Tetrahedron Letters, Vol. 33, No. 3, pp. 373-376, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

A NEW ROUTE TO 2-ARYL-4-QUINOLONES VIA PALLADIUM-CATALYZED CARBONYLATIVE COUPLING OF o-IODOANILINES WITH TERMINAL ARYLACETYLENES

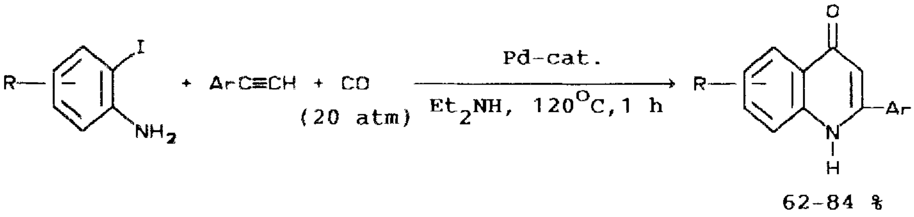
V.N.Kalinin*, M.V.Shostakovsky, and A.B.Ponomaryov

Nesmeyanov Institute of Organoelement Compounds
117813,Vavilova 28, Moscow, USSR

Abstract: o-Iodoanilines undergo Pd-catalyzed intramolecular heterocyclization with terminal arylacetylenes in the presence of carbon monoxide to give 2-aryl-4-quinolones.

Substituted 4-quinolones demonstrate various pharmacological activity[1]. The general method for preparation of 2-substituted 4-quinolones is a condensation reaction of anilines with β-ketoesters followed by cyclization of β-anilinoacrylates formed[2]. In the case of 2-phenyl-4-quinolone the application of 2,2-dimethyl-5-methyl-thiobenzylidene-1,3-dioxan-4,6-dione instead of β-ketoester is more effective[3]. Heterocyclization of 2'-aminochalcones under the action of stoichiometric amount of Pd(II) complexes also gives 2-aryl-4-quinolones in good yields[4].

Now we present a novel conveniuent preparative method of synthesis of these compounds by carbonylation of a mixture of o-iodoanilines and therminal arylacetylenes in the presence of a palladium catalyst:



Various o-iodoanilines and therminal arylacetylenes give 2-aryl-4-quinolones in good yields (table 1). It should be noted that o-iodoanilines react both as a base and hydrochloride form (entries 2,7), the yield of the product being decreased in the latter case (entries 1,2). To study the conditions under which 2-aryl-4-quinolones are formed the interaction between phenylacetylene and o-iodoaniline was chosen as a model reaction. The carbonylation of phenylacetylene and o-iodoaniline (120 ^{o}C, 20 atm, 1 h) proceeds both in secondary and tertiary amines (diethylamine- 83% , triethylamine - 70% , piperidine - 60%, morpholine - 61%) and in organic solvents (benzene - 68% , HMPA - 21%) containing 4 eq. of diethylamine.

Among palladium catalysts tested the complex $PdCl_2$(dppf) (dppf= 1,1'-bis(diphenylphosphino)ferrocene) proved to be the most effective (entry 1). When $PdCl_2(PPh_3)_2$ and $PdCl_2(CH_3CN)_2$ were used as the catalysts the yields of 2-phenyl-4-quinolone were 74 % and 55 % respectively. It's interesting to note that the common palladium (II) chloride showed significant catalytic activity (60 % of 2-phenyl-4-quinolone were formed).

The decrease in carbon monoxide pressure down to 5 atm practically does not influence on the yield of the product (76 %), however when the reaction is carried out at 1 atm of carbon monoxide the yield of the product was 33 % only.

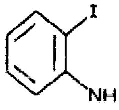
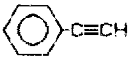
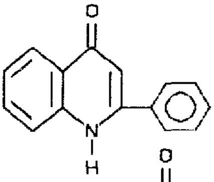
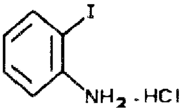
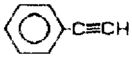
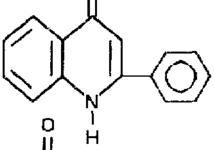
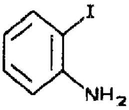
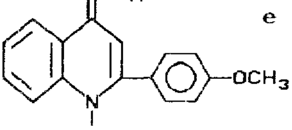
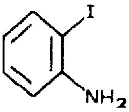
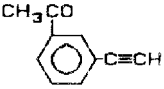
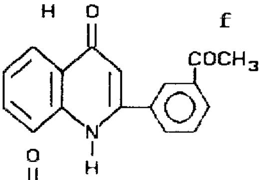
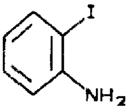
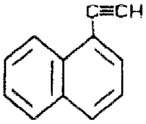
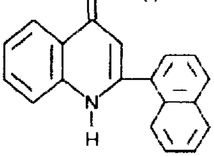
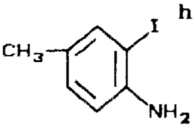
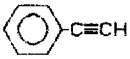
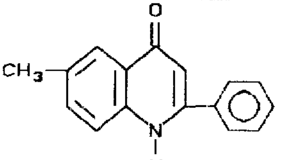
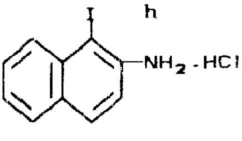
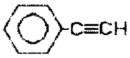
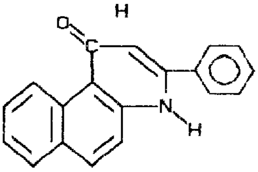
The decrease in the temperature of the reaction decreases the rate of the process. For example, 43 % of 2-phenyl-4-quinolone is formed at 60^{o}C (20 atm CO, 1 hour).

It should be noted that the starting materials for the reaction presented are widely available since a number of o-iodoanilines are easily formed by the direct reaction of iodine with appropriate anilines[6], and several conveniuent methods of synthesis of terminal arylacetylenes have been developed now[7].

TYPICAL PROCEDURE

4-Methyl-2-iodoaniline (1.00 g, 4.29 mmol), phenylacetylene (0.86 g, 8.58 mmol), diethylamine (15 ml), and $PdCl_2$(dppf) (0.031 g, 0.0429 mmol) were placed into 100 ml stainless steel autoclave.The mixture was stirred under CO (20 atm) at 120^{o}C for 1 hour. After cooling product formed was collected by suction and purified by recrystallization from ethanol. 6-Methyl-2-phenyl-4-quinolone (0.71 g, 70%) was obtained as white crystals. M.p. 291-293^{o}C, lit. m.p. 296-297^{o}C [5].

Synthesis of 2-aryl-4-quinolones[a] Table 1

Entry	Aniline	Arylacetylene	Product[b]	Yield,%[c] (isolated yield,%)
1				[d] 83 (70)
2				77
3				[e] 69
4				[f] 67
5				[g] 63
6	[h] 			84 (70)
7	[h] 			[i] 62

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[a] 2-Iodoaniline (0.91 mmol), terminal arylacetylene (1.83 mmol),diethylamine (3 ml),and $PdCl_2$(dppf) (0.091 mmol) were placed into the autoclave and heated at 120°C under CO (20 atm) for 1 hour. [b] The products were characterized by ^1H NMR-,mass-, and IR-spectra. [c] Yield was determined by TLC and UV-spectroscopy. [d] M.p. 253.5°C (EtOH), lit.m.p. 254°C[5]. [e] M.p. 294-296°C (EtOH),lit.m.p.236-238 C°[4]. [f] M.p.267-269°C (EtOH). [g] M.p.284-285°C (EtOH). [h] Note 6. [i] 5 mol.% of $PdCl_2$(dppf) were used; m.p. 272.5-274°C (DMF).

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(Received in Japan 30 May 1991)