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A convenient microwave assisted arylzinc generation-Negishi coupling protocol ☆

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Abstract—Arylzinc reagents were readily prepared from aryl iodides using a Zn–Cu couple in a microwave environment. A sequential arylzinc formation-Negishi cross-coupling protocol suitable for parallel high-throughput synthesis has been developed.

Microwave dielectric heating has become an important tool in organic chemistry and, particularly, in high-throughput synthesis.[1] Many chemical reactions can be performed more rapidly and in higher yields under microwave irradiation than using conventional conditions. Among these, the advantages of dielectric heating have been demonstrated in transition metal catalyzed C–C bond forming reactions involving organozinc reagents.[2] However, the generation of organometallic species directly from *metals* under dielectric heating conditions has found only very limited application in organic synthesis.[3] To the best of our knowledge, there is no report on the synthesis of main group organometallic and organozinc reagents from the corresponding metals in a microwave environment.

A complicating factor in the heating of a metal–organic solvent system by microwaves is destructive electrical arcing. Whittaker and Mingos have demonstrated that the use of low microwave power and small, well-dispersed metal particles in a polar, high boiling point solvent can substantially diminish the arcing.[4] These findings have opened doors to synthetic applications of metals under microwave conditions. Given the importance of arylzinc reagents in C–C bond forming chemistry,[5] we decided to apply microwave dielectric heating to facilitate generation of arylzinc species from aryl iodides and zinc.[6]

Initially, we made certain that the microwave irradiation of zinc in organic solvents can be carried out safely under the conditions reported by Whittaker and Mingos.[7] Thus, dielectric heating of zinc *dust*[8] at various temperatures was performed in DMF as well as in ethereal solvents such as 1,4-dioxane, THF and DME, which are routinely used for the preparation of organozinc species. To our delight, temperature and pressure profiles of the heating did not show any unusual behavior such as a quick rise in temperature or a sudden change of pressure, demonstrating that microwave irradiation of zinc *dust* under the tested conditions is a safe and reliable procedure.[9] These results rendered further studies of microwave assisted zinc insertion into aryl-iodine bonds feasible. Ethyl 4-iodobenzoate **1a** was chosen as the substrate and yields of the corresponding arylzinc iodide **2a** were determined by performing a GC analysis of the hydrolysis and iodolysis products.[10]

Activation of zinc dust is necessary to initiate the insertion of the metal into an aryl-iodine bond. Therefore, representative activation protocols such as treatment with aqueous HCl prior to use[11] as well as addition of 1,2-dibromoethane/TMS-Cl[12] and iodine[13] were examined. None of these activation methods brought about the formation of the desired arylzinc iodide **2a** under the conditions tested (Table 1, entries 1–3). Attempts using 0.5 equiv of CuI as an additive[14] (entry 4) and replacing the zinc dust with the commercially available Zn–Cu couple[15] (entry 5) also proved to be unsuccessful. In contrast, the Zn–Cu couple prepared from zinc dust according to the *LeGoff* procedure[16] afforded the arylzinc reagent **2a** in reasonable yields (entry 6). Consequently, further studies were carried out using the in-house prepared Zn–Cu couple.

Keywords: Microwaves; Organometallic reagents; Zinc; Cross-coupling; Palladium; Nickel.

☆ Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2004.03.118

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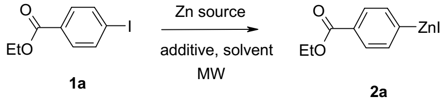
Table 1. Evaluation of zinc activation methods for the generation of organozinc iodide **2a**



Entry	Zn source	Additive or activation method	Solvent	Temp (0 °C)	Time (min)	Yield of **2a** (%)[a]
1	Dust	HCl wash	DMF	100	10	6[b]
2	Dust	Iodine	DMF	100	10	3[b]
3	Dust	1,2-DBE, TMSCl	DMF	100	10	7[b]
4	Dust	CuI[c]	DMF	100	10	14[b]
5	Zn–Cu couple[d]	—	DMF	100	10	0[b]
6	Zn–Cu couple	—	DMF	100	10	87
7	Zn–Cu couple	TMEDA[f]	TMU	100	15	55
8	Zn–Cu couple[e]	—	DMF	100	10	72
9	Dust	1,2-DBE, TMSCl	DME	160	30	4[b]
10	Zn–Cu couple	—	DME	160	30	52
11	Zn–Cu couple	TMEDA[f]	DME	140	30	81
12	Zn–Cu couple	TMEDA[f]	THF	140	30	80

[a] Reactions were run using 1.0 mmol of aryl iodide, 6.0 mmol of the zinc source in 2.0 mL of solvent; yields were determined by GC analysis of hydrolyzed and iodolyzed aliquot.

[b] The major product was the unreacted starting iodide **1a**.

[c] 0.5 mmol of CuI was added.

[d] The Zn–Cu couple was purchased from *Aldrich* and *Acros*.

[e] Twofold increase in concentration of reactants was employed.

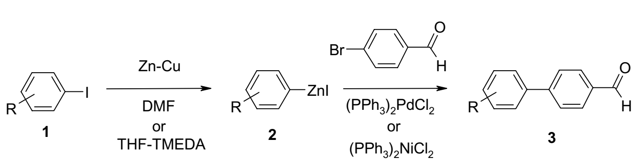
[f] 1 mmol of TMEDA was added.

Zinc insertion readily occurs in polar solvents such as DMF[17] and 1,1,3,3-tetramethylurea (TMU) (entries 6–7). Arylzinc iodide **2a** was also formed in less polar ethereal solvents such as DME and THF[18] provided that 1 equiv of TMEDA was added (Table 1, entries 10–12).[19] A typical concentration of aryl iodide **1a** was 0.5 M and a sixfold excess of the Zn–Cu couple was required to achieve the best yields of arylzinc iodide **2a**. Higher concentrations of both reactants caused a slight attenuation in yield, presumably due to diminished stirring efficiency (Table 1, entry 8 vs entry 6).

Table 2 illustrates the scope of the procedure.[20] The time and temperature profiles of the oxidative addition of zinc depended on the structure of the aryl iodide.[21] For aryl iodides possessing electron withdrawing substituents, microwave heating at 100 °C for 10 min was sufficient to form the corresponding organozinc species **2a–d** in 70–87% yields (Table 2, entries 1a, 2–4). *ortho*-Substituted iodo-arene[22] **1k** as well as heterocyclic iodides **1l–m** required even milder conditions to generate the corresponding organozinc species (Table 2, entries 11–13). In contrast, higher temperatures and longer times were required in the case of the less reactive aryl iodides **1g–i** possessing electron donating substituents (Table 2, entries 7–9). Selective formation of bromo- and chloro-substituted arylzinc iodides **2h,j** (Table 2, entries 8,10) was possible, as aryl bromides and chlorides were completely unreactive under standard conditions. Poor yields in the case of the ketone **1e** (Table 2, entry 5) could be attributed to the undesired quench of the generated arylzinc iodide **2e** by a proton from the ketone moiety. This assumption was supported by the particularly high amount of deiodinated product (55%, GC yield) observed after iodolysis of the reaction aliquot.

To demonstrate the suitability of this methodology for high-throughput synthesis, the design of a sequential microwave assisted arylzinc formation-Negishi coupling protocol was addressed. 4-Bromobenzaldehyde was employed in the cross-coupling with the arylzinc species under microwave conditions (see Table 2). Among the various catalysts tested, $(PPh_3)_2PdCl_2$ was the most

Table 2. Microwave assisted preparation of arylzinc iodides **2** and *Negishi* cross-coupling with 4-bromobenzaldehyde



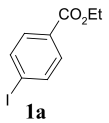
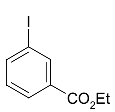
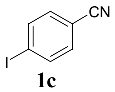
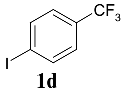
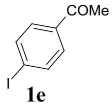
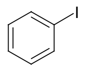
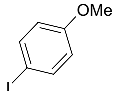
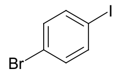
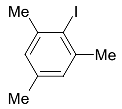
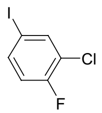
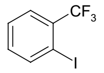
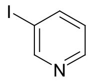
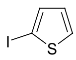
Entry	Aryl iodide (ArI)	Temp (°C)	Time (min)	Yield of ArZnI **2** (%)[a]	Yield of aldehyde **3** (%)[b]
1a	 **1a**	100	10	87	85
1b	**1a**	140	30	80	71[c]
2	 **1b**	100	10	70	82
3	 **1c**	100	10	87	95
4	 **1d**	100	10	77	85

Table 2 (*continued*)

Entry	Aryl iodide (ArI)	Temp (°C)	Time (min)	Yield of ArZnI **2** (%)[a]	Yield of aldehyde **3** (%)[b]
5	 **1e**	100	10	15	N/A
6	 **1f**	100	15	89	78[d]
7	 **1g**	125	15	75	76[e]
8	 **1h**	125	15	86	67
9	 **1i**	130	15	72	57
10	 **1j**	100	2	81	82
11	 **1k**	80	2	60	87
12	 **1l**	80	5	71	92
13	 **1m**	60	3	79	96

[a] Reactions were carried out using 1.0 mmol aryl iodide **1**, 6.0 mmol of a Zn–Cu couple in DMF (2.0 mL); yields were determined by GC analysis of hydrolyzed and iodolyzed aliquot.

[b] Reactions were run using a solution of arylzinc reagent, 0.7 mmol of 4-bromobenzaldehyde and 0.03 mmol $(PPh_3)_2PdCl_2$ in 1.0 mL DMF at 120 °C for 5 min; yields of isolated products were calculated based on 4-bromobenzaldehyde.

[c] The reaction was run using a THF solution of arylzinc reagent, 0.7 mmol of 4-bromobenzaldehyde and 0.03 mmol $(PPh_3)_2NiCl_2$ in 1.0 mL THF at 120 °C for 5 min; the yield of isolated product was calculated based on 4-bromobenzaldehyde.

[d] The *Negishi* cross-coupling was performed at 120 °C for 10 min.

[e] The *Negishi* cross-coupling was performed at 100 °C for 15 min.

efficient in DMF as solvent, while $(PPh_3)_2NiCl_2$ was the catalyst of choice for the cross-coupling reaction in THF. Heating the arylzinc iodide **2a** and 4-bromobenzaldehyde in DMF at 120 °C for 5 min in the presence of 3 mol% of $(PPh_3)_2PdCl_2$ afforded an 85% isolated yield (based on 4-bromobenzaldehyde) of biaryl aldehyde **3a**. The analogous Ni-catalyzed reaction in THF was slightly less efficient affording 71% of the desired product **3a**. Although both catalyst systems demonstrated comparable efficiency in the *Negishi* reaction, the superiority of DMF as the solvent for the microwave assisted generation of arylzinc species dictated the application of $(PPh_3)_2PdCl_2$ to catalyze the cross-coupling reaction. Subsequently, a series of biaryl aldehydes **3** (Table 2) was synthesized in good to excellent yields using the sequential microwave assisted arylzinc formation-Negishi coupling protocol.[20]

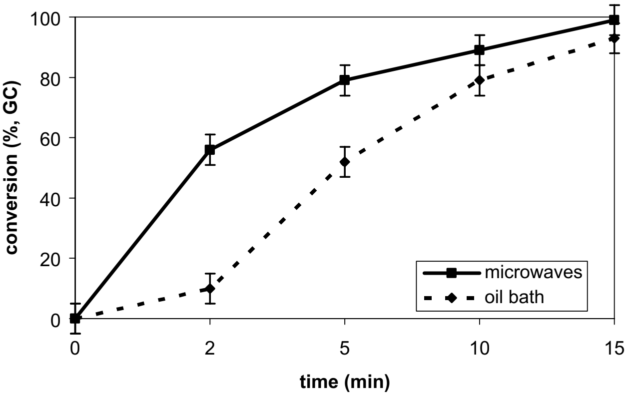


Figure 1. Conversion rates of iodo-mesitylene **1i** to mesitylzinc iodide **2i** under conventional heating conditions (oil bath) and under microwave irradiation.

Additional experiments were conducted to study the possible acceleration of the reaction by microwaves. Thus, the rates of formation of the mesitylzinc iodide **2i** were measured both under dielectric heating conditions and in an oil bath[23] (Fig. 1). Indeed, initial acceleration of the reaction rate under dielectric heating conditions was observed (56% vs 10% after 2 min and 79% vs 52% after 5 min) and this could be attributed to the more rapid dielectric heating process.

In conclusion, we have shown that the use of a Zn–Cu couple under dielectric heating conditions allows the preparation of arylzinc species directly from aryl iodides. The reaction benefits from reduced reaction time, operational simplicity and ease of automation. To demonstrate the suitability of the methodology developed for parallel high-throughput organic synthesis, a sequential arylzinc formation-Negishi cross-coupling protocol has been designed. Further studies to expand the application of the Zn–Cu couple in conjunction with microwaves are currently in progress.

Note added in proof: Related work on the generation of arylzinc halides from *Rieke* zinc and subsequent Negishi coupling under microwave conditions has recently appeared: Walla, P.; Kappe, C.O. *Chem. Commun.* **2004**, 564.

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6. Most methods for direct generation of arylzinc species from aryl iodides and zinc suffer from relatively long reaction times (up to 24 h). On the other hand, the use of highly reactive *Rieke* zinc is associated with sophisticated handling techniques and therefore can hardly be automated. Subsequently, fast and operationally simple arylzinc preparation procedures are highly desirable, especially for high-throughput synthesis.
7. Whittaker and Mingos have used an in-house modified domestic microwave oven with multimode cavity to study the arcing phenomenon.[3] Our experiments were performed on a purpose-built *Smith Synthesizer* by Personal Chemistry (Uppsala, Sweden) with a monomode cavity and temperature control.
8. Zinc *dust* was purchased from *Acros*.
9. Zinc sources of larger particle size such as *powder* or *granules* are reported to be more susceptible to arcing.[3,4] On the other hand, a successful application of Zn *powder* in a microwave environment to catalyze Friedel–Crafts acylation has been recently reported: Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, 2877.
10. For a detailed description of GC analysis of zinc organometallics see: Knochel, P.; Jones, P.; Langer, F. Organozinc chemistry: an overview and general experimental guidelines. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; *The Practical Approach in Chemistry Series*; Oxford University Press: New York, 1999; pp 1–21.
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15. The Zn–Cu couple was purchased from *Aldrich* and *Acros*. To the best of our knowledge, the use of a Zn–Cu couple for the generation of *aryl* zinc species is not precedented in the literature.
16. LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048, A slightly modified procedure was used. Thus, zinc dust (35 g) was added in one portion to a hot (80–90 °C) and rapidly stirred solution of 2.0 g cupric acetate monohydrate in 50 mL of glacial acetic acid. After 30 s (time should not be exceeded!) the flask was cooled in an ice-water bath for 1 min, filtered and washed with 50 mL acetic acid, followed by 4–5 portions of dry Et_2O (50 mL each). The solid material was ground in a pestle and after drying in vacuo for 8 h at 90 °C the resulting dark grey zinc-copper couple was ready for use. No attenuation of activity of thus prepared Zn–Cu couple was observed after storage for 3 months under an argon atmosphere.
17. Extra dry DMF (*Acros*, water content <50 ppm) was used in all experiments.
18. THF and DME were distilled from sodium benzophenone ketyl under argon.
19. Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336.
20. General experimental procedure. An oven dried process vial equipped with a Teflon-coated stirring bar[10] was charged with the Zn–Cu couple (392 mg, 6.0 mmol), aryl iodide (if solid at room temperature; 1.0 mmol), flushed with argon and closed using an aluminium open-top seal with PTFE-faced septum. The aryl iodide (if liquid at room temperature; 1.0 mmol), TMEDA (if reaction was performed in THF or DME; 150 μL, 1.0 mmol) and solvent (2 mL) were introduced via a syringe and the reaction mixture was microwave-irradiated for the appropriate time and temperature (see Table 2). After cooling the suspension was centrifuged (5 min at 3000 rpm) and the supernatant solution containing the arylzinc reagent was used in the Negishi cross-coupling reaction (vide infra). An aliquot of the supernatant solution was subjected to hydrolysis and iodolysis to determine the yield of the arylzinc reagent by GC analysis. A separate oven dried process vial, equipped with a Teflon-coated stirring bar was charged with $(PPh_3)_2PdCl_2$ (if reaction was performed in DMF; 21.1 mg, 0.03 mmol) or with $(PPh_3)_2NiCl_2$ (if reaction was performed in THF or DME; 19.6 mg, 0.03 mmol), 4-bromobenzaldehyde (130 mg, 0.7 mmol) and 1 mL of solvent, flushed with argon and closed using an open-top seal with PTFE-faced septum. The contents of the vial were stirred vigorously for 2 min where upon the supernatant solution of arylzinc iodide was introduced via a cannula and the reaction mixture was heated by microwave irradiation at 120 °C for 5 min. After cooling, the resulting black reaction mixture was diluted with EtOAc (3 mL) and filtered through a Celite plug (2 × 2 cm) followed by rinsing with EtOAc. After solvent removal (rotary evaporator) the residue was purified by flash column chromatography on silica gel. All biaryl aldehydes **3** were characterized by spectral data (^{1}H NMR, GC–MS) and analytical data (melting points).
21. For relative rates of the formation of various arylzinc species see: Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155.
22. Amano, M.; Saiga, A.; Ikegami, R.; Ogata, T.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 8667.
23. Experimental procedure for reactions in an oil bath. The temperature of the oil bath was adjusted to ensure a temperature of 130 °C *inside* a well-stirred oven dried process vial (measured using a thermocouple thermometer with a hypodermic probe). An oven dried process vial equipped with a Teflon-coated stirring bar was charged with Zn–Cu couple (392 mg, 6.0 mmol), iodo-mesitylene **1i** (246 mg, 1.0 mmol), flushed with argon and closed using open-top seals with a PTFE-faced septum. DMF (2 mL) was introduced via syringe and the reaction mixture was placed into the pre-heated oil bath. After the appropriate time the reaction mixture was cooled in an ice bath. Formation of mesitylzinc iodide **2i** was determined by GC analysis of hydrolyzed and iodolyzed aliquots. Each datapoint on the curve (Fig. 1) represents a single experiment.