Microwave-induced electrostatic etching: generation of highly reactive magnesium for application in Grignard reagent formation†

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A detailed study regarding the influence of microwave irradiation on the formation of a series of Grignard reagents in terms of rates and selectivities has revealed that these heterogeneous reactions may display a beneficial microwave effect. The interaction between microwaves and magnesium turnings generates violent electrostatic discharges. These discharges on magnesium lead to melting of the magnesium surface, thus generating highly active magnesium particles. As compared to conventional operation the microwave-induced discharges on the magnesium surface lead to considerably shorter initiation times for the insertion of magnesium in selected substrates (*i.e.* halothiophenes, halopyridines, octyl halides, and halobenzenes). Thermographic imaging and surface characterization by scanning electron microscopy showed that neither selective heating nor a "specific" microwave effect was causing the reduction in initiation times. This novel and straightforward initiation method eliminates the use of toxic and environmentally adverse initiators. Thus, this initiation method limits the formation of by-products. We clearly demonstrated that microwave irradiation enables fast Grignard reagent formation. Therefore, microwave technology is promising for process intensification of Grignard based coupling reactions.

Introduction

The use of microwave heating[1] in accelerating organic reactions as compared to conventional heating techniques (referred to as a positive microwave effect[2]) has attracted increased attention of organic chemists over the past decade.[3] A novel approach to apply microwave technology in organometallic chemistry has been elaborated. Previously reported results[4] teach that heterogeneous reaction mixtures are most promising to show a positive microwave effect. One of the most common and useful heterogeneous organometallic reactions is the Grignard reagent formation.[5] Detailed studies on Grignard reagent formations have been previously reported.[6–9] Nevertheless, performing the reaction can be difficult, the initiation times for the reaction are often not reproducible, and may depend on the experimental skills of the chemist. The reproducibility of the initiation step can be improved by various techniques.[10–14] A relatively novel activation method is the application of microwave irradiation. In literature the formation of Grignard reagents by microwave irradiation in sealed vessels at temperatures above the normal boiling points of the solvents has been reported.[15–16] In these reported experiments the pressure was much higher than atmospheric which is not advantageous when working on a larger scale. However, we were the first to report[4] the microwave-heated formation of these reagents at atmospheric pressure and without using an initiator (*e.g.* iodine, dibromoethane.). It was demonstrated that microwave heating can, for certain substrates, replace the initiators as an initiation method. During irradiation in an inert argon atmosphere violent blue arcing is observed (see Fig. 1). The mechanism of this particular activation is, however, unknown which challenged us to gain more insight in these arcing phenomena. Especially the role of selective heating and the electrical discharges were studied in detail. Also the applicability of the activation method was screened for a series of substrates.

Fig. 1 Violent blue arcing induced by irradiating magnesium turnings with microwaves.

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Results and discussion

The influence of microwave irradiation on magnesium: is selective heating the cause of the reduced initiation times?

It is obvious that microwave irradiation considerably reduces the inhibition period of the initiation accompanying the Grignard reagent formation. However, it is unclear whether selective heating of the magnesium is the rationale of the reduction of the inhibition period. In the first place, to get insight into the interaction of magnesium with microwaves, heating experiments in the absence of all reagents except magnesium and solvent were conducted. Magnesium samples of different sizes were compared and the temperature-time history was recorded, see Fig. 2.

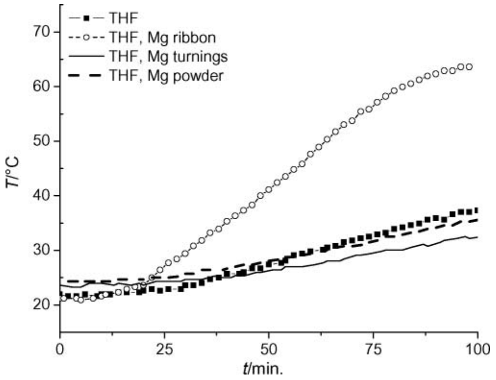


Fig. 2 Temperature-time history of solvent (20 mL) and magnesium samples of different sizes (0.2 g) under microwave irradiation (100 W). (Filled squares): THF, (open circles): THF and magnesium ribbon, (solid line): THF and magnesium turnings, (dashed line): THF and magnesium powder.

The results in Fig. 2 demonstrate that the size of the metal particles strongly influences the heating rate of the mixture. A magnesium ribbon submerged in THF showed rapid heating of the mixture resulting in boiling at the surface of the ribbon. Arcing was not observed. Magnesium turnings submerged in THF on the other hand showed a heating pattern similar to that of pure THF and substantial arcing. Also magnesium powder showed a temperature-time history similar to that of pure THF. In this case arcing was not observed. Hence, the appearance of the magnesium plays a dominant role in the interaction of magnesium with microwaves. The similar temperature-time history observed for pure THF and the turnings in THF suggests that no significant heat transfer from the magnesium particles to the solvent occurs. These observations point to the absence of selective heating of the magnesium turnings. To further detect any selective heating, thermographic imaging[17] was applied. A camera was placed above an open 6 cm diameter reaction tube to detect infrared radiation emitted from a sample. The image was recorded by transmission in an argon atmosphere. As expected the recording of the microwave-irradiated magnesium turnings in THF did not show selective heating. The thermographic images of the irradiation of a magnesium ribbon are shown in Fig. 3a and 3b. Fig. 3a depicts a magnesium ribbon submerged in THF showing the selective heating of the ribbon. Note that THF is not transparent for the wavelength used by this infrared camera and the heating ring shown in the picture is a result of natural convection. In this temperature range no boiling of the solvent occurs, thus eliminating the effect of preferred nucleation sites for boiling on the magnesium surface. Fig. 3b shows a magnesium ribbon partly above the THF surface. Surprisingly, the part of the ribbon at the gas/THF surface displays no heating, as seen by the darker color in the middle of the vessel. It can be concluded that heating of the magnesium occurs in a layer at the magnesium/THF boundary and is only observed for relatively large metal objects (*i.e.* a ribbon). Therefore, selective heating of the magnesium turnings is certainly not the origin of the decrease in initiation time.

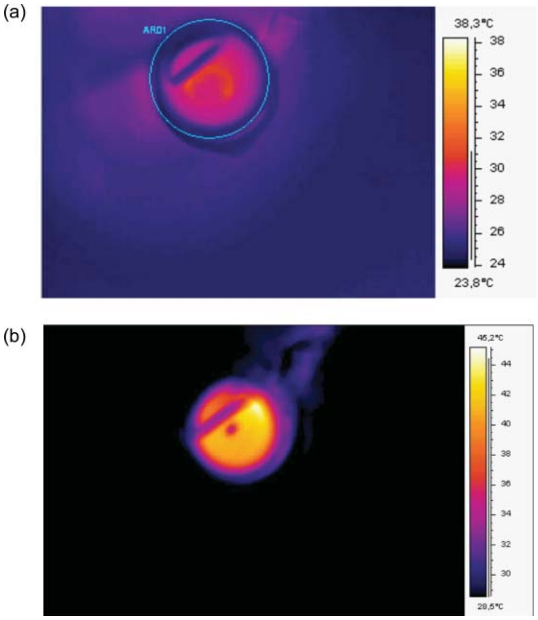


Fig. 3 **a** Thermographic imaging: magnesium ribbon submerged in THF. The dark rod in the upper left corner of the vessel is a tube supplying argon above the solvent surface. The pale and diffuse half circle is the ribbon submerged in THF. **b** Thermographic imaging: circular magnesium ribbon in upright position partially above the gas/THF surface.

The influence of microwave irradiation on magnesium: electrical discharges

The interaction of microwave irradiation with magnesium turnings used for Grignard reagent formation causes charge generation on the magnesium surface leading to a charge imbalance on the surface of the magnesium. With large particles, such as ribbons, a current on the metal is generated resulting into selective heating. For smaller particles the charge is more or less trapped and released by an electrical breakdown of the dielectric medium between two opposite charged particles resulting into an arc. The possibility that these electrical discharges give rise to the large decrease in initiation and reaction time was further investigated using SEM (scanning electron microscopy) and XPS (X-ray photoelectron spectroscopy).

The arcing influences the surface of the magnesium dramatically which is already noticeable by low magnification as shown in Fig. 4. The microwave-heated turnings in THF were compared with those treated by refluxing THF through oil-bath heating to ensure exclusion of any solvent effects at the surface. The impact area of the arcing is clearly visible in Fig. 4b. Fig. 5

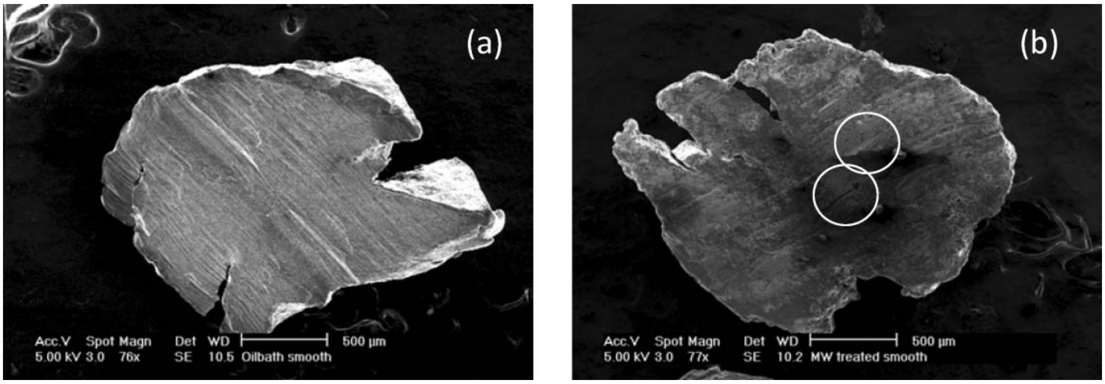


Fig. 4 SEM images of a magnesium turning treated in refluxing THF by a) oil-bath heating and b) microwave heating. The circles indicate the impact area of the microwave-induced electrical discharges.

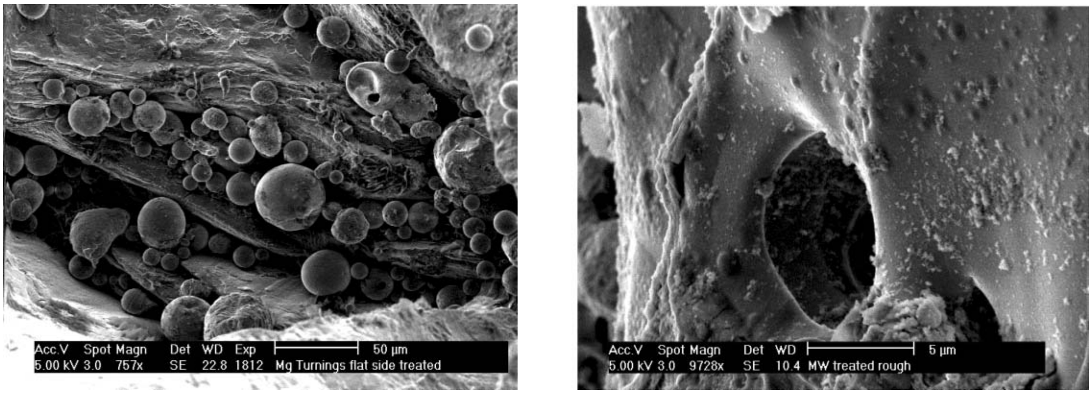


Fig. 5 SEM images of magnesium turnings after microwave irradiation: left: spherical objects that remain in the cavities of the surface after removal of THF and right: impact area of the arc showing disruption of the magnesium surface and formation of cavities.

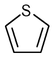
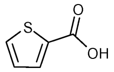
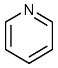
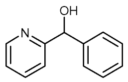
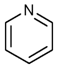
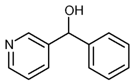
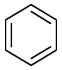
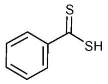
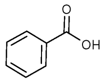
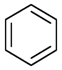
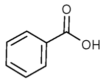
(right) shows that the impact of the arcs on the surface causes a distortion of the magnesium surface. Probably this distortion also influences the magnesium oxide/magnesium hydroxide layer. A magnesium oxide/magnesium hydroxide layer is always present on non-activated magnesium.[18] This layer prevents an immediate reaction with organic halides. The etching causes metallic magnesium (Mg^0) to be exposed to the reactant. During the investigation of the arcing phenomenon it was also discovered that, when arcing is induced in the absence of a reactive organic halide, the solvent becomes turbid. A black dispersion of small magnesium particles is produced. The shape of the particles in this dispersion is predominantly spherical, see Fig. 5 (left). The formation of these spherical magnesium particles is induced by the impact of high electrical currents, caused by the arc, at the magnesium surface. These currents give rise to extremely high local temperatures, which are not generated by the direct absorption of microwave energy, and melting of the magnesium occurs. The molten magnesium is transferred to the solvent phase and is cooled almost instantaneously which leads to a preservation of the spherical geometry that is adopted in the molten state. The size of the produced particles varies between about 5 µm and 50 µm, see Fig. 5 (left). The generation of this type of spherical debris by electrical discharges in electrical discharge machining (EDM)[19] is known but the impact on synthetic chemistry was never investigated. The results of the elemental analysis of these particles by XPS showed a large degree of magnesium carbide formation after prolonged arcing without traces of a reactive organic halide. This may suggest that the arcing only facilitates side reactions with the solvent. In the presence of reactive organic halides, the formation of arcing-induced magnesium carbide from the solvent is severely hampered. This observation, combined with the fast oxidation observed for the spherical particles after short exposure to air, stresses the reactive nature of the magnesium produced by microwave-induced electrical discharges. This reactive nature is mainly due to the high surface area to volume ratio and lack of inhibiting magnesium oxide/hydroxide layers.

Application of microwave-induced electrical discharges in the Grignard reagent formation

To demonstrate the applicability of microwave-induced electrical discharges for the Grignard reagent formation a series of halogenated compounds was tested. The time-conversion histories of the Grignard reagent formation was monitored by GC-MS analyses of small aliquots quenched by saturated ammonium chloride. For the determination of the yield of the Grignard reagent a suitable consecutive reaction had to be performed. A series of quenching reactions was evaluated. The ease of purification and isolation of the product, the absence of ketone corresponding to the produced alcohol accompanied by equimolar amounts of benzyl alcohol by-products, and quantitative yields

Table 1 Grignard reagent synthesis of selected substrates under microwave irradiation and conventional heating (oil bath), step 1, and subsequent quenching reactions, step 2

$$R{-}X + Mg \xrightarrow{\text{Step 1}} R{-}MgX \xrightarrow{\text{Step 2}} P$$

Entry	*R*	X	Conditions step 1	Conditions step 2	Product (P)
1		2-Br	A	C	
2		2-Br	B	C	
3		2-Cl	A	C	
4		2-Cl	B	C	
5		2-Br	A	D	
6		2-Br	B	D	
7		2-Cl	A	D	
8		2-Cl	B	D	
9		3-Br	A	D	
10		3-Br	B	D	
11		Br	A	E	
12		Br	B	C	
13		I	A	C	
14		I	B	C	
15	n-C_8H_{17}	Br	A	C	n-$C_8H_{17}COOH$
16	n-C_8H_{17}	Br	B	C	n-$C_8H_{17}COOH$
17	n-C_8H_{17}	Cl	A	C	n-$C_8H_{17}COOH$
18	n-C_8H_{17}	Cl	B	C	n-$C_8H_{17}COOH$

A: oil-bath reflux (66 °C), B: microwave, reflux (66 °C), max power = 300 W, C: dry CO_2, −78 °C, D: benzaldehyde, 66 °C, E: CS_2, room temperature.

for the addition reaction, *i.e.* the Grignard reagent present reacts quantitatively with the CO_2, made the reaction with carbon dioxide the best choice for analyzing reactive Grignard reagents. The maximum of 90% yield is due to the loss of starting material during the Grignard reagent formation. The analogous reaction with CS_2 was also almost completely selective and gave an approximately 100% yield for the addition reaction of the Grignard reagent. Relatively unreactive, or insoluble, Grignard reagents, *i.e.* 3-halopyridine Grignard reagents, can be reacted with benzaldehyde at reflux temperature showing moderate yields and minor by-product formation. The undesired formation of the ketone corresponding to the secondary alcohol together with equimolar amounts of benzyl alcohol is clearly a consecutive process that does not change the overall conclusions. Unstable Grignard reagents, resulting from 2-halopyridine derivatives, tend to polymerize into insoluble tars making the subsequent quenching reaction redundant. Table 1 depicts a selection of substrates that were subjected to microwave-induced arcing and conventional heating to facilitate the synthesis of their corresponding Grignard reagents.

Table 2 depicts the initiation and reaction times with corresponding yields for these reactions. The lower isolated yields under microwave irradiation are mainly caused by a difficult layer separation in the work-up procedure of the formed acid due to residual magnesium carbide particles. The yields determined in the crude reaction mixture were similar under both heating methods. Further optimization of the work-up procedure may minimize these losses.

The previously reported 2-halothiophenes[4] are included in the investigation for reference purposes. A large decrease in the initiation time, compared to conventional heating, was observed for 2-chlorothiophene and 2-bromothiophene (entries 1–4) when the reaction was performed with microwave-induced electrical discharges. Surprisingly, the formation of the Grignard reagent from 3-bromothiophene and 3-chlorothiophene failed using both heating methods, stressing the unreactive nature of the 3-position of thiophene. When heating the reaction mixture of the halopyridines (entries 5–10) the intensity of arcing under microwave irradiation is less pronounced. This is mainly due to the higher dielectric loss[20] of the pyridine derivatives, ensuring a higher absorption of

Table 2 Grignard reagent synthesis of selected substrates under microwave irradiation and conventional heating (oil bath), step 1, and subsequent quenching reactions, step 2

Entry	Initiation time step 1 (min)[e]	Reaction time step 1 (min)[f]	Yield (%)
1	20	45	86[a]
2	0–1	15	73[a]
3	75	120	82[a]
4	5	40	73[a]
5	0–1	10[b]	trace[c]
6	0	10[b]	trace[c]
7	125	200	trace[c]
8	75	110	trace[c]
9	30	180	37 (8)[d]
10	50	200	41 (19)[d]
11	0–1	10[b]	88[a]
12	0	10[b]	87[a]
13	0–1	10[b]	30[a]
14	0	10[b]	30[a]
15	0–1	10[b]	87[a]
16	0	10[b]	70[a]
17	80	150	85[a]
18	—	—	0

[a] Isolated yield. [b] Addition time of the substrate. [c] Tar formation. [d] Between brackets: % of product representing ketone corresponding to the produced alcohol accompanied by equimolar amounts of benzyl alcohol. [e] Time at which Grignard reagent starts to form. [f] Time at complete conversion.

the microwave irradiation by the solvent/reagent mixture. The higher absorption of the microwave irradiation by the solvent leads to a diminished charge build-up at the magnesium surface. The lower intensity of arcing for these substrates gives rise to a smaller influence of microwave irradiation on the initiation time: 75 (entry 8) instead of 125 (entry 7) minutes for 2-chloropyridine. The formation of the Grignard reagent from 3-bromopyridine (entries 9 and 10) is slightly retarded under microwave irradiation indicating some competitive carbide formation reaction. The influence of magnesium carbide formation is most clearly seen from the Grignard reagent formation of *n*-octyl chloride (entries 17 and 18). Although this substrate is reactive under conventional heating conditions with an initiation time of 80 min, the reaction does not occur with microwave irradiation. The formation of magnesium carbide species from the activated magnesium is believed to occur at a higher rate than the generation of Grignard reagent for *n*-octyl chloride leading to an inhibiting layer on the surface of the magnesium turnings. This layer causes the Grignard formation reaction to be completely inhibited for *n*-octyl chloride under microwave-induced electrical discharges. The formation of magnesium carbide is a competitive process, rendering the generation of very poorly reactive halides less probable. Short exposure to microwave irradiation and subsequent transferring the mixture to oil-bath heating (and therefore without additional electrostatic discharges) gave comparable results as for oil-bath heating only. The results in Table 2 demonstrate that 2-bromopyridine (entries 5 and 6), bromobenzene (entries 11 and 12), iodobenzene (entries 13 and 14) and *n*-octyl bromide (entries 15 and 16) are very reactive towards magnesium. The lower yield for iodobenzene, under both heating methods, was mainly caused by the insolubility of the formed Grignard reagent and the formation of biphenyl. Due to the short initiation time of the very reactive substrates a clear difference between thermal activation and activation by electrical discharges is difficult to quantify. Nevertheless, these same results clearly show that for microwave irradiation the instantaneous initiation is consistent and for conventional heating a scatter was observed, meaning an increased reproducibility for these substrates with microwave irradiation. The very exothermic reaction of the active substrates with magnesium demands the drop-wise addition of these substrates. The addition time governs the overall reaction time, thus obscuring the influence of area enlargement of the magnesium by electrical discharges on the reaction rate. Although no quantitative distinction between conventional and microwave heating for the reactive species can be made, the comparable yields for both heating techniques make the application of microwave heating for the production of Grignard reagents for the active substrates feasible and increase the reproducibility. Therefore, it can be concluded that microwave heating leads to a higher reproducibility of the Grignard reaction than conventional heating.

Conclusion

The use of metals in combination with microwave heating can cause dramatic electrical discharges. The suppression of these discharges has been a point of interest[21] to expand the scope of microwave heating in organic syntheses. The deliberate generation of these discharges (with of course the due caution) gives rise to effects that cannot be easily mimicked by other methods. One of these effects is the generation of highly active magnesium that can be directly used for the formation of Grignard reagents. Selective heating of the metal during microwave irradiation does not occur with magnesium turnings and is obviously not the origin of the observed decrease in initiation time. The formation of highly active magnesium spheres and the etching of the magnesium surface resulting from the interaction of the microwaves with the metal explain the large decrease in initiation times for selected substrates. This novel and straightforward initiation method generates magnesium with a reactivity similar to that of Riekes[22] magnesium and eliminates the use of highly toxic and environmentally adverse initiators and therefore limits the formation of by-products.

Experimental section

All chemicals were purchased from Sigma-Aldrich and used as received unless otherwise indicated. All presented results have been reproduced. ^{1}H-NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standard. All reactions have been reproduced at least two times.

Microwave heating

A commercially available, automated multimode microwave oven MicroSynth from Milestone s.r.l. (Italy) was used. This oven operates at 2.45 GHz and is temperature controlled by fiber-optic sensor. To eliminate significant temperature distributions the temperature was monitored by insertion of a calibrated fiber-optic sensor in the reaction mixture while stirring properly. The maximum power input could be adjusted between 0 and 1000 Watt.

Thermal imaging

An infrared camera (FLIR Systems ThermaCAMTM P65) was placed outside the cavity of the microwave unit and was focused on an open vessel containing the THF/magnesium sample. The images were recorded real time *via* IEEE-1394 FireWire DV-output during irradiation. The mixture was covered with a blanket of argon to ensure safety (no oxygen should be present during the electrical discharges).

Scanning electron microscopy

SEM was performed on a Philips XL30 ESEM-FEG electron microscope in the high-vacuum mode. The acceleration voltage used was 5.0 kV. Samples were prepared by either placing a droplet of a suspension of the particles in THF on an aluminium stub followed by evaporation of the THF or by mounting the particles with carbon tape on an aluminium stub. NOTE: The activated magnesium may be pyrophoric and create a flare which is hazardous to the eyes when exposed to air. Due caution should always be taken in the handling of activated magnesium.

X-ray photoelectron spectroscopy

The XPS measurements are carried out with a Kratos AXIS Ultra spectrometer, equipped with a monochromatic Al Kα X-ray source and a delay-line detector (DLD). Spectra were obtained using the aluminium anode (Al Kα = 1486.6 eV) operating at 150 W. For survey scans a constant pass energy of 160 eV was used and for region scans a constant pass energy of 80 eV. The background pressure was 2×10^{-9} mbar.

Grignard reagent formation of the reactive substrates under conventional heating (entries 1, 5, 11, 13, 15 in Table 1)

Magnesium turnings (0.44 g, 18 mmol) were introduced in an oven-dried 25 mL three neck round-bottomed flask. 2-Bromothiophene (2.28 g, 14 mmol) was dissolved in dry THF (10 mL, distilled from mol sieves 3 Å). A volume of 1 mL of the 2-bromothiophene solution was added to the Mg in an argon atmosphere and the mixture was heated by a preheated oil bath ($T = 85$ °C) to reflux. As soon as initiation took place, the oil bath was lowered and the remaining solution was added dropwise in 10 min to maintain a gentle reflux. Additional heating with an oil bath was applied for 30–60 min. The solution of Grignard reagent was separated from the remaining Mg with a syringe.

Grignard reagent formation of the reactive substrates under microwave heating (entries 2, 6, 12, 14, 16 in Table 1)

Magnesium turnings (0.44 g, 18 mmol) were introduced in an oven-dried 25 mL three neck round-bottomed flask. 2-Bromothiophene (2.28 g, 14 mmol) was dissolved in dry THF (10 mL, distilled from mol sieves 3 Å). A volume of 1 mL of the 2-bromothiophene solution was added to the Mg in an argon atmosphere (Note: no oxygen, or fire supporting oxygen rich compounds, should be present upon the occurrence of the electrical discharges) and irradiated with microwave energy (maximum power-input 350 W) to reflux. As soon as initiation took place the remaining solution was added dropwise in 10 min to maintain a gentle reflux (the microwave oven was in an OFF state during this period). Additional irradiation with microwave energy (maximum power input 200 W) was applied for 30–60 min. The solution of Grignard reagent was separated from the remaining Mg with a syringe.

Grignard reagent formation of the relatively non-reactive substrates under conventional heating (entries 3, 7, 9, 17, in Table 1)

Magnesium turnings (0.44 g, 18 mmol) and 2-chlorothiophene (1.66 g, 14 mmol), dissolved in dry THF (10 mL, distilled from mol sieves 3 Å), were introduced in an oven-dried 25 mL three neck round-bottomed flask under an argon atmosphere. The mixture was heated by a preheated oil bath ($T = 85$ °C) to reflux. Additional heating was applied for 30–200 min. The solution of Grignard reagent was separated from the remaining Mg with a syringe.

Grignard reagent formation of the relatively non-reactive substrates under microwave heating (entries 4, 8, 10, 18 in Table 1)

Magnesium turnings (0.44 g, 18 mmol) and 2-chlorothiophene (1.66 g, 14 mmol), dissolved in dry THF (10 mL, distilled from mol sieves 3 Å), were introduced in an oven-dried 25 mL three neck round-bottomed flask under an argon atmosphere. (Note: no oxygen, or fire supporting oxygen rich compounds, should be present upon the occurrence of the electrical discharges). The reaction mixture was heated by microwave irradiation (maximum power input 350 W) to reflux. Additional irradiation with microwaves (maximum power-input 200 W) was applied for 30–200 min. The solution of Grignard reagent was separated from the remaining Mg with a syringe.

Quenching the Grignard reagents with CO_2 (entries 1, 2, 3, 4, 12, 13, 14, 15, 16, 17, 18 in Table 1)

The solution of the Grignard reagent was added dropwise to an excess of freshly prepared dry, solid CO_2 (prepared by passing sublimated CO_2 over 3 stages of concentrated sulfuric acid and depositing it in a liquid nitrogen cooled flask). After addition of the reagent another layer of dry CO_2 was deposited. The mixture was slowly heated to room temperature in 15 min, acidified with 10 wt% HCl (10 mL) and extracted with toluene (3 × 10 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated. Optional purification method: the crude residue was dissolved in toluene (15 mL) and extracted with 1.0 M KOH (2 × 10 mL). The aqueous layer was acidified with conc. HCl and extracted with toluene. The toluene layer was dried with $MgSO_4$, filtered and evaporated yielding the pure product. Benzoic acid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.63 (m, 1H), 8.14 (m, 2H), 11.72 (s, 1H); Nonanoic acid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H), 1.25–1.30 (m, 12H), 1.63 (t, 2H), 10.63 (br s, 1H), 2-Thiophenecarboxylic acid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.1 (dd, 1H), 7.90 (dd, 1H), 7.66 (dd, 1H), 9.76 (br s, 1H).

Quenching the Grignard reagents with CS_2 (entry 11 in Table 1)

The solution of the Grignard reagent was added dropwise at room temperature to a flask containing a large excess of CS_2 dissolved in THF (10 mL, distilled from mol sieves 3 Å). The solution was stirred for 1 h and subsequently acidified with 10 wt% HCl (10 mL) and extracted with toluene (3 × 10 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated. Benzodithio acid: ^1H-NMR (400 MHz, $CDCl_3$) δ: 6.38 (br s, 1H) 7.40 (t, 2H), 7.60 (t, 1H), 8.05 (d, 2H).

Quenching the Grignard reagent with benzaldehyde (entries 5, 6, 7, 8, 9, 10 in Table 1)

The solution of the Grignard reagent was added dropwise to a flask containing a two-fold molar excess of benzaldehyde dissolved in THF (10 mL, distilled from mol sieves 3 Å) at reflux temperature. The solution was stirred for 1 h and subsequently acidified with saturated NH_4Cl (10 mL) and extracted with toluene (3 × 10 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated. Phenyl (2-pyridinyl)methanol: ^1H-NMR (400 MHz, $CDCl_3$) δ: 4.69(s, 1H), 5.74 (s,1H), 7.23–7.49 (m, 7H), 7.62 (td, 1H), 8.56 (d, 1H). Phenyl-(3-pyridyl)methanol: ^1H-NMR (400 MHz, $CDCl_3$) δ: 8.52 (d 1H), 8.37 (dd, 1H), 7.78 (dd, 1H) 7.20 (m, 5H), 7.15 (dd, 1H), 5.82 (s, 1H), 4.7 (s, 1H) 3.15–4.36 (br s, 1H).

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