Tetrahedron Letters 49 (2008) 5961–5964

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iron/copper-catalyzed C–C cross-coupling of aryl iodides with terminal alkynes

Chandra M. Rao Volla, Pierre Vogel *

Laboratoire de Glycochimie et Synthèse Asymétrique (LGSA), Swiss Federal Institute of Technology Lausanne (EPFL), Batochime, 1015 Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 24 June 2008
Revised 23 July 2008
Accepted 29 July 2008
Available online 31 July 2008

Keywords:
Sonogashira–Hagihara coupling
Iron
Copper
Synergic effect

ABSTRACT

Synergic effect of iron and copper salts as catalysts for the Sonogashira–Hagihara cross-couplings of aryl iodides with terminal alkynes is demonstrated. High yields of cross-coupled products are obtained under conditions that are smoother than those using only CuI as catalyst. Furthermore no expensive or/and toxic ligand is required.

1. Introduction

Aryl alkynes are important compounds for material sciences and medicinal chemistry.[1] These compounds are best obtained by the Sonogashira–Hagihara cross-coupling reaction of terminal alkynes with aryl halides or triflates, originally using palladium catalysts together with phosphine or diamine ligands.[2] Transition metal-free Sonogashira–Hagihara reactions of aromatic iodides and bromides with terminal alkynes have been reported, but they require very high temperature, phase-transfer catalyst, and microwave activation. Furthermore, they are limited to aromatic alkynes.[3] Sonogashira–Hagihara cross-couplings have been reported using less harsh conditions in the presence of copper,[4] ruthenium,[5] or nickel[6] catalysts and adequate ligands. Li and co-workers[7] reported that CuI/DABCO is an effective catalyst for Sonogashira–Hagihara cross-couplings of aryl halides and vinyl halides. Highly dispersed Cu metal on alumina is a good catalyst for the cross-coupling of aryl iodides with phenylacetylene.[8] CuI/ligand couples are good catalysts for C–C, C–N, and C–O Ullmann-type coupling reactions.[9] The discovery in 1954 by Kharasch and Reinmuth,[10] then in 1971 by Tamura and Kochi[11] that Grignard reagents and alkyl halides can be cross-coupled in the presence of iron catalysts has stimulated several studies toward the substitution of expensive and toxic transition metals and ligands by iron catalysts in C–C bond forming reactions.[12–18] Iron salts are cheap, non-toxic, and environmentally benign.[19] A recent report by Bolm and co-workers[20] on iron-catalyzed Sonogashira reaction urges us to present our own studies on this topic.[21] Aromatic iodides and terminal alkynes undergo C–C cross-coupling reactions in the presence of iron salt and CuI as catalysts and under relatively smooth conditions that do not require the presence of expensive or toxic ligand. Iron-catalysis has been recently extended to allylic alkylation, allylic aminations,[22] and carbon-heteroatom cross-coupling reactions.[21,23,24]

2. Results

Our initial attempts used 4-iodotoluene and phenylacetylene as the coupling partners in the presence of iron(III) acetylacetonate and copper(I) iodide, without any external ligand. The reaction was carried out in DMF at 140 °C with Cs_2CO_3 as the base of choice (Table 1). We find that the reaction is completed in 36 h giving 1-(4-methylphenyl)-2-phenylethyne in 93% yield (Table 1, entry 1). The crucial roles played by both iron and copper salts were clear as reactions done in the absence of either iron or copper led only to low yields of product (entries 2 and 3). Without iron and copper catalysts the coupling did not occur at all (entry 4), thus demonstrating the synergic effect of iron and cuprous salts. This type of synergic effect of Fe/Cu has been disclosed in the arylmagnesation of internal alkynes.[25] Reaction time was somewhat shorter in DMSO (entry 6) or NMP (*N*-methylpyrrolidinone) (entry 7). The beneficial effect of NMP was also observed for other iron-catalyzed C–C coupling reaction.[13,18] Among several iron salts, (Table 1, entries 9–13) iron(III)acetylacetonate appeared to be the best catalyst. Nakamura has shown the importance of fluoride ion in iron-catalyzed Corriu–Kumada coupling reaction.[17c] In our case $FeF_3{\cdot}(H_2O)_3$ (entry 10) was not as efficient as $Fe(acac)_3$. To our surprise, although $FeCl_3$ + CuI (entry 9) did catalyze the reaction almost as well as $Fe(OAc)_2$ + CuI (entry 12), $FeCl_2$ + CuI (entry 11),

* Corresponding author. Tel.: +41 21 693 93 71; fax: +41 21 693 93 50.
E-mail address: pierre.vogel@epfl.ch (P. Vogel).

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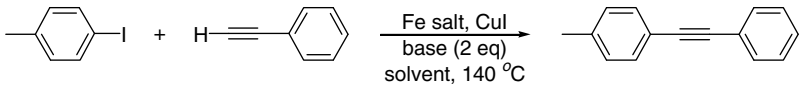
doi:10.1016/j.tetlet.2008.07.151

Table 1
Iron/copper-catalyzed coupling of 4-iodotoluene with phenylacetylene



Entry	Fe source (mol %)	CuI (mol %)	Ligand (15 mol %)	Base	Solvent	Time (h)	Yield[a] (%)
1	$Fe(acac)_3$ (10)	10	—	Cs_2CO_3	DMF	36	93
2	$Fe(acac)_3$ (10)	—	—	Cs_2CO_3	DMF	48	—
3	—	10	—	Cs_2CO_3	DMF	48	6
4	—	—	—	Cs_2CO_3	DMF	36	—
5	$Fe(acac)_3$ (10)	10	—	Cs_2CO_3	DMF	2.5	94[b]
6	$Fe(acac)_3$ (10)	10	—	Cs_2CO_3	DMSO	21	87
7	$Fe(acac)_3$ (10)	10	—	Cs_2CO_3	NMP	20	95
8	$Fe(acac)_3$ (5)	10	—	Cs_2CO_3	NMP	48	68
9	$FeCl_3$ (10)	10	—	Cs_2CO_3	NMP	48	55
10	$FeF_3{\cdot}3H_2O$ (10)	10	—	Cs_2CO_3	NMP	48	76
11	$FeCl_2$ (10)	10	—	Cs_2CO_3	NMP	48	Traces
12	$Fe(OAc)_2$ (10)	10	—	Cs_2CO_3	NMP	48	61
13	$Fe(OAc)_2$ (10)	—	—	Cs_2CO_3	NMP	48	—
14	$Fe(acac)_3$ (7)	10	TMEDA	Cs_2CO_3	NMP	40	89
15	$Fe(acac)_3$ (7)	10	DMEDA	Cs_2CO_3	NMP	40	85
16	$Fe(acac)_3$ (7)	10	HMTA	Cs_2CO_3	NMP	36	91
17	$Fe(acac)_3$ (10)	10	—	K_3PO_4	NMP	48	71
18	$Fe(acac)_3$ (10)	10	—	Et_3N	NMP	21	Traces

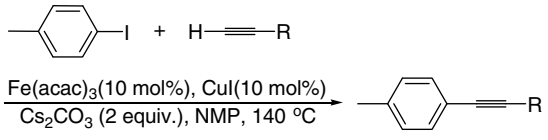
[a] Yields were determined after flash chromatography.
[b] Reaction was done in a microwave reactor. acac = Acetylacetonate, DMF = dimethylformamide, DMSO = dimethylsulfoxide, NMP = *N*-methylpyrrolidone, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, DMEDA = *N*,*N*′-dimethylethylenediamine, HMTA = hexamethylenetetramine.

$Fe(OAc)_2$ alone (entry 13) did not catalyze it. This shows the importance of the oxygenated σ-ligands of the iron salt. Cahiez et al. reported the beneficial effect of TMEDA and HMTA as additives in iron-catalyzed cross-coupling of alkyl halides with Grignard reagents.[13d,e]

Addition of external ligands such as Et_3N, TMEDA, DMEDA, or HMTA did not help the reaction (entries 14–16). Substitution of Cs_2CO_3 by K_3PO_4 retarded somewhat the reaction, whereas Et_3N as base alone gave the product only in trace amounts (entries 17 and 18). When the reaction was carried out in *m*-xylene in the presence of 1 equiv of NMP, low yield of the coupling product was observed. Although the reaction takes 20 h for completion, the reaction time can be greatly decreased by using a microwave reactor (2.5 h for nearly same yields) (Table 1, entry 5). Our best conditions (Table 1, entry 7) were then applied to the cross-coupling of a variety of terminal acetylenes with 4-iodotoluene (Table 2). In most cases, the reaction was over in ca 20 h at 140 °C except for (4-methoxyphenyl)acetylene which required 36 h (entry 10) for a 79% yield. A wide variety of terminal acetylenes with aryl, alkyl, 3-pyridinyl, and cyclohexen-1-yl substituents gave the corresponding products of cross-coupling in good to excellent yields.

In order to extend the scope of the reaction further, we explored the cross-coupling of various electrophilic partners with phenylacetylene (Table 3). Apart from 4-iodonitrobenzene all aryl iodides assayed led to good yields of isolated products. With 4-bromo-, 4-chlorotoluene, and 4-methylbenzenesulfonyl chloride (entries 2–4) no product of cross-coupling could be observed. In the latter case, the sulfonyl chloride decomposed rapidly giving a small amount of products of homocoupling. Interestingly, the cross-coupling reaction was successful for electron-poor (entries 6–10, 15,

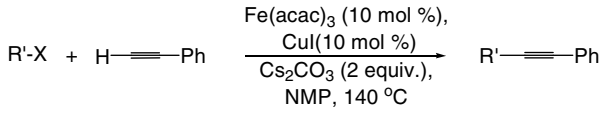
Table 2
Iron/copper-catalyzed coupling of various terminal alkynes with 4-iodotoluene



Entry	R	Time (h)	Yield[a] (%)
1	Phenyl	20	95
2	Phenyl	2.5	94[b]
3	4-Methylphenyl	20	92
4	*n*-Octyl	18	91
5	*n*-Hexyl	18	96
6	*t*-Butyl	18	86
7	*n*-Butyl	18	87
8	3-Pyridyl	21	92
9	4-Methoxyphenyl	36	79
10	Cyclohexen-1-yl	20	94

[a] Yields of isolated products after flash chromatography.
[b] Reaction was done in a microwave reactor.

Table 3
Iron/copper-catalyzed cross-coupling of aryl halides with phenylacetylene



Entry	R′	X	Time (h)	Yield[a] (%)
1	4-Methylphenyl	I	20	95
2	4-Methylphenyl	Br	24	0
3	4-Methylphenyl	Cl	24	0
4	4-Methylphenyl	SO_2Cl	24	0[b]
5	Phenyl	I	20	94
6	4-Fluorophenyl	I	18	96
7	4-(Trifluoromethyl)phenyl	I	18	98
8	4-Nitrophenyl	I	24	0[c]
9	4-Cyanophenyl	I	18	87
10	4-Acetylphenyl	I	18	89
11	2-Methylphenyl	I	20	91
12	3-Methylphenyl	I	20	85
13	1-Naphthyl	I	20	93
14	4-Methoxyphenyl	I	36	83
15	4-Bromophenyl	I	18	96
16	4-Chlorophenyl	I	18	97

[a] Yield of isolated products after flash chromatography.
[b] Starting material was decomposed after 3 h under the reactions conditions, small amount of homocoupling of phenylacetylene was observed.
[c] Starting material was decomposed to give a mixture of products (nitrobenzene and aniline).