Rapid Homogeneous-Phase Sonogashira Coupling Reactions Using Controlled Microwave Heating

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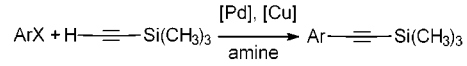
A microwave-enhanced, rapid and efficient homogeneous-phase version of the Sonogashira reaction is presented. It has been applied to the coupling of aryl iodides, bromides, triflates, and aryl chloride, as well as pyridine and thiophene derivatives with trimethylsilylacetylene. Excellent yields (80−95%) for substrates containing a large variety of substituents in different positions are obtained in 5−25 min.

Introduction

Arylalkynes are interesting intermediates for the preparation of a variety of target compounds. Recent examples include heterocyclic compounds,[1] molecular-scale electronic devices,[2] cyclophanes,[3] estradiol derivatives,[4] enediyne antibiotics,[5] and natural products with antitumor or phytotoxical activity.[6] An early approach to these compounds was provided by the palladium(0)-catalyzed coupling of terminal alkynes and aryl iodides in the presence of copper(I) and a base,[7] now known as Sonogashira coupling (Scheme 1). Recently, several procedures were published describing the application of this coupling to the less reactive aryl bromides[8] and triflates[1c] involving long reaction times.

Attempts to improve this reaction would have to address some of its weaknesses: the demand for a reactive arene derivative, long reaction times, and the limited choice of reaction medium. Microwave heating has emerged as a versatile method to speed up many chemical reactions, delivering high yields in a few minutes,[9] and has consequently been applied to the Sonogashira reaction. When microwave heating was first used in a heterogeneous phase system, several hours or even days were required for full conversion.[10] Recently, a fast, solventless, microwave-assisted heterogeneous Sonogashira coupling on alumina has been achieved,[11] but the reaction was limited to aryl iodides. To date, a microwave-assisted Sonogashira reaction in the homogeneous phase has not been reported. In fact, it has been recommended to avoid homogeneous conditions, because of the difficulty of controlling the reaction rate in the presence of volatile liquid reactants and metal catalyst that can cause thermal runaway.[11]

Scheme 1



Results and Discussion

Here, we describe the first microwave-enhanced, rapid, and efficient homogeneous-phase Sonogashira reaction of aryl iodides, bromides, and triflates and an aryl chloride with trimethylsilylacetylene. Our optimized reaction conditions give excellent yields for aryl halides containing a large variety of substituents in different positions. To demonstrate the scope of the procedure, we also examined couplings of heterocyclic aryl halides (the preparative results are summarized in Table 1), substrates that commonly appear to give more unpredictable results when a metal catalyst is used.[1b−c,12,13]

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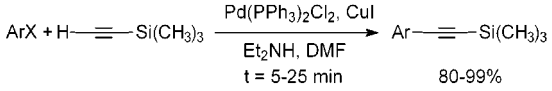
Table 1. Sonogashira Coupling of Aryl Halides and Trifluoromethane Sulfonates with Trimethylsilylacetylene



		this work		literature		
	Ar-X	this work yield (%) (method)[a]	reaction time (min)	yield (%)	conditions	ref
1	2-iodoaniline	98 (A1), 98 (A2)	5 h, 5	96	20 h, 25 °C	19
		92 (B)	5			
2	3-iodoaniline	99 (A1), 96 (A2)	5 h, 5	72	20 h, 25 °C	19
		99 (B)	5			
3	4-iodoaniline	97 (A1), 95 (A2)	5 h, 5	90	18 h, 25 °C	19
		98 (B)	5			
4	3-bromoaniline	83 (C)	25			
5	4-bromoaniline	87 (C)	25			
6	methyl-2-iodobenzoate	90 (B)	5	98	16 h, 40 °C	20
7	methyl-2-bromobenzoate	93 (C)	25	88	16 h, 25 °C	8a
8	methyl-3-bromobenzoate	83 (C)	25	87	16 h, 25 °C	8a
9	methyl-4-bromobenzoate	93 (C)	25	88	16 h, 25 °C	8a
10	2-iodoanisole	99 (B)	5	100	3 h, 25 °C	21
11	3-iodoanisole	99 (B)	5	95	−, 40 °C	22
12	4-iodoanisole	99 (B)	5	b	5h 80 °C	23
13	2-bromoanisole	87 (C)	25	61	48 reflux	24
14	3-bromoanisole	89 (C)	25			
15	4-bromoanisole	90 (C)	25	90	0.5−15 h, 25 °C	8b
16	iodobenzene	89 (B)	5	100	20 h, 25 °C	25
17	bromobenzene	87 (C)	25	33	24 h, 100 °C	26
18	phenyltriflate	94 (D)	5	87	3−17 h, 90 °C	27
19	4-cyano-phenyltriflate	99 (D)	5	97	3 h, 25 °C	28
20	1-iodo-4-trifluoromethyl-benzene	97 (B)	5			
21	1-bromo-4-trifluoromethyl-benzene	92 (C)	25	97	16 h, 20 °C	29
22	3-bromopyridine	80 (C)	25	80	5 h, 80 °C	13
23	2-chloropyridine	97 (C)	25	80	12 h, 120 °C	13
24	2-iodothiophene	86 (B)	5	95	2 h, 25 °C	30
25	3-iodothiophene	88 (B)	5	80	no details	1a
26	3-bromothiophene	81 (C)	25	28[c]	4 h, heat	1b

[a] Methods: (A) thermic conditions, room temperature, isolated yield; (B−D) microwave irradiation, 120 °C, yield determined by ^{1}H NMR; in C, triphenylphosphine was added; in D, lithium chloride was added. [b] No yield reported. [c] Obtained as byproduct.

It is known that the relative reactivity of organic halides in palladium-catalyzed reactions is R-Cl < R-Br ∼ R-OTf < R-I, reflecting the reactivity toward oxidative addition.[8b,14] For the same reason, electron-withdrawing substituents on aromatic halides increase the reaction rate,[15] as does the increasing acidity of the acetylenic hydrogen (arylacetylenes are more reactive than alkylacetylenes).

The microwave irradiations were performed under controlled conditions that make the procedure highly safe, reliable, and reproducible. Single mode irradiation with monitoring of temperature, pressure, and irradiation power vs time (Figure 1) was used throughout. Contrary to earlier procedures,[9] the reaction temperature was kept constant throughout the reaction in the single mode cavity by an automatic power control. When carrying out reactions with microwave irradiation in closed vessels in the presence of volatile substances such as diethylamine and trimethylsilylacetylene, extra caution is advisable. In addition to the high pressure generated by the vapor pressure of these components, the metal catalysts might precipitate and cause a "thermal runaway", increasing the pressure further. Therefore, the use of special heavy-walled process vials is highly recommended.

Our optimization studies were focused on the coupling of the comparatively unreactive iodoanilines and 4-bromoanisole with the moderately reactive trimethylsilylacetylene. The conditions producing full conversion of these compounds were then applied to further substrates. As catalyst, several palladium complexes were tested: $Pd_2(dba)_3$ and $Pd_3(AcO)_6$ gave only moderate yields. Excellent yields were obtained when $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ was used. Of these, $Pd(PPh_3)_2Cl_2$ was preferred because of its lower sensitivity to air. It is known that a small amount of Cu(I) in the reaction mixture results in faster reactions, and this applies also for our microwave-enhanced reaction. For example, in the absence of CuI, with 7% palladium catalyst 4-bromoanisole gave only 70% yield in 25 min at 120 °C (product 15E).[16] Upon addition of 5% CuI, 5% $Pd(PPh_3)_2Cl_2$ was sufficient to reach 90% yield (Table 1, entry 15C). As has been described for other microwave-assisted reactions, DMF was found to be the more advantageous solvent compared to THF. This has been attributed to it's higher rate of energy absorbance when subjected to microwave irradiation.[17]

In reactions involving the less reactive aryl bromides and 2-chloropyridine, triphenylphosphine was added to the reaction mixture to improve the stability of the palladium catalyst.[8a] Since this additive can complicate the workup procedure, it's amount was lowered to 20%,

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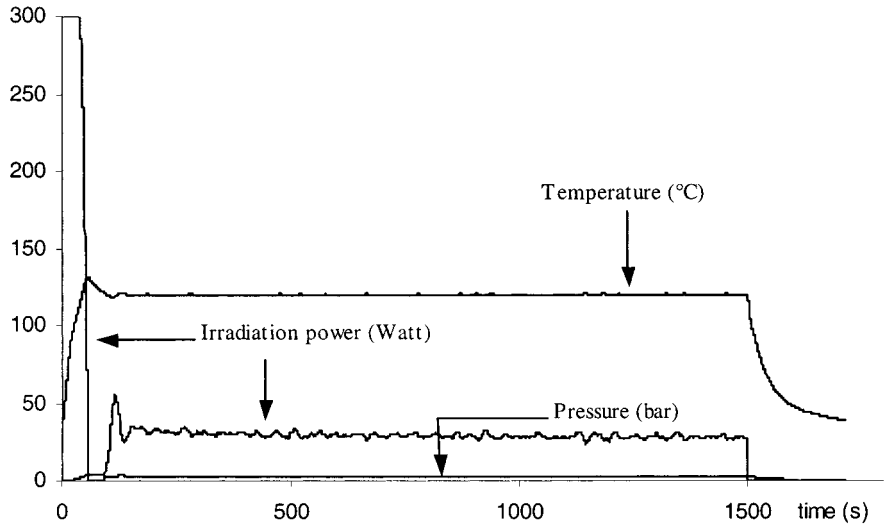

Figure 1. Temperature, pressure, and irradiation power monitored during microwave-assisted preparation of compound 15C.

as compared to 50% used in corresponding reactions of aryl bromides with acetylenes.[8a] In the case of aryl triflates, LiCl was added to the reaction mixture as an additive.[1c] A large excess of diethylamine was found to be favorable for the reaction. A small excess (1.1 equiv) of the rather expensive trimethylsilyl acetylene was found to be sufficient for full conversion, despite the high reaction temperature, which is likely to be due to the use of sealed reaction vessels.

During optimization, the reaction temperature was varied between 60 and 240 °C, with 120 °C giving optimal reaction enhancement. At higher temperatures, fast decomposition of the palladium catalyst was observed.

For comparative reasons, the Sonogashira coupling of 2-, 3-, and 4-iodoanilines was also performed without microwave heating both at room temperature (entries 1A1, 2A1, 3A1 in Table 1) and at temperatures corresponding to those used with microwave irradiation (entries 1A2, 2A2, 3A2 in Table 1). For all substrates, reported highest yields and conditions of nonmicrowave syntheses are included in Table 1. As can be seen, our optimized conditions give good to excellent yields within much shorter reaction times than the alternative methods. Furthermore, entries 1A2, 2A2, and 3A2 support earlier investigations that explain the effect of microwave irradiation to be entirely thermal.[18]

The aryl iodides and trifluoromethane sulfonates reacted at much higher rates than the aryl bromides. In general, the amount of palladium catalyst and/or the reaction time could be reduced when the aryl halide was unsubstituted or when it was carrying electron-withdrawing substituents. As an example, the coupling of 4-iodobenzotrifluoride with trimethylsilylacetylene in the presence of only 1% Pd catalyst and 2% CuI cocatalyst at 120 °C gave 92% yield after 10 min (product 20F). Increasing the amounts of Pd to 2% and Cu(I) to 4% gives only a slightly higher yield of 97% after 5 min (product 20B). However, it should be emphasized that the reaction conditions described in Table 1 were not optimized in every individual case, but the conditions optimized for the iodoanilines and 4-bromoanisole were applied. For example, the amount of catalyst could have been decreased in the reactions involving aryl iodides and triflates by adding triphenylphosphine to improve the palladium complex stability or by letting the reactions run longer than 5 min. Further studies in this direction are in progress.

Experimental Section

General Comments. All reactions were conducted under nitrogen in heavy-walled glass Smith process vials sealed with aluminum crimp caps fitted with a silicon septum. The inner diameter of the vial filled to the height of 2 cm was 1.3 cm. The microwave heating was performed in a Smith Synthesizer single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden). Reaction mixtures were stirred with a magnetic stir bar during the irradiation. The temperature, pressure and irradiation power were monitored during the course of the reaction. The average pressure during the reaction was 3−4 bar. After completed irradiation, the reaction tube was cooled with high-pressure air until the temperature had fallen below 39 °C (ca. 2 min). ^{1}H NMR spectra were recorded for $CDCl_3$ solutions at 400 MHz at room temperature. Chemical shifts are referenced indirectly to TMS via the residual solvent signal ($CHCl_3$, δ = 7.26). Mass spectra (EI, 70 eV) were obtained with a mass-selective detector interfaced with a gas chromatograph equipped with a 25m × 0.20 mm HP-1 capillary column. All products obtained by microwave heating were purified by extraction, selective dissolution, and filtration of the solution through Celite, leaving triphenylphosphine residues as the only impurity.[31] For exact quantification, hydroquinone diacetate was added as an internal standard to an aliquot of this product and the mixture was subjected to ^{1}H NMR analysis.

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Materials. The starting materials were purchased from commercial suppliers and were used without purification with the exception of 4-iodoaniline, which was recrystallized from ethanol twice. 2-Iodoaniline (98%), 3-iodoaniline (98%), methyl 2-bromobenzoate (98%), methyl 4-bromobenzoate (99%), bromobenzene (99%), and 2-chloropyridine (99%) were obtained from Aldrich. 4-Iodoaniline (97%), 4-iodoanisole (98%), and 2-bromothiophene (purum) were purchased from Fluka. Methyl 2-bromobenzoate (98%), methyl 3-bromobenzoate (98%), and 1-iodo-4-trifluoromethylbenzene (99%) were from Lancaster. 2-Iodoanisole (97%), 3-iodoanisole (97%), 2-bromoanisole (97%), 4-bromoanisole (98%), iodobenzene (98%), 2-iodothiophene (98%), and 3-bromothiophene (96%) were from Janssen Chimica, Belgium. 4-Bromoaniline (98%) and 3-bromopyridine (98%) were from Merck. 1-Bromo-4-trifluoromethylbenzene (99%) was from Acros. 3-Bromoanisole (99%) was from Ega Chemie and 3-bromoaniline from Theodor Schuchardt GmbH&Co, München. The reagents diethylamine (98%), trimethylsilylacetylene (98%), and $Pd(PPh_3)_2Cl_2$ (98%) were from Aldrich, cuprous iodide (99%) and triphenylphosphine (98%) were from Merck, and dimethylformamide (99%) was from Fluka. The $Pd(PPh_3)_4$ (99%) was received from Acros. The aryl triflates were prepared following literature procedures.[32] All products are known and were identified by comparison with their reported MS and NMR literature data.

Method A1. The aryl iodide (0.9 mmol), $Pd(PPh_3)_2Cl_2$ (12.8 mg, 0.02 mmol), CuI (6.9 mg, 0.04 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were mixed and stirred under nitrogen in a heavy-walled Smith process vial at 25 °C for 5 h. Then, the reaction mixture was poured into 0.1 M aqueous HCl (5−10 mL) and extracted three times with diethyl ether (5−10 mL). The combined organic layers were washed with concentrated aqueous $NaHCO_3$ solution (5−10 mL) and water (5−10 mL), re-extracting the aqueous phases in each case two times with diethyl ether, and then concentrated under reduced pressure. Then, the residue was purified by flash chromatography (silica gel 60, particle size 0.040−0.063 mm, Merck; hexane/ethyl acetate 12:1). The combined product fractions were concentrated on a rotatory evaporator, followed by removal of remaining solvent under reduced pressure overnight.

Method A2. Procedure as described for method A1 except for temperature (120 °C) and reaction time (5 min) and the workup procedure as described for method B. The Smith Process Vial, containing a magnetic stir bar, was placed in an oil bath that was kept at 120 °C. The reaction mixture assumed the temperature of the oil bath within 1 min and was stirred at this temperature for 5 min.

Method B. The aryl iodide (0.90 mmol), $Pd(PPh_3)_2Cl_2$ (12.8 mg, 0.02 mmol), CuI (6.9 mg, 0.04 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were stirred under nitrogen in a heavy-walled Smith process vial at 120 °C for 5 min in the microwave cavity. The mixture was then poured into 0.1 M aqueous HCl (5−10 mL) and extracted three times with diethyl ether (5−10 mL). The combined organic layers were washed with concentrated aqueous $NaHCO_3$ solution (5−10 mL) and water (5−10 mL), re-extracting the aqueous phases in each case two times with diethyl ether (5−10 mL), then concentrated under reduced pressure. After the residue was treated with pentane, it was filtered through Celite. Then the solvent was evaporated on a rotatory evaporator and the product was quantified by ^{1}H NMR.

Method C. The aryl bromide or chloride (0.90 mmol), $Pd(PPh_3)_2Cl_2$ (31.9 mg, 0.05 mmol), CuI (8.7 mg, 0.05 mmol), triphenylphosphine (47.7 mg, 0.18 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were stirred under nitrogen in a heavy-walled Smith process vial at 120 °C for 25 min in the microwave cavity. Then the reaction mixture was treated with diethyl ether, filtered, and poured into 0.1 M aqueous HCl (5−10 mL). Subsequent workup followed the procedure described in method B.

Method D. The aryl triflate (0.90 mmol), $Pd(PPh_3)_2Cl_2$ (12.8 mg, 0.02 mmol), CuI (6.9 mg, 0.04 mmol), lithium chloride (57.8 mg, 1.36 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were stirred under nitrogen in a heavy-walled Smith process vial at 120 °C for 5 min. Subsequent workup followed the procedure described for method B.

Method E. The aryl bromide (0.90 mmol), $Pd(PPh_3)_2Cl_2$ (44.7 mg, 0.06 mmol), triphenylphosphine (47.7 mg, 0.18 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were stirred under nitrogen in a heavy-walled Smith process vial at 120 °C for 20 min in the microwave cavity. Subsequent workup followed the procedure described for Method C.

Method F. The aryl iodide (0.90 mmol), $Pd(PPh_3)_2Cl_2$ (6.4 mg, 0.02 mmol), CuI (3.5 mg, 0.04 mmol), trimethylsilylacetylene (0.14 mL, 1.00 mmol), diethylamine (1.5 mL, 13.60 mmol), and dimethylformamide (0.5 mL) were stirred under nitrogen in a heavy-walled Smith process vial at 120 °C for 10 min in the microwave cavity. The subsequent workup followed the procedure described for method B.

The weighted yields of method B, C, D, E, and F include triphenylphosphine; the exact yields obtained by NMR quantification can be seen in Table 1 or are mentioned in the text.

2-(Trimethylsilylethynyl)aniline. Method A1, entry 1A1: brown oil, 167.8 mg, 0.90 mmol, 98%. Method A2, entry 1A2: brown oil, 204.4 mg. Method B, entry 1B: brown oil, 210.0 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 1.7, 7.5 Hz, 1H, ArH), 7.11 (ddd, J = 1.7, 7.5, 8.2 Hz, 1H ArH), 6.68 (dd, J = 1.1, 8.2 Hz, 1H, ArH), 6.66 (ddd, J = 1.1, 7.5, 7.5 Hz, 1H, ArH), 4.07 (br s, 2H, NH_2), 0.27 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 189 (61, M^+), 174 (100).

3-(Trimethylsilylethynyl)aniline. Method A1, entry 2A1: brown oil, 167.8 mg, 0.90 mmol, 99%. Method A2, entry 2A2: brown oil, 244.4 mg. Method B, entry 2B: brown oil; 259.1 mg. Method C, entry 4C: yellow oil, 239.5 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 7.7, 8.0 Hz, 1H, ArH), 6.87 (ddd, J = 0.7, 1.1, 7.7 Hz, 1H, ArH), 6.79 (dd, J = 1.1, 2.6 Hz, 1H, ArH), 6.63 (ddd, J = 0.7, 2.6, 8.0 Hz, 1H, ArH), 3.6 (br s, 2H, NH_2), 0.25 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 189 (42, M^+), 174 (100).

4-(Trimethylsilylethynyl)aniline. Method A1, entry 3A1: yellowish solid, 164.9 mg, 0.88 mmol, 97%. Method A2, entry 3A2: yellowish solid, 259.8 mg. Method B, entry 3B: brown oil, 191.1 mg. Method C, entry 5C: yellow oil, 257.9 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (AA′XX′, 2H, ArH), 6.55 (AA′XX′, 2H, ArH), 3.80 (br s, 2H, NH_2), 0.22 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 189 (42, M^+), 174 (100).

Methyl 2-(Trimethylsylilethynyl)benzoate. Method B, entry 6B: brown oil, 275.3 mg. Method C, entry 7C: 249.8 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (ddd, J = 0.6, 1.5, 7.9 Hz, 1H, ArH), 7.57 (ddd, J = 0.6, 1.5, 7.7 Hz, 1H, ArH), 7.43 (ddd, J = 1.5, 7.5, 7.9 Hz, 1H, ArH), 7.36 (ddd, J = 1.5, 7.5, 7.7 Hz, 1H, ArH), 3.90 (s, 3H, $ArCOOCH_3$), 0.25 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 232 (4, M^+), 217 (27), 187 (100).

Methyl 3-(Trimethylsylilethynyl)benzoate. Method C, entry 8C: yellowish oil, 259.4 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (ddd, J = 0.6, 1.7, 1.7 Hz, 1H, ArH), 7.96 (ddd, J = 1.1, 1.7, 7.9 Hz, 1H, ArH), 7.63 (ddd, J = 1.1, 1.7, 7.7 Hz, 1H, ArH), 7.37 (ddd, J = 0.6, 7.7, 7.9 Hz, 1H, ArH), 3.90 (s, 3H, $ArCOOCH_3$), 0.25 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 232 (14, M^+) 217 (100).

Methyl 4-(Trimethylsylilethynyl)benzoate. Method C, entry 9C: yellowish oil, 262.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (AA′XX′, 2H, ArH), 7.51 (AA′XX′, 2H, ArH), 3.90 (s, 3H, $ArCOOCH_3$), 0.25 (s, 9H, $RSi(CH_3)_3$); MS m/z (relative intensity) 232 (14, M^+) 217 (100).

2-(Trimethylsilylethynyl)anisole. Method B, entry 10B: brown oil, 263.2 mg. Method C, entry 13C: yellowish oil, 248.6 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 1.8, 7.5 Hz,

(31) For preparative purposes, triphenylphosphine-free product might be isolated by flash chromatography; see method A.

(32) Saá, J. M.; Dopico, M.; Martorell, G.; Gracía-Raso, A. *J. Org. Chem.* **1990**, *55*, 991.

1H, ArH), 7.28 (ddd, J = 1.8, 7.5, 7.7 Hz, 1H, ArH), 6.88 (ddd, J = 0.9, 7.5, 7.5 Hz, 1H, ArH), 6.86 (dd J = 0.9, 7.7 Hz, 1H, ArH), 3.87 (s, 3H, $ArOCH_3$), 0.27 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 204 (51, M^+), 189 (100).

3-(Trimethylsilylethynyl)anisole. Method B, entry 11B: brown oil, 249.1 mg. Method C, entry 14C: orange oil, 239.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J = 7.7, 8.2 Hz, 1H, ArH), 7.08 (ddd, J = 0.9, 1.5, 7.7 Hz, 1H, ArH), 7.0 (dd, J = 1.5, 2.6 Hz, 1H, ArH), 6.87 (ddd, J = 0.9, 2.6, 8.2, 1H, ArH), 3.79 ppm (s, 3H, $ArOCH_3$), 0.26 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 204 (29, M^+), 189 (100).

4-(Trimethylsilylethynyl)anisole. Method B, entry 12B): brown oil, 287.3 mg. Method C, entry 15C: yellowish oil, 167.2 mg. Method E, entry 15E: yellowish oil, 280.7 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (AA′XX′, 2H, ArH), 6.81 (AA′XX′, 2H, ArH), 3.79 (s, 3H, $ArOCH_3$), 0.25 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 204 (29, M^+), 189 (100).

Trimethyl(2-phenyl-1-ethynyl)silane. Method B, entry 16B: brown oil, 201.4 mg. Method C, entry 17C: yellowish oil, 214.2 mg. Method D, entry 18D: 197.1 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H, ArH), 7.30 (m, 3H, ArH), 0.27 (s, 9H, $RSi(CH_3)_3$); MS (70 eV) *m/z* (relative intensity) 174 (24, M^+), 159 (100).

4-(Trimethylsilylethynyl)benzonitrile. Method D, entry 19D: yellowish-orange solid, 221.9 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (AA′XX′, 2H, ArH), 7.53 (AA′XX′, 2H, ArH), 0.26 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 199 (14, M^+) 184 (100).

4-(α.α.α-Trifluoromethyl)trimethylsilylphenylacetylene. Method B, entry 20B: brown oil, 253.2 mg. Method C, entry 21C: yellowish oil, 264.3 mg. Method F, entry 20F: yellowish oil, 251.7 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 4H, ArH), 0.26 (s, 9H, $RSi(CH_3)_3$). MS *m/z* (relative intensity) 242 (13, M^+), 227 (100).

3-(Trimethylsilylethynyl)pyridine. Method C, entry 22C: yellowish oil, 251.4 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 0.9, 2.2 Hz, 1H, ArH) 8.48 (dd, J = 1.7, 5.0 Hz, 1H, ArH), 7.7 (ddd, J = 1.7, 2.2, 8.0 Hz, 1H, ArH), 7.19 (ddd, J = 0.9, 5.0, 8.0 Hz, 1H, ArH), 0.23 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 175 (21, M^+), 160 (100).

2-(Trimethylsilylethynyl)pyridine. Method C, entry 23C: yellowish oil, 187.0 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J = 1.5, 4.7 Hz, 1H, ArH), 7.57 (dd, J = 1.7, 7.7 Hz, 1H, ArH), 7.39 (ddd, 1.1, 7.7, 7.7 Hz, 1H, ArH), 7.16 (ddd, J = 1.7, 4.7, 7.7 Hz, 1H, ArH), 0.22 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 175 (27, M^+), 160 (100).

2-(Trimethylsylilethynyl)thiophene. Method B, entry 24B: brown oil, 224.0 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, m), 6.95 (1H, dd, J = 3.6, 5.1 Hz), 0.25 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 180 (26, M^+), 165 (100).

3-(Trimethylsilylethynyl)thiophene. Method B, entry 25B: brown oil, 207.3 mg. Method C, entry 26C: yellowish oil, 221.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, dd, J = 1.3, 3.1 Hz), 7.23 (1H, dd, J = 3.1, 5.2 Hz), 7.13 (1H, dd, J = 1.3, 5.2 Hz), 0.26 (s, 9H, $RSi(CH_3)_3$); MS *m/z* (relative intensity) 180 (27, M^+), 165 (100).

Conclusions

In summary, we have developed homogeneous reaction conditions for a microwave-assisted Sonogashira coupling, involving various aryl halides or pseudohalides with a wide variety of substitution patterns, including pyridine and thiophene derivatives. The reaction conditions provide good to excellent yields within a few minutes, as compared to hours or days when conventional literature conditions are used. However, some results also indicate that microwave heating might be replaced by an alternative heat source. The advantage of the microwave equipment is that it provides full control of reaction parameters.

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