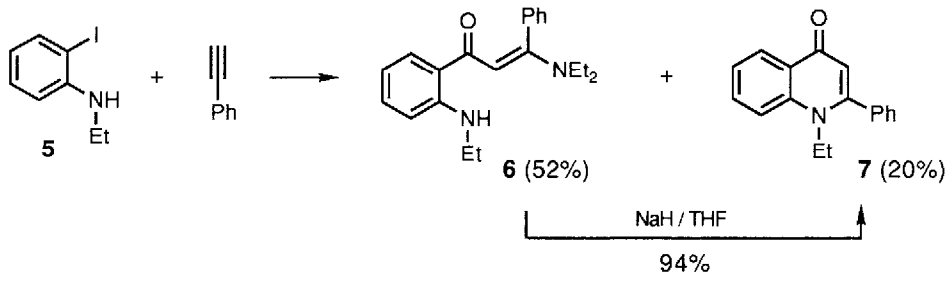
results. Although the formation of a usual carbonylation product, *i.e.* *N,N*-diethyl aroylamide, was suspected under this condition, neither such a simple amide nor intermediary acetylenic ketones **3** were detected in each attempt. Use of solvent such as DMF, THF, and so on resulted in the decrease in the yield. The results of the carbonylative coupling leading to a variety of 2-substituted quinolinones[6] are collected in Table 1.[8]

Table 1. Carbonylative Formation of Quinolinones [a)]

Entry	1	2	4 (%)
1	**a**		**a** (90)
2	**b**		**a** (55)
3	**a**		**b** (95)
4	**a**		**c** (85)
5	**a**		**d** (88)
6	**a**		**e** (75) [b)]
7	**a**		**f** (64)
8	**a**		**g** (61)
9	**a**		**h** (66)
10	**a**		**i** (62)

a) The reaction was carried out by using **1** (1 mmol), terminal acetylene **2** (2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), in Et_2NH (3 mL) at 120 °C for 6 h at 20 $Kgcm^{-2}$ of CO pressure. b) 1-Octyne (3 mmol) was used.

Iodoaniline **1a** is preferred to bromoaniline **1b** to gain a higher yield. When the reaction was carried out with **1a** and phenylacetylene **2a**, the expected product **4a** was obtained in 90% yield (Entry 1), while the bromide **1b** produced **4a** in 55% (Entry 2). The reaction of the aryl acetylenes generally gave better yields than that of the aliphatic acetylenes as can be seen in Table 1 (compare Entries 1-5 with Entries 6-10). Acidity of the acetylene proton may be a crucial factor for this result. Functional groups such as acetal, THP, and ester are found to be compatible with the reaction conditions and the corresponding quinolinones were afforded in satisfactory yields. These functionalized quinolinones would be versatile precursors for the synthesis of the above mentioned intriguing compounds.



When the amino group of 2-haloaniline is primary, the ensuing nucleophilic cyclization readily proceeded as shown in Table 1. On the contrary, the reaction of the alkylated aniline homologue **5** under the same reaction conditions afforded the corresponding cyclized product **7** in only 20% yield. The enamine **6** was obtained in 52% yield as a main product, which is apparently formed by the 1,4-addition of diethylamine to the intermediary acetylene ketone.[6] Further heating of the enamine **6** in THF in the presence of sodium hydride caused smooth cyclization leading to the quinolinone **7**, quantitatively.

Thus, a new methodology to obtain a variety of quinolinone derivatives has been developed by palladium-catalyzed carbonylative coupling of 2-haloaniline and terminal acetylene compounds with carbon monoxide under mild conditions.

We are grateful to the SC-NMR Laboratory of Okayama University for obtaining high resolution NMR spectra.

References and Notes

(1) Tsuji, J. *Organic Synthesis with Palladium Compounds;* Springer-Verlag: Berlin, 1980; p145-146; Heck, R. F. *Palladium Reagents in Organic Syntheses;* Academic Press: London, 1985; Chapter 8; Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis;* Pergamon Press: Oxford, 1982; p378-394.

(2) Torii, S.; Okumoto, H.; Xu, L-H. *Tetrahedron Lett.* in press.

(3) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1990**, 31, 4073. However, a different result is also reported. See: Catellani, M.; Chiusoli, G. P.; Costa, M. *Pure & Appl. Chem.* **1990**, 62, 623.

(4) Crumplin, G. C.; Midgley, J. M.; Smith, J. T. *Part A, Mechanism of Action of Nalidixic Acid and its Congeners;* in *Topics in Antibiotic Chemistry;* John Wiley & Sons: New York, 1980; Vol. 3.

(5) Aimi, A.; Nishimura, M.; Miwa, A.; Hoshino, H.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1989**, 30, 4991; Aimi, A.; Hoshino, H.; Nishimura, H.; Sakai, S.; Haginiwa, J. *ibid.* **1990**, 31, 5169.

(6) Hormi, O. E. O.; Peltonen, C.; Heikkilä, L. *J. Org. Chem.* **1990**, 55, 2513; Chen, B.; Huang, X.; Wang, J. *Synthesis* **1987**, 482 and references cited therein.

(7) A palladium-catalyzed carbonylative coupling to produce aryl acetylene ketones has been reported. Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1981**, 333.

(8) General procedure: A mixture of aryl halide **1** (1 mmol), terminal acetylene **2** (2 mmol), and $PdCl_2(PPh_3)_2$ (0.05 mmol) in diethylamine (3 mL) was stirred at 120 °C under carbon monoxide of 20 $Kgcm^{-2}$ for 6 h. After usual work up, the quinolinone **4** was isolated by column chromatography or recrystallization. The spectral data (^1H (200 MHz), ^{13}C NMR (50 MHz), and IR) are shown below.

4a: IR (KBr) 3460, 1636, 1599, 1584, 1549, 1506 cm^{-1}; ^1H NMR (MeOH-d_4) 6.58 (s, 1 H), 7.40-7.82 (m, 8 H), 8.29 (d, J = 7.90 Hz, 1 H); ^{13}C NMR (MeOH-d_4) 108.48, 119.71, 125.40, 125.75, 125.97, 128.55 (2C), 130.29 (2C), 131.93, 133.70, 135.46, 141.95, 153.57, 180.64.

4b: IR (KBr) 3426, 1632, 1599, 1580, 1543, 1504 cm^{-1}; ^1H NMR (DMSO-d_6) 3.84 (s, 3 H), 6.31 (br, 1 H), 7.08-7.18 (m, 2 H), 7.32 (ddd, J = 1.02, 6.93, 8.03 Hz, 1 H), 7.65 (ddd, J = 1.43, 6.93, 8.33 Hz, 1 H), 7.68-7.83 (m, 3 H), 8.09 (dd, J = 1.43, 8.03 Hz, 1 H), 11.69 (br, 1 H); ^{13}C NMR (DMSO-d_6) 55.49, 106.61, 114.51 (2C), 118.81, 123.24, 124.79, 124.90, 126.31, 129.01 (2C), 131.78, 140.65, 149.84, 161.18, 177.02.

4c: IR (KBr) 3444, 1719, 1638, 1599, 1578, 1549, 1512 cm^{-1}; ^1H NMR (DMSO-d_6) 1.34 (t, J = 7.08 Hz, 3 H), 4.35 (q, J = 7.08 Hz, 2 H), 6.40 (d, J = 1.46 Hz, 1 H), 7.35 (ddd, J = 1.17, 6.85, 8.03 Hz, 1 H), 7.68 (ddd, J = 1.32, 6.85, 8.01 Hz, 1 H), 7.78 (br d, J = 8.01 Hz, 1 H), 7.96-8.14 (m, 5 H), 11.86 (br, 1 H); ^{13}C NMR (DMSO-d_6) 14.29, 61.25, 108.13, 118.94, 123.62, 124.88, 125.08, 128.01 (2C), 129.73 (2C), 131.49, 132.16, 138.53, 140.65, 148.88, 165.31, 177.11.

4d: IR (KBr) 3464, 1636, 1601, 1557, 1510 cm^{-1}; ^1H NMR (DMSO-d_6) 6.12 (s, 2 H), 6.32 (s, 1 H), 7.09 (d, J = 8.05 Hz, 1 H), 7.27-7.42 (m, 3 H), 7.62 (ddd, J = 1.35, 6.87, 8.30 Hz, 1 H), 7.75 (d, J = 8.30 Hz, 1 H), 8.07 (dd, J = 1.35, 8.05 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 101.84, 106.68, 107.63, 108.71, 119.11, 121.88, 123.22, 124.66, 124.78, 128.29, 131.69, 140.86, 147.92, 149.16, 149.97, 176.69.

4e: IR (KBr) 3432, 1642, 1599, 1547, 1502 cm^{-1}; ^1H NMR (MeOH-d_4) 0.88 (t, J = 6.32 Hz, 3 H), 1.25-1.41 (m, 6 H), 1.65-1.75 (m, 2 H), 2.68 (t, J = 7.69 Hz, 2 H), 6.22 (s, 1 H), 7.36 (ddd, J = 1.39, 6.79, 8.18 Hz, 1H), 7.60 (br d, J = 8.39 Hz, 1 H), 7.71 (ddd, J = 1.60, 6.79, 8.39 Hz, 1 H), 8.32 (dd, J = 1.60, 8.18 Hz, 1 H); ^{13}C NMR (MeOH-d_4) 12.48, 21.68, 28.02, 28.25, 30.74, 33.10, 106.92, 117.18, 123.14, 123.58, 123.79, 131.47, 139.70, 155.22, 178.71.

4f: IR (neat) 3380, 1638, 1603, 1557, 1514 cm^{-1}; ^1H NMR (MeOH-d_4) 1.51-1.83 (m, 6 H), 3.49-3.96 (m, 2 H), 4.52-4.76 (m, 3 H), 6.36 (s, 1 H), 7.30-7.38 (m, 1 H), 7.59-7.64 (m, 2 H), 8.21 (d, J = 8.24 Hz, 1 H); ^{13}C NMR (MeOH-d_4) 18.33, 24.42, 29.39, 61.48, 64.58, 98.17, 105.96, 117.42, 123.16, 123.90, 124.02, 131.55, 139.48, 150.46, 178.65.

4g: IR (KBr) 3472, 1630, 1597, 1562, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) 1.46-1.82 (m, 6 H), 1.58 (s, 6 H), 3.41-3.98 (m, 2 H), 4.63 (dd, J = 2.54, 6.50 Hz, 1 H), 6.26 (s, 1 H), 7.20-7.29 (m, 1 H), 7.51 (br, 1 H), 7.52 (br, 1 H), 8.28 (d, J = 8.06 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 20.88, 24.81, 27.18, 27.71, 32.08, 64.62, 77.20, 95.88, 105.97, 117.96, 123.34, 124.84, 125.52, 131.71, 139.35, 156.48, 178.92.

4h: IR (KBr) 3320, 1734, 1647, 1601, 1551, 1516 cm^{-1}; ^1H NMR ($CDCl_3$) 1.84 (s, 3 H), 2.06-2.10 (m, 2 H), 2.84 (t, J = 7.81 Hz, 2 H), 4.06 (t, J = 6.34 Hz, 2 H), 6.26 (s, 1 H), 7.36 (dd, J = 7.08, 7.79 Hz, 1 H), 7.58 (ddd, J = 1.46, 7.08, 8.19 Hz, 1 H), 7.77 (d, J = 7.79 Hz, 1 H), 8.33 (dd, J = 1.22, 8.19 Hz, 1 H), 13.09 (br, 1 H); ^{13}C NMR ($CDCl_3$) 20.66, 27.88, 30.66, 63.13, 107.96, 118.63, 123.65, 124.74, 124.92, 131.86, 140.70, 154.22, 170.87, 178.70.

4i: IR (KBr) 3298, 1729, 1647, 1599, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) 2.06 (m, 2 H), 2.32 (t, J = 7.84 Hz, 2 H), 2.78 (t, J = 7.75 Hz, 2 H), 3.56 (s, 3 H), 6.24 (s, 1 H), 7.31 (dd, J = 7.15, 8.14 Hz, 1 H), 7.56 (ddd, J = 1.28, 7.15, 8.34 Hz, 1 H), 7.75 (br d, J = 8.14 Hz, 1 H), 8.31 (dd, J = 1.28, 8.34 Hz, 1 H), 12.77 (br, 1 H); ^{13}C NMR ($CDCl_3$) 24.08, 32.92, 33.22, 51.58, 108.18, 118.63, 123.67, 124.78, 125.04, 131.86, 140.66, 154.18, 173.28, 178.73.

(Received in Japan 15 October 1990)