Carbonylation of Organic Halides in the Presence of Terminal Acetylenes; Novel Acetylenic Ketone Synthesis

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Summary Aryl, heterocyclic, and vinylic halides react with carbon monoxide and terminal acetylenes at 120 °C or below and 80 atm or below in the presence of triethylamine and a catalytic amount of a palladium(II) complex to form acetylenic ketones in 46·7—92·9% yield.

CARBONYLATION of organic halides is an important C–C bond formation process used in the synthesis of organic acids, esters, amides, and aldehydes.[1] However, little attention has been paid to unsymmetrical ketone synthesis, which requires the formation of two C–C bonds, under catalytic carbonylation conditions.[2,3] We report herein a convenient synthesis of acetylenic ketones *via* carbonylation of organic halides in the presence of terminal acetylenes [equation (1)]. Acetylenic ketones are not only versatile intermediates in

$$\mathrm{RX + CO + HC{\equiv}CR'} \xrightarrow[-\mathrm{NR''_3{\cdot}HX}]{\mathrm{NR''_3}} \mathrm{R{\cdot}CO{\cdot}C{\equiv}R'} \qquad (1)$$

organic syntheses,[4] particularly for heterocyclic compounds such as isoxazoles, pyrazoles, and triazoles, but also are biologically active.[5]

TABLE. Acetylenic ketone synthesis from RX, CO, and HC≡CR′ in the presence of NEt_3.

RX	HC≡CR′ (R′)	Catalyst	P_{CO} /atm	T/°C	t/h	Conversion[a] %	R·CO·C≡CR′[b] %	RC≡CR′[b] %
PhI	Ph	$PdCl_2(PPh_3)_2$	20	120	1	97·5	47·8	23·4
PhI	Ph	$PdCl_2$(dppf)[c]	20	120	4	100	85·6	0·8
PhI	Ph	$PdCl_2$(dppf)	1	80	26	96·6	92·9	2·6
PhI	n-C_4H_9	$PhPdI(AsPh_3)_2$	20	120	4	91·9	(44·8)	0
PhI	$PhCH_2CH_2$	$PdCl_2$(dppf)	20	100	1	n.d.	(63·1)	0
$MeOC_6H_4I$-p	Ph	p-$MeC_6H_4PdI(AsPh_3)_2$	20	120	4	98·0	(77·3)	5·0
$EtO_2CC_6H_4I$-p	Ph	$PdCl_2$(dppf)	20	90	8	100	(79·3)	n.d.
$O_2NC_6H_4I$-p	Ph	$PdCl_2$(dppf)	20	100	1·5	100	(58·4)	0
PhBr	Ph	$PdCl_2$(dppf)	20	120	24	78·5	73·6	0·5
α-NaphBr[d]	Ph	$PdCl_2$(dppf)	20	120	6	88·2	(78·6)	1·4
ClC_6H_4Br-p	Ph	$PdCl_2$(dppf)	20	120	24	n.d.	(63·3)[e]	0
2-Br Then[f]	Ph	$PdCl_2(PPh_3)_2$	80	120	3	61·6	(55·1)	5·5
MeCH=CMeBr	Ph	$PdCl_2$(dppf)	20	120	43	n.d.	46·7	n.d.
PhCH=CHBr	Ph	$PdCl_2$(dppf)	20	90	2	n.d.	(80·8)	1·3
EtOCH=CHBr	Ph	$PdCl_2$(dppf)	20	120	19	78·0	(57·5)	0

[a] Conversion refers to consumption of the halides; n.d. = not determined. [b] Based on the amount of halide used. The figures in parentheses indicate isolated yields. [c] Dppf refers to 1,1′-bis(diphenylphosphino)ferrocene. [d] α-NaphBr = α-naphthyl bromide. [e] 1-(4′-Chlorophenyl)-3-phenylprop-2-ynone. [f] 2-Br Then = 2-bromothiophen.

The synthesis of 1,3-diphenylprop-2-ynone is typical of the general procedure. A 27 ml stainless steel autoclave, containing iodobenzene (1·88 mmol), phenylacetylene (2·00 mmol), $PdCl_2$[1,1′-bis(diphenylphosphino)ferrocene] ($1·88 \times 10^{-2}$ mmol), and triethylamine (3 ml) in a nitrogen atmosphere, was pressurized up to 20 atm with carbon monoxide. The mixture was stirred at 120 °C for 4 h. G.l.c. analysis then showed that 1,3-diphenylprop-2-ynone was formed in 85·6% yield along with tolan (diphenylacetylene) in 0·8% yield. Routine work-up followed by preparative layer chromatography isolated the ketone.

Some representative results for other combinations of halides and acetylenes are collected in the Table, which shows that the reaction can be successfully applied to a variety of aryl and alkenyl halides. Although most examples shown in the Table were run at 20 atm of carbon monoxide, the reaction also worked quite well under atmospheric pressure without significant loss of selectivity, thus offering a mild, simple, and selective modification of the procedure. For most halides, $PdCl_2$[1,1′-bis(diphenylphosphino)ferrocene] was the best catalyst among a wide range of Pd^{II}–phosphine or –arsine complexes. For instance, the use of $PdCl_2(PPh_3)_2$ in the carbonylation of iodobenzene with phenylacetylene resulted in extensive formation of tolan. In addition, this complex catalysed the dimerisation of the initial acetylenes into the 1,3-diyne derivatives as, in many cases, a side reaction. Note that the present preparation does not require any highly reactive reagents such as alkali-metal acetylides, the use of which imposes severe limitations on conventional acetylenic ketone syntheses because of undesirable side reactions. The major drawback which we have not overcome yet is the lack of carbonylation in the case of aromatic bromides having highly electron-withdrawing substituents; the reaction of p-bromobenzonitrile gave only 1-(4′-cyanophenyl)-2-phenylethyne, exclusively.

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