A Microwave-Assisted Heck Reaction: Modifying Conventional Heating Protocols

Introduction

Nearly any conventionally heated synthetic transformation can be adapted for microwave heating. The power of microwave irradiation has been harnessed in nanomaterial assembly,[1] polymerization reactions,[2] and small molecule synthesis,[3] compatible with air-sensitive reagents and transition-metal catalysts.[4] Benefits of microwave heating include decreased waste generation and increased product purity. Perhaps the largest benefit of microwave-assisted synthesis, however, is the dramatic reduction of reaction time. Because modern microwave reactors like the Discover SP™ can safely maintain high-pressure atmospheres, reactions can be performed at temperatures exceeding reflux, expediting reaction rates and reducing reaction times.

$$k = Ae^{-Ea/(RT)} \qquad \text{Equation 1}$$

Standard incremental temperature screening procedures can be employed when adapting a conventional synthesis to a microwave-assisted synthesis. A convenient generalization supported by the Arrhenius equation (**Equation 1**), is that a reaction rate will double every 10 °C the temperature increases. With this generalization, a microwave reaction time approximation can be derived, presented in **Equation 2**, where T = microwave heating temperature, T_0 = conventional heating temperature, x = the temperature increase coefficient, t = microwave heating time and t_0 = conventional heating time. (For a chart representation of **Equation 2**, see page 3).

$$T = T_0 + (10\,^{\circ}\mathrm{C})x,\ t \approx \frac{t_0}{2^x} \qquad \text{Equation 2}$$

To demonstrate the ready modification of a conventionally heated transformation to microwave heating, a Heck reaction of iodobenzene with methyl acrylate[5] (**Figure 1**) was adapted for microwave irradiation. Under conventional heating protocol, the transformation is limited to 80 °C (boiling point of MeCN) and takes 20 h for completion. However, after applying the approximation depicted in **Equation 2**, simply doubling the temperature to 160 °C (x = 8) via microwave irradiation could lead to a reaction time under 10 min.

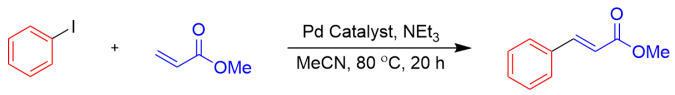

Figure 1: Conventionally heated Heck reaction of iodobenzene with methyl acrylate.[5]

Materials and Methods

Reagents

Acetonitrile (MeCN), iodobenzene, methyl acrylate, palladium(II) acetate ($Pd(OAc)_2$), toluene, and triethylamine (NEt_3) were obtained from Sigma Aldrich (St. Louis, MO).

Procedure

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with palladium(II) acetate (15 mg, 0.065 mmol, 5.0 mol %.). Then, the vial was sealed with a Teflon-lined silicon cap and purged with N_2. While purging with N_2, iodobenzene (0.15 mL, 1.3 mmol, 1.0 equiv.), methyl acrylate (0.23 mL, 2.6 mmol, 2.0 equiv.), triethylamine (0.22 mL, 1.6 mmol, 1.2 equiv.) and solvent (acetonitrile or toluene, 3.0 mL), if applicable, were added to the vessel via syringe addition. The vessel was then placed in the Discover SP microwave cavity, where the solution was heated to the specified temperature. After heating for the specified amount of time, the solution was cooled to room temperature and analyzed via gas chromatography.

Results

Optimization of reaction temperature was first pursued (**Table 1**). A 10 min reaction time is common in microwave synthesis and was therefore employed as the heating period while optimizing temperature. As expected, at 80 °C low conversion to product was observed (13% conversion, **Table 1**, entry 1). Initial adjustments of 40 °C per run provided an efficient manner to identify optimal reaction temperature, with 44% conversion at 120 °C (**Table 1**, **entry 2**) and 79% conversion at 160 °C (**Table 1**, **entry 3**). However, when increased to 200 °C, though conversion further increased to 85%, significant amounts of by-product were observed (**Table 1**, **entry 4**), and reduction of temperature to 180 °C yielded similar results (**Table 1**, **entry 5**). Further reduction to 170 °C, however, maintained the high level of conversion (82%, **Table 1**, **entry 6**) with minimal levels of by-product formation.

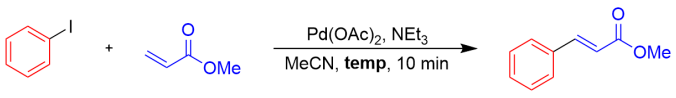

Table 1: Optimization of reaction temperature for microwave-assisted Heck reaction.

Entry	Temperature (°C)	Conversion (%)[a]
1	80	13
2	120	44
3	160	79
4	200	85[b]
5	180	85[b]
6	170	82

[a] Determined by GC analysis. [b] Significant by-product formation.

Upon establishing 170 °C as the optimal reaction temperature, additional reaction conditions were surveyed. Using PowerMAX™ cooling and a fiber optic probe for temperature measurement, by-product formation was further minimized, but no increase in conversion was observed (**Table 2**, **entry 1**). Extending reaction time to 15 min did not improve conversion to product, and increased by-product formation (**Table 2**, **entry 2**). Reduction of reaction time (**Table 2**, **entries 3–4**) was met with comparable levels of yield and purity to the 10 min reaction employing PowerMAX cooling and fiber optic temperature monitoring (**Table 2**, **entry 1**).

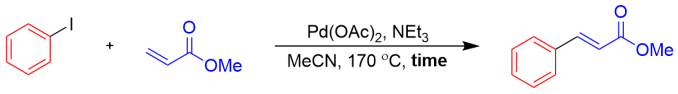

Table 2: Optimization of reaction time for microwave-assisted Heck reaction.

Entry	Time	Conversion (%)[a]
1	10	82[b]
2	15	85
3	5	72
4	3	78

[a] Determined by GC analysis. [b] Performed using PowerMAX and fiber optic probe

Lastly, the effects of solvent identity were investigated (**Table 3**). Acetonitrile, a moderate microwave absorbing solvent, already proved effective in this transformation (**Table 3**, **entry 1**). A switch to toluene, a low microwave absorbing solvent, was met with a dramatic decrease in reaction conversion (25%, **Table 3**, **entry 2**). Performing the reaction neat, however, significantly increased product conversion to 93% while maintaining minimal production of by-product (**Figure 2**). Upon purification, the product alkene was isolated in an 87% yield (**Table 3**, **entry 3**).

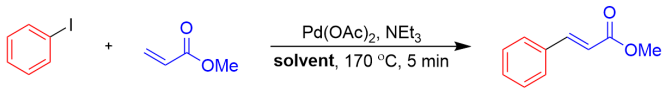

Table 3: Optimization of reaction solvent for microwave-assisted Heck reaction.

Entry	Temperature (°C)	Conversion (%)[a]
1	MeCN	82
2	toluene	25
3	none	93 (87)[b]

[a] Determined by GC analysis. [b] Isolated yield.

Temperature	Time													
T = Conventional	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	16 h	18 h	24 h	48 h	96 h	172 h
T + 10 °C	30 min	1 h	1.5 h	2 h	3 h	4 h	5 h	6 h	8 h	9 h	12 h	24 h	48 h	96 h
T + 20 °C	15 min	30 min	45 min	1 h	1.5 h	2 h	2.5 h	3 h	4 h	5 h	6 h	12 h	24 h	48 h
T + 30 °C	8 min	15 min	23 min	30 min	45 min	1 h	75 min	1.5 h	2 h	2.5 h	3 h	6 h	12 h	24 h
T + 40 °C	4 min	8 min	12 min	15 min	23 min	30 min	38 min	45 min	1 h	75 min	1.5 h	3 h	6 h	12 h
T + 50 °C	2 min	4 min	6 min	8 min	12 min	15 min	20 min	23 min	30 min	38 min	45 min	1.5 h	3 h	6 h
T + 60 °C	1 min	2 min	3 min	4 min	6 min	8 min	10 min	12 min	15 min	20 min	23 min	45 min	1.5 h	3 h
T + 70 °C		1 min	2 min	2 min	3 min	4 min	5 min	6 min	8 min	10 min	12 min	23 min	45 min	1.5 h
T + 80 °C			1 min	1 min	2 min	2 min	3 min	3 min	4 min	5 min	6 min	12 min	23 min	45 min
T + 90 °C					1 min	1 min	2 min	2 min	2 min	3 min	3 min	6 min	12 min	23 min
T + 100 °C							1 min	1 min	1 min	2 min	2 min	3 min	6 min	12 min
T + 110 °C										1 min	1 min	2 min	3 min	6 min
T + 120 °C												1 min	2 min	3 min
T + 130 °C													1 min	2 min
T + 140 °C														1 min

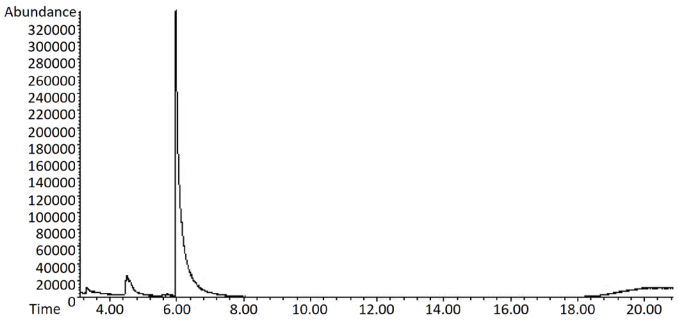

Figure 2: GC chromatogram of solvent-free, microwave-assisted Heck reaction (**Table 3**, **entry 6**).

Conclusion

The conventionally heated Heck reaction of iodobenzene with methyl acrylate was successfully adapted for microwave-assisted synthesis. Although the transformation requires 20 h for completion at 80 °C under conventional heating protocol, it can be accomplished in 5 min at 170 °C when employing microwave irradiation. In addition to extensive time savings (the entire optimization was performed in about 4 h), the high-temperature, high-pressure capabilities of the Discover SP allowed the transformation to be performed solvent-free, minimizing waste generation.

References

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