Efficient Iron/Copper Cocatalyzed Alkynylation of Aryl Iodides with Terminal Alkynes

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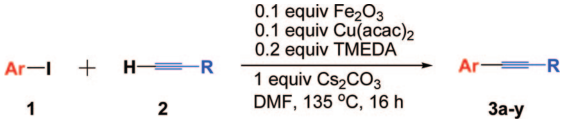

We developed a highly efficient and practical protocol for the coupling of terminal alkynes with aryl iodides that is catalyzed by inexpensive and environmentally benign Fe/Cu. A broad spectrum of substrates can participate in the process effectively to produce desired products in good yields. The versatility, generality, low cost, and environmental friendliness, in combination with exceptionally high reaction rates, render this method particularly attractive for industrial applications.

Introduction

Cross-coupling reactions mediated by transition metals are presently considered the cornerstones in the field of organic synthesis.[1] Reactions leading to C(sp)−C(sp^2) bond formation are often the key steps involved in a wide range of organic processes.[2] Among these, the Sonogashira-type reactions, which involve the coupling of aryl or vinyl halides with terminal alkynes, have been studied in detail as powerful tools for preparing arylalkynes and conjugated enynes, which are the precursors for natural products, pharmaceuticals, and molecular organic materials.[3] In the past decade, an effort was made to develop efficient catalytic systems.[4−7] A significant step toward the development of the Sonogashira reaction was achieved by Fu et al., who treated various aryl bromides with alkynes based on the system $(PhCN)_2PdCl_2/PtBu_3/CuI$ at room temperature.[5a] Gelman and Buchwald reported that phenylacetylene coupled with various aryl chlorides in the presence of a palladium catalyst utilizing the $P(Cy)_2Ar$ as ligand to produce the coupling product in good yields.[6c] However, the coupling reactions of

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(4) For representative articles on the palladium-catalyzed Sonogashira cross-coupling reactions, see: (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2003**, *345*, 1146. (b) Genin, E.; Amengual, R.; Michelet, V.; Savignac, M.; Jutand, A.; Neuville, L.; Genêt, J. P. *Adv. Synth. Catal.* **2004**, *346*, 1733. (c) Gil-Moltó, J.; Karlström, S.; Nájera, C. *Tetrahedron* **2005**, *61*, 12168. (d) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391. (e) Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295. (f) Soares do Rêgo Barros, O.; Favero, A.; Nogueira, C. W.; Menezes, P. H.; Zeni, G. *Tetrahedron Lett.* **2006**, *47*, 2179. (g) Li, P. H.; Wang, L. *Adv. Synth. Catal.* **2006**, *348*, 681. (h) Guan, J. T.; Weng, T. Q.; Yu, G. A.; Liu, S. H. *Tetrahedron Lett.* **2007**, *48*, 7129.

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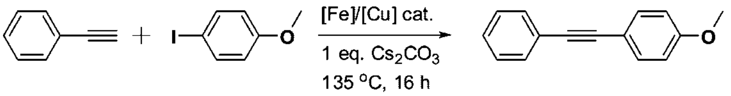
10.1021/jo801942h CCC: $40.75

TABLE 1. Optimization of the Catalysis Conditions



entry	solvent	[Fe] cat.	[Cu] cat. (0.1 equiv)	ligand[a]	yield (%)
1[b]	DMF	$FeCl_3$	$Cu(acac)_2$	DMEDA	69
2[c]	DMF	Fe_2O_3	$Cu(acac)_2$	DMEDA	85
3[d]	DMF	Fe_2O_3 $Fe(acac)_3$		DMEDA	0
4	DMF		$Cu(acac)_2$	DMEDA	48
5[c]	DMF	Fe_2O_3		DMEDA	0
6[c]	DMF	Fe_2O_3	$Cu(acac)_2$		70
7[c]	DMF	Fe_2O_3	$Cu(acac)_2$	TMEDA	91
8[c,e]	DMF	Fe_2O_3	$Cu(acac)_2$	TMEDA	56
9[c]	toluene	Fe_2O_3	$Cu(acac)_2$	TMEDA	63
10[c]	DMSO	Fe_2O_3	$Cu(acac)_2$	TMEDA	62

[a] DMEDA = *N*,*N*′-dimethylethylenediamine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [b] 0.1 equiv of $FeCl_3$ was used. [c] 0.1 equiv of Fe_2O_3 was used. [d] 0.1 equiv of $Fe(acac)_3$ and 0.1 equiv of Fe_2O_3 were used. [e] NaOEt was used as base.

this type are usually performed using an expensive palladium catalyst in the presence or absence of a copper(I) cocatalyst. Iron complexes, which offer attractive industrial prospects in terms of low price and environmentally benign features, used alone or in combination with other metals,[8,9] are rarely reported to be used in the formation of this type of bond. Significant progress in this field has been made very recently. Bolm et al. demonstrated a novel iron-catalyzed arylation of terminal alkynes by utilizing catalytic amounts of $FeCl_3$ in conjunction with *N*,*N*′-dimethylethylenediamine (DMEDA).[8e] Taillefer et al. reported the Cu-catalyzed Sonogashira-type coupling using 0.3 equiv of 1,3-diphenylpropane-1,3-dione as the ligand.[7b] Vogel's group obtained similar results in the case of aryl iodides with terminal alkynes catalyzed by $Fe(acac)_3$ and CuI.[10] Although these methods are encouraging, there is a considerable scope for improvement. For example, Bolm's method requires long reaction times (72 h), and the reaction of aliphatic alkyne was less successful in this catalytic system. Furthermore, these methods suffer from a relatively narrow scope of substrates. No examples of the coupling of heterocyclic alkynes with aryl halides or heterocyclic halides have been reported. Clearly, the development of improved procedures in which more sustainable catalysts and wide applications are used has remained an elusive goal.

Results and Discussion

In this study, we report a general and practical method for the coupling of terminal alkynes with aryl iodides, which is based on a simple and inexpensive method of iron−copper cocatalysis. The reported reactions proceed in the presence of a catalytic amount of [$Cu(acac)_2$] (acac = acetylacetonate) and Fe_2O_3 to yield the products, and these conditions have been employed for a wide range of substrates, including aliphatic alkynes, heterocyclic alkynes, various substituted aryl alkynes, and aryl iodides or heterocyclic iodides.

As reported in previous studies, the Sonogashira-type reaction proceeded more rapidly in the presence of more electron-poor halides.[3] For our initial experiments, we chose to study the cross-coupling of phenylacetylene and *p*-iodoanisole, a relatively challenging test substrate because of its electron richness, as the model reaction for screening the catalyst and optimizing the reaction conditions. As illustrated in Table 1, the preliminary survey was carried out in *N*,*N*-dimethylformamide (DMF) at 135 °C using cesium carbonate as a base. The coupling reaction provided promising results in the presence of catalytic amounts of both [$Cu(acac)_2$] and $FeCl_3$ (69% yield; Table 1, entry 1). Remarkably, the yield afforded by Fe_2O_3 was better than that afforded by $FeCl_3$ (85% yield; Table 1, entry 2). We observed that there was no coupling when [$Cu(acac)_2$] was replaced by [$Fe(acac)_3$] (Table 1, entry 3). In the absence of an iron source, catalytic amounts of [$Cu(acac)_2$] afforded a moderate yield of the coupling product (48% yield; Table 1, entry 4). However, the catalytic amount of Fe_2O_3 was unable to promote the reaction in the absence of a copper source (Table 1, entry 5), indicating that the nature of the copper source had a pronounced impact on this process (Table 1, entries 1−3 and 5). In addition, the use of [$Cu(acac)_2$] appears to be important for the reaction to proceed (Table 1, entries 1−5). Remarkably, switching the ligand DMEDA with cheaper tetramethylethylenediamine (TMEDA) led to a superior yield (Table 1, entries 6 and 7). The more effective base among those that we surveyed is Cs_2CO_3 (Table 1, entries 7 and 8). Previous studies indicated that toluene, dimethyl sulfoxide (DMSO), and DMF were the most effective solvents for the Sonogashira-type coupling reactions.[2f,6d,7] Further optimization of these reaction conditions revealed that DMF was superior to others solvents (Table 1, entries 7, 9, and 10).

Under our optimized reaction conditions (0.1 equiv of [$Cu(acac)_2$], 0.1 equiv of Fe_2O_3, 0.2 equiv of TMEDA, 1.0 equiv of Cs_2CO_3, and DMF, 135 °C, 16 h), we accomplished

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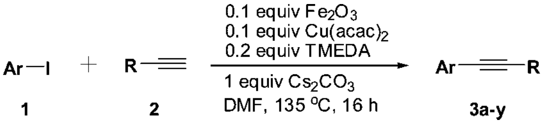
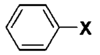
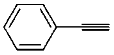
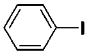
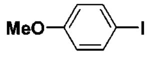
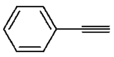
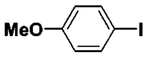
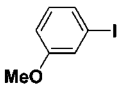
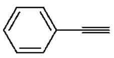
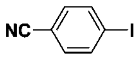
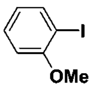
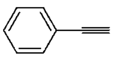
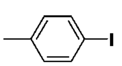
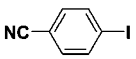
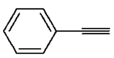
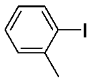
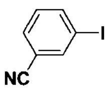
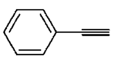
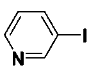
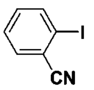
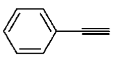
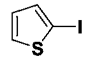
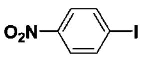
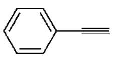
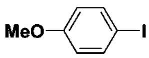
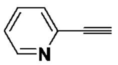
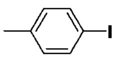
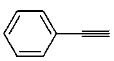
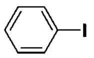
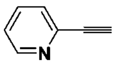
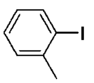
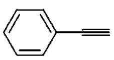
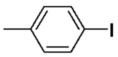
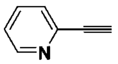
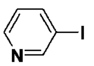
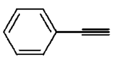
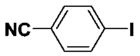
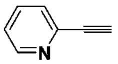
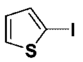
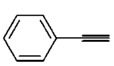
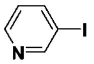
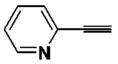
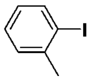
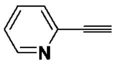
TABLE 2. **Sonogashira-Type Coupling of Aryl Iodides ArI with Alkynes RC≡CH**[a]



Entry	Aryl iodide	Alkyne	Product	Yield [%]	Entry	Aryl iodide	Alkyne	Product	Yield [%]
1			**3a**	92 (X=I) 42 (X=Br)	13		n-C_6H_{13}—≡	**3m**	94
2			**3b**	91	14		n-C_6H_{13}—≡	**3n**	93
3			**3c**	90	15		n-C_6H_{13}—≡	**3o**	94
4			**3d**	87	16		n-C_6H_{13}—≡	**3p**	96
5			**3e**	94	17		n-C_6H_{13}—≡	**3q**	94
6			**3f**	90	18		n-C_6H_{13}—≡	**3r**	91
7			**3g**	88	19		n-C_6H_{13}—≡	**3s**	79
8			**3h**	90	20			**3t**	90
9			**3i**	93	21			**3u**	88
10			**3j**	92	22			**3v**	85
11			**3k**	93	23			**3w**	91
12			**3l**	71	24			**3x**	83
					25			**3y**	90

[a] Reaction conditions: 0.1 equiv of [Cu(acac)$_2$], 0.1 equiv of Fe$_2$O$_3$, 0.2 equiv of TMEDA, 1.0 equiv of Cs$_2$CO$_3$, DMF, 135 °C, 16 h.

Sonogashira-type cross-couplings of a wide array of electronically and structurally diverse aryl halides.

As shown in Table 2, the corresponding products were obtained in good to excellent yields. Consistent with the results of previous studies, bromobenzene was found to be less efficient than iodobenzene (Table 2, entry 1).[3] The electronic effects on the reactions were limited. Both electron-neutral and electron-poor aryl iodides reacted with alkynes to provide excellent yields of the reaction products. Remarkably, even extremely electron-rich aryl iodides coupled efficiently with alkynes in the presence of this catalytic system (Table 2, entries 2−4, 14, and 20). Although sterically hindered substrates are often problematic,[3] it is also tolerant of ortho substitution in aryl iodides without any difficulty (Table 2, entries 4, 7, 10, 17, and 25). In further experiments for establishing the scope of this method, we investigated the cross-coupling of alkynes with heterocyclic iodides, thus allowing access to heterocyclic alkyne derivatives which are present in numerous appealing compounds. Pyridyl iodide was found to afford excellent yields of the corresponding products (Table 2, entries 11, 18, and 24). The use of less reactive thienyl iodide resulted in moderate yields (Table 2, entries 12 and 19). Notably, both the aryl alkynes and aliphatic alkynes were effective in the formation of the C(sp)−C(sp^2) bond (Table 2, entries 1−19). More remarkable is the efficient coupling between 2-ethynylpyridine and electron-rich, electron-neutral, electron-deficient, and heterocyclic aryl iodides (Table 2, entries 20−24). Furthermore, sterically demanding ortho substituents did not hamper the coupling, and good yields were obtained (Table 2, entry 25). These successful reactions reveal that the present catalytic system is also effective for the cross-coupling reactions of aryl iodides with heterocyclic alkynes. In general, it is remarkable that all reactions were very clean, and the desired products were obtained in high yields without undesirable amounts of alkyne homocoupling products, which were often generated in the presence of copper(I).[1]

Conclusions

In summary, we developed a highly efficient and practical protocol for the coupling of terminal alkynes with aryl iodides that is catalyzed by the inexpensive and environmentally benign Fe/Cu to create the C(sp)−C(sp^2) bond. A broad spectrum of substrates can participate in the process effectively under the optimized conditions to produce good yields of the desired products. The versatility, generality, low cost, and environmental friendliness, in combination with exceptionally high reaction rates, render this method particularly attractive for industrial applications.

Experimental Section

General Procedure for the Synthesis of 3a (Table 2, Entry 1). A mixture of 1-iodobenzene (51 μL), phenylacetylene (50 μL), and Cs_2CO_3 (148 mg) was dissolved in DMF (1.5 mL). Subsequently, 0.1 equiv of $Cu(acac)_2$, 0.1 equiv of Fe_2O_3, and 0.2 of equiv TMEDA were added to this mixture. The vial was sealed, and this mixture was then heated in an oil bath for 16 h at 135 °C. The reaction was then cooled to ambient temperature, and the crude reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed twice with brine, and the combined aqueous phases were extracted with ethyl acetate. The organic layers were dried using Na_2SO_4, concentrated, and purified by flash column chromatography (petroleum ether/ethyl acetate) to yield the expected product. The data obtained are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57−7.54 (m, 4H), 7.40−7.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 128.3, 128.2, 123.2, 89.351. MS (EI, *m/z*): 178 $[M]^+$. HRMS (EI) calcd for $C_{14}H_{10}$ $[M]^+$, 178.0783; found, 178.0791.

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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