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A DIRECT APPROACH TO 2-SUBSTITUTED 1,4-DIHYDRO-4-OXO-QUINOLINE-3-CARBOXYLATES BY PALLADIUM-CATALYZED CARBONYLATIVE CYCLIZATION

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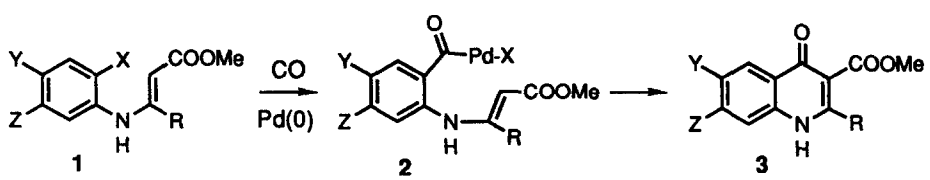
Summary; Carbonylation of 3-substituted 3-(2-haloarylamino)prop-2-enoates in the presence of palladium catalyst under 20 $Kgcm^{-2}$ of CO at 120 °C resulted in the heterocyclization to form a variety of 2-substituted 1,4-dihydro-4-oxo-quinoline-3-carboxylates in good yields.

Since a remarkable effect of nalidixic acid on Gram-negative bacteria was found,[1] a large number of its analogues have been synthesized and evaluated.[2,3] The structural frame of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid is indispensable for the bioactivity.[2,3] Synthetic efforts have been focused on the construction of such a highly oxidized framework, and the modification of the substituents has been also performed at the positions 1 and 7.[3] Although we have investigated more flexible and efficient synthetic paths by the utilization of an electrochemical oxidation,[4] some restrictions are still left to obtain the optionally functionalized quinolinone derivatives.

Herein, we wish to demonstrate a straightforward approach to provide the quinolinone derivatives **3** containing a variety of substituents at optional positions by palladium-catalyzed carbonylative heterocyclization as shown in the following scheme. This method is of practical importance because of the wide choice of the group R in addition to the fact that the benzene ring may carry a diverse number of substituents. Carbonylation of aromatic halides with palladium catalyst has been widely used in organic synthesis.[5] The intermediary acylpalladium species such as **2** can react with carbon nucleophiles leading to the ketones.[6] However, attempts to construct heterocyclic rings by employing enamine as a nucleophile have not been reported.



Carbonylation of the iodide **1a** proceeded even under balloon pressure of carbon monoxide at 120 °C to give the desired product **3a** in 54% yield. However, the reaction was too slow in a practical sense and accompanied 22% of 2-methyl-3-methoxycarbonylindole as the usual Heck reaction product without insertion of carbon monoxide.[7] Increase of the pressure up to 20 $Kgcm^{-2}$ caused the envisioned cyclization efficiently, whereas 30 $Kgcm^{-2}$ was required for the bromide **1b** to obtain a similar yield. Investigation of the reaction conditions revealed that the combination of palladium acetate, triphenylphosphine, and potassium carbonate in DMF is an optimized choice. A representative procedure for the palladium-catalyzed carbonylative cyclization

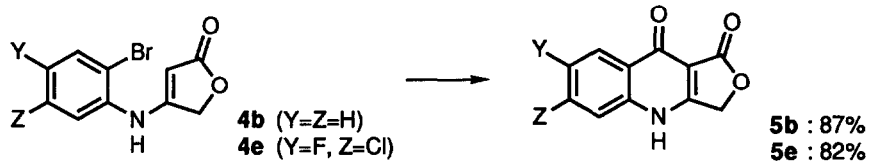
is as follows. A mixture of **1a** (243 mg, 0.767 mmol), palladium acetate (9.8 mg, 0.043 mmol), triphenylphosphine (43 mg, 0.163 mmol), and potassium carbonate (323 mg, 2.3 mmol) in DMF (3 mL) was stirred at 120 °C under 20 $Kgcm^{-2}$ of carbon monoxide for 20 h. Since the crude material sometimes contains a small amount of quinolinone carboxylic acid, the residue obtained by evaporation of the solvent was treated with diazomethane. Concentration followed by column chromatography afforded the quinolinone **3a** (137 mg) in 82% yield. The results of the attempted carbonylative cyclization producing a variety of substituted quinolinone-3-carboxylic acid esters are listed in Table 1.[8]

Table 1. Carbonylative Cyclization to Form Quinolinone Framework

Entry	1	X	Y	Z	R	3 (%)
1	**a**	I	H	H	Me	**a** (82)
2	**b**	Br	H	H	Me	**a** (82)
3	**c**	I	H	H	CH_2COOMe	**c** (67)
4	**d**	I	H	H	COOMe	**d** (24)
5	**e**	Br	F	Cl	Me	**e** (75)
6	**f**	Br	F	F	Me	**f** (37)
7	**g**	Br	F	Cl	CH_2COOMe	**g** (55)

The reaction was carried out by using **1** (0.7 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), K_2CO_3 (3 equiv.), DMF (3 mL) at 120 °C for 20 h under 20 $Kgcm^{-2}$ of CO pressure for the iodides and 30 $Kgcm^{-2}$ for the bromides. The crude products were treated with diazomethane before purification.

As a result, **3a** was obtained in 82% yield from both the iodide **1a** (Entry 1) and the bromide **1b** (Entry 2). Reaction of the enamine **1c** substituted with acetic acid ester moiety produced the corresponding compound **3c** in a satisfactory yield (Entry 3). Quinolinone **3d** involving methoxycarbonyl group at the 2 position was also prepared (Entry 4). On the other hand, most of the commonly used quinolinone antibiotics often consist of not only fluorine atom at the 6 position but also a variety of amino pendants at the 7 position which can be incorporated by a simple displacement of halogen atoms with amines.[3,4] For the preparation of such molecules, **3e** and **3g** are considered to be the most versatile intermediates. The carbonylation of the halides **1e** and **1g** containing three different halogen atoms under 30 $Kgcm^{-2}$ of carbon monoxide pressure smoothly lead to the expected products **3e** and **3g** in 75% and 55% yields respectively as indicated in Entries 5 and 7. Both fluorine and chlorine atoms remained intact. However, difluoride **1f** gave a lower yield (Entry 6). Furthermore, other functionalized enamines **4** were submitted to the carbonylative heterocyclization under the similar conditions to those of the bromides **1e** through **1g**. Reaction of the lactone **4e** resulted in the successful formation of the desired product **5e** in 82% yield and **5b** was also obtained in a comparable yield. Hydrolysis of the lactone **5** may provide other intriguing quinolinone carboxylic acids.



Thus, several versatile intermediates for the synthesis of the quinolinone-3-carboxylic acid antibiotics could be afforded in two steps which are composed of condensation of anilines and ketones[8] and subsequent carbonylation. A variety of interesting appendages, whose introduction was difficult in the previous synthetic methods in spite of much interest, could be readily attached at the 2-position. The chlorides **3e**, **3g**, and **5e** are properly substituted for further elaboration directed toward the synthesis of the highly functionalized quinolinone antibiotics, since the substitution of their chlorine atom with amine nucleophiles is well preceded and also various kinds of substituents can be introduced to the nitrogen atom at the position 1 by a simple alkylation.[3,4] Consequently, this study has resulted in the straightforward synthesis of the 1,4-dihydro-4-oxo-quinoline system, suitably equipped for conversion to a variety of quinolinone analogues, by the palladium-catalyzed carbonylative heterocyclization. This strategy, by virtue of its convergent nature and its potentiality to accommodate functionalized elements at the C2, offers much flexibility for the design of quinolinone derivatives, which is needed to explore the biologically active compounds.[9]

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

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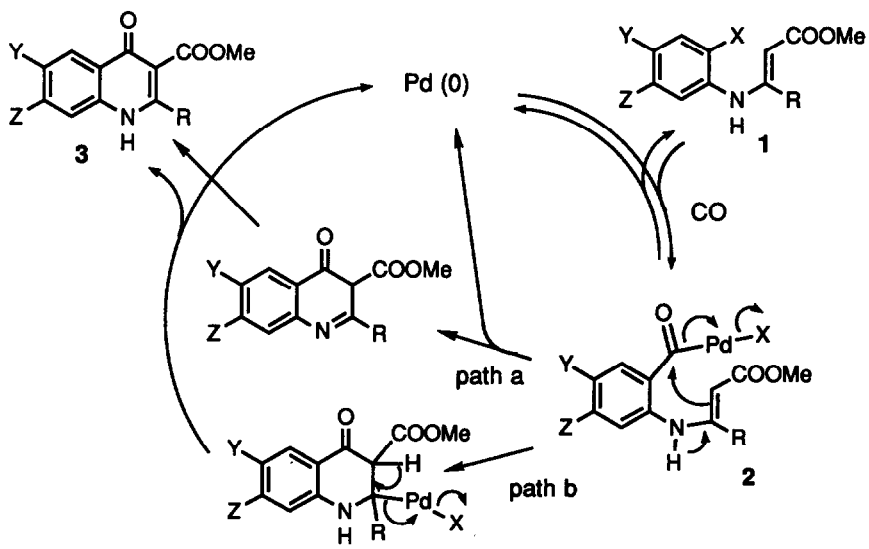
(8) The starting materials **1** were prepared by the conventional condensation of ketones and anilines with acid catalyst in high yields, see reference 7. The products were fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

(9) A plausible reaction path is illustrated in the following figure, in which two routes, path a and b, from **2** to **3** are possible. We suppose that the cyclization is completed by the intramolecular acylation of the enamine with the intermediary acylpalladium **2** (path a), although the insertion of the olefin (path b) can not be excluded at this stage. Because, our palladium-catalyzed heteroring formation occurs in *endo*-fashion, while most of the previously reported carbocyclization have been demonstrated to proceed in *exo*-mode. In addition, the reported carbocyclizations in *exo*-mode were achieved by intramolecular insertion of olefin. See the following references: (a) Zhang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem.* **1988**, 53, 5588. (b) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, 107, 8289. (c) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, 30, 5883. (d) Yamamoto, K.; Terakado, M.; Murai, K.; Miyazawa, M.; Tsuji, J.; Takahashi, K.; Mikami, K. *Chem. Lett.* **1989**, 955. *endo*-Cyclization in the absence of phosphine ligands is reported, see: Negishi, E.; Tour, J. M. *Tetrahedron Lett.* **1986**, 27, 4869.



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