Microwave Irradiation as a High-Speed Tool for Activation of Sluggish Aryl Chlorides in Grignard Reactions

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Abstract: Grignard reagents have been generated from reluctant aryl chlorides and bromides using controlled microwave heating to establish a safe, productive and reproducible method. In the synthesis of a novel HIV-1 protease inhibitor, microwave irradiation was both used to generate the starting arylmagnesium halide and to promote a subsequent Kumada coupling.

Key words: Grignard reactions, arylations, cross-coupling, microwave, inhibitors

The need for rapid synthesis to meet the ever growing demand of new chemical entities in drug discovery endeavours has made critical the development of better and faster synthesis methods.[1,2] To address this issue, our group has previously developed several high-speed transition metal-catalyzed methods for the decoration and optimization of peptidomimetic core structures.[3,4] Complementary to the essential participation of largely covalent transition metal organyl intermediates in homogeneous catalysis, the much more nucleophilic alkali and alkali earth metal counterparts are of great importance in stoichiometric transformations. In contrast to the extensively exploited lithium reagents, the corresponding magnesium reagents have been less frequently used, probably due to the occasionally unreliable and demanding metallation of the starting organohalides, especially in small-scale applications. Accordingly, Knochel has reported on several transhalogenation procedures using pre-formed Grignard reagents to facilitate magnesiation under mild conditions.[5] The importance and versatility of Grignard reagents in nucleophilic reactions with carbonyl derivatives is, however, indisputable and has been demonstrated in the production of several pharmaceuticals.[6] Furthermore, Grignard reagents are also frequently used as reactants in several important transmetallation-based coupling protocols, including transition metal-catalyzed C–C bond formations (e.g., Kumada couplings).[7–9]

The direct generation of Grignard reagents from aliphatic halides is a well-established process but aryl halides are comparatively less readily reactive.[10] In particular, the use of electron-rich aryl chlorides are commonly associated with low conversions and yields, unless specialized, high-pressure equipment is used.[11] Thus, a robust and rapid procedure for the preparation of organomagnesium reagents from magnesium metal seems worthwhile.

Today, most reported examples of microwave-enhanced (MW) transformations are performed in homogeneous media, in which the polar solvent acts as the heat absorbant.[12,13] Surprisingly, there are few examples of heterogeneous organometallic reactions in the microwave chemistry literature. The possible problems with interfacial polarization, a heating phenomena associated with differences in conductivity, may have prevented investigation of solid metals in organometallic synthesis.[14] However, in this project more than 500 reactions were performed in the absence of arcing or overpressurization incidents. By using septum sealed reaction vials and controlled microwave heating, it was possible to raise the reaction temperature well above the boiling point of the solvent, thus decreasing reaction times (Figure 1). Since oxidative magnesiation of inert halides often requires constant re-activation of the metal surface during the reaction, a closed reaction vessel also preserves the anhydrous environment necessary to retain active magnesium throughout the process. Herein, we would like to report a microwave-assisted lab-scale[15] protocol for fast generation of Grignard reagents employing reluctant aryl chlorides[16] and bromides as inexpensive and readily available starting materials.

A primary screen of reaction conditions revealed that activation of the magnesium metal was conveniently performed by the dry stir method,[17] and proved that freshly

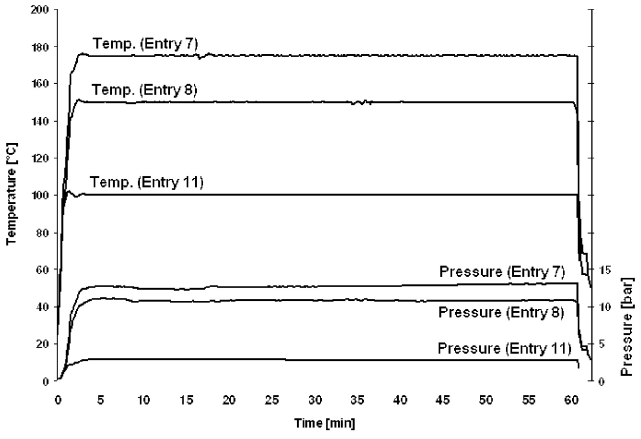

Figure 1 Temperature and pressure profiles for Grignard formation from **1k**, **1h** and **1g** (entries 11, 8, 7, Table 1), in THF (bp 66 °C, 1 atm).

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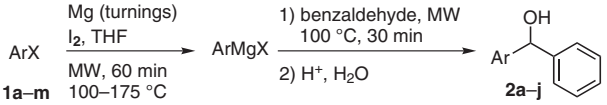
distilled THF was the best solvent in terms of microwave compatibility and promotion of aryl magnesiation. After the initial metallation step, benzaldehyde was added to the Grignard reagent to deliver the diarylmethanol product **2** (Scheme 1).



Scheme 1

Microwave heating at 150 °C for one hour, using only a catalytic amount of iodine as the sole activator[10] initiated Grignard formation of most aryl chlorides (see Table 1). The only exception was the sterically hindered 2-chloro-*m*-xylene (**1g**) that required a slightly elevated temperature (175 °C) for sufficient conversion. The reaction pressure at 175 °C never exceeded 14 bar (Figure 1). A second irradiation at 100 °C for 30 minutes resulted in full conversion of benzaldehyde in all cases when an excess of aryl halide **1** (1.0 mmol) compared to benzaldehyde (0.5 mmol) was used, in accordance with the standard procedure (condition A, Table 1). As evident from entries 1–9 in Table 1, a rather broad scope of aryl chlorides could be employed. Both electron-rich, electron-poor and sterically hindered precursors produced excellent yields (89–99%). The aryl bromides **1j–m** could, as expected, be activated at a lower temperature (100 °C), providing almost quantitative yields of **2** (entries 10–13). With aryl chlorides biaryl formation was the most prominent side reaction. Using equimolar amounts of benzaldehyde (condition B) and the aryl chlorides **1e** or **1h**, the outcome was not equally impressive since side reactions increased (i.e., reduction of benzaldehyde and biaryl formation, entry 14 and 15). Notably, the corresponding 2-bromotoluene furnished better yield (entry 16). Metallation of π-deficient heteroaromatic halides is known to require low temperature to minimize side reactions and was accordingly found to be incompatible with this protocol.[18]

Table 1 Microwave-Heated Generation of Grignard Reagents from Sluggish Aryl Halides and Subsequent Addition of Benzaldehyde

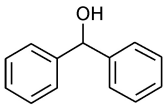
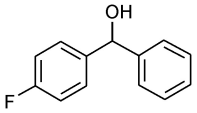
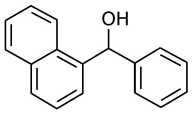
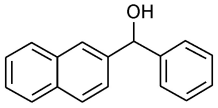
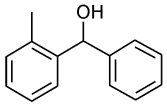
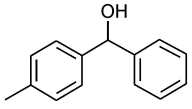
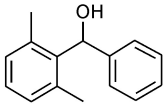
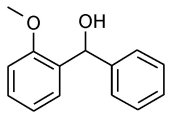
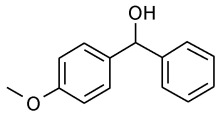
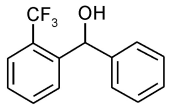
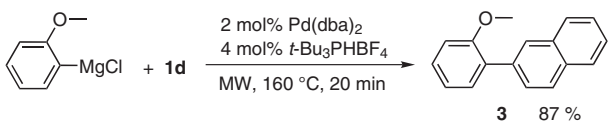
Entry	Aryl halide	Condition,[a] temp (°C)	Product	Yield (%)[b]
1	Chlorobenzene **1a**	A 150	 **2a**	94
2	1-Chloro-4-fluorobenzene **1b**	A 150	 **2b**	91
3	1-Chloronaphthalene **1c**	A 150	 **2c**	99
4	2-Chloronaphthalene **1d**	A 150	 **2d**	99
5	2-Chlorotoluene **1e**	A 150	 **2e**	93
6	4-Chlorotoluene **1f**	A 150	 **2f**	93
7	2-Chloro-*m*-xylene **1g**	A 175	 **2g**	89[c]

Table 1 Microwave-Heated Generation of Grignard Reagents from Sluggish Aryl Halides and Subsequent Addition of Benzaldehyde (continued)

Entry	Aryl halide	Condition,[a] temp (°C)	Product	Yield (%)[b]
8	2-Chloroanisole **1h**	A 150	 **2h**	89
9	4-Chloroanisole **1i**	A 150	 **2i**	93
10	2-Bromo-trifluoromethylbenzene **1j**	A 100	 **2j**	97
11	1-Bromonaphthalene **1k**	A 100	**2c**	99
12	2-Bromotoluene **1l**	A 100	**2e**	99
13	2-Bromoanisole **1m**	A 100	**2h**	99
14	2-Chlorotoluene **1e**	B 150	**2e**	58
15	2-Chloroanisole **1h**	B 150	**2h**	61
16	2-Bromotoluene **1l**	B 100	**2e**	81

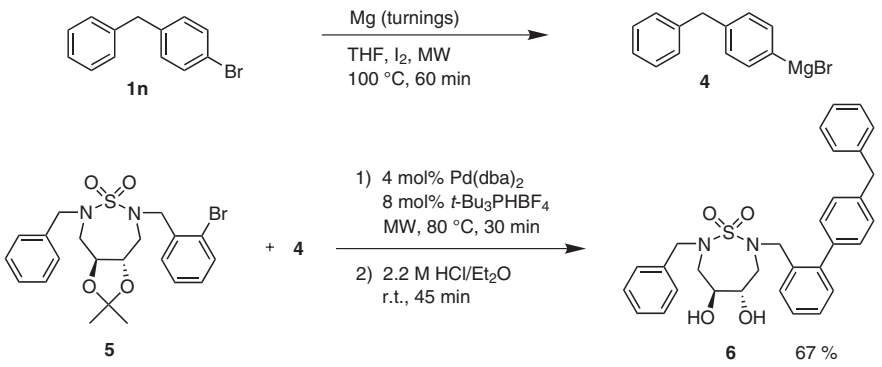
[a] Condition **A**: aryl chloride (1.0 mmol), Mg (turnings) (4.0 mmol), I_2 (one crystal) and freshly distilled THF (2.5 mL) were exposed to microwave radiation for 60 min. Benzaldehyde (0.5 mmol) was added via syringe followed by an additional microwave heating at 100 °C for 30 min, after which the reaction was quenched with 0.1 M HCl in H_2O; condition **B**: same as **A** but with 1.0 mmol benzaldehyde.
[b] Isolated yield of **2** (based on benzaldehyde) after column chromatography with purity ≥95% (GC-MS and ^{1}H NMR).
[c] One drop of 2-bromo-*m*-xylene was added to initiate Grignard formation.

Aryl Grignard reagents are commonly employed in biaryl bond forming processes typically catalyzed by palladium or nickel, i.e., Kumada–Tamao–Curriu cross-couplings.[19–21] Aryl chlorides as Grignard precursors in these types of couplings have not been as frequently reported as the corresponding bromides, especially with sterically hindered substrates due to their difficult preparation. Rewardingly, employing the presented microwave protocol with **1h** as the Grignard substrate, followed by a subsequent Pd-catalyzed coupling with **1d** furnished, after some optimization, the unsymmetrical biaryl product **3** in 87% yield (Scheme 2).



Scheme 2

In the development of a novel unsymmetrical HIV-1 protease inhibitor, we needed to attach a *p*-diphenyl methane group in the P2′-position of the sulfamide template structure (Scheme 3). A Suzuki coupling procedure appeared problematic, since the requisite aryl boronic acid was not commercially available. Using the presented magnesiation methodology on aryl bromide **1n** to generate the reactant for a Kumada coupling evaded the problem. Unfortunately, the protocol presented in Scheme 2 was not compatible with **5** due to deterioration. Therefore, it was essential to use a bromo-substituted template to be able to carry out the transformation at a sufficiently low temperature. Thus, a cross-coupling between **5** and the Grignard reagent **4** smoothly delivered the desired inhibitor **6** in 67% yield after 30 minutes of microwave irradiation at 80 °C and deprotection (Scheme 3). Biological evaluation using a HIV-1 protease assay showed 17% inhibition at 5 μM.[22]



Scheme 3

In conclusion, this study demonstrates the possibility of performing the Grignard reaction with reluctant aryl chlorides using a microwave heating protocol in a reliable manner. The transformations can be conducted without the necessity of entrainment carriers[23] or sophisticated reagents like Rieke's magnesium.[24,25] The benefits of the methodology have been illustrated in the rapid synthesis of a novel HIV-1 protease inhibitor.

The microwave reactions were performed in a SmithSynthesizer producing controlled radiation at 2450 MHz with a power of 0–300 W. The reaction temperature and pressure were determined using the built-in on-line sensors. ^{1}H NMR and ^{13}C NMR spectra were recorded at 399.8 and 100.6 MHz, respectively. Chemical shifts are reported as δ values (ppm) and indirectly referenced to TMS via the solvent residual signal. Analytical HPLC/MS was performed using a Chromolith SpeedROD RP-18e column, 50 × 4.6 mm (4 mL/min, 20–100% MeCN in H_2O, 3 min gradient) employing UV detection (214 and 254 nm) and a mass selective detector (ESI). GC-MS was performed with an instrument equipped with a mass selective detector (EI, 70 eV) and a CP-SIL 5 CB Low bleed column (30 m × 0.25 mm) to analyze conversion and reaction mixture composition. THF was freshly distilled over Na/benzophenone. All other chemicals were commercially available and used as received. Compounds **2a**,[26] **2b**,[27] **2c**,[28] **2d**,[29] **2e**,[26] **2f**,[26] **2g**,[30] **2h**,[31] **2i**,[31] **2j**,[27] and **3**[32] were previously described. Compound **5** was prepared following a literature procedure.[33] Spectral data were in agreement with the proposed structures.

General Method for Synthesis of Grignard Reagents from Aryl Halides and Subsequent Addition of Benzaldehyde

Aryl halide, **1** (1.0 mmol), Mg turnings (4.0 mmol, 97 mg), I_2 (one crystal) were mixed in a process vial under air and immediately capped with a Teflon coated septum. The vial was set under vacuum and back filled with nitrogen gas, in order to remove humid air. THF (2.5 mL) was added via a syringe. The microwave synthesizer was set to the required temperature for 60 min (see Table 1). After Grignard formation, the benzaldehyde was added (0.5 mmol, 53 mg, condition A; or 1.0 mmol, 106 mg, condition B) directly to the reaction mixture with a syringe and additionally heated for 30 min at 100 °C. After cooling, the reaction mixture was acidified with 0.1 M HCl (30 mL) and extracted with CH_2Cl_2. The organic solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography, using 4:1 to 1:4 iso-hexane–CH_2Cl_2 as the eluent, providing the diarylmethanol products **2** (>95% purity by ^{1}H NMR and GC-MS).

Procedure for Kumada Coupling Using Aryl Chlorides

2-Chloronaphthalene (0.25 mmol, 41 mg), $Pd(dba)_2$ (5 μmol, 3 mg), *t*-Bu_3PHBF_4 (10 μmol, 3 mg) were placed in a 5 mL process vial. Grignard reagent prepared from *o*-chloroanisole (1 mmol, 143 mg) following the procedure outlined in Table 1, was added via syringe and the reaction mixture was heated in the microwave at 160 °C for 20 min. After addition of 0.1 M HCl (30 mL), the reaction mixture was extracted with CH_2Cl_2. Subsequent evaporation of the organic solvent under reduced pressure and flash column chromatography using 9:1 isohexane–CH_2Cl_2 as the eluent, yielded the pure product **3** in 87% yield as a white solid (>95% purity by ^{1}H NMR and GC-MS). Spectral data were consistent with that within the literature.[32]

3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-[2-(4-benzylphenyl)benzyl]-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6)

Compound **5** (0.041 mmol, 20 mg), $Pd(dba)_2$ (1.7 μmol, 1 mg) and *t*-Bu_3PHBF_4 (3.4 μmol, 1 mg) were transferred to a 5 mL process vial and capped with a Teflon coated septum. Grignard reagent **4**, prepared using the General Method starting from (4-bromophenyl)phenylmethane (0.33 mmol, 82 mg), was added via syringe and the reaction mixture was microwave heated at 80 °C for 30 min. After cooling, the reaction mixture was filtered through Celite and concentrated under reduced pressure, followed by flash column chromatography using 1:4 iso-hexane–CH_2Cl_2 as the eluent. The protective group was removed using 2.2 M HCl/Et_2O (1 mL) and MeOH (2 mL) at r.t. for 45 min. Concentration and flash column chromatography using 1% MeOH in CH_2Cl_2 furnished the pure product in 67% yield over two steps as a white solid; mp 65–68 °C. LC-MS: t_R = 2.18 min, *m/z* = 529 [M + H$^+$]. ^{1}H NMR (acetone-d_6): δ = 7.68 (ddd, *J* = 0.69, 1.42, 7.72 Hz, 1 H), 7.45–7.18 (m, 17 H), 4.69 (d, *J* = 16.4 Hz, 1 H), 4.65 (d, *J* = 15.8 Hz, 1 H), 4.49 (d, *J* = 16.4 Hz, 1 H), 4.48 (d, *J* = 15.8 Hz, 1 H), 4.17 (d, *J* = 4.5 Hz, 1 H), 4.10 (d, *J* = 4.3 Hz, 1 H), 4.05 (s, 2 H), 3.52 (m, 1 H), 3.38 (m, 1 H), 3.25 (ddd, *J* = 1.2, 9.9, 14.9 Hz, 1 H), 3.21 (ddd, *J* = 1.2, 9.7, 15.1 Hz, 1 H), 3.06 (dd, *J* = 3.5, 15.1 Hz, 1 H), 2.97 (dd, *J* = 3.1, 14.9 Hz, 1 H). ^{13}C NMR (acetone-d_6): δ = 142.6, 142.2, 141.5, 139.3, 138.5, 135.6, 130.9, 130.1, 129.8, 129.7, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 128.1, 126.9, 73.1, 72.9, 53.1, 50.9, 49.0, 48.6, 42.1. Anal. Calcd for $C_{31}H_{32}N_2O_4S$ (%): C, 70.43; H, 6.10; N, 5.30. Found: C, 70.21; H, 6.29; N, 5.19.

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