Video Article

A Microwave-Assisted Direct Heteroarylation of Ketones Using Transition Metal Catalysis

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Abstract

Heteroarylation introduces heteroaryl fragments to organic molecules. Despite the numerous available reactions reported for arylation via transition metal catalysis, the literature on direct heteroarylation is scarce. The presence of heteroatoms such as nitrogen, sulfur and oxygen often make heteroarylation a challenging research field due to catalyst poisoning, product decomposition and the rest. This protocol details a highly efficient direct α-C(sp3) heteroarylation of ketones under microwave irradiation. Key factors for successful heteroarylation include the use of XPhos Palladacycle Gen. 4 Catalyst, excess base to suppress side reactions and the high temperature and pressure achieved in a sealed reaction vial under microwave irradiation. The heteroarylation compounds prepared by this method were fully characterized by proton nuclear magnetic resonance spectroscopy (^{1}H NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C NMR) and high-resolution mass spectrometry (HRMS). This methodology has several advantages over literature precedents including broad substrate scope, rapid reaction time, greener procedure and operational simplicity by eliminating the preparation of intermediates such as silyl enol ether. Possible applications for this protocol include, but are not limited to, diversity-oriented synthesis for the discovery of biologically active small molecules, domino synthesis for the preparation of natural products and ligand development for new transition metal catalytic systems.

Video Link

The video component of this article can be found at https://www.jove.com/video/60441/

Introduction

Microwaves interact with materials through ionic conduction or dipolar polarization to provide rapid and homogeneous heating. Microwave-assisted organic reactions have gained increasing popularity in research laboratories after the first report for rapid organic synthesis in 1986[1]. Though the exact nature of microwave heating is not clear and the existence of a "nonthermal" microwave effect is still under debate, significant rate enhancements for microwave-assisted organic reactions have been observed and reported[2]. Sluggish reactions that normally take hours or days to finish have been reported to be completed within minutes under microwave irradiation[3,4,5,6]. Difficult organic reactions that require high activation energy such as cyclizations and construction of sterically hindered sites were reported to be successful under microwave irradiation with improved reaction yields and purity[7]. Combined with other features such as solvent-free reactions and domino reactions, microwave-assisted organic synthesis offers unparalleled advantages in the design of eco-friendly reactions.

Unlike its arylation equivalent, which has been widely studied, heteroarylation, especially on the α-C(sp3) of carbonyl compounds, has been rarely reported in the literature[8,9,10]. The few literature reports of α-heteroarylation of carbonyl compounds had great limitations such as a stoichiometric amount of catalysts, narrow substrate scope, and isolation of reaction intermediates[11,12,13]. There are several challenges for the direct α-heteroarylation of ketones that remain to be solved in order to make it a general approach. First, heteroatoms tend to coordinate to the transition metal catalyst and cause catalyst poisoning[14,15]. Second, the α-H in the mono(hetero)arylation product is more acidic than those in the starting material. Thus, it tends to react further to make the undesired (bishetero)arylation or (multihetero)arylation products. Third, carbonyl compounds often have a lower cost than heteroaryl compounds, so it is practical to use excess carbonyl compounds to drive the reaction to completion. However, excess carbonyl compounds would often cause self-condensation, a frequently encountered problem in the transition metal-catalyzed α-heteroarylation of carbonyl compounds.

In this report, we describe our recent study on the direct α-C(sp3) heteroarylation of ketones using a microwave-assisted reaction protocol. To address the first challenge, catalyst poisoning discussed above, strongly coordinating and sterically hindered ligands were utilized to minimize the catalyst poisoning by heteroatoms. Bulky ligands were also expected to slow down the side reactions such as (bishetero)arylation or (multihetero)arylation[16,17], the second challenge mentioned above. To minimize the effect of the third challenge, the formation of the ketone self-condensation side products, more than 2 equivalents of base was employed to convert ketones to their corresponding enolates. The long reaction time and high reaction temperature, together with the challenges specifically associated with the direct α-C(sp3) heteroarylation of ketones, render it a suitable candidate for microwave-assisted organic synthesis research.

Protocol

CAUTION:

- Microwave reaction vials should be operated under 20 bar for the microwave reactor equipped with a 4 x 24MG5 rotor. If the reaction uses very volatile solvents, generates gas, or if solvents decompose, it is necessary to calculate the pressure at certain reaction temperatures to make sure the total pressure in the vial is less than 20 bar.
- Standard techniques in organic synthesis for glove box, flash chromatography and nuclear magnetic resonance (NMR) are utilized in this protocol.
- Appropriate Personal Protective Equipment (PPE) should be used during the experiment. These include safety goggles, a lab coat, nitrile gloves, long pants and closed-toe shoes.
- Consult all Safety Data Sheets (SDS) prior to the use of the chemicals in this procedure, as some of the chemicals are hazardous, corrosive, toxic or flammable.
- All chemical waste should be disposed of properly in designated waste containers.

1. Reaction set up

1. Use the following amounts of reagents for the example reaction in **Figure 1** - the formation of 1-phenyl-2-(pyridin-3-yl)ethanone (compound **1a**) from acetophenone and 3-iodopyridine.
2. Oven-dry microwave reaction vials equipped with stirring bars overnight. Purge argon vigorously into toluene for 30 min to degas the solvent prior to use.
3. Preparation of reagents and supplies for glove box usage
    1. Gather two 100 µL syringes, four small spatulas, two glass pipets, two microwave seals, two microwave caps, two microwave stirring bars, at least four pieces of pre-folded weighing paper, four Kimwipes, four rubber bands, and two 100 mL beakers along with all the necessary reactants/solvents.
    2. Put the microwave vials, seals, and caps in one of the 100 mL beakers, then cover the beaker with a Kimwipe and wrap a rubber band around the beaker to keep the Kimwipe in place.
    3. Place the beaker and the rest of the items from step 1.3.1 into the transport box and take it into the glove box workstation.
4. Transport the reagents and supplies in step 1.3 into the glove box.
    1. Inside the purged glove box, weigh 115 mg of NaO^tBu (molecular weight (MW) 96.1, 1.2 mmol, 2.4 eq.) directly into the microwave reaction vial.
    2. Use a glass pipet to add half of the degassed toluene (1 mL) into microwave reaction vial.
    3. Weigh 9 mg of precatalyst XPhos Pd G4 (MW 860.5, 0.01 mmol, 2 mol%) and add it into the microwave vial. Dip a spatula into the solution in the vial and swirl to ensure the complete transfer of the catalyst.
    4. Use a suitable microliter syringe to add 64.4 µL of acetophenone (MW 120.15, 66.1 mg, 0.55 mmol, 1.1 eq.) into the microwave vial.
    5. Weigh 103 mg of 3-iodopyridine (MW 205.0, 0.5 mmol, 1.0 eq.) and add it into the microwave vial.
    6. Add the remaining half of degassed toluene so that the total reaction mixture is about 3 mL.
    NOTE: The reaction solution volume should not exceed ¾ of the total volume capacity of the microwave reaction vial. For the standard glass vials used in this protocol, the vial volume is 4 mL and the recommended reaction volume is 0.3 mL – 3 mL.
    7. Line up the seal and the cap carefully and put them on the microwave reaction vial. The cap should be finger tight.
    8. Take the chemicals, supplies and trash out of the glove box.

2. Microwave irradiation

1. Take the assembled reaction vial to the microwave reactor and place it on the silicon carbide (SiC) plate on the rotor. For multiple reaction vials, space them evenly across the four silicon carbide (SiC) plates on the rotor.
2. Parameter set-up
NOTE: The most important parameters are the IR sensor temperature limit, microwave power and time.
    1. Set the Infrared (IR) sensor temperature limit to 113 °C.
    NOTE: IR sensor-measured temperatures tend to be lower than reaction solution temperatures due to a non-preventable temperature gradient between the sample and the outside of the vessel. There is a linear relationship between these two temperatures: IR T (°C) = Reaction T (°C)/1.152. When the IR sensor temperature is 113 °C, the actual reaction temperature will be 130 °C using the equation given above.
    2. Program the microwave power and time for each step:
    Step 1: Power ramp = 1300 W, 10 min, Fan Level = 1, Stirrer = High
    Step 2: Power hold = 1300 W, 10 min, Fan Level = 1, Stirrer = High
    Step 3: Cooling = 60 °C, Fan Level = 3
    NOTE: The microwave power will adjust automatically when the actual reaction temperature reaches the target temperature.
3. Run the reaction under microwave irradiation. Record the actual reaction time and temperature.

3. Product isolation

1. After the microwave reaction vial cools to ambient temperature, transfer the reaction mixture into a separatory funnel using a minimal amount of ethyl acetate (EtOAc).

2. Use acid-base extraction to isolate the crude product.
    1. Add 2 mL of saturated NH_4Cl to the separatory funnel.
    2. Add 10 mL of EtOAc to the separatory funnel and extract the product. Separate the organic layer and save it in a clean, dry beaker. Repeat the extraction two more times, and combine the organic layers.
    3. Dry the combined organic layer with anhydrous Na_2SO_4 for 20 min.
    4. Decant the clear solution into a round bottom flask and evaporate the solvent by rotatory evaporation under reduced pressure to yield the crude product.
    5. Record the shape, color and mass of the crude product.
3. Take ^1H and ^{13}C NMR spectra for the crude product to confirm the presence of the characteristic peaks for the expected product.
4. Combine the crude product from the NMR sample with the rest of the crude product for flash chromatography purification below.
5. Use automated flash chromatography to purify the final product.
    1. Sample loading: Dissolve the crude product in 1-2 mL of acetone, followed by the addition of 1.5 g of silica gel to make a slurry. Use rotatory evaporation to remove acetone very carefully so that the product is loaded on the silica gel. Transfer the resulting silica gel to an empty flash chromatography loading cartridge.
    2. Assemble the loading cartridge, prepacked column, test tube rack and solvent lines for the automated medium pressure liquid chromatography (MPLC) system.
    3. Set up the solvent gradient and other parameters for the MPLC system and run the flash chromatography.
    NOTE: The automated flash chromatography solvent gradients are suggested based on the heteroaryl product structural features:
    1) If the product has one or zero nitrogen atoms (N) or hydroxyl groups (OH), use EtOAc/hexanes (0% to 100% over 12 min) with an extension at 100% EtOAc gradient for 2-6 min.
    2) If the product has two or more nitrogen atoms (N) or hydroxyl groups (OH), use CH_3OH/CH_2Cl_2 (0% to 30% over 12 min) with an extension at 30% CH_3OH gradient for 1-3 min.
    4. Combine the desired MPLC fractions and evaporate the solvent to collect the pure product. Dry the purified product under high vacuum for at least 1 h to remove residual solvent.

4. Product characterization

1. Weigh 5 - 10 mg of the final purified product, dissolve it in deuterated chloroform ($CDCl_3$) (or other appropriate deuterated solvent), and take a ^1H NMR spectrum.
2. Weigh 10 - 30 mg of the final purified product, dissolve it in $CDCl_3$ (or other appropriate deuterated solvent), and take a ^{13}C NMR spectrum.
3. Analyze the NMR spectra to confirm the product structure.
4. Recover the NMR sample in a 1 dram vial by evaporating the solvent.
5. Once the NMR spectra support the correct structure, submit a 1 mg sample for HRMS testing to confirm the molecular formula.

Representative Results

The direct α-C(sp3) heteroarylation of ketones can be performed using this efficient microwave-assisted protocol. Selected examples of heteroaryl ketones synthesized in this study are shown in **Figure 1**. Specifically, compound **1a** was synthesized and isolated as a pale-yellow oil (0.49 mmol, 192 mg, 98 %). Its ^1H and ^{13}C NMR spectra are shown in **Figure 2** to confirm the structure and purity. The presence of a two-proton singlet signal δ 4.26 ppm in the ^1H spectrum confirmed the successful C-C coupling between the ketone α carbon and the heteroaryl halide. The structures of all the synthesized heteroaryl compounds were confirmed by ^1H NMR, ^{13}C NMR and HRMS[18].

For microwave-assisted organic reactions using non-polar or weakly polar solvents, the biggest challenge is to raise the reaction temperature to the desired range. The microwave reactor used in our study has a few unique features to achieve this purpose. First, it is equipped with four silica carbide (SiC) plates (**Figure 3A**) which have excellent microwave absorption ability that help to conduct the heat to reaction vials[19]. Second, the controlled microwave heating in sealed reaction vessels (**Figure 3B**) can achieve high temperature and high pressure and thus dramatically reduce reaction times. Third, it has two standard magnetrons of 850 W that can deliver up to 1500 W microwave power over the full power range. The microwave irradiation is continuously controlled by sophisticated software and wireless sensors to achieve homogeneous heating. The maximum available power for an experiment depends mainly on the solvent and number of vessels used.

The most frequently used solvent in our heteroarylation is toluene, a non-polar weak microwave absorber. Thus, the microwave power in our experiments was set to 1300 W, the highest recommended power. The high microwave power and silica carbide (SiC) plates are extremely important to help toluene achieve the desired reaction temperature. As seen in **Figure 4**, the reaction progress graph, the reaction mixture achieved the desired temperature of 130 °C in less than 10 min. This is important for efficient and successful heteroarylation reactions since the temperature has great impact on reaction yields, especially when the reaction time is only a few minutes.

As mentioned above, extreme caution is necessary if the experiment is performed in volatile solvents under microwave irradiation. Among the several solvents we tested for the heteroarylation, tetrahydrofuran (THF) has a boiling point of 66 °C and is used as an example of a volatile solvent to explain the total pressure calculation. Three components need to be considered for total pressure calculation: the solvent vapor, the inert gas introduced during the reaction set up, and any possible gas evolved during the reaction. First, under the current reaction temperature of 130 °C, THF will have a vapor pressure of 4121.5 mmHg or **5.49 bar**. This can be estimated from the Antoine Equation:

$$log_{10}(P) = A - [B / (T + C)]$$

where P is the calculated vapor pressure in mmHg and T is the temperature in Celsius (°C). The coefficients A, B and C for THF in the temperature range of 121 to 265 °C are 7.42725, 1532.81 and 272.081, respectively[20].

Second, the pressure of the inert nitrogen will increase as the reaction temperature increases. The volume of the nitrogen is estimated to be 1 mL, which is the difference between the vial volume (4 mL) and the reaction solution volume (3 mL). Using the approximation that nitrogen volume does not change throughout the reaction, the final nitrogen pressure under the reaction temperature can be found to be **1.39 bar** using the equation below:

$P_1/T_1 = P_2/T_2$

where P_1 is 1 atm or 1.01325 bar, T_1 is room temperature (293 K) and T_2 is reaction temperature in Kelvin (130 °C; 403 K).

Finally, there is no gas evolved during the heteroarylation reaction, so product gas pressure is not needed for total pressure consideration. For those reactions that evolves gas (H_2, NH_3, CO_2, etc), the following formula can be used to calculate the pressure increase caused by the evolved gas:

$PV = nRT$

where V is the volume above the solution in the reaction vial, n is the molar amount of gas evolved, R is the gas constant (8.314×10^{-2} $L \cdot bar \cdot K^{-1} \cdot mol^{-1}$), and T is the reaction temperature in Kelvin.

Overall, the total pressure in a sealed vial at the reaction temperature when the volatile solvent THF is utilized for this heteroarylation is estimated to be:

$P(total) = P(THF\ vapor\ pressure) + P(N_2) + P(evolved\ gas) = 5.49\ bar + 1.39\ bar + 0 =$ **6.88 bar**

This number is well below the microwave vial pressure limit of 20 bar, therefore, THF is a safe solvent to use in the reported direct heteroarylation reaction.

Besides the reaction conditions, the purification is also crucial for the successful preparation of heteroaryl compounds. The purification of heteroaryl compounds is often laborious and difficult due to the lone pair electrons on the heteroatom and the aromatic ring. Recrystallization is not ideal for small-scale reactions, so flash chromatography is the main technique we rely on. We struggled with several different modifications to improve the separation, such as adding 1% Et_3N or toluene to the solvents. Eventually we settled on a slight modification of the EtOAc/hexanes solvent system by adding additional time at 100% EtOAc gradient at the end of the elution. This allowed us to isolate the compounds with one nitrogen very well (**Figure 5A**) as these compounds tend to elute around 70% - 100% EtOAc gradient. However, when this method was utilized for compounds with two or more nitrogen atoms, it took an additional 5 to 10 min to elute the column at the 100% EtOAc gradient to obtain the product. The CH_3OH/CH_2Cl_2 solvent system was employed alternatively to purify compounds with two or more nitrogen atoms to get faster elution (**Figure 5B**).

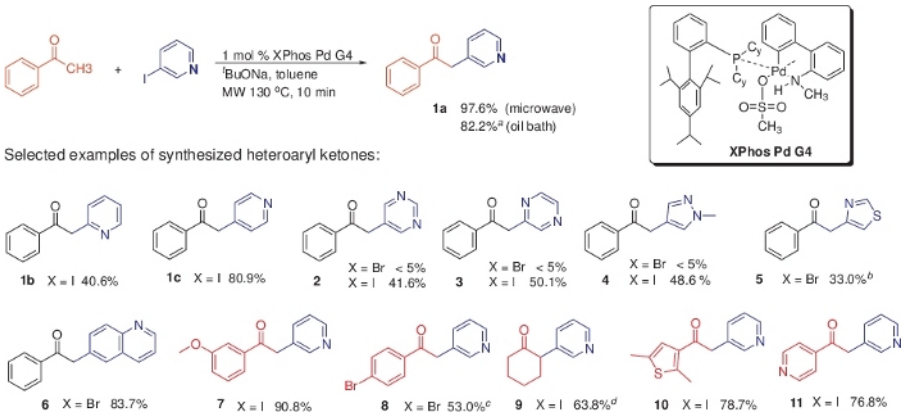

Figure 1: Reaction scheme and selected examples for the microwave-assisted Pd-catalyzed heteroarylation of ketones. Reaction conditions are as follows unless otherwise noted: 1.0 equiv. heteroaryl halide, 1.1 equiv. ketone, 1 mol % XPhos Pd G4 catalyst, 2.4 equiv. ^{t}BuONa, toluene, microwave irradiation at 130 °C for 10 min.

[a] Reaction was conducted under traditional thermal conditions at 100 °C for 4 h.

[b] Reaction was conducted at room temperature for 3 days.

[c] $Pd_2(dba)_3$ was used as the catalyst and XPhos was used as the ligand. The catalyst and ligand were premixed in toluene for 30 min under Ar before the addition of the rest of the reagents. Reactions were conducted under microwave irradiation at 120 °C for 20 min.

[d] Reaction was conducted under microwave irradiation at 130 °C for 20 min due to the less reactive secondary α-carbon in cyclohexanone.

[e] This figure has been modified from Quillen, A., et al.[18]. Adapted with permission from Quillen, A., et al. Palladium-Catalyzed Direct α-C(sp3) Heteroarylation of Ketones under Microwave Irradiation. *The Journal of Organic Chemistry.* **84** (12), 7652-7663 (2019). Copyright 2019 American Chemical Society. Please click here to view a larger version of this figure.

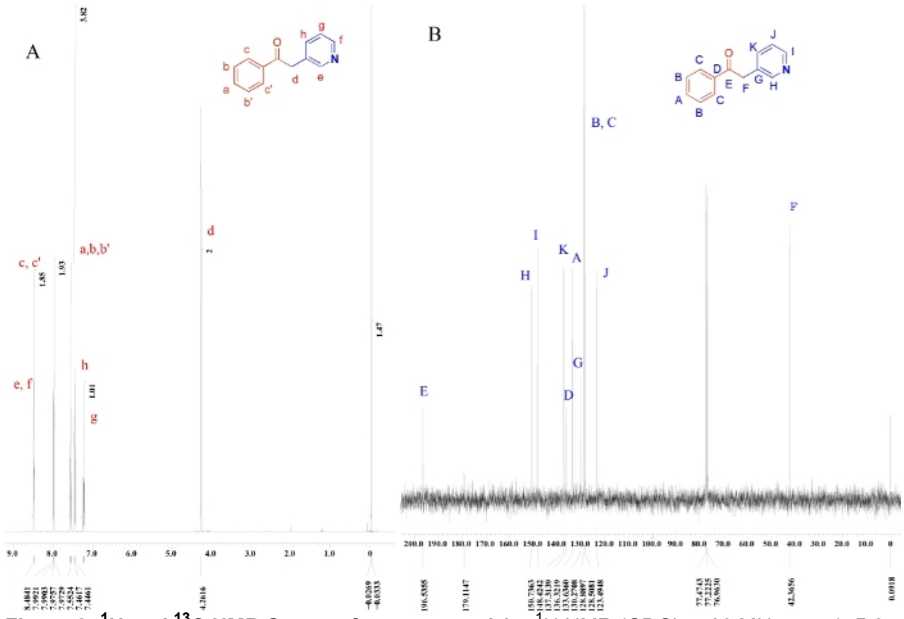

Figure 2: ^{1}H and ^{13}C NMR Spectra for compound 1a. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.53 (1H, s), 8.49 (1H, d, *J* = 5.05 Hz), 8.00 (2H, d, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 6.85 Hz), 7.56 (1H, t, *J* = 7.8 Hz), 7.46 (2H, t, *J* = 7.8 Hz), 7.24 (1H, dd, *J* = 7.8,4.6 Hz), 4.26 (2H, s). ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ196.5, 150.7, 148.4, 137.3, 136.3, 133.6, 130.3, 128.9, 128.5, 123.5, 42.4. Please click here to view a larger version of this figure.

Figure 3: Silicon carbide (SiC) plates and microwave reaction vial assembly. (**A**) Four SiC plates are placed on the rotor inside the microwave reactor. Each plate can hold up to 24 reaction vials and up to 96 reactions can be set up for each experiment. (**B**) A close-up view of the microwave reaction vial, seal and cap. The microwave vial and seal are disposable, and the microwave cap is made of polyether ether ketone (PEEK) and it is reusable. Please click here to view a larger version of this figure.

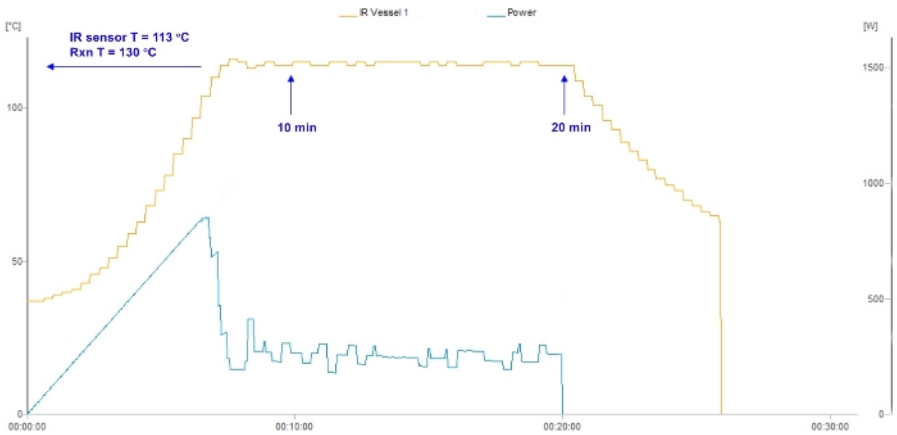

Figure 4: Representative reaction progress graph: microwave power (blue) and IR sensor temperature (orange) versus reaction time. The IR sensor temperature reached 113 °C at 8 min during the ramp step, indicating the reaction solution temperature reached 130 °C. The microwave power was held at between 300 W and 500 W during the hold step. Please click here to view a larger version of this figure.

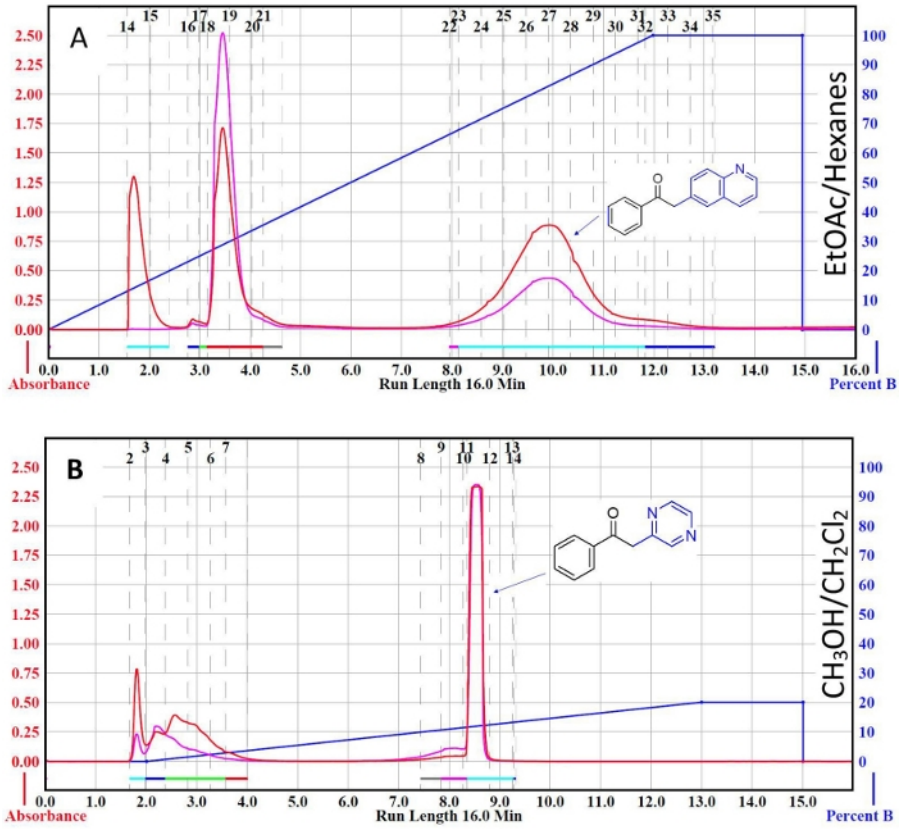

Figure 5: Representative flash chromatography purification plot. (**A**) Compound **6** eluted with EtOAc/hexanes (0% to 100% over 12 min) with an extension of 100% EtOAc for 3 min. (**B**) Compound **3** eluted with CH_3OH/CH_2Cl_2 (0% to 30% over 12 min) with an extension of 30% CH_3OH for 2 min. Please click here to view a larger version of this figure.

Discussion

The methodology described herein was developed to access valuable synthesis building blocks – heteroaryl compounds. Compared to precedent literature reports on heteroarylation, the choice of this current catalytic system showed several significant advantages. First, it avoids the use of protecting groups, the isolation of reactive intermediates, the stoichiometry requirement of catalysts, and the extended reaction times[11,17]. Second, the SiC plates offer a great opportunity for parallel synthesis in diversity-oriented drug discovery[19]. In theory, up to 96 reactions in 0.5 – 1 mmol scale can be set up and performed under microwave irradiation. Practically, the limiting factor would be the work up and purification for each reaction. Third, this method fulfills several principles for green chemistry including design for energy efficiency, catalysis, prevention of chemical waste, etc[21]. Thus, it is a more environmentally friendly method to build valuable molecular entities.

There are many steps involved in this protocol, and there are many factors that can affect the reaction outcomes (e.g., catalysts, ligands, bases, solvents, temperature and time). The critical steps in this protocol are as follows: (1) the choice of catalyst and catalyst addition. Our starting point to optimize the reaction conditions involved the screening of various catalysts. XPhos Pd G4 (structure shown in **Figure 1**), a palladium pre-catalyst with bulky ligands, stood out as an excellent candidate among the catalysts we tested. The additional available catalysts included $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, (SIPr)Pd(allyl)Cl, $Fe[C_5H_4P^tBu_2]_2$ and Ni(COD)[18]. Due to the small scale of the reaction, the catalyst can easily be lost during its addition. Therefore, it is important to dip the spatula with the catalyst into the solvent to ensure the complete transfer of the catalyst. (2) the monitoring and calibration of the microwave reaction temperature. The reaction temperature dramatically impacts the product yield and purity: low or poor yields were observed when the reaction temperatures were below 120 °C, while too many side products or starting material decomposition was observed when the reaction temperatures exceeded 140 °C. During the heteroaryl experiments in our lab, the actual reaction temperatures were closely monitored and recorded. Since the actual reaction temperature is highly dependent on the microwave power, it is recommended to calibrate the microwave power every six months.

In order to gain insight on different heating methods, a comparison of the heteroarylation between microwave irradiation and traditional heating was performed. Traditional thermal heating conditions for the direct heteroarylation to form compound **1a** was performed at 100 °C for 4 h to give 82.2 % isolated yield, which was lower than the microwave irradiation yield (97.6%, **Figure 1**)[18]. Additionally, the overall purity of the crude products using traditional heating was lower than those obtained under microwave irradiation. This is probably because the long heating under high temperature caused more condensation or polymerization side products[3,22]. Thus, the rapid heating and cooling under microwave irradiation helps to avoid these side reactions and contributes to cleaner products.

The main strengths of this heteroarylation protocol include highly efficient reactions, broad substrate scope, improved yields, purity and parallel synthesis ability. Depending on the exact experiment, modifications and troubleshooting might be necessary to obtain optimal results. For example, the substrate structures vary greatly, and this may impact their chemical reactivity. For iodopyridines, 3-iodopyridine and 4-iodopyridine gave much higher yields than 2-iodopyridine, likely due to the increased chance of catalyst poisoning when the N atom is located closer to the reactive site (compounds **1a**, **1c** v.s. compound **1b**, **Figure 1**)[18]. Some substrates decompose at high temperature and cause reaction failures. For these compounds, the reaction mixture can be stirred at room temperature instead of using microwave irradiation to facilitate the possible preparation of heteroarylation product (e.g., compound **5** in **Figure 1**). On the other hand, some substrates react sluggishly due to steric hindrance (e.g., a secondary carbon instead of a primary carbon at the α position of the ketone substrate). Longer reaction time or higher reaction temperature might be necessary to obtain a decent yield in some cases (e.g., compound **9** in **Figure 1**).

The strong, nucleophilic bases required in the reported heteroarylation impose some limitations on this protocol. Functional groups that are not compatible with the strong bases are not suitable for this reaction. For example, ketone substrates with active methylene groups (1-phenyl-1,3-butanedione, 1,3-cyclohexanedione, ethyl levulinate, etc.) did not give expected products due to the strong basicity of NaO^tBu[23]. For these reactions, the use of a weaker base might give improved results. For substrates bearing electrophilic groups such as cyano or nitro groups, no α-heteroarylation was observed possibly due to their interactions with the strong, nucleophilic bases.

In conclusion, a highly efficient microwave-assisted, palladium-catalyzed direct α-heteroarylation of ketones was developed. This protocol enables rapid synthesis and structure modification to prepare heteroaryl compounds as pharmaceutical candidates, coordinating ligands for chemical catalysis, or useful precursors for material chemistry. A domino approach using heteroarylation as a key reaction to synthesize isocoumarin compounds is currently under study in our lab and will be reported in the near future. Other possible applications for this protocol include, but are not limited to, diversity-oriented synthesis for the discovery of biologically active small molecules and ligand development for new transition metal catalytic systems.

Disclosures

The authors have nothing to disclose.

Acknowledgments

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