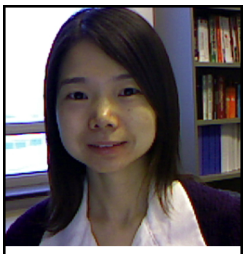
Send Orders for Reprints to reprints@benthamscience.ae

150 *Current Microwave Chemistry,* **2015,** *2,* **150-158**

A Rapid One-step Synthesis of Isoflavanone Compounds Under Microwave Irradiation

Timothy Dunn, Thuy Do, Nathan Johnson, Quintin Hauser, KC Russell and Lili Ma*

Department of Chemistry, Northern Kentucky University, Nunn Drive, Highland Heights, KY 41099, USA



Lili Ma

Abstract: A rapid one-step synthesis of isoflavanones from salicylaldehydes and alkynes in the presence of gold(I) catalyst under microwave irradiation was developed. Various reaction conditions including catalysts, solvents, reaction time and temperature were investigated. This reaction is compatible with a variety of functional groups on salicylaldehydes or aromatic alkynes such as alkoxy, alkyl, halogen, amino, thiophenyl and pyridyl groups. NMR spectroscopy was used to monitor the reaction progress and to investigate the initial step in the mechanistic pathway.

Keywords: Alkyne, annulation, aromatase inhibitor, breast cancer, catalysis, chemical shifts, drug discovery, gold catalysis, hydroxyaldehyde, isoflavanone, mechanism, medicinal chemistry, microwave irradiation, natural products, nucldear maganetic resonance, reaction intermediate.

INTRODUCTION

One subclass of flavonoids are isoflavanones (3-phenylchroman-4-ones). Because of their rarity they have not been well studied. Approximately 100 isoflavanones have been identified in nature. Some of these compounds have been shown to possess antipyretic, antioxidant and anticancer activities [1]. Representative naturally occurring isoflavanones include perbergin [2], sativanone [3], and sophoronol A [4], which possess various hydroxylation or methoxylation patterns (Fig. **1**). To date there are only two studies that have reported the aromatase inhibitory effects of eight naturally occurring isoflavanones [5]. Based on the results of our previous studies on anti-breast cancer agents, we decided to prepare a small library of isoflavanone compounds [6, 7]. One of the complications with current methods is that several steps or extremely long reaction times are needed. The problem is exacerbated when the reactions cannot be carried out in parallel. Therefore, the development of a fast and efficient method to synthesize isoflavanone libraries is highly desirable.

Current methods to synthesize isoflavanone derivatives rely heavily upon toxic metals or sensitive reagents, such as *N*-heterocyclic carbene-catalyzed hydroarylation of *O*-allylated hydroxyaldehydes [8], Friedel-Crafts acylation of 2-phenyl-3-phenoxyacids [9], addition of *O*-hydroxyalkynes to aldehydes [10], 1,4-addition to α,β-unsaturated ketones [11], coupling of aryllead with 3-phenythio-chroman-4-one [12], reaction of benzyl 2-hydroxyphenylketones with bis (dimethylamino)methane [13], hydrogenation or hydride reduction of isoflavones [14-17], and alkylation of isoflavones [18]. However, these reactions suffer from the use of toxic reagents, laborious steps, harsh reaction conditions, staring materials or catalysts that are not readily available and sometimes poor selectivity for the desired products.

Very recently, Li reported the AuCN-catalyzed annulation reactions of salicyaldehydes and alkynes in toluene at 150°C for 36 hours to produce isoflavanones [19, 20]. Considering the variety and commercial availability of hydroxyaldehydes (salicyladehydes) and alkynes, we envisioned that this reaction can be utilized to synthesize isoflavanone derivatives. Additionally, gold-catalyzed reactions have distinct advantages such as low toxicity, air and oxygen tolerance, broad substrate scope, diverse product scaffolds, atom economy and biocompatibility [21, 22]. The reported long reaction time and the large amount of $^{n}Bu_3P$ ligand required under thermal reaction conditions hindered the rapid production of isoflavanone derivatives and motivated us to explore this reaction under microwave irraddiation. The first microwave-assisted gold-catalyzed reaction was reported by Che in 2006 [23]. It is surprising that few papers have investigated microwave-assisted gold-catalyzed reactions [24-26]. Considering the many advantages of microwave-assisted reactions and its wide application in organic synthesis [27-30], it is attractive to apply microwave conditions to study gold-catalyzed annulation reactions. Herein, we describe our recent findings on the microwave-assisted synthesis of isoflavanones by the gold-catalyzed annulation reaction of salicyaldehydes and aryl alkynes.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions for the microwave production of isoflavones the reaction between salicylaldehye and phenylacetylene was used as a model. We first established a suitable internal reference compound so that the reaction process could be monitored by Nuclear Magnetic Resonance (NMR) spectroscopy. Several inert compounds such as nitromethane, diethyl phthalate, bibenzyl

*Address correspondence to this author at the Department of Chemistry, Northern Kentucky University, Nunn Drive, Highland Heights, KY 41099; Tel: (859) 572- 6961; Fax: (859) 572-5162; E-mail: mal1@nku.edu

2213-3356/15 $58.00+.00

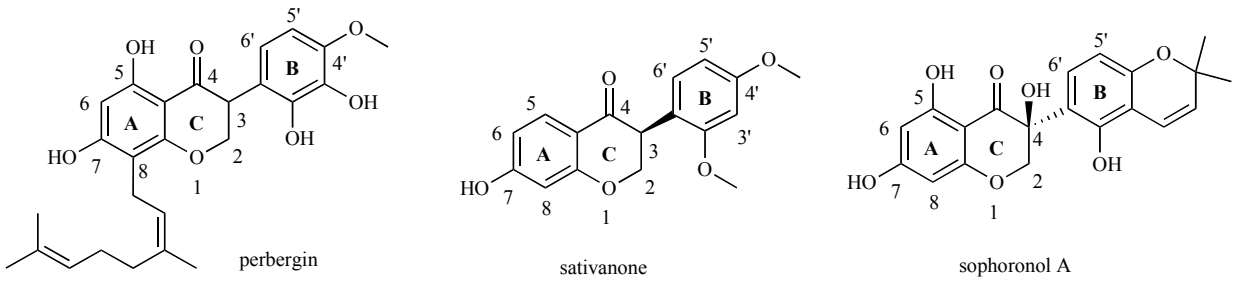
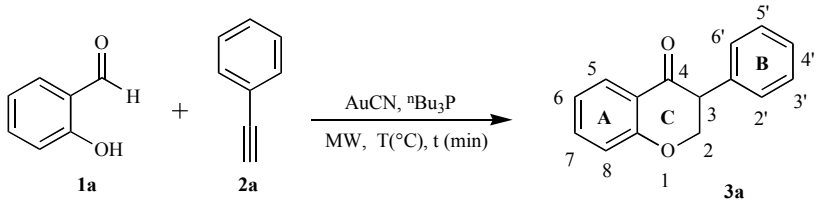


Fig. (1). Structure of naturally occurring isoflavanones.

Table 1. Preliminary study on microwave-assisted isoflavanone formation reaction.[a]



1a **2a** **3a**

Entry	AuCN	$^{n}Bu_3P$	T (°C)	t (min)	C[b] (M)	Conversion (%)[c]	Yield (%)[c]	Selectivity (%)[c]
1	2%	10%	200	**10**	1.0	15.2	12.9	84.8
2	2%	10%	200	**20**	1.0	25.8	14.8	57.4
3	2%	10%	200	**30**	1.0	30.0	13.4	44.7
4	2%	10%	200	**40**	1.0	32.7	11.3	34.6
5	10%	20%	**150**	10	1.0	18.6	4.1	22.0
6	10%	20%	**175**	10	1.0	31.2	12.1	38.8
7	10%	20%	**200**	10	1.0	43.0	19.7	45.8
8	5%	25%	165	10	**0.1**	22.6	5.0	22.1
9	5%	25%	194	10	**0.5**	64.7	48.4	74.8
10	5%	25%	200	10	**1.0**	61.6	38.6	62.7
11	5%	25%	200	10	**2.0**	32.3	22.1	68.3
12[d]	5%	25%	150	1440	0.5	88.0	33.9	38.5

[a] Reaction conditions: CEM Discover microwave reactor, sealed vial, power = 200 Watts, hydroxyaldehyde (1.0 mmol), phenylacetylene (3.0 mmol), toluene (2 mL).
[b] Reaction mixture concentration.
[c] Determined by ^{1}H NMR using diethyl phthalate as an internal reference.
[d] Under thermal condition.

and mesitylene were examined in the model reaction between salicylaldehye **1a** and phenylacetylene **2a** to produce isoflavanone **3a** (Table **1**) under thermal conditions. The ^{1}H NMR signal from ethoxy ethlylene group in diethyl phthalate was δ4.52 ppm, and the product aliphatic protons (-CH_2CH-) showed signals at δ4.68 and δ4.00, respectively. The clear and distinct signal from diethyl phthalate made this compound a suitable internal NMR reference (5 μL, 2.5%). The yield, which is the percentage of desired product, was determined from the ratio of the isoflavanone methine peak (-CH-) at δ4.00 to the original aldehyde peak at δ 9.96. The reaction conversion, which measures how much of the starting material has reacted, was determined by measuring disappearance aldehyde of starting material. The reaction selectivity was the ratio of desired product to total products which was also determined from NMR spectra.

We then started to explore the optimal reaction conditions such as time, temperature, catalyst to ligand ratio and concentration. Under thermal conditions, this reaction required 24-48 hours at 150°C in toluene. Based on the time-temperature prediction chart [31], 1 h conventional heating at 150°C is equivalent to 2 min at 200°C under microwave irridiation. Therefore, this reaction was predicted to need 48-96 minutes in a microwave reactor. The microwave power was set to 200 W since toluene is non-polar and absorbs microwaves very poorly. The model reaction was run in the presence of 2% AuCN catalyst and 10% $^{n}Bu_3P$ ligand for 10, 20, 30 and 40 minutes (Table **1**, Entries 1-4). With increased reaction time, the conversion of the starting materials increased. However, the yield and selectivity for desired product decreased. Therefore, the optimal reaction time under microwave irradiation was set to 10 minutes.

Given the fact of the short reaction time and poor microwave absorbance solvent, it would be beneficial to increase the amount of gold catalyst since metal particles absorbs and transmits microwave very well. So for the next series of experiments, optimization of reaction temperature, the AuCN was increased to 10% and $^{n}Bu_3P$ ligand was increased to 20%. The model reaction was examined at the following temperatures: 150°C, 175°C and 200°C. As shown in Table **1** (Entries 5-7), with increased temperature, both reaction yields and selectivity increased.

During the optimization of time and temperature, we noticed the amount of gold catalyst and catalyst/ligand ($Au/^{n}Bu_3P$) ratio also played an important role on the reaction outcomes. Under thermal conditions, it was necessary to use a large amount of $^{n}Bu_3P$ ligand with a catalyst/ligand ratio of 1:25 in order to achieve good yields [20]. The $^{n}Bu_3P$ ligand is very toxic and is easily oxidized to tri-n-butylphosphine oxide in air. We systematically investigated the catalyst loading amount (2%, 5%, 7.5% and 10%) and $Au/^{n}Bu_3P$ ratio (1:1, 1:2, 1:3, 1:5, 1:10, 1:12.5 and 1:25) in an attempt to reduce the use of $^{n}Bu_3P$. It was found that the optimal conditions were 5% AuCN and 1:5 catalyst/ligand ratio. Too much $^{n}Bu_3P$ caused a significant decrease in the yield of the desired product. It is necessary to point out that in order to reach the 200°C reaction temperature, the amount of gold catalyst should be no less than 5 mg for 1 mL reaction mixture, since gold particles help to absorb and transmit the microwave energy to the reaction mixture. The $^{n}Bu_3P$ ligand should be less than 30%; otherwise too many side products were observed. Several experiments were then carried out in an attempt to identify the side products. When only salicylaldehyde, AuCN and $^{n}Bu_3P$ were subjected to microwave irradiation at 200°C for 10 min, only starting materials were recovered. On the other hand, when phenylacetylene, AuCN and $^{n}Bu_3P$ ligand were subjected to the same conditions, the phenylacetylene was consumed and an intractable black precipitate formed at the bottom of the reaction vial. This suggests the side products may come from polymerization of phenylacetylene, including tricyclization of phenylacetylene [32]. Polymeric side products are very typical for thermal reactions involving alkynes such as Bergman cyclization.

This reaction was further tested at different concentrations of hydroxyaldehyde: 0.1 M, 0.5 M, 1 M and 2 M in toluene (Table **1**, Entries 8-11). For reactions conducted at 0.1 M concentrations, the yields were typically between 5% and 20%. For 0.5 M reaction solutions, the yields ranged from 25% to 45%. Further increasing the concentration of the reaction mixture resulted in lower yields and decreased selectivity. In addition to the above conditions, a solventless reaction was also attempted under microwave irradiation. Unfortunately, the solventless reaction gave 12.0% yield and 21.7% selectivity, indicating a substantial degree of side reactions occurred. Thereore, the optimal concentration was 0.5 M. Compared to microwave-assisted reactions, similar reactions conducted under thermal conditions using the optimized conditions required 1 to 2 days and resulted in decreased selectivity (Table **1**, Entry 12).

After suitable choices of reaction temperature (200°C), time (10 min), concentration (0.5 M) and catalyst/ligand ratio (1:5) were identified for the annulation reaction under microwave irradiation, a variety of catalysts, ligands and solvents were screened. In addition to AuCN, other gold(I) and gold(III) catalysts, $KAu(CN)_2$, AuCl and $AuCl_3$, also catalyzed the annulation reaction of salicyaldehyde and phenylacetylene with reasonable yields (Table **2**, Entries 2 - 4). Microwave irradiation of a toluene solution of hydroxylaldehyde and phenylacetylene catalyzed by palladium or rhodium catalysts produced **3a** in yields less than 10% (Table **2**, Entry 5-6). Four phosphine ligands (Ph_3P, $^{t}Bu_3PH{\bullet}BF_4$, SPhos and XPhos) and one NHC ligand ($SIMesH{\bullet}BF_4$) were screened for this reaction. No reaction occurred in the presence of these ligands, and only starting materials were recovered in these experiments.

When chosing solvents, the first practical consideration is microwave power. Generally speaking, low power (50 W) is used for polar protic solvents with good microwave absorbance such as water and ethanol. Medium power (125 W) is used for polar solvents such as 1-methyl-2-pyrrilidone (NMP), *N, N*-dimethylformamide (DMF), acetonitrile, *etc*. High power is used for non-polar or weakly polar solvents. The second practical consideration is maximum temperature achievable for a solvent. For solvents unable to reach the annulation temperature, poor yields may be expected. There was no or little product observed when reactions were carried out in protic solvents such as water and ethanol or strongly polar solvents such as CH_3NO_2, CH_3CN and DMF. A control study using 2 equiv. of water showed that the presence of water prohibited the reaction. Also, if the toluene was not dried over CaH_2 before use, the reaction yield decreased about 10 ~ 15%. Other solvents such as *N*-methylpyrolidone (NMP), dimethylformamide (DMF), 1,4-dioxane, tetrahydrofuran (THF), CH_2Cl_2 and 1,2-dichlorobenzene gave low yields (Table **2**, Entries 7 - 10). Noticeably, the reaction conducted in 1,2-dichlorobenzene showed a high selectivity of 85.3% (Table **2**, Entry 11). Encouraged by this result, we subsequently tested the reaction in 1,2-dichlorobenzene at elevated temperature (Table **2**, Entry 12) in an attempt to increase the reaction yield. However, the yields didn't improve while the selectivity decreased dramatically to 43.6% (Table **2**, Entry 13). On the other hand, the highest selectivity of 97.2% was achieved when the temperature was reduced to 150°C (Table **2**, Entry 13). An attempt to increase the reaction yield by increasing the reaction time under such conditions was not successful. (Table **2**, Entry 14).

To summarize, the optimized reaction conditions for the gold-catalyzed annulation reaction of hydroxyaldehye and alkynes under microwave irradiation were 5% AuCN catalyst, 25% $^{n}Bu_3P$ ligand at 200°C for 10 min in toluene with a concentration of 0.5 M. These conditions were subsequently applied on a variety of salicylaldehydes and alkynes to test the substrate scope. A set of different aliphatic and aromatic alkynes were examined first in the microwave-assisted annulation reaction. All final compunds were purified through column chromtagraphy and micro-scale recrystallization using Craig tubes to ensure the purity was at least 95%. Isoflavanone compounds were not formed when aliphatic alkynes such as hex-1-yne and but-3-yn-1-ylbenzene were utilized, probably due to the poor coordination between aliphatic alkynes and gold(I) catalyst. When it came to heteroaryl aromatic alkynes, it was found that their reactivity

Table 2. Investigation on catalysts, ligands and reaction solvents of isoflavanone formation[a].

Entry	Catalyst	Solvent	Power[b] (W)	T (°C)	Conv. (%)[c]	Yield (%)[c]	Selec. (%)[c]
1	AuCN	Toluene	200	200	61.7	42.2	68.4
2	$KAu(CN)_2$	Toluene	200	200	38.0	20.7	53.8
3	AuCl	Toluene	200	200	35.4	18.7	52.8
4	$AuCl_3$	Toluene	200	200	39.4	25.9	65.7
5	$Pd(PPh_3)_4$	Toluene	200	200	93.7	4.0	4.3
6	$RhCl(PPh_3)_3$	Toluene	200	200	49.8	7.7	15.5
7	AuCN	NMP	44	200	32.5	9.0	27.7
8	AuCN	1,4-dioxane	200	174	61.7	7.3	11.8
9	AuCN	THF	200	165	41.8	21.3	50.8
10	AuCN	CH_2Cl_2	114	140	31.0	21.4	69.0
11	AuCN	1,2-dichlorobenzene	200	200	24.5	20.9	85.3
12	AuCN	1,2-dichlorobenzene	200	230	44.0	19.2	43.6
13	AuCN	1,2-dichlorobenzene	200	150	17.7	17.2	97.2
14[d]	AuCN	1,2-dichlorobenzene	200	150	76.9	36.7	47.7

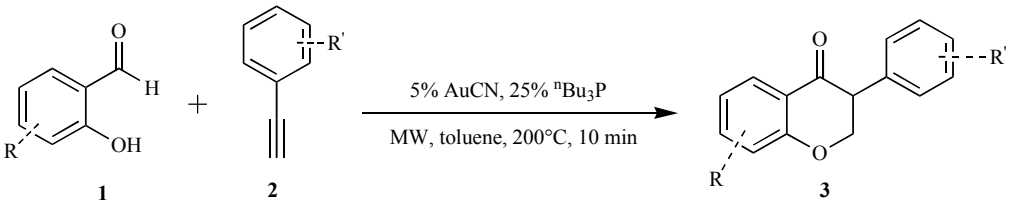
[a] Reaction conditions: hydroxyaldehyde (1.0 mmol), phenylacetylene (1.0 mmol), 5% catalyst and 25% $^nBu_3P$ under microwave irradiation for 10 minutes.

[b] Microwave irradiation power.

[c] Determined by ^1H NMR using diethyl phthalate as an internal reference.

[d] Reaction mixture was irradiated under microwave for 30 minutes.

Table 3. Microwave-assisted one-step synthesis of isoflavanone compounds[a].



1 **2** **3**

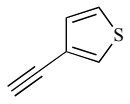
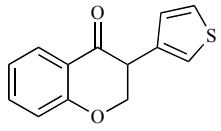
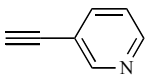
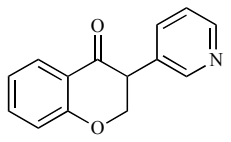
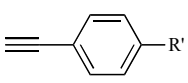
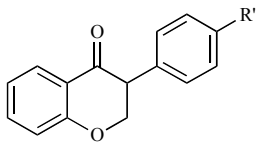
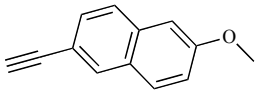
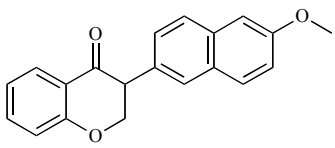
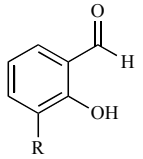
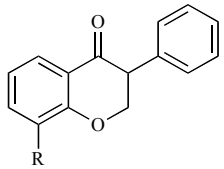
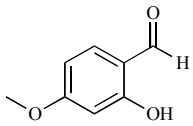
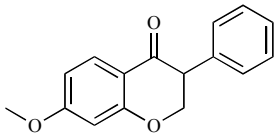
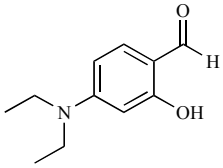
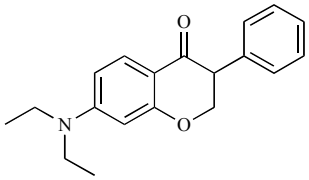
Aldehyde	Alkyne	Product		Yield (%)[b]	Purity (%)[c]
1a	 **2b**		**3b**	28.7	99.8
1a	 **2c**		**3c**	28.0	99.7
1a	 **2d-2g**		R'= **3d** OCH_3 **3e** CH_3 **3f** CF_3 **3g** F	36.5 28.7 19.6 8.3	99.5 99.4 97.5 99.5

Table 3. Contd……

Aldehyde	Alkyne	Product		Yield (%)[b]	Purity (%)[c]
1a	 **2h**		**3h**	47.7	97.7
 **1b -d**	**2a**		R = **3i** OCH_3 **3j** CH_3 **3k** F	43.7 31.4 21.5	94.5 98.9 99.2
 **1e**	**2a**		**3l**	32.5	97.7
 **1f**	**2a**		**3m**	13.0	98.9

[a] Reaction conditions: hydroxyaldehyde (1.0 mmol), phenylacetylene (3.0 mmol), 5% catalyst, 25% $^{n}Bu_3P$ under microwave irradiation at 200°C for 10 minutes.
[b] Isolated yield after column chromatography and micro-scale recrystallization.
c Purity established by HPLC.

depended on the substrate structures. 3-Ethynylthiophene **2b** reacted with **1a** to produce **3b** in 28.7% isolated yield and 99.8% HPLC purity. For *N*-heterocyclic compounds, 3-ethylnylpyridine **2c** reacted with **1a** to give isoflavanone **3c**, while 2-ethylnylpyridine and 5-ethynyl-1-methyl-1*H*-imidazole failed to produce the desired product. We are currently investigating alternative routes using palladium-catalyzed direct heteroarylation to prepare these compounds. For aryl alkynes with different substituents at the 4'-position, the results seemed to obey the Hammett relationship (Table **3**, compounds **3d-3g**). Specifically, the yields decreased when the functional groups changed from strong electron donating group CH_3O- to strong electron withdrawing group fluorine. This reaction was also active toward 2-ethynyl-6-methoxynaphthalene **2h** to produce compound **3h** in 47.7% yield. Finally, a selection of salicylaldehydes was investigated. The substituents at the hydroxyaldehyde C3 position might affect the reactivity in a trend related to the Hammett relation, as observed for compounds **3i**, **3j** and **3k**. In addition to the above salicylaldehydes, 4-ethynyl-*N,N*-dimethylaniline (**1f**) also reacted with phenylacetylene to give compounds **3m**. Therefore, this reaction is compatible with many functional groups such as methyl, methoxy, halides and amines.

The possibility of forming of gold-nano particles that may act as catalysts was excluded based on the complete homogeneity of the reaction. The literature reported mechanism for this reaction [20] includes the following steps: oxidative addition of the aldehyde C-H bond to form an acyl gold(III) hydride, hydrometalation with phenylacetylene to form an α,β-unsaturated ketone, addition of the hydroxy group in aldehyde to α,β-unsaturated ketone and reductive elimination to give the desired product. However, there was a contradiction between the above mechanism and other preceding mechanistic insights on gold catalyzed reactions. Due to the decreased electron-electron repulsion in the 5d orbitals, gold is a 'soft' transition metal and preferentially activating 'soft' electrophiles such as alkenes, alkynes, etc. Given the alkynophilicity of gold catalysts, it is hard to explain why the 'soft' gold catalyst preferentially reacts with a 'hard' aldehyde in the presence of a 'soft' alkyne. Also, the homogenous gold-catalyzed oxidation often requires the presence of an external oxidant [33-35]. Therefore, we propose that the intial step of this annulation reaction is the coordination between gold catalyst and alkyne substrate. To test this hypothesis, we carried out a series of experiments using isotope labeled compounds and NMR spectroscopy to monitor the reaction progress. The first experiment was performed with 1 equivalent salicylaldehyde, 0.5 equivalent of AuCN, 2.5 equivalent of $^{n}Bu_3P$ in Toluene-d8 using benzyl ether as internal reference compound. The mixture was heated at 150°C in pressure NMR tubes and ^{1}H and ^{13}C NMR spectra were taken at 10 minutes, 5, 16 and 24 hours during the heating process. The ^{1}H NMR signal for aldehyde group (9.96 ppm) didn't change in terms of chemical shift and intergral value. The second experiment was carried out subsequently under similar conditions except that phenylace-

tylene was used in instead of salicylaldehyde. Interestingly, one of the ^{13}C NMR signals from the alkyne group (83.8 ppm) gradually disappeared during the reaction. Corresondingly, a new signal appeared at 102.8 ppm and gradually increased (Fig. **2**). Comparison of these two experiments strongly suggested that gold(I) did not coordinate with salicylaldehyde; instead, it coordinated with phenylacetylene. To confirm this point, we performed a third experiment using 1 equivalent terminally deterium-labeld phenyacetylene, 0.5 equivalent of AuCN and 2.5 equivalent of $^{n}Bu_3P$. This experiment showed that the 83.8 ppm signal was a triplet due to the presence of deterium, therefore this signal was ascribed to the terminal carbon in phenylacetylene. While this triplet gradually disappeared during the reaction process, a new singlet at 102.2 ppm started to show up and its intensity gradually increased. The dramatic downfiled shift (18.4 ppm) indicated the build-up of an appreciable level of positive charge on the alkyne terminal carbon, which is in agreement with literature reported downfield shift (15-22 ppm) during organogold intermediate formation [36]. Therefore, these results provided direct evidence for our hypothesis that gold catalyst cooridinate to alkyne instead of aldehyde in the initial step of the catalyltic cycle. The investigation using on the following steps involved in the mechanism is currently ongoing in our lab.

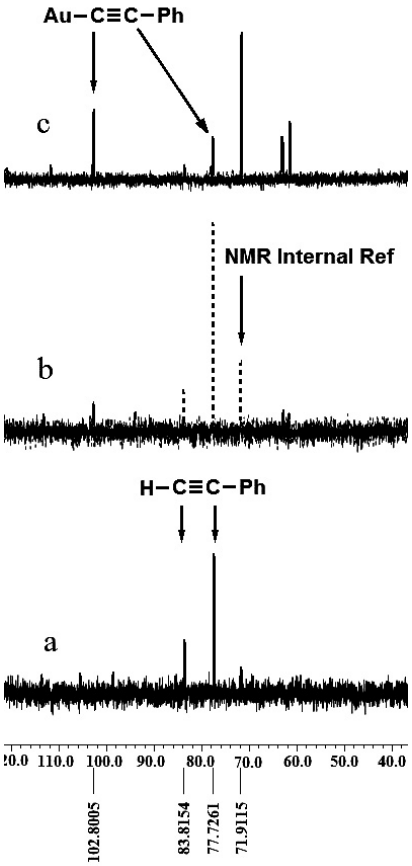


Fig. (2). ^{13}C NMR spectra. Reaction conditions: phenylacetylene (0.2 mmol, 20.4 mg), benzyl ether (internal NMR reference, 5.0 μL), $^{n}Bu_3P$ (0.5 mmol, 101.2 mg) and AuCN (0.1 mmol, 22.3 mg) in toluene-d8. **a**), r.t., 10 min; **b**), 150°C, 3 hours; **c)**, 150°C, 24 hours.

CONCLUSION

In conclusion, a rapid microwave-assisted gold(I)-catalyzed annulation reaction of hydroxyaldhehydes and alkynes to form isoflavanone compounds in one step was developed. The optimized reaction conditions under microwave irradiation was 5% AuCN, 25% $^{n}Bu_3P$, 200°C for 10 minutes. The solvent choice could be toluene or 1,2-dichlorobenzene. This reaction is compatible with a variety of functional groups on salicylaldehydes or aromatic alkynes such as alkoxyl, alkyl, halogen, amino, thiophenyl and pyridyl groups. The mechanistic investigation on this gold(I)-catalyzed annulation reaction is ongoing in our lab, but currently pointing to an initial coordination of the catalyst to the aryl alkyne.

EXPERIMENTAL

General

Reagents and solvents were obtained from Aldrich and used without further purification unless otherwise noted. Toluene was freshly distilled from CaH_2 prior to use. The microwave-assisted reactions were conducted on a single-mode Discover System from CEM Corporation. Power cooling was turned off manually during the reaction to ensure that the reaction temperature reached 200°C. Thin-layer chromatography was performed using precoated silica gel F254 plates (Whatman). Column chromatography was performed using pre-packed RediSep Rf Silica columns on a CombiFlash Rf Flash Chromatography system **(**Teledyne Isco). NMR spectra were obtained on a Joel 500 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) relative to the tetramethylsilane (TMS) signal at 0.00 ppm. Coupling constants, *J*, were reported in Hertz (Hz). The peak patterns were indicated as follows: s, singlet; d, doublet; t, triplet; dt, doublet of triplet; dd, doublet of doublet; m, multiplet; q, quartet. Analytical reverse-phase HPLC was carried out using a system consisting of a 1525 binary HPLC pump and 2996 photodiode array detector (Waters Corporation, Milford, MA). A Nova-Pak C18 column (4μm, 3.9 × 150 mm), also from Waters, was used with a mobile phase of methanol and water (60:40, vol./vol.) plus 0.25% acetic acid, flow rate 1.2 mL/min and UV detection wavelength at 250 nm. Control and data acquisition was done using the Empower 2 software (Waters Corporation, Milford, MA). Synthesized compounds were prepared in methanol to make 1.0 mg/mL stock solution and 10μL solution was injected for HPLC testing. The purity of all the compounds was assessed by HPLC at 254 nm. All final compounds were confirmed to be ≥ 95% purity by analysis of their peak area. Mass spectra were obtained on a Waters TQD Tandem Quadrapole Mass Spectrometer, and data was collected in electrospray positive mode (ESI+). High resolution mass spectra were recorded on a Micromass Q-TOF 2 or a Thermo Scientific LTQ-FT™ mass spectrometer operating in electrospray (ES) mode.

Typical Procedure for Microwave-Assisted Gold-Catalyzed Isoflavanone Synthesis

The microwave-assisted isoflavanone synthesis were conducted on a single-mode Discover System from CEM

Corporation. To an oven-dried standard microwave reaction vial (capacity 10 mL) equipped with a stirring bar was added AuCN (0.05 mmol, 0.05 equiv., 11.0 mg), $^{n}Bu_3P$(0.25 mmol, 0.25 equiv., 61.7 μL), aldehyde (1 mmol, 1 equiv.), alkyne (3 mmol, 3 equiv.), diethyl phthalate (5 μL, 2.5%, internal NMR reference), and 2 mL of freshly distilled toluene. The reaction vial was then sealed with a Teflon septum cap, and the sample was subjected to microwave irradiation at a power of 200 W for 10 min (hold time) at 200°C. After being cooled down, the vial was opened, and the crude mixture was loaded directly on silica gel and was purified by Medium Performance Liquid Chromatography eluting with an ethyl acetate/hexanes gradient to afford the desired products. To ensure ≥ 95% purity, products were further purified by microscale recrystallization using Craig tubes.

2-(4-Phenoxyphenyl)-2,3-dihydro-1H-benzo[f]chromen-1-one (3b) [7]. Synthesized from 2-hydroxy-1-naphthaldehyde (0.4 mmol, 1 equiv, 68.9 mg) and 1-ethynyl-4-phenoxybenzene (1.2 mmol, 3 equiv, 217 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. White solid. Yield: 35.1%.

6-Methoxy-3-(4-phenoxyphenyl)chroman-4-one (3c) [7]. Synthesized from 2-hydroxy-5-methoxybenzaldehyde (0.4 mmol, 1 equiv, 49.8 lL), and 1-ethynyl-4-phenoxybenzene (1.2 mmol, 3 equiv, 217.04 μL) according to the general procedure described above. Light yellow solid. Yield 36.3%.

3-(4-Methoxyphenyl)chroman-4-one (3d) [7]. Synthesized from salicylaldehyde (1 mmol, 1 equiv, 104.7 μL), and 4-ethynylanisole (3 mmol, 3 equiv, 389 μL) according to the general procedure described above. Yellow solid. Rf = 0.14 (10% EtOAc/Hex). Yield, 36.5%.

3-p-Tolylchroman-4-one (3e) [7]. Synthesized from salicylaldehyde (1 mmol, 1 equiv, 104.7 μL), and 4-ethynyltoluene (3 mmol, 3 equiv, 380.5 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Light yellow solid. Yield, 28.7%.

3-(4-(Trifluoromethyl)phenyl)chroman-4-one (3f) [6]. Synthesized from salicylaldehyde (1 mmol, 1 equiv, 104.7 μL), and 1-ethynyl-4-trifluoromethylbenzene (3 mmol, 3 equiv, 489.4 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Light yellow solid. Yield: 19.6%.

3-(4-Fluorophenyl)chroman-4-one (3g) [6]. Synthesized from 1-ethynyl-4-fluorobenzene (1 mmol, 1 equiv, 114.4 μL) and salicylaldehyde (3 mmol, 3 equiv, 314.2 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Yellow solid. Yield: 28.3%.

3-(6-methoxynaphthalen-2-yl)chroman-4-one (3h). Synthesized from 2-ethynyl-6-methoxy-naphthalene (1.5 mmol, 3 equiv., 273.3 mg) and salicylaldehyde (0.5 mmol, 1 equiv., 52.4 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Rf = 0.57 (10% EtOAc/Hex). Yield, 47.7%. Purity, 97.7%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 7.98 (d, J = 3.9 Hz, 1H), 7.70 (m, 4H), 7.53 (m, 2H), 7.25 (d, J = 0.9 Hz, 1H), 4.75 (t, J = 7.58 Hz, 2H), 4.21 (m, 1H), 3.92 (s, 3H), 1.55 (d, J = 0.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 192.4, 161.7, 157.9, 136.1, 134.1, 130.1, 129.4, 129.1, 127.9, 127.5, 126.9, 121.7, 119.2, 118.0, 105.7, 71.6, 55.4, 52.3. HRMS Calculated for $C_{20}H_{16}O_3Na$ [M+Na] 327.0997, found 327.0999.

8-Methoxy-3-phenylchroman-4-one (3i) [7]. Synthesized from o-vanillin (1 mmol, 1 equiv, 166 mg), and phenylacetylene (3 mmol, 3 equiv, 330 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Yellow solid. Yield, 43.7%.

8-Methyl-3-phenylchroman-4-one (3j) [7]. Synthesized from 2-hydroxy-3-methyl-benzaldehyde (1 mmol, 1 equiv, 120.0 μL) and phenylacetylene (3 mmol, 3 equiv, 330 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Yellow solid. Yield, 31.4%.

8-Fluoro-3-phenylchroman-4-one (3k) [6]. Synthesized from 3-fluorosalicylaldehyde (0.5 mmol, 1 equiv, 70.1 mg) and phenylacetylene (1.5 mmol, 3 equiv, 164.7 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Orange yellow solid. Yield: 21.5%.

7-Methoxy-3-phenylchroman-4-one (3l) [7]. Synthesized from 2-hydroxy-4-methoxybenzaldehyde (1 mmol, 1 equiv, 159.2 mg) and phenylacetylene (3 mmol, 3 equiv, 330 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Light yellow solid. Yield, 37.1%.

7-(diethylamino)-3-phenylchroman-4-one (3m). Synthesized from 4-(diethylamino)-salicylaldehyde (1 mmol, 1 equiv., 193 mg) and phenylacetylene (3 mmol, 3 equiv., 330 μL) according to the general procedure for the synthesis of isoflavanone derivatives described above. Rf = 0.18 (10% EtOAc/Hex). Yield, 13.0%. Purity, 98.9% ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 7.82 (d, J = 8.7 Hz, 1H), 7.25-7.31 (m, 6H), 6.37 (d, J = 7.8 Hz, 1H), 6.08 (s, 1H), 4.59 (m, AB of ABX, 2H), 3.85 (dd, X of ABX, J = 7.8, 5.0 Hz, 1H), 3.40 (q, J = 7.2 Hz, 4H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 190.0, 163.6, 153.8, 136.6, 129.7, 128.8, 128.7, 127.4, 110.1, 106.6, 96.6, 72.0, 52.0, 44.8, 12.7. HRMS Calculated for $C_{19}H_{21}NO_2Na$ [M+Na] 318.1470, found 318.1462.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This project was supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103436. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This study was also supported by Center for Integrated Science and Mathematics (CINSAM) and Northern Kentucky University Office of Research, Grants and Contracts Seed Grant. We thank Dr. Grant Edwards for his help with HPLC and

Dr. Isabelle Lagadic for the assistance with microwave reactor.

ABBREVIATIONS

DMF = *N, N*-dimethylformamide

HPLC = High Pressure Liquid Chromatography

MW = Microwave

NMP = methyl-2-pyrrilidone

NMR = Nuclear Magnetic Resonance

THF = tetrahydrofuran

REFERENCES

[1] Kanagalakshmi, K.; Premanathan, M.; Priyanka, R.; Hemalatha, B.; Vanangamudi, A. Synthesis, anticancer and antioxidant activities of 7-methoxyisoflavanone and 2,3-diarylchromanones. *Eur. J. Med. Chem.,* **2010**, *45* (6), 2447-52.

[2] Rajaonson, S.; Vandeputte, O.M.; Vereecke, D.; Kiendrebeogo, M.; Ralambofetra, E.; Stevigny, C.; Duez, P.; Rabemanantsoa, C.; Mol, A.; Diallo, B.; Baucher, M.; El Jaziri, M., Virulence quenching with a prenylated isoflavanone renders the Malagasy legume dalbergia pervillei resistant to Rhodococcus fascians. *Environ. Microbiol.,* **2011**, *13* (5), 1236-52.

[3] Umehara, K.; Nemoto, K.; Matsushita, A.; Terada, E.; Monthakantirat, O.; De-Eknamkul, W.; Miyase, T.; Warashina, T.; Degawa, M.; Noguchi, H. Flavonoids from the heartwood of the thai medicinal plant dalbergia parviflora and their effects on estrogenic-responsive human breast cancer cells. *J. Nat. Prod.,* **2009**, *72* (12), 2163-2168.

[4] Zhang, G.-P.; Xiao, Z.-Y.; Rafique, J.; Arfan, M.; Smith, P.J.; Lategan, C.A.; Hu, L.-H. Antiplasmodial isoflavanones from the roots of sophora mollis. *J. Nat. Prod.,* **2009**, *72* (7), 1265-1268.

[5] Ibrahim, A.R.; Abul-Hajj, Y.J. Aromatase inhibition by flavonoids. *J. Steroid Biochem. Mol. Biol.,* **1990**, *37* (2), 257-60.

[6] Amato, E.; Bankemper, T.; Kidney, R.; Do, T.; Onate, A.; Thowfeik, F.S.; Merino, E.J.; Paula, S.; Ma, L., Investigation of fluorinated and bifunctionalized 3-phenylchroman-4-one (isoflavanone) aromatase inhibitors. *Biorg. Med. Chem.,* **2014**, *22* (1), 126-34.

[7] Bonfield, K.; Amato, E.; Bankemper, T.; Agard, H.; Steller, J.; Keeler, J.M.; Roy, D.; McCallum, A.; Paula, S.; Ma, L. Development of a new class of aromatase inhibitors: Design, synthesis and inhibitory activity of 3-phenylchroman-4-one (isoflavanone) derivatives. *Bioorg. Med. Chem.,* **2012**, *20* (8), 2603-2613.

[8] Hirano, K.; Biju, A.T.; Piel, I.; Glorius, F. N-Heterocyclic carbene-catalyzed hydroacylation of unactivated double bonds. *J. Am. Chem. Soc.,* **2009**, *131* (40), 14190-14191.

[9] Vicario, J.L.; Badia, D.; Carrillo, L. An easy and straightforward approach to the asymmetric synthesis of isoflavanones. *Tetrahedron: Asymmetry.,* **2003**, *14* (4), 489-495.

[10] Park, J.Y.; Ullapu, P.R.; Choo, H.; Lee, J.K.; Min, S.-J.; Pae, A.N.; Kim, Y.; Baek, D.-J.; Cho, Y.S. TMSOTf-Promoted addition of alkynes to aldehydes: A novel synthesis of chroman-4-ones. *Eur. J. Org. Chem.,* **2008**, (32), 5461-5469.

[11] Simas, A.B.C.; Furtado, L.F.O.; Costa, P.R.R. 4-Chromenesulphones: synthesis and transformation to isoflavonoid models. *Tetrahedron. Lett.,* **2002**, *43* (39), 6893-6895.

[12] Deesamer, S.; Kokpol, U.; Chavasiri, W.; Douillard, S.; Peyrot, V.; Vidal, N.; Combes, S.; Finet, J.-P. Synthesis and biological evaluation of isoflavone analogues from *Dalbergia oliveri*. *Tetrahedron.* **2007**, *63* (52), 12986-12993.

[13] Valenti, P.; Belluti, F.; Rampa, A.; Bisi, A. A simple one-pot synthesis of isoflavanones. *Synth. Commun.,* **1999**, *29* (22), 3895-3899.

[14] Stachulski, A.V.; Berry, N.G.; Low, A.C.L.; Moores, S.L.; Row, E.; Warhurst, D.C.; Adagu, I.S.; Rossignol, J.-F. Identification of isoflavone derivatives as effective anticryptosporidial agents *in vitro* and *in vivo*. *J. Med. Chem.,* **2006**, *49* (4), 1450-1454.

[15] Vasquez-Martinez, Y.; Ohri, R.V.; Kenyon, V.; Holman, T.R.; Sepulveda-Boza, S. Structure-activity relationship studies of flavonoids as potent inhibitors of human platelet 12-hLO, reticulocyte 15-hLO-1, and prostate epithelial 15-hLO-2. *Biorg. Med. Chem.,* **2007**, *15* (23), 7408-25.

[16] Salakka, A.K.; Jokela, T.H.; Wahala, K. Multiple hydride reduction pathways in isoflavonoids. *Beilstein. J. Org. Chem.,* **2006**, *2*, 16.

[17] Goto, H.; Terao, Y.; Akai, S. Synthesis of various kinds of isoflavones, isoflavanes, and biphenyl-ketones and their 1,1-diphenyl-2-picrylhydrazyl radical-scavenging activities. *Chem. Pharm. Bull.* **2009**, *57* (4), 346-360.

[18] Wang, C.L.; Li, H.Q.; Meng, W.D.; Qing, F.L. Trifluoromethylation of flavonoids and anti-tumor activity of the trifluoromethylated flavonoid derivatives. *Bioorg. Med. Chem. Lett.,* **2005**, *15* (20), 4456-4458.

[19] Skouta, R.; Li, C.-J. Rapid syntheses of (±)-pterocarpans and isoflavones *via* the gold-catalyzed annulation of aldehydes and alkynes. *Tetrahedron. Lett.,* **2007**, *48* (47), 8343-8346.

[20] Skouta, R.; Li, C.J. Gold(I)-catalyzed annulation of salicylaldehydes and aryl acetylenes as an expedient route to isoflavanones. *Angew. Chem. Int. Ed.,* **2007**, *46* (7), 1117-9.

[21] Nolan, S.P. Catalytic gold rush. *Nature.* **2007**, *445*, 496-497.

[22] Widenhoefer, R.A. Recent developments in enantioselective gold(I) catalysis. *Chem. Eur. J.,* **2008**, *14* (18), 5382-91.

[23] Liu, X.-Y.; Li, C.-H.; Che, C.-M., Phosphine gold(I)-catalyzed hydroamination of alkenes under thermal and microwave-assisted conditions. *Org. Lett.,* **2006**, *8* (13), 2707-2710.

[24] Wang, M.-Z.; Wong, M.-K.; Che, C.-M., Gold(I)-catalyzed intermolecular hydroarylation of alkenes with indoles under thermal and microwave-assisted conditions. *Chem. Eur. J.,* **2008**, *14* (27), 8353-8364.

[25] Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. Synthesis of substituted 1,2-dihydroquinolines and quinolines from aromatic amines and alkynes by gold(I)-catalyzed tandem hydro-amination-hydroarylation under microwave-assisted conditions. *Org. Lett.,* **2007**, *9* (14), 2645-2648.

[26] Miranda, L.D.; Marrero, J.G.; Bautista, E.; Maldonado, E.; Ortega, A. Microwave-assisted gold(I) catalyzed pyran ring opening in brevifloralactone: synthesis of the hawtriwaic acid core. *Tetrahedron. Lett.,* **2009**, *50* (6), 633-635.

[27] Santagada, V.; Frecentese, F.; Perissutti, E.; Fiorino, F.; Severino, B.; Caliendo, G. Microwave assisted synthesis: A new technology in drug discovery. *Mini Rev Med Chem.,* **2009**, *9*, 340-358.

[28] Yılmaz, F.; Mentese, E. A rapid protocol for the synthesis of N-[2-(alkyl/aryl)-4-phenyl-1Himidazol-1-yl] benzamides *via* microwave technique. *Current Microwave Chemistry.,* **2014**, *1*, 47-51.

[29] Xia, Y.; Chen, L.-y.; Lv, S.; Sun, Z.; Wang, B. Microwave-assisted or Cu–NHC-catalyzed cycloaddition of azido-disubstituted alkynes: Bifurcation of reaction pathways. *J Org Chem.,* **2014**, *79* (20), 9818-9825.

[30] Malvacio, I.; Vera, M.A.; Moyano, E.L., Microwave assisted synthesis of ethyl-quinolon-4-one-3-carboxylates and hydrolysis to quinolon-4-one-3-carboxylic acids. *Current Microwave Chemistry.,* **2014**, *1*, 52-58.

[31] Prediction Chart, http://www.biotagepathfinder.com/texts.jsp?textName=prediction (Accessed on 6-10-2014).

[32] Anju, V.P.; Roy, D.K.; Anju, R.S.; Ghosh, S. Transition-metal variation as a probe into the catalytic activity of metallaboranes. *J. Organomet. Chem.,* **2013**, *733*, 79-81.

[33] Li, H.; Guan, B.; Wang, W.; Xing, D.; Fang, Z.; Wan, X.; Yang, L.; Shi, Z. Aerobic oxidation of alcohol in aqueous solution catalyzed by gold. *Tetrahedron.* **2007**, *63* (35), 8430-8434.

[34] Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. Highly selective aerobic oxidation of alcohol catalyzed by a gold(I) Complex with an Anionic Ligand. *J. Am. Chem. Soc.,* **2005**, *127* (51), 18004-18005.

[35] Zhang, G.; Cui, L.; Wang, Y.; Zhang, L., Homogeneous gold-catalyzed oxidative carboheterofunctionalization of alkenes. *J. Am. Chem. Soc.,* **2010**, *132* (5), 1474-1475.

[36] Seidel, G.; Lehmann, C.W.; Furstner, A. Elementary steps in gold catalysis: the significance of gem-diauration. *Angew. Chem.,* **2010**, *49* (45), 8466-70.

Received: October 30, 2014 Revised: December 13, 2014 Accepted: December 16, 2014