Video Article

Facile Preparation of 4-Substituted Quinazoline Derivatives

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Abstract

Reported in this paper is a very simple method for direct preparation of 4-substituted quinazoline derivatives from a reaction between substituted 2-aminobenzophenones and thiourea in the presence of dimethyl sulfoxide (DMSO). This is a unique complementary reaction system in which thiourea undergoes thermal decomposition to form carbodiimide and hydrogen sulfide, where the former reacts with 2-aminobenzophenone to form 4-phenylquinazolin-2(1H)-imine intermediate, whilst hydrogen sulfide reacts with DMSO to give methanethiol or other sulfur-containing molecule which then functions as a complementary reducing agent to reduce 4-phenylquinazolin-2(1H)-imine intermediate into 4-phenyl-1,2-dihydroquinazolin-2-amine. Subsequently, the elimination of ammonia from 4-phenyl-1,2-dihydroquinazolin-2-amine affords substituted quinazoline derivative. This reaction usually gives quinazoline derivative as a single product arising from 2-aminobenzophenone as monitored by GC/MS analysis, along with small amount of sulfur-containing molecules such as dimethyl disulfide, dimethyl trisulfide, *etc.* The reaction usually completes in 4-6 hr at 160 ºC in small scale but may last over 24 hr when carried out in large scale. The reaction product can be easily purified by means of washing off DMSO with water followed by column chromatography or thin layer chromatography.

Video Link

The video component of this article can be found at https://www.jove.com/video/53662/

Introduction

Substituted quinazolines, as a unique type of heterocycles, have been known for a variety of biological activities, including antibiotic,[1] antidepressant,[2] anti-inflammatory,[3,4] anti-hypertensive,[3] antimalarial,[5] and anti-tumoral,[6] among others. What is more, 4-substituted quinazolines, *e.g.*, 4-aryl-quinazolines, with anti-plasmodial activity[7] have been recognized as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors,[8] CNS depressants,[9] and antibiotics against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*.[10] Because of its wide spectrum of biological activities, synthetic methods for substituted quinazolines have been largely explored. As an example, more than 25 synthetic methods have already been reported for the preparation of 4-phenylquinazolines.[11] Representative methods include the formation of 4-phenylquinazolines from 2-aminobenzophenones and formamide in the presence of boron trifluoride etherate ($BF_3{\cdot}Et_2O$)[12] or formic acid,[13] or from the reaction of 2-aminobenzophenones with urotropine and ethyl bromoacetate,[14] or the reaction with aldehyde and ammonium acetate in the presence of an oxidizing agent.[15]

Different from the above reactions using moisture sensitive reagent (*e.g.*, $BF_3{\cdot}Et_2O$) or expensive reagent (*e.g.*, urotropine and ethyl bromoacetate), a facile method that can easily convert 2-aminobenzophenones into corresponding 4-phenylquinazolines in dimethyl sulfoxide (DMSO) in the presence of thiourea has been explored. Extensively mechanistic studies on this reaction indicate that it is a complementary reaction in which thiourea undergoes thermal decomposition to form carbodiimide and hydrogen sulfide, where carbodiimide reacts with 2-aminobenzophenone to form 4-phenylquinazolin-2(1H)-imine intermediate, whilst DMSO is used not only as a solvent, but also the reagent to generate sulfur-containing reducing reagent when it reacts with hydrogen sulfide (also arising from thiourea). Then, the sulfur-containing reducing agents reduce the 4-phenylquinazolin-2(1H)-imine intermediate to form 4-phenyl-1,2-dihydroquinazolin-2-amine that undergoes elimination of ammonia to form 4-phenylquinazoline. This reaction is usually carried out at temperature from 135-160 °C, and can be easily performed by means of traditional oil bath heating on hotplate or under microwave irradiation. This reaction is generally illustrated in **Figure 1** below.

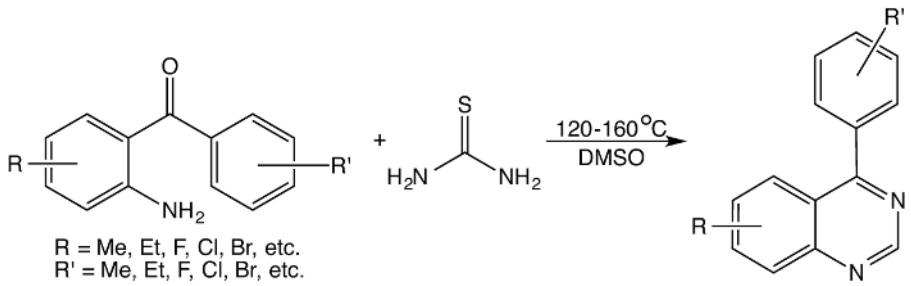

Figure 1: A general reaction between 2-aminobenzophenone and thiourea in DMSO. Please click here to view a larger version of this figure.

Protocol

Caution: Please consult all relevant material safety data sheets (MSDS) before use. Whilst 2-aminobenzophenones are odorless, some sulfur-containing molecules are generated in this reaction. Therefore, good condition of ventilation should always be used. Please use all appropriate safety practice when performing the reactions at temperature higher than 140 °C, as pressure may go above 5 bars as recorded under microwave irradiation. When the temperature is set at 160 °C, the highest pressure recorded is 21 bars, which is almost the upper limit the microwave reactor can handle. Although pressure is not an issue when the reaction is carried out in oil bath under refluxing, good ventilation should always be used.

1. Preparation of 4-Phenylquinazoline in Small Scale Under Microwave Irradiation

1. Preparation of Reaction Mixture
    1. Add a compatible magnetic stir bar to a 2-5 ml microwave reaction tube.
    2. Use analytical balance and weigh 0.0866 g of 2-aminobenzophenone (yellow powder), 0.0988 g of thiourea (white crystal, 3 equivalents) into the above reaction tube.
    Note: The optimal ratio between 2-aminobenzophenone and thiourea is 1:3.
    3. Transfer 5 ml of DMSO to the reaction tube.
    Note: The amount of DMSO is quite flexible, 5 ml of DMSO is just about enough to meet the minimal requirement of volume for correct absorption of microwave according to manufacturer's guide. However, under thermal condition, much less solvent is needed for reaction of this scale.
    4. Seal the reaction tube with a compatible aluminum cap containing rubber septum inlet.
    5. Vigorously shake the tube on a vortexer for 1-2 min to dissolve the reactants.
    Note: Thiourea may not completely dissolve in DMSO at room temperature, but it will fully dissolve when heat is applied.
    6. Use a micro-syringe to withdraw 5 µl of reaction mixture to a 2 ml glass sampling tube containing 0.35 ml of ethyl acetate (EtOAc) for gas chromatography/mass spectroscopy (GC/MS) analysis before the reaction starts.

2. Formation of 4-phenylquinazoline Under Microwave Irradiation
    1. Turn on microwave reactor, put the microwave reaction tube in one of the eight tube holders.
    2. Setup reaction parameters through touch screen, such as the location of tube (*e.g.*, from well 1 to 8), type of tube (*e.g.*, 2-5 ml), reaction temperature (at 150 °C), pre-stirring duration (1 min), microwave absorption level (high), stirring speed (600 rpm), and reaction time (5 hr).
    3. Once all parameters are setup correctly, click "run" button, the robot will automatically pick up the reaction tube from the tube holder (or well) and put it inside the heating hole. Then, the microwave reactor will run the reaction according to the parameters set up previously.
    4. When microwave irradiation completes, wait until temperature drops to close to 30 ºC, the robot will pick up the reaction tube and put it back to the original holder.
    5. Use micro-syringe to withdraw 5 µl of reaction mixture (clear yellow solution, no insoluble substance observed) and add it to another 2 ml glass sampling tube containing 0.35 ml of EtOAc for GC/MS analysis.
    6. As GC/MS analysis indicates that the reaction is only half completed, set up the microwave reaction of the same tube for another 5 hr at the same temperature.
    Note: Reaction time varies depending on the amount of starting material used, the concentration of reaction solution, the substituting groups on 2-aminobenzophenones, and more importantly, the reaction temperature. For example, a reaction of 0.3 g 2-aminobenzophenone in 3 ml of DMSO will complete in 6 hr at 160 °C, but lasts more than 14 hr at 140 °C under both microwave irradiation and hotplate heating. It is also recommended to monitor the reaction periodically with GC or GC/MS analysis. People without access to GC or GC/MS should then use thin layer chromatography (TLC) to monitor the reaction, although it is not the best tool.

3. GC/MS Analysis of Reaction Mixture
    1. Make sure GC/MS is setup properly according to manufacturer's protocol.
    2. Put the glass sampling tubes on auto-sampler tray.
    3. Click "GCMS_3" shortcut on the monitor to initiate the data acquisition program that controls and coordinates the functions of injector, GC and mass spectrometer. Load a proper method by clicking the "Method" on the drop down menu and highlighting "Load Method." The selected method contains all necessary parameters for both GC and quadruple mass spectrometer to analyze the target samples. If there is no such method, create a necessary method.
        1. For a new sample, if modify some of the GC parameters to suit a particular sample, highlight the "Edit Entire Method" by clicking "Method" from the drop down menu and change the relevant parameters accordingly. The GC parameters that are often changed are the initial temperature and the duration to hold that temperature, the rate of increasing temperature, the final temperature

and the duration to maintain the temperature, the injection amount, the times to wash the injection needle before and after the injection, the equilibration time and post run time, and the post run temperature.

2. For this experiment, set the initial GC temperature at 70 °C (1 min), with an increasing rate of temperature at 20 °C/min, and the final temperature at 250 °C (5 min). Use a total running time of 15 min. Use an injection volume of 2 µl, with 4 pre-wash and 4 after-washes of needle. Use pure helium as the carrier gas used under this condition.
   Note: A method for GC/MS analysis contains the pre-set parameters to run both GC and MS instruments. The parameters for GC include the initial temperature of oven to heat the GC column and the number of minutes to retain that temperature, the rate to raise the temperature of oven, the final temperature of the oven and the number of minutes to retain the final temperature before the GC analysis completes; the amount of sample injected; the split rate of the carrier gas; the number of times to wash the needle before sample is injected; and the number of times to wash the needle after the sample is injected; *etc.* The choice of initial and final temperatures as well as the rate of raising temperature depends on the nature of analyzed sample. In general, non-polar molecules of low boiling points are analyzed at relatively low initial temperature.

4. Tune the Mass Spectrometer According to Manufacturer's Protocol.
   1. Once a running method is selected, click "Instrument" on top of the drop down menu, and highlight "Tune MSD." Then another window appears in front of the data acquisition window. One can select either "Tune MSD" or "QuickTune", and click "OK" button to start the tuning process of mass spectrometer. The "QuickTune" option takes about 3 min to complete, whereas the "Tune MSD" option runs about 10 min. Under normal circumstance, "QuickTune" option is good enough to calibrate the mass spectrometer with accuracy up to 0.1 Dalton. The tuning process will measure the relative abundance of peak 69, 219 and 502 of perfluorotributylamine (PFTBA) as well as the amount of N_2, O_2, H_2O, CO_2, *etc.*
      Note: The mass spectrometer must be calibrated every other day in order to have an accurate measurement of mass. The tuning is to adjust the parameters for the mass spectrometer to work properly, such as the voltage of quadruple, vacuum of mass detector, the background noise, the standard peaks to gauge the mass spectrometer, *etc.* One can choose either autotune or manual tune mode to calibrate the mass spectrometer, *i.e.*, by selecting "QuickTune" or "Tune MSD" option.

5. Acquire the GC/MS Data
   1. Edit data acquisition sequence. Click the "Sequence" on top of the drop down menu to highlight "Edit Sequence", and a new window pops up, in which the information about samples should be input, such as the type of sample (sample, blank, calibration, QC, *etc.*), the location of sample vial (from 1 to 100), sample name, data file name, comments of sample, *etc.* When all sample information has been input, click "OK" button. Then click the "Sequence" on top of the drop down menu to highlight "Save Sequence As.." and input the sequence name in a proper folder.
   2. Acquire the GC/MS data. Click the "Sequence" on top of the drop down menu to highlight "Run Sequence", choose a proper "Data File Directory" to save the acquired data, and then click the "Run Sequence" button to start the data acquisition process.

6. Analyze the GC/MS Results
   Note: Molecules can be characterized by the minutes they are eluted from the GC column, so-called the retention time. Under the same GC condition (*i.e.*, the above mentioned GC parameters), the retention time of a particular molecule is very reproducible. The compound can be further confirmed by its mass spectrum. One can easily identify a compound in terms of retention time and mass spectrum, and check the purity of a compound as well.
   1. Double click the "GCMS_3 Data Analysis" shortcut on the monitor to bring up the software that deliberately processes the acquired data from the GC/MS machine.
   2. During the data acquisition process, to see the instant result of the analyzed sample, click "File" from the drop down menu and highlight "Take Snapshot" to get the synchronized GC spectrum of sample. Often, people will process the data after the acquisition process completes. In this case, click "File" from the drop down menu to highlight "Load Data File" and select the correct data file, or browse the data directory and double click the data file, to show the whole GC spectrum of the sample. A vertical line appears at the position where mouse is pointed to inside the window of GC spectrum.
   3. Move mouse to the center of a peak where the vertical line hits the highest point of the peak, and double click the right button of mouse to bring up the mass spectrum of the sample in a new window below the window of GC spectrum. One can zoom the mass spectrum by holding the left button and select the region to zoom for the detail of mass spectrum.
   4. Identify the compounds by double clicking the right button of mouse inside the mass spectrum window to obtain two new windows. The small front window with a name of "PBM Search Results: C:\Database\W8N08.L" brings up 20 molecules from the database that most likely match the analyzed mass spectrum, and ranks the 20 molecules in order of their similarities. The large back window contains two panels, of which the top panel displays the original mass spectrum of the analyzed peak inside the GC spectrum, and the bottom panel displays the mass spectrum of the selected molecule from the list of small front window. Often, common organic compounds can be confirmed by comparing its mass spectrum with the standard mass spectrum collected in the database. Although new compounds or molecules not collected in the database cannot be directly confirmed, their identities can be obtained through the matching of expected molecular weight and possible fragments with their structures.
   5. Identify the same compound in different samples by comparing its retention time on the GC spectrum. Under the same condition of data acquisition, the same compound should appear with the same retention time on the GC spectrum.
   6. Analyze the purity of sample by clicking the "Chromatogram" on the drop down menu, highlighting either "Integrate" or "AutoIntegrate", and selecting "Percent Report".
   7. Print both GC spectrum and mass spectra corresponding to the peaks inside the GC spectrum in either portrait or landscape format by selecting "Printer Setup" when one click "File" on the drop down menu. Also, print the spectra directly into pdf format by selecting a pdf converter.

4. Extraction of Reaction Mixture
   Note: The isolation process has been carried out in fume hood, as small amount of sulfur-containing molecules with unpleasant smell are generated in this reaction.

1. Open the microwave reaction tube with manufacturer provided plier, and transfer the reaction mixture into a 125 ml separating funnel. Add 20 ml of EtOAc to this funnel followed by 10 ml of water.
   Note: If the reaction solution is left at room temperature over one day, long needle shape crystals may appear in the solution depending on the concentration of solution. Thus, it is wise to leave the large-scale reaction mixture at room temperature to form crystal and isolate the product of crystal directly if time is not a factor.
2. Shake the separating funnel vigorously, and drain the bottom aqueous layer. Then add another 10 ml of water to the separating funnel, and repeat this process.
3. Concentrate the remaining EtOAc solution down to about 1 ml by rotatory evaporation.

5. Purification of 4-phenylquinazoline by Preparative TLC
   1. Transfer the concentrated EtOAc solution with Pasteur pipette to a 20 cm x 20 cm preparative TLC plate in such a way that the stripe of sample on the TLC plate is less than 1 cm wide and is about 1 cm from the edge. Dip this plate to a glass chamber containing 150 ml of hexane and EtOAc (2:1). Watch the movement of solvent frontier approaching the top of the TLC plate, and take out the plate when solvent frontier is about 1 cm from the top edge.
      1. Draw two straight lines on the TLC plate with pencil to mark the place before sample is loaded. Also, dip the TLC plate in glass chamber in such a way that the stripe of sample is at the bottom but still about 2 mm above the solvent level.
   2. Under ultra-violet (UV) light, use a pencil to mark the band with green fluorescence, and scratch off the marked band on the TLC plate to a weighing paper (with a relative mobility of R_f = 0.68, Hexane/EtOAc = 2:1).
      Note: Due to high sensitivity of UV absorption, one may observe multiple weak bands on the plate. However, the very top bands often correspond to sulfur-containing molecules, such as dimethyl disulfide, dimethyl trisulfide; others bands below 4-phenylquinazoline are visible but their amount are too little to be isolated and characterized.
   3. To a glass pipette filled with glass wool, transfer the scratched silica gel powder to the pipette by folding the weighing paper diagonally to allow the powder of silica gel falls into the pipette, and tap the pipette against a hard surface to pack the silica gel tight. Wash the pipette with acetone (8-15 ml) into a 2-drum scintillation vial.
   4. Transfer 0.35 ml of the eluted acetone solution to another 2 ml glass sampling tube for GC/MS analysis, and directly dry the remaining acetone solution on a rotatory evaporator. Put the whole scintillation vial containing the purified compound in vacuum desiccator for further drying.
      Note: Up to this step, the product is purified and can be used for further characterization (*e.g.*, nuclear magnetic resonance (NMR) spectroscopy) or additional transformations.

2. Preparation of 4-Phenylquinazoline in Small Scale via Hotplate Heating

Note: The procedures for the GC/MS analysis of reaction mixture, extraction of reaction mixture, and purification of reaction product are very similar to the ones described in section 1 (1.1.1-1.3.4, 1.4.1-1.4.3, and 1.5.1-1.5.5, respectively), so that most of these steps will be omitted below.

1. Preparation of reaction mixture for hotplate heating
   1. Weigh 0.0240 g of 2-aminobenzophenone and 0.0280 g of thiourea into a 2 ml glass vial, then transfer 0.5 ml of DMSO to the same vial, and close the vial with a screw cap.
      Note: The amount of DMSO used under this condition is much less than the one under microwave irradiation. Due to small scale of this reaction, magnetic stirring is not needed anymore, so for the vortex stirring of the solution to dissolve the reactants. However, in a relative large reaction scale, for example, in 2-drum scintillation vial or round-bottomed flask, magnetic stirring is still needed.

2. Preparation of 4-phenylquinazoline via Hotplate Heating
   1. Inside fume hood, put a heating block on top of hotplate, and set temperature to 160 °C.
   2. When temperature reaches 160 °C, insert the glass vial into one of the wells in heating block. With about half an hour interval, take out of the vial and hand shake it for 2-3 sec, and put it back to the well again. After 6 hr, take out of the vial and leave it inside the fume hood to cool down.
   3. Transfer 5 µl of the reaction mixture to another 2 ml glass sampling tube containing 0.35 ml of EtOAc, and submit the sample for GC/MS analysis.

3. Once the reaction completes, work out the product as described in section 1. See the details in section 1.1.1-1.3.4, 1.4.1-1.4.3, and 1.5.1-1.5.5 for GC/MS analysis, extraction of reaction mixture, and purification of product, respectively.

Representative Results

The GC analysis of reaction mixture before the reaction, 5 hr after reaction under microwave irradiation, and 10 hr after reaction under microwave irradiation at 150 °C are presented in **Figure 2**, which clearly illustrates the process of this neat reaction. The mass spectra of 2-aminobenzophenone and 4-phenylquinazoline are presented in **Figure 3** and **Figure 4**, respectively. An apparent mechanism for the reaction between 2-aminobenzophenone and thiourea that a person with good knowledge of Organic Chemistry may postulate is shown in **Figure 5**. In comparison, the reaction in DMSO on hotplate at 160 ºC is similarly tracked by GC/MS as shown in **Figure 6**, along with the mass spectrum of 4-phenylquinazolin-2(1H)-one byproduct. Based on many experimental facts, a full explanation for the generation of 4-phenylquinazoline is illustrated in **Figure 7**. The mass spectra of dimethyl disulfide (MeSSMe) and dimethyl trisulfide (MeSSSMe) are shown in **Figure 8** and **Figure 9**, respectively. The comparison of the reaction between 2-aminobenzophenone and thiourea in DMF and in DMF but with a small amount of DMSO is illustrated in **Figure 10**.

On the basis of GC/MS analysis, it is quite clear that the conversion of starting material into product is nearly quantitative (**Figure 2**). Due to small difference of molecular weight between the starting material (*e.g.*, 2-aminobenzophenone, MW = 197, retention time = 9.673 min) and the product of substituted quinazoline derivative (*e.g.*, 4-phenylquinazoline, MW = 206, retention time = 9.962 min), the retention times of starting material and product on GC are very similar, but still separable. More than 10 different 2-aminobenzophenones have been tested for this reaction and similar results are obtained.[16]

Discussion

This clean reaction (as shown in **Figure 2**) appears very intriguing at beginning as molecular weight of the product is only increased by 9 with respect to that of starting material (as shown in **Figure 3** and **Figure 4**). This sounds impossible because the atomic weight of carbon is 12. Very likely, introduction of one carbon atom into a molecule will increase the molecular weight by at least 12 if the accompanying hydrogen atom(s) were not included. Therefore, the reaction has confused us for quite a bit of time.

In a quick glimpse of the reaction between 2-aminobenzophenone and thiourea, one may postulate that a simple addition of the amino group of 2-aminobenzophenone to the thiocarbonyl group of thiourea followed by addition of the amino group connecting to thiocarbonyl group to the carbonyl group inside the 2-aminobenzophenone will form a structure with a molecular weight of 238 (**Figure 5**). However, as shown in **Figure 2**, thiourea decomposes quickly because it cannot be detected after the reaction mixture is heated for 5 hr; under this condition, almost 50% of starting material still remains. If thiourea is the real species to react with 2-aminobenzophenone as postulated in **Figure 5**, then there will always be starting material remaining in the reaction solution because no more thiourea is available to react with the residual starting material. Thus, this sound mechanism does not represent the real reaction path and is also inconsistent with the change of molecular weight from 197 of starting material to 206 of the product. It is well known that an even number of molecular weight suggests an even number of nitrogen atom inside the molecule. Thus, the product either does not have nitrogen atom at all or contains even number of nitrogen atoms, most likely with two nitrogen atoms in this case; otherwise, the molecular weight of the product cannot be just increased by 9.

After extensive structural characterizations, including ^{1}H NMR, ^{13}C NMR, and especially X-ray crystallography, it is clear that the product is 4-phenylquinazoline.[16] But how is it formed? Computational study shows that hydrogen sulfide and carbodiimide can be formed from thermal decomposition of thiourea.[17] If the carbodiimide is the species to react with 2-aminobenzophenone, even though thiourea disappears in the reaction solution, carbodiimide would remain in the solution. With this knowledge, it is possible that the amino group inside 2-aminobenzophenone initially reacts with carbodiimide to form 1-(2-benzoylphenyl)guanidine intermediate, which cyclizes to form 4-phenylquinazolin-2(1H)-imine intermediate. However, such intermediate is unstable, and can be hydrolyzed to 4-phenylquinazolin-2(1H)-one, as shown in **Figure 6C**, under the condition of heating on hotplate. In addition, the decomposition of this intermediate does not lead to the formation of 4-phenylquinazoline either, because the direct transformation of this intermediate to 4-phenylquinazoline would require the removal of a nitrogen atom. This is impossible, as both bonds connecting to this nitrogen atom must break to get rid of a fragment of NH, a highly unstable reactive species. However, if 4-phenylquinazolin-2(1H)-imine intermediate were reduced, then the elimination of ammonia under high temperature would take place very easily (**Figure 7**). Then, there must be a reducing reagent that participates in the reaction and reduces 4-phenylquinazolin-2(1H)-imine to 4-phenyl-1,2-dihydroquinazolin-2-amine. As mentioned early, thermal decomposition of thiourea generates hydrogen sulfide, along with carbodiimide. Hydrogen sulfide may react with solvent DMSO to generate organic sulfur-containing molecules that function as reducing reagents, although hydrogen sulfide itself has been applied as the reducing agent as well.[18-20] The most possible sulfur-containing organic reducing agent might be methanethiol, as supported by detection of dimethyl disulfide (retention time = 3.287 minutes in **Figure 2**, Mass spectra in **Figure 8**) and dimethyl trisulfide (retention time = 3.691 minutes in **Figure 2**, Mass spectra in **Figure 9**).

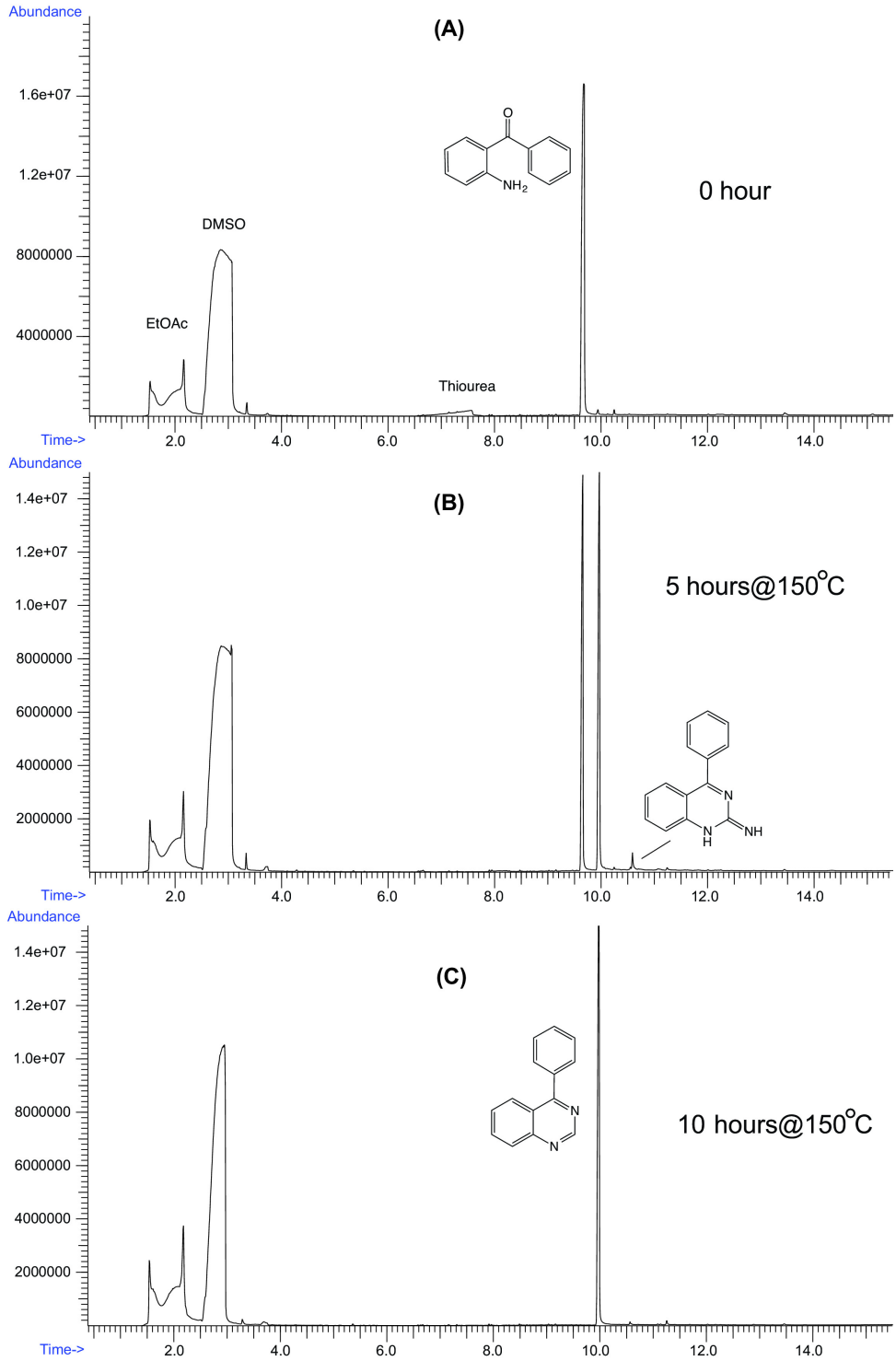

Figure 2: GC analysis of reaction between 2-aminobenzophenone and thiourea in DMSO at 150 ºC under microwave irradiation. The GC conditions are: initial temperature at 70 °C (1 min), increasing temperature rate at 20 °C/min, final temperature at 250 °C (5 min). Total running time is 15 min. The injection amount is 2 µl, with 4 pre-wash and 4 after-wash of needle. (**A**) Reaction mixture before heat is applied; (**B**) reaction mixture after being heated at 150 ºC for 5 hr(imine intermediate observable); (**C**) reaction mixture after being heated at 150 ºC for 10 hr. Please click here to view a larger version of this figure.

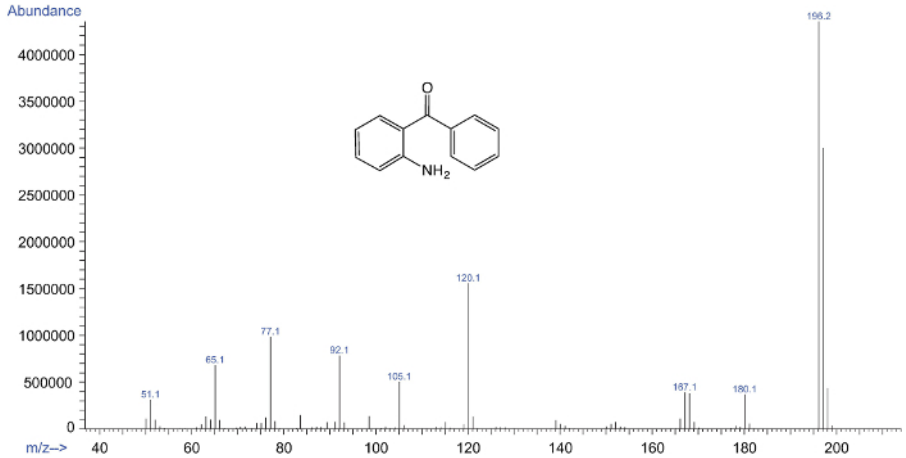

Figure 3: Mass spectrum of 2-aminobenzophenone (EI mode, quadruple). Molecular formula: $C_{13}H_{11}NO$, molecular weight: 197. Typical fragments are 198, M^++1 (9.8%), 197: M^+ (68.6%), 196, M^+-1 (100.0%), 180: M^+-17 (NH_3 lost, 8.3%), 120: M^+-77 (phenyl C_6H_5 lost, 35.9%), 105: benzoyl cation ($C_6H_5CO^+$, 11.4%), 92: M^+-benzoyl (M^+-C_6H_5CO, 18.0%), 77: phenyl cation (22.4%). Please click here to view a larger version of this figure.

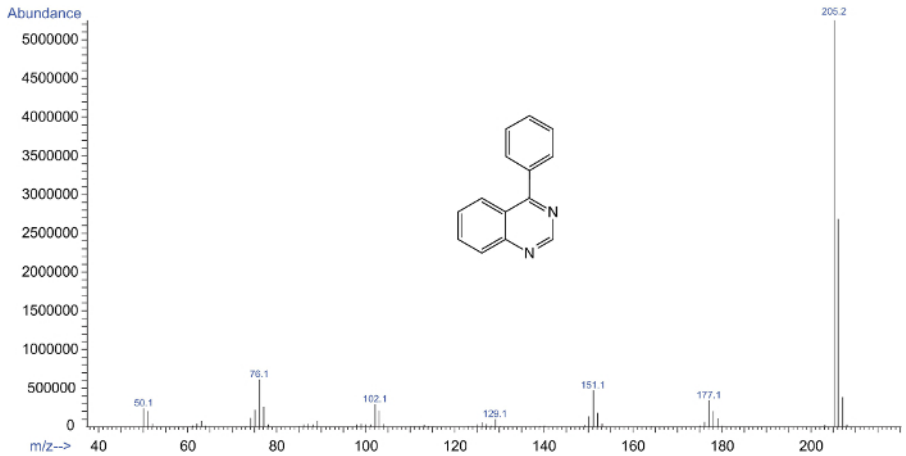

Figure 4: Mass spectrum of 4-phenylquinazoline (EI mode, quadruple). Molecular formula: $C_{14}H_{10}N_2$, molecular weight: 206.25. Typical fragments are 207: M^++1 (7.2%), 206: M^+ (50.8%), 205: M^+-1 (100.0%), 177: M^+-1-HCN-1 (6.6%), 151: M^+-1-C_4H_4-H_2 (8.9%), 129: M^+-C_6H_5 (1.6%), 102: M^+-C_4H_4-C_4H_4 (5.3%). Please click here to view a larger version of this figure.

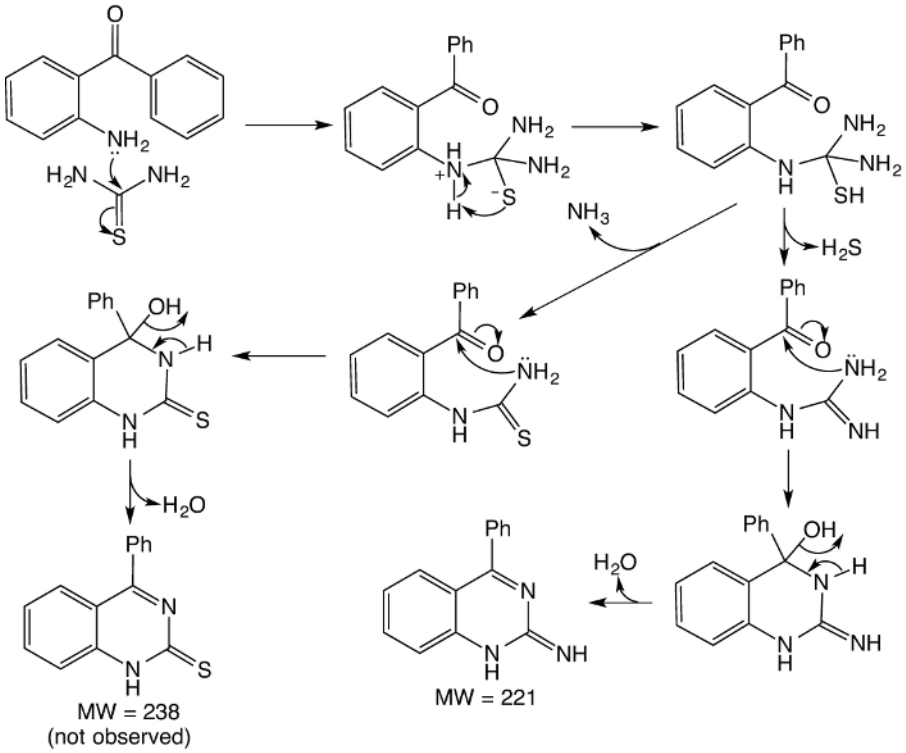

Figure 5: The apparent mechanism for reaction between 2-aminobenzophenone and thiourea. Please click here to view a larger version of this figure.

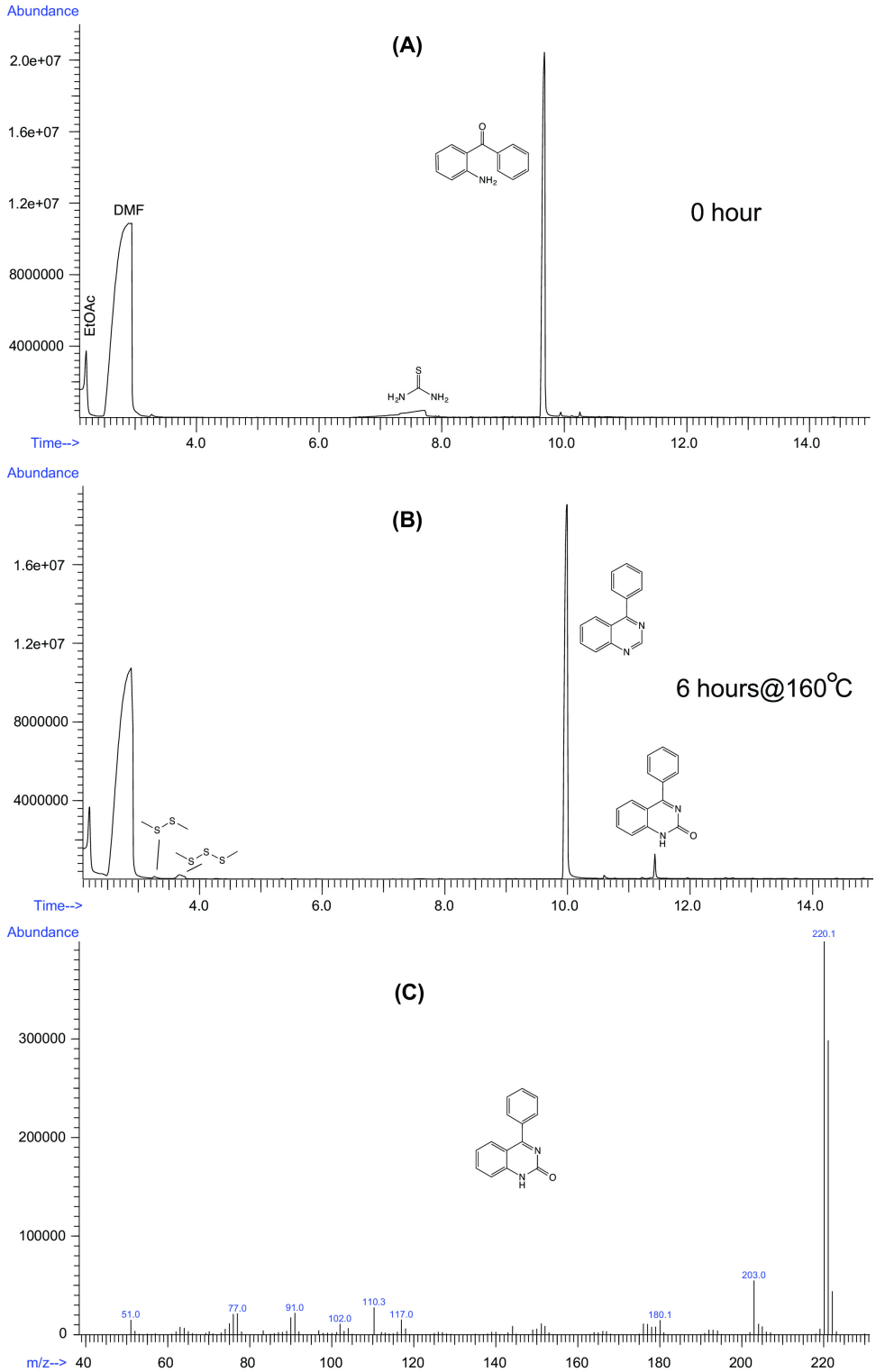

Figure 6: GC/MS analysis of reaction between 2-aminobenzophenone and thiourea in DMSO on hotplate at 160 ºC. (**A**) A mixture of 0.0240 g 2-aminobenzophenone and 0.0280 g of thiourea in 0.5 ml DMSO before heat is applied; (**B**) reaction mixture after being heated at 160 ºC for 6 hr; (**C**) mass spectrum of 4-phenylquinazolin-2(1H)-one byproduct after the solution was heated at 160 ºC for 6 hr. Please click here to view a larger version of this figure.

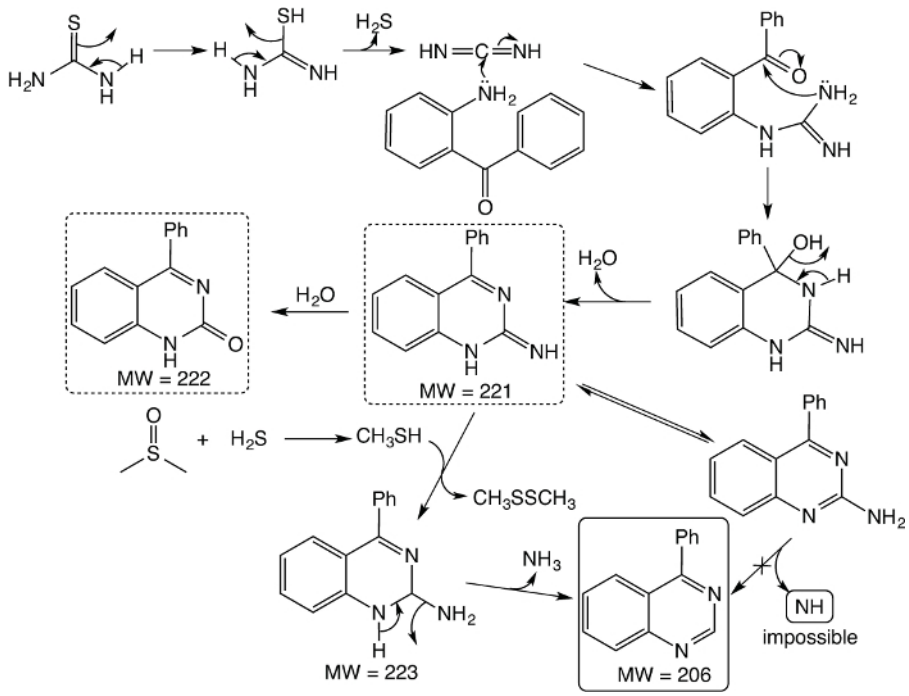

Figure 7: The true reaction mechanism for the formation of 4-phenylquinazoline from 2-aminobenzophenone and thiourea. Please click here to view a larger version of this figure.

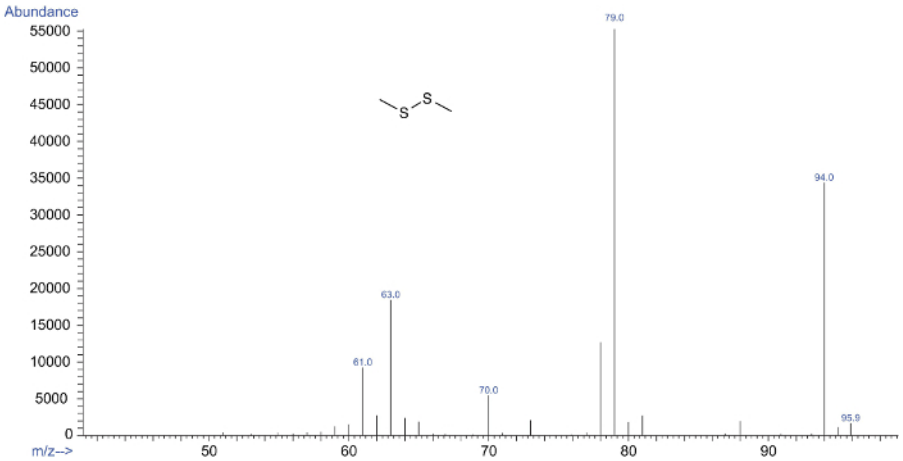

Figure 8: Mass spectrum of dimethyl disulfide (EI mode, quadruple). Molecular formula: $C_2H_6S_2$, molecular weight: 94.19. Typical fragments are 95.9: M^++2 (2.9%), 94: M^+ (62.0%), 79: M^+-CH_3 (100.0%). Please click here to view a larger version of this figure.

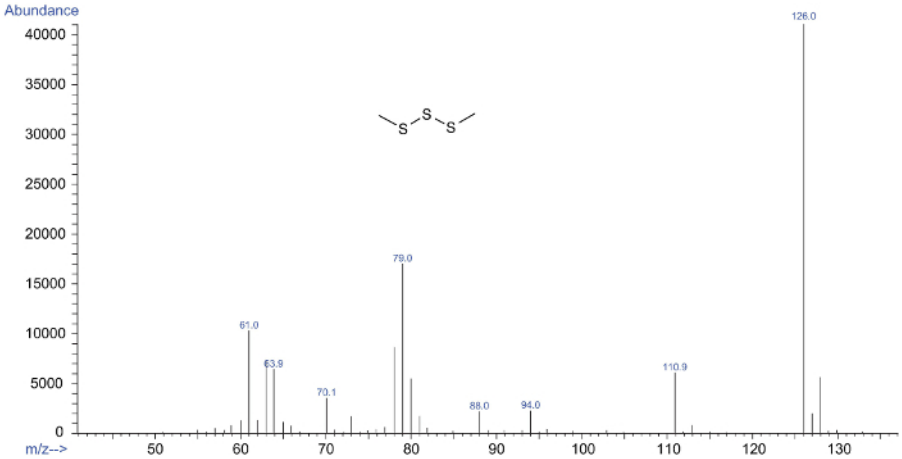

Figure 9: Mass spectrum of dimethyl trisulfide (EI mode, quadruple). Molecular formula: $C_2H_6S_3$, molecular weight: 126.25. Typical fragments are 128: M^++2 (13.7%), 126: M^+ (100.0%), 110.9: M^+-CH_3 (14.6%). Please click here to view a larger version of this figure.

For this simple reaction, the critical steps are the control of heating temperature and afterwards purification. As the carbodiimide is the real species that reacts with 2-aminobenzophenone to form 4-phenylquinazolin-2(1H)-imine intermediate, the formation of carbodiimide from thermal decomposition of thiourea is very important. Early study indicated that thiourea starts to decompose at temperature between 140 and 180 °C,[21] which is also consistent with computational study of thiourea.[17] However, when thiourea is dissolved in polar solvent like DMSO, it starts to decompose at a lower temperature. This temperature has been observed around 120 °C or above in order to have a reasonable reaction rate for the formation of 4-phenylquinazoline from 2-aminobenzophenone. On the other hand, this reaction cannot be setup at a very high temperature either. The upper limit of reaction temperature depends on the boiling point of solvent, and possibly the temperature at which additional side products from thermal decomposition of thiourea are generated. For example, it has been reported that carbon disulfide is the primary product when thiourea is heated at temperature between 182 and 240 °C.[22] Also, under condition of microwave irradiation, the whole reaction system is sealed in a reaction tube of limited space, too high temperature can cause very high pressure and potential explosion. Therefore, the ideal reaction temperature is recommended between 150 and 165 °C. While the pressure may not be an issue under thermal refluxing, a high reaction temperature will cause the evolving of hydrogen sulfide that is required to generate reducing reagents from the reaction with DMSO. Another critical step in this protocol is the purification of product. As 4-phenylquinazoline is less polar than starting material, the solubility of product in DMSO is less than that of the starting material. When the reaction is completed, often product of crystal appears if the reaction solution is left at room temperature for a day or longer. In this case, the crystal can be simply filtrated and washed with solvent to obtain pure product. In addition, the concentration of reactants also influences the way to purify the products. At the same reaction temperature, the higher the concentration of solution is, the longer time the reaction takes to complete. Particularly, when the reaction solution is too concentrated, an oil layer of product forms and floats on top of DMSO solution. This is the case when 3 g of 2-aminobenzophenone and 3.5 g of thiourea react in a 20 ml microwave tube with 7 to 8 ml of DMSO. In this case, no crystal forms, and the product can only be separated from solvent through extraction. Meanwhile, the product can be contaminated with sulfur-containing molecules such as dimethyl disulfide and dimethyl trisulfide, which will be removed by column chromatography. This is the procedure recommended for purification of large-scale reaction.

Regarding the modification of this reaction, it can be carried out in a different polar solvent, such as *N,N*-dimethylformamide (DMF), in the presence of DMSO. In this case, small amount of DMSO is used as the reagent rather than the solvent, for the purpose of generating reducing agent. Under this condition, besides DMSO, less sulfur-containing molecules are present so that unpleasant smell can be well handled. However, this modification will slow down the overall reaction rate. Also, a tiny amount of byproduct originating from DMF is noticeable by GC/MS analysis, although it may not affect the overall purification process. On the other hand, a reaction of large scale can be performed in a round-bottomed flask under refluxing. As it is open to air in the fume hood during refluxing, low volatile molecules including dimethyl disulfide and dimethyl trisulfide will evolve from the reaction system, so that less unpleasant smell will be detected. It should be pointed out that this reaction is very reproducible that has been repeated in multiple times. If the starting materials are mixed correctly in DMSO, and the solution is heated between 150 and 165 °C, it is guaranteed to have the expected final product, so that almost no trouble-shooting is necessary. However, the reaction rate does change when a different 2-aminobenzophenone is used, due to the substituent effect and steric effect.

The significance of this reaction is its simplicity and neatness, with very few minor byproducts. As shown in **Figure 2**, almost no other side products arising from 2-aminobenzophenone can be observed by GC analysis. Although one peak appears at a retention time (*i.e.*, 10.553 min) higher than 4-phenylquinazoline, such peak is very small and disappears as the reaction proceeds to completion. Spectroscopy study on this peak indicates that it is 4-phenylquinazolin-2(1H)-imine intermediate.[16] In addition, very cheap starting material such as thiourea is used in this reaction, instead of other expensive reagents like urotropine or ethyl bromoacetate. Besides the preparation of 4-phenylquinazolines from 2-aminobenzophenones, this reaction can be easily extended to prepare other aromatically fused molecules containing quinazoline scaffold, such as perimidines that have important industrial applications as dyes and pigments. Moreover, this reaction can also be extended to 2-aminophenyl alkyl ketones to prepare quinazolines with an alkyl group at position 4, instead of an aryl group. But it is limited to only those 2-aminophenyl alkyl ketones without active α-hydrogen(s) on the carbon atom adjacent to the carbonyl group, because if an active hydrogen exists at this α-carbon atom, potential tautomerization can occur to form enol that undergoes Aldol condensation to form other side products, instead of quinazoline derivatives.

For this reaction, the optimal ratio between 2-aminobenzophenone and thiourea is 1:3. Computational study of thermal decomposition for thiourea shows that besides a pair of hydrogen sulfide and carbodiimide, ammonia and thiocyanic acid are generated as well, indicating that not all thiourea will be converted into carbodiimide.[17] Therefore, at least one equivalent of thiourea is needed for this reaction. On the other

hand, as small sulfur-containing molecule will be generated from this reaction, it is wise not to use too much thiourea for this reaction due to the unpleasant smell of sulfur-containing by-products.

It is clear that the reaction between 2-aminobenzophenone and thiourea in DMSO is a unique complementary reaction system, in which thermal decomposition of thiourea produces the required reactive species (*i.e.*, carbodiimide) that couples with 2-aminobenzophenone to form the imino intermediate (*i.e.*, 4-phenyl-quinazolin-2(1H)-imine), whereas hydrogen sulfide reacts with DMSO to generate organic sulfur-containing molecule that functions as reducing agent to reduce the imino intermediate. Then, elimination of ammonia from 4-phenyl-1,2-dihydroquinazolin-2-amine affords 4-phenylquinazoline. The reaction has been tested in other aprotic polar solvents, such as DMF, ethylene glycol, but the reaction is not as good as the one in DMSO. For example, the reaction between 2-aminobenzophenone and thiourea in ethylene glycol affords primarily (5Z,11Z)-6,12-diphenyl-dibenzo[b,f][1,5]-diazocine, the dimerization product of 2-aminobenzophenone.[16] While the reaction between 2-aminobenzophenone and thiourea in DMF can afford 4-phenylquinazoline, this reaction is not as clean as the one in DMSO, as shown by the unknown byproducts in **Figure 10B**. Apparently, this reaction is not as fast as the one in DMSO either. However, the addition of small amount of DMSO into DMF solution certainly improves the reaction in terms of both reaction rate and reduction of side products (**Figure 10D** and **Figure 10E**). This result clearly shows the role of DMSO in this reaction, not only as a solvent, but also as a reagent to generate reducing reagent. Therefore, this is a complementary reaction system. As a simple and clean reaction to make quinazoline derivatives, the reported protocol can be applied to the preparation of heterocycles containing the fused pyrimidine scaffold in the future. Many heterocyclic molecules containing the pyrimidine moiety have been used in medicines as well as colorants.

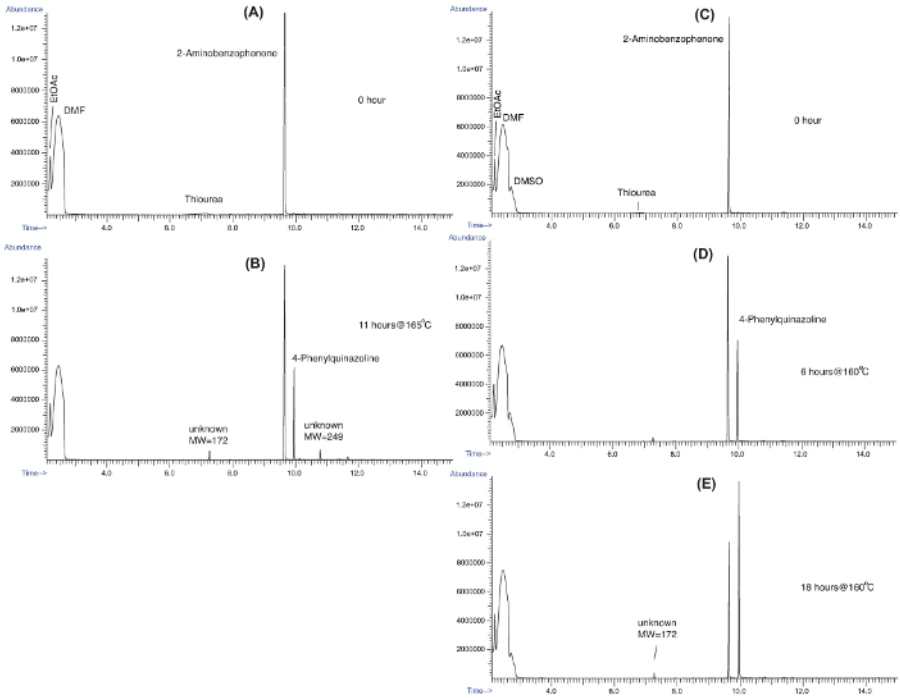

Figure 10: GC/MS analysis of the reaction between 2-aminobenzophenone and thiourea in DMF and in DMF with DMSO present. (**A**) A mixture of 0.0318 g of 2-aminobeznophenone and 0.0382 g of thiourea in 2 ml of DMF before heated is applied; (**B**) the DMF solution after being heated at 165 ºC for 11 hr under microwave irradiation; (**C**) a mixture of 0.0663 g of 2-aminobenzophenone, 0.0767 g of thiourea, 0.5 ml of DMSO and 5.0 ml of DMF before heated is applied; (**D**) the solution in (C) after being heated at 160 ºC for 6 hr under microwave irradiation; (**E**) the solution in (C) after being heated at 160 ºC for 18 hr under microwave irradiation. Please click here to view a larger version of this figure.

Disclosures

Except for the contents described in patent (pending), the authors have nothing else to disclose.

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