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Rapid Microwave Promoted Sonogashira Coupling Reactions on Solid Phase

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Abstract: A microwave-enhanced, rapid, and efficient solid-phase version of the Sonogashira reaction is presented. It has been applied to the coupling of aryl iodides and bromides with various acetylene derivatives giving excellent yields in 15−25 min. The scopes of homogeneous, solventless, and solid-phase conditions for Sonogashira coupling of aryl halides are compared.

The Sonogashira cross-coupling is an important example of metal-catalyzed carbon−carbon bond-forming reactions.[1] It has been applied to the preparation of various target compounds, many of them being of pharmaceutical interest.[2] Some weaknesses of the original procedure are long reaction times (hours to days), limited choice of aryl halides, and complicated workup procedures.[3] Recently, we have developed an improved methodology that allows the use of aryl iodides, as well as less reactive aryl bromides, triflates, and chlorides under homogeneous conditions using microwave heating.[2] A microwave-assisted solventless procedure for the Sonogashira coupling of aryl iodides has also been reported by others.[4] In this paper, we describe an efficient solid-phase version of the Sonogashira reaction of aryl iodides and bromides using controlled microwave heating.

Solid-phase organic synthesis (SPOS) is an efficient methodology for the production of combinatorial libraries and is extensively used by the pharmaceutical and the agricultural industries. The application of a polymer support offers the advantage of automatization and ease of purification. However, this approach often is limited by the narrower choice of reactants and reaction medium and by longer reaction times. Examples for a Sonogashira coupling on solid phase were reported recently,[5] but these procedures suffer from the demand of long reaction times (5−120 h) and the large amount of catalysts required (10−40%). Enhancements of SPOS by the use of microwave heating have so far received limited attention,[6] possibly because of the difficulty of controlling the reaction rate and the requirement of special heavy-walled vials for microwave irradiation that makes resin handling rather complicated.

In the present paper, we describe a microwave-promoted version of the Sonogashira reaction of aryl iodides and bromides on Rink amide linker attached to polystyrene resin. Single mode microwave irradiation with an automatic power control keeping the reaction temperature constant was used throughout. Pressure, temperature, and irradiation power vs time were monitored. A unique, modified Smith Process vial was used that provided the possibility of both simplified resin handling and microwave heating. The vial was equipped with a polypropylene frit and screw cap at one end and was sealed with an aluminum crimp cap fitted with a silicon septum at the other end.[7]

Our optimization studies have been performed for the coupling of moderately reactive trimethylsilylacetylene with 3-haloaryl-substituted resins. The conditions producing full conversion of these compounds were then applied to further substrates. In reactions involving the more reactive aryl iodides, the use of 5% $Pd(PPh_3)_2Cl_2$ catalyst and 10% CuI cocatalyst at 120 °C, in a 3:1 mixture of diethylamine and DMF, gave full conversion within 15 min. To achieve cross-coupling of aryl bromides with full conversion within 25 min, the presence of 10% palladium catalyst, 20% of CuI, and 20% PPh_3 was required when using the same temperature and solvent mixture. During the trifluoroacetic acid mediated cleavage of products from the resin, the $SiMe_3$ group of **1** was lost, as has been reported for similar conditions.[5c,f] Likewise, the Boc or Fmoc[8] protecting groups of **4** and **5** were removed, and an acid-catalyzed rearrangement of **3** to the thermodynamically most stable conjugated α,β-unsaturated ketone was observed. The Sonogashira coupling of polymer-bound 3-chlorophenol was attempted using similar conditions as for the coupling of aryl bromides, but was without success. The use of an *o*-tolylphospine complex of palladium in the presence of Cs_2CO_3 base was recently described to be advantageous for coupling of aryl chlorides.[9] Therefore, reactions were performed using 10% of palladium *o*-tolylphosphine catalyst and 1 equiv of $ZnCl_2$ cocatalyst in the presence of Cs_2CO_3, but without giving any improvement. In the Heck reaction of aryl bromides, the presence of Tl^{3+} additive was proposed to promote halide abstraction.[10]

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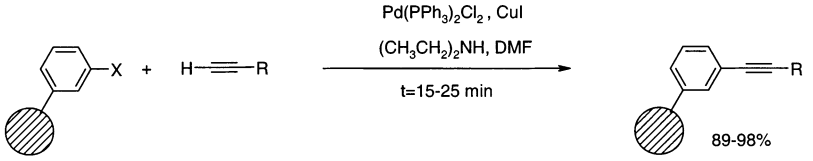
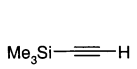
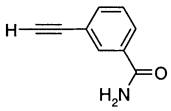
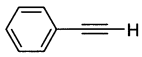
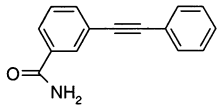
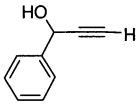
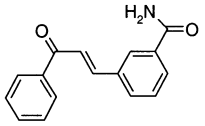
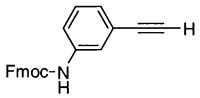
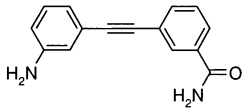
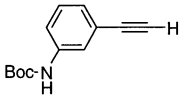
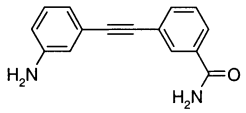
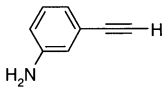
TABLE 1. Sonogashira Coupling of Arylacetylenes on Iodophenyl and Bromophenyl Resins



	R-C≡CH	3-iodophenyl resin yield[A]	3-bromophenyl resin yield[B]	product
1[C]		94%	97%	
2		89%	92%	
3		92%	98%	
4[C]		-	95%	
5[C]		98%	94%	
6[C]		0 %	0 %	-

[a] Method A, 120 °C, 15 min, 5% Pd, 10% Cu. [b] Method B, 120 °C, 25 min, 10% Pd, 20% Cu, 20% PPh_3. [c] Yield determined by ^1H NMR.

However, in our hands the use of $Tl(OAc)_3$ additive had no beneficial effect.

The results of selected cross-coupling experiments, containing highest yields and reaction conditions, are included in Table 1.

Whereas aryl iodides react readily in all media, the Sonogashira coupling of aryl bromides is limited to homogeneous-phase[2] as well as solid-phase conditions. Cross-coupling of the least reactive aryl chlorides could only be performed using homogeneous catalysis.[2,8] The presence of a primary amine during Sonogashira coupling was tolerated under homogeneous[2] and solventless[4] conditions, whereas no conversion was observed on solid phase. This observation might be explained by the relative rates of the competing processes: Rapid coupling of aryl halides at elevated temperature under homogeneous (5 min) and solventless (2.5 min) conditions occurs faster than catalyst decomposition. On solid phase with longer reaction times (15−25 min), due to the slower diffusion of the reactants, the cross-coupling—inside of the resin—cannot compete with the amine-mediated decomposition of the catalyst taking place in solution. Amines can be used when they are protected by Fmoc or Boc groups (**4** and **5**). Because of the lower affinity of palladium to oxygen, free alcohols were tolerated under all conditions.

The amount of catalysts and additives required for the coupling of aryl iodides on solid phase (5% Pd, 10% Cu, 15 min) was slightly higher than under homogeneous conditions (2% Pd, 4% Cu, 5 min),[2] but nevertheless considerably lower than that needed for a solventless reaction (37% Pd, 37% Cu and 70% PPh_3, 2.5 min).[4] The presence of triphenylphosphine additive can complicate the workup procedure when solventless or homogeneous conditions are applied. Therefore, to improve the stability

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of the Pd catalyst in homogeneous-phase reactions, the use of polymer-bound triphenylphosphine was investigated, but remained without effect. Using aryl bromides on solid phase in a heavy-walled Smith vial equipped with a polypropylene frit, the Sonogashira couplings could be rapidly performed, and the resin-bound substrates could easily be separated from PPh_3.

In conclusion, we have developed a general procedure for rapid Sonogashira coupling of aryl iodides and bromides on solid phase. Furthermore, a modified heavy-walled glass vial equipped with a polypropylene frit is introduced, allowing both microwave heating and simplified resin handling. The described procedure should prove valuable for the fast automatized generation of chemical libraries.

Experimental Section

General Comments. For a general description of methods and microwave irradiation procedures, see ref 2.

Materials. The starting materials were purchased from commercial suppliers and were used without purification with the exception of (3-ethynylphenyl)carbamic acid *tert*-butyl ester (3-ethynyl-Boc-aniline) and (3-ethynylphenyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (3-ethynyl-Fmoc-aniline), which were prepared from 3-ethynylaniline using standard protection procedures.[11]

Method A. Loading of 3-Iodobenzoic Acid onto the Rink Amide Resin (A1). To 500 mg of Rink amide linker attached to polystyrene resin (loading 0.78 mmol/g) were added DMF (3 mL), 3-iodobenzoic acid (0.78 mmol, 193.5 mg), PyBOP[12] (0.78 mmol, 405.8 mg), and diisopropylethylamine (1.34 mmol, 0.4 mL). The mixture was stirred in a modified heavy-walled Smith Process Vial under microwave irradiation at 110 °C for 20 min, then washed with DMF, ethanol, and dichloromethane to yield 3-iodophenyl-derivatized Rink amide resin. The substitution level of the iodophenyl-derivatized resin was determined to be 0.48 mmol/g by cleavage and quantification of 3-iodophenylamide following procedure A3.

Sonogashira Coupling on Iodophenyl Resin (A2). The 3-iodophenyl-resin obtained in procedure A1 (500 mg, 0.48 mmol/g), $Pd(PPh_3)_2Cl_2$ (8.2 mg, 0.012 mmol), CuI (4.5 mg, 0.024 mmol), the acetylene derivative **1**−**6** (0.43 mmol), diethylamine (1.5 mL, 13.60 mmol), and DMF (0.5 mL) were stirred in a modified heavy-walled Smith Process Vial at 120 °C for 15 min in the microwave cavity. The mixture was then washed with DMF, ethanol, and dichloromethane.

Cleavage and Purification of the Arylacetylene (A3). Four milliliters of 95% trifluoroacetic acid was added to the resin, and the mixture was stirred in a modified heavy-walled Smith Process Vial at 70 °C for 20 min in the microwave cavity. The mixture was then filtered, and the resulting solution was concentrated on a rotatory evaporator. The residue was extracted with aqueous sodium hydroxide solution (pH = 12), reextracting the aqueous phase with dichloromethane twice. After filtration of the combined organic layers through $MgSO_4$, they were concentrated under reduced pressure. The further purification of 3-ethynylbenzamide and 3-(3-aminophenylethynyl)benzamide was omitted because of their tendency to adsorb on silica, and these compounds were therefore quantified by ^{1}H NMR using hydroquinone diacetate as an internal standard. In the case of all other arylacetylene derivatives, the obtained residue was purified by column chromatography (silica gel 60, particle size 0.040−0.063 mm, hexane/ethyl acetate stepwise gradient from 12:1 to 1:1). The combined product fractions were concentrated on a rotatory evaporator, followed by removal of remaining solvent under reduced pressure overnight.

Method B. Loading of 3-Bromobenzoic Acid onto the Rink Amide Resin (B1). Procedure A1 was followed with the exception of using a resin with a loading of 0.69 mmol/g and using 3-bromobenzoic acid (0.78 mmol, 156.8 mg) instead of the iodo-derivative, yielding 3-bromophenyl-derivatized Rink amide resin. The substitution level was determined to be 0.39 mmol/g by cleavage of 3-bromophenylamide following procedure A3.

Sonogashira Coupling on Bromophenyl Resin (B2) and Cleavage and Purification of the Arylacetylenes (B3). The 3-bromophenyl resin obtained in procedure B1 (500 mg, 0.39 mmol/g), $Pd(PPh_3)_2Cl_2$ (13.7 mg, 0.020 mmol), CuI (7.4 mg, 0.039 mmol), triphenylphosphine (20.5 mg, 0.078 mmol), the acetylene derivative **1**−**6** (0.43 mmol), diethylamine (1.5 mL, 13.60 mmol), and DMF (0.5 mL) were stirred in a modified heavy-walled Smith Process Vial at 120 °C for 25 min in the microwave cavity. Subsequent workup followed the procedure described for methods A2 and A3.

3-Iodobenzamide.[13] Method A: 59.0 mg, 0.239 mmol, 62%, white solid, corresponding to a loading rate of 0.48 mmol/g. Mp: 183−184 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 8.22 (dd, J = 1.1, 1.1 Hz, 1H, H-2), 7.89 (ddd, J = 1.1, 1.6, 7.9 Hz, 1H, H-6), 7.86 (ddd, J = 1.1, 1.6, 7.9 Hz, H-4), 7.23 (dd, J = 7.9, 7.9 Hz, H-5). ^{13}C NMR (100 MHz, CD_3OD): δ 169.2, 140.5, 136.5, 135.7, 130.0, 126.6, 93.4. EI-MS m/z (relative intensity): 247 (M^+, 100), 231 (84), 203 (40), 127 (16), 76 (82). IR ν (cm^{-1}): 3404, 3202, 1665.

3-Bromobenzamide.[14] Method B: 39.2 mg, 0.195 mmol, 57%, white solid, giving a loading rate of 0.39 mmol/g. Mp: 153−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J = 1.8, 1.8 Hz, 1H, H-2), 7.68 (ddd, J = 1.1, 1.8, 7.8 Hz, 1H, H-6), 7.56 (J = 1.1, 1.8, 7.8 Hz, H-4), 7.23 (dd, J = 7.8, 7.8 Hz, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 135.3, 134.9, 130.7, 130.1, 126.1, 122.6. EI-MS m/z (relative intensity) 201 (M^+, 73), 200 (M^+, 59), 185 (96), 183 (100), 76 (18). IR ν (cm^{-1}): 3560, 3180, 1640.

3-Ethynylbenzamide. (**1A**) Method A: 91.5 mg, white solid containing 32.8 mg, 0.226 mmol, 94% product. (**1B**) Method B: 57.9 mg, yellowish solid containing 27.9 mg, 0.191 mmol, 97% product. ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (ddd, J = 0.6, 1.3, 1.3 Hz, 1H, H-2), 7.86 (ddd, J = 1.3, 1.8, 7.9 Hz, 1H, H-6), 7.62 (ddd, J = 1.3, 1.8, 7.7 Hz, 1H, H-4), 7.45 (ddd, J = 0.6, 7.7, 7.9 Hz, 1H, H-5). ^{13}C NMR (100 MHz, CD_3OD): δ 170.0, 134.8, 134.1, 130.8, 128.5, 127.6, 122.9, 82.2, 78.4. EI-MS m/z (relative intensity): 145 (M^+, 63), 129 (79), 101 (100), 75 (71), 51 (39). IR ν (cm^{-1}): 3682, 3622, 2398, 1518. Anal. (C_9H_7NO) C, H, N.

3-Phenylethynylbenzamide. (**2A**) Method A: 47.0 mg, white solid (0.212 mmol, 89%). (**2B**) Method B: 39.7 mg 27.9 mg, white solid (0.179 mmol, 92%). Mp: 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 1.5, 1.7 Hz, 1H, H-2), 7.75 (ddd, J = 1.3, 1.7, 7.9 Hz, 1H, H-6), 7.63 (ddd, J = 1.3, 1.5, 7.9 Hz, 1H, H-4), 7.46−7.51 (m, 2H, AA′ part of AA′BB′C), 7.40 (dd, J = 7.9, 7.9 Hz, 1H, H-5), 7.29−7.35 (m, 3H, BB′C part of AA′BB′C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 134.7, 133.6, 131.5, 130.6, 128.6, 128.5, 128.4, 127.2, 123.8, 122.7, 90.2, 88.2. EI-MS m/z (relative intensity): 221 (M^+, 100), 205 (61), 176 (79), 151 (32), 88 (18). IR ν (cm^{-1}): 3522, 3413, 2392, 1674. Anal. ($C_{15}H_{11}NO$) C, H, N.

(*E*)-3-(3′-Oxo-3-phenylprop-1-enyl)benzamide.[13] (**3A**) Method A: 55.9 mg, white solid (0.222 mmol, 92%). (**3B**) Method B: 48.4 mg, white solid (0.193 mmol, 98%). Mp: 153−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, J = 1.8, 1.8 Hz, 1H, H-2), 8.06 (m, 2H, AA′ part of AA′BB′C), 7.83 (d, J = 15.8 Hz, 1H, C=C−H), 7.81 (ddd, J = 1.1, 1.8, 7.7 Hz, 1H, H-6), 7.79 (ddd, J = 1.1, 1.8, 7.7 Hz, 1H, H-4), 7.62 (d, J = 15.8 Hz, 1H, C=C−H), 7.61 (ddd, J = 1.1, 1.1, 7.7 Hz, 1H, H-5), 7.52 (m, 3H, BB′ and C part of AA′BB′C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 170.3, 143.1, 137.8, 135.2, 134.4, 133.1, 131.9, 129.5, 129.1,

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128.6, 128.5, 127.2, 122.9. EI-MS *m/z* (relative intensity): 251 (M^+, 81), 207 (100), 178 (25), 157 (48), 129 (19), 105 (65), 77 (91). IR ν (cm^{-1}): 3413, 3353, 1665, 1607.

3-(3′-Aminophenylethynyl)benzamide. (**4B**) Method B: 91.1 mg, yellowish solid containing 44.3 mg, 0. 188 mmol, 95% product. (**5A**) Method A:, 129.5 mg, white solid containing 57.8 mg, 0.245 mmol, 98% product. (**5B**) Method B: 130.3 mg, yellowish solid containing 43.9 mg, 0.186 mmol, 94% product. ^{1}H NMR (400 MHz, CD_3OD): δ 9.06 (dd, J = 1.7, 1.8 Hz, 1H, H-2), 8.88 (ddd, J = 0.8, 1.7, 7.8 Hz, 1H, H-6), 8.67 (ddd, J = 0.8, 1.8, 7.8 Hz, 1H, H-4), 8.49 (dd, J = 7.8, 7.8 Hz, 1H, H-5), 8.13 (dd, J = 7.7, 7.7 Hz, 1H, H-5′), 7.93 (dd, J = 2.1, 2.1 Hz, 1H, H-2′), 7.89 (ddd, J = 0.8, 2.1, 7.7 Hz, 1H, H-6′), 7.77 (ddd, J = 0.8, 2.1, 7.7 Hz, 1H, H-4′). ^{13}C NMR (100 MHz, CD_3OD): δ 170.2, 147.8, 134.3, 134.1, 130.4, 129.0, 128.5, 127.0, 124.0, 123.2, 121.0, 117.6, 115.7, 90.5, 87.0. EI-MS *m/z* (relative intensity): 236 (M^+,100), 220 (21), 191 (19), 165 (41), 139 (7). IR ν (cm^{-1}): 3683, 3615, 3544, 3404, 2391, 1674, 1210. Anal. ($C_{15}H_{12}N_2O$) C, H, N.

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Supporting Information Available: A description of the modified heavy-walled glass microwave vial. This material is available free of charge via the Internet at http://pubs.acs.org.

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