

PALLADIUM-CATALYZED SYNTHESIS OF FLAVONES AND CHROMONES VIA
CARBONYLATIVE COUPLING OF o-IODOPHENOLS WITH TERMINAL ACETYLENES

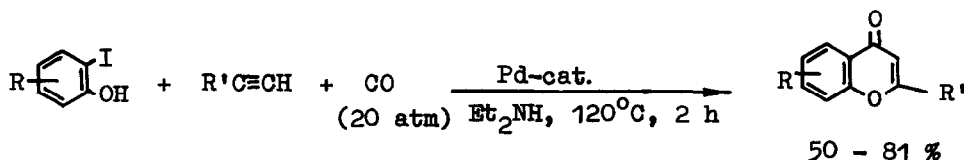
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Abstract. o-Iodophenols react with terminal acetylenes under carbon monoxide in the presence of palladium catalyst to give flavones or 2-substituted chromones.

A number of flavones and chromones have been reported as natural products, biologically active substances, and drugs ^{1,2}. The most common routes to obtain these compounds are the condensation of β -keto esters or diethyl acetylenedicarboxylate with phenols and of o-hydroxyacetophenones with various acylating agents ³⁻⁵. Flavones are often synthesized by condensation of o-hydroxyacetophenones with aromatic aldehydes followed by heterocyclization of 2-hydroxychalcones formed ⁶ and intermolecular cyclization of o-hydroxyaryl(arylethynyl)ketones in the presence of secondary amines ⁷.

Now we report a reaction of o-iodophenols with terminal acetylenes under carbon monoxide in the presence of secondary amine and catalytic amount of palladium complex to be a convenient preparative method of synthesis of flavones and 2-substituted chromones:



The influence of the nature of a solvent, amine, catalyst, carbon monoxide pressure, and temperature on the yield of the flavone was studied (Table 1), o-iodophenol and phenylacetylene being chosen for a model reac-

Table 1

Synthesis of flavone by carbonylative coupling of o-iodophenol
with phenylacetylene ^a

Entry	Catalyst	Solvent	Amine	CO, atm	Yield of flavone, %
1	PdCl ₂ (dppf) ^b	---	Diethylamine ^c	20	81
2	"	---	Piperidine ^c	"	77
3	"	---	Triethylamine ^c	"	61
4	"	---	Pyridine ^c	"	55
5	PdCl ₂ (dppf) ^d	DMF	Piperidine	"	56
6	"	THF	"	"	52
7	"	PhOMe	"	"	50
8	"	C ₆ H ₆	"	"	46
9	"	HMPA	"	"	76
10	Pd(PPh ₃) ₄	---	Diethylamine ^c	"	74
11	PdCl ₂ (PPh ₃) ₂	---	"	"	74
12	PdCl ₂ (MeCN) ₂	---	"	"	64
13	NiCl ₂ (PPh ₃) ₂	---	"	"	18
14	PdCl ₂ (dppf)	---	"	10	73
15	"	---	"	5	31
16	"	---	"	1	28
17	"	---	"	20 ^e	52

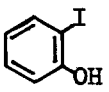
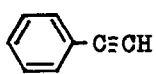
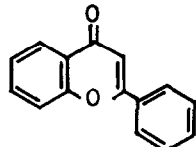
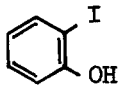
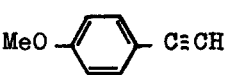
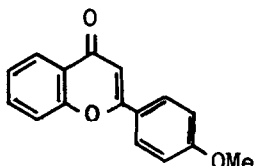
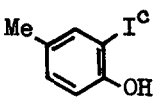
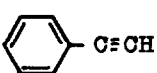
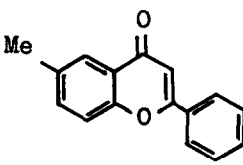
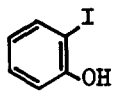
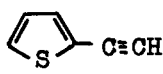
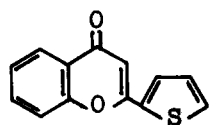
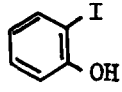

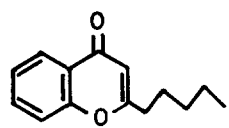
^a o-Iodophenol (0.91 mmol), phenylacetylene (1.82 mmol), catalyst (0.0091 mmol), amine (1.82 mmol), and solvent (3 ml) were placed into the autoclave and heated at 120°C under CO pressure during 2 hours. ^b dppf = bis(diphenylphosphino)ferrocene. ^c Amine was used as a solvent. ^d 0.018 mmol (2 mol.%) of a catalyst were used. ^e The reaction was carried out at 90°C.

tion. The best results were obtained using secondary amines (piperidine and diethylamine) both as a solvent and a base (entries 1,2). This reaction could be carried out in the presence of 2 eq. of amine in various solvents as well, but except for HMPA (entry 9) the yields of flavone were lower (entries 5-8).

The reaction is catalyzed by palladium complexes both containing and not containing phosphine ligands (entries 10-12). Flavone was formed in

Table 2

Synthesis of flavones and chromones ^a

Iodophenol	Acetylene	Product	Yield ^b , %
			81
			54
			67
			50
			58

^a *o*-Iodophenol (0.91 mmol), terminal acetylene (1.82 mmol), diethylamine (3 ml) and PdCl₂(dppf) (0.0091 mmol) were placed into the autoclave and heated at 120°C² under CO (20 atm) during 2 hours. ^b Yield was determined by TLC and UV-spectroscopy. Note 8.

18% yield when NiCl₂(PPh₃)₂ was used as a catalyst (entry 13).

The yield of flavone was not decreased considerably when the reaction was carried out under 10 atm of carbon monoxide (entry 14). It should be noted that the reaction of *o*-iodophenol with phenylacetylene even under 1 atm of carbon monoxide gave flavone in 28% yield (entry 16). Carbonylation of *o*-iodophenol at 90°C also yields flavone, the reaction rate being

decreased (entry 17).

Palladium-catalyzed carbonylative coupling of o-iodophenols proceeds either with aryl- or heteroaryl- and alkylacetylenes giving the corresponding 2-substituted chromones in good yields (Table 2).

Typical procedure. Diethylamine (3 ml), o-iodophenol (200 mg, 0.91 mmol), phenylacetylene (0.20 ml, 1.82 mmol) and PdCl₂(dppf) (6.0 mg, 0.0091 mmol) were placed into the autoclave. The reaction was carried out under CO (20 atm) at 120°C with magnetic stirring for 2 hours. The yield of flavone formed was determined by TLC and UV spectroscopy (81%). The product was isolated by TLC on silica gel (hexane:chloroform=1:2 as eluent) and recrystallized from hexane. M.p. 96-98°C, lit. m.p. 97-98°C⁷.

The products were characterized by UV-, IR-, mass-, NMR¹H- and NMR¹³C-spectra.

REFERENCES AND NOTES

1. The Flavanoids. Advances in research since 1980. Ed. by I.B.Harborne, London, New-York, Chapman & Hall, 1988, pp. 235-302.
2. Comprehensive Heterocyclic Chemistry. Ed. by A.R.Katritzky, Pergamon Press, 1984, v. 3/2B, p. 874.
3. S.Sethna and R.Rhadke in "Organic Reactions". Ed. by R.Adams, Wiley, New-York, 1953, v. 7, ch. 1.
4. S.Ruhemann and H.E.Stapleton, J.Chem.Soc., 77, 1179 (1900).
5. a) T.A.Geissman, J.Am.Chem.Soc., 71, 1498 (1949); b) J.Allan and R.Robinson, J.Chem.Soc., 2334 (1926); c) H.M.Lynch, T.M.O'Toole and T.S.Wheeler, J.Chem.Soc., 2063 (1952); d) W.D.Ollis and D.Weight, J.Chem.Soc., 3826 (1952).
6. a) V.T.Ramakrishnan and J.Kagan, J.Org.Chem., 35, 2901 (1970); b) A.Schiavello and C.Sebastiani, Gazz.Chim.Ital., 79, 909 (1949); c) A.Schöuberg and G.Schütz, Chem.Ber., 93, 1466 (1960); d) A.Kasahara, T.Izumi and M.Ooshima, Bull.Chem.Soc.Japan, 47, 2526 (1974); e) M.Meyer-Dayan, B.Bodo, C.Deschamps-Vallet and D.Molho, Tetrahedron Lett., 3359 (1978); f) Y.Hoshino, T.Ooshinata and N.Takeno, Bull.Chem.Soc. Japan, 59, 2351 (1986); g) Y.Hoshino, T.Ooshinata and N.Takeno, Nippon Kagaku Kaishi, 2104 (1985).
7. S.P.Korshunov, N.V.Korzova and V.M.Kazantseva, Zh.Org.Khim., 22, 1847 (1986).
8. The product was synthesized by the reaction of p-cresol with iodine in the presence of copper (II) acetate according to the procedure reported by C.A.Horiuchi and J.Y.Sato, Bull.Chem.Soc.Japan, 57, 2691 (1984).