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Unprecedented Cu(I)-Catalyzed Microwave-Assisted Three-Component Coupling of a Ketone, an Alkyne, and a Primary Amine

Olga P. Pereshivko, Vsevolod A. Peshkov, and Erik V. Van der Eycken*

Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC),
Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F,
B-3001 Leuven, Belgium

erik.vandereycken@chem.kuleuven.be

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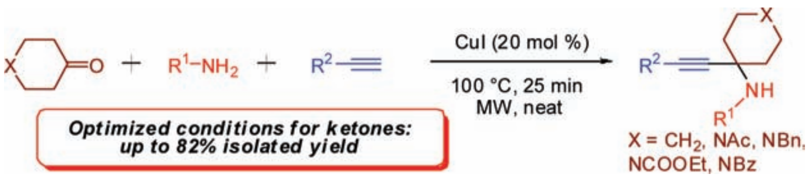
ABSTRACT



An efficient, microwave-assisted Cu(I)-catalyzed one-pot coupling of a ketone, an alkyne, and a primary amine (KA^2 coupling) is described, giving access to secondary propargylamines.

Propargylamines are widely used as intermediates for the synthesis of various nitrogen-containing biologically active compounds and natural products.[1] The three-component coupling of an aldehyde, an alkyne, and an amine, commonly called A^3 coupling, is a convenient and general approach to propargylamines.[2] The scope of this three-component reaction has been explored under various conditions.[3] Different examples of asymmetric variants have also been reported.[4] A tentative mechanism of the A^3 coupling involves C−H activation of the alkyne by a metal catalyst.[3b,d,f] The in situ generated metal acetylide reacts with the iminium ion arising from the aldehyde and the amine, resulting in the formation of the propargylamine with concomitant regeneration of the catalyst. The reaction of an imine[5] or an enamine[6] with an alkyne in the presence of a suitable catalyst leads to the same result. Moreover, the enantioselective addition of a terminal alkyne to an imine or enamine provides access to optically pure propargylamines.[5,7]

Despite the huge advancements, A^3-coupling reactions were mainly optimized for anilines and secondary amines resulting in the formation of *N*-arylpropargylamines or

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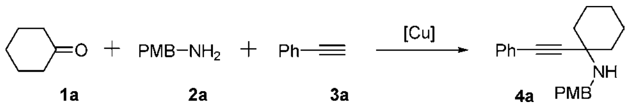
Table 1. Optimization of the KA^2-Coupling Conditions^a



entry	**1a/2a/3a** (mmol)	cat. (mol %)	time (min)	conditions	yield^b (%)
1	1:1.2:1.2	CuI (20)	25	neat, MW, 100 °C	51^c
2	1:1:1.2	CuI (20)	25	neat, MW, 100 °C	61
3	**1.2:1:1.2**	**CuI (20)**	**25**	**neat, MW, 100 °C**	**76**
4	1.2:1:1.2	CuI (20)	25	neat, MW, 80 °C	43
5	1.2:1:1.2	CuI (20)	25	neat, MW, 120 °C	62
6	1.2:1:1.2	CuI (20)	25	toluene, MW, 100 °C	54
7	1.2:1:1.2	CuI (20)	20h	toluene, conv, 100 °C	59
8	1.2:1:1.2	CuI (20)	15	neat, MW, 100 °C	54
9	1.2:1:1.2	CuI (10)	25	neat, MW, 100 °C	63
10	1.2:1:1.2	CuBr (20)	25	neat, MW, 100 °C	72

[a] When the reaction was run under microwave irradiation a maximum power of 80 W was used. [b] Isolated yields based on 4-methoxybenzylamine. [c] Isolated yield based on cyclohexanone.

tertiary propargylamines. Primary amines are considered as being difficult substrates thus, limiting access to secondary propargylamines.[8] However, these amines are potent synthetic intermediates for the synthesis of pyrroles,[9] quinolines,[10] and oxazolidinones.[11] Recently, we have reported an optimized protocol for the synthesis of secondary alkylpropargylamines via a microwave-assisted A^3-coupling reaction.[12] We were rather surprised to found that the aldehyde could be replaced by a ketone in this process, as to the best of our knowledge, there are no examples in the literature describing the application of ketones in the A^3 coupling. Herein, we report an unprecedented Cu(I)-catalyzed coupling of a ketone, an alkyne, and a primary amine. We will call this novel three-component reaction a KA^2 coupling.

The reaction conditions of the KA^2 coupling were optimized using cyclohexanone **1a**, 4-methoxybenzylamine **2a**, and phenylacetylene **3a** (Table 1). When a (1:1.2:1.2) mixture of the respective compounds together with 20 mol % of CuI catalyst was irradiated under solventless conditions at a ceiling temperature of 100 °C and a maximum power of 80 W for 25 min, the desired propargylamine **4a** could be isolated in 51% yield (Table 1, entry 1). Changing the relative amounts of the three components it was found that the optimal ratio was (1.2:1:1.2) providing the desired compound in 76% yield (Table 1, entries 1−3). A lower reaction temperature of 80 °C reduced the yield of the propargylamine **4a** to 43% (Table 1, entry 4), while increasing the temperature to 120 °C also resulted in a decreased yield of 62% due to the formation of several unidentified byproducts (Table 1, entry 5). Solventless conditions proved to be most suitable for the reaction as the use of toluene resulted in a substantially decreased yield of 54% (Table 1, entry 6). When the reaction in toluene was conducted under conventional heating at the same temperature, the desired propargylamine **4a** was obtained in a comparable moderate yield of 59% after an extended reaction time of 20 h (Table 1, entry 7). A shorter irradiation time of 15 min (Table 1, entry 8) or a diminished concentration of the CuI catalyst to 10 mol % (Table 1, entry 9) all resulted in lower yields. The application of CuBr instead of CuI delivered compound **4a** in a comparable yield (Table 1, entries 3 and 10).

The scope of the reaction was evaluated for various ketones, primary amines, and alkynes applying the optimal conditions (Table 1, entry 3). Both aromatic and aliphatic alkynes were explored as reaction partners, but the last afforded the target compounds **4e**,**f** only in low to moderate yields (Table 2, entries 5 and 6), even when 2 equiv of alkyne was used. To expand the scope of the protocol, a variety of primary amines was evaluated. All reactions seemed to be working well when 6-membered (hetero)cyclic ketones were used. When cyclohexanone (**1a**) was used, the desired compounds **4a**−**d**,**g**−**l** were obtained in 46−82% yield (Table 2, entries 1−4 and 7−12). When N-protected piperidinones **1b**−**e** were used, yields between 38% and 82% were obtained (Table 2, entries 13−16). 2-Methylcyclohexanone (**1f**) delivered the adducts **4q** (mixture of diastereomers (10:1)) in only 33% yield (Table 2, entry 17), clearly showing that sterical hindrance might play an important role for the yield of the reaction. The fact that 3-methylcyclohexanone (**1g**) is working well (Table 2, entry 18) confirms this conclusion. It seemed that also conformational factors are playing a crucial role in this process, as when cycloheptanone (**1h**) was used the yield dropped to 21% (Table 2, entry 19). It is probably that ketimines from 6-membered (hetero)cyclic ketones (see the mechanism bellow) are more accessible for

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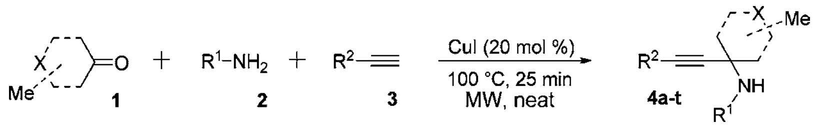
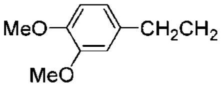
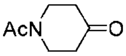
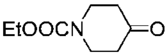
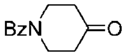
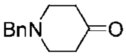
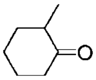
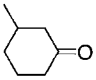
Table 2. Scope and limitations of the KA^2 Coupling[a]



entry	ketone	R^1	R^2	product	yield (%)[b]
1	Cyclohexanone (**1a**)	PMB (**2a**)	Ph (**3a**)	(**4a**)	76
2	Cyclohexanone (**1a**)	PMB (**2a**)	4-methoxyphenyl (**3b**)	(**4b**)	75
3	Cyclohexanone (**1a**)	PMB (**2a**)	3-fluorophenyl (**3c**)	(**4c**)	64
4	Cyclohexanone (**1a**)	PMB (**2a**)	thiophene-3-yl (**3d**)	(**4d**)	75
5	Cyclohexanone (**1a**)	PMB (**2a**)	Hexyl (**3e**)[c]	(**4e**)	31
6	Cyclohexanone (**1a**)	PMB (**2a**)	Cyclopropyl (**3f**)[c]	(**4f**)	48
7	Cyclohexanone (**1a**)	Hexyl (**2b**)	Ph (**3a**)	(**4g**)	61
8	Cyclohexanone (**1a**)	Cyclohepthyl (**2c**)	Ph (**3a**)	(**4h**)	46
9	Cyclohexanone (**1a**)	$MeOCH_2CH_2$ (**2d**)	Ph (**3a**)	(**4i**)	62
10	Cyclohexanone (**1a**)	 (**2e**)	Ph (**3a**)	(**4j**)	68
11	Cyclohexanone (**1a**)	3-clorobenzyl (**2f**)	*p*-tolyl (**3g**)	(**4k**)	82
12	Cyclohexanone (**1a**)	Bn (**2g**)	Ph (**3a**)	(**4l**)	74
13	 (**1b**)	PMB (**2a**)	Ph (**3a**)	(**4m**)	64
14	 (**1c**)	PMB (**2a**)	Ph (**3a**)	(**4n**)	82
15	 (**1d**)	PMB (**2a**)	Ph (**3a**)	(**4o**)	61
16	 (**1e**)	PMB (**2a**)	Ph (**3a**)	(**4p**)	38
17	 (**1f**)	PMB (**2a**)	Ph (**3a**)	(**4q**)	33 (10:1 dr)
18	 (**1g**)	PMB (**2a**)	Ph (**3a**)	(**4r**)	75 (3:1 dr)
19	Cycloheptanone (**1h**)	PMB (**2a**)	Ph (**3a**)	(**4s**)	21
20	Acetone (1i)	PMB (**2a**)	Ph (**3a**)	(**4t**)	30

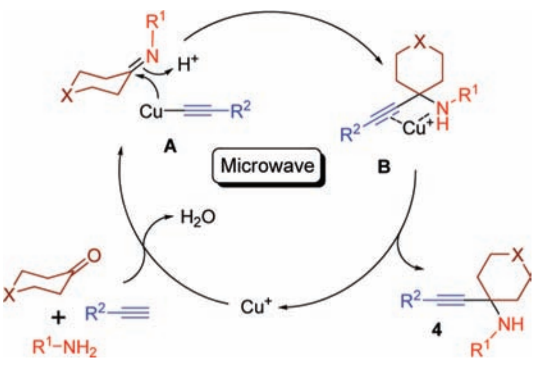
[a] A mixture of amine **1** (1.0 mmol), alkyne **2** (1.2 mmol), ketone **3** (1.2 mmol), and CuI (20 mol %) was irradiated at a ceiling temperature of 100 °C and a maximum power of 80 W for 25 min. [b] Isolated yields are reported. [c] 2 mmol of alkyne was used.

copper acetylide attack than imines from other ketones.[13] Remarkably, the reaction with acetone (**1i**) resulted in a low yield of 30% (Table 2, entry 20).

A tentative mechanism for the KA^2 coupling is proposed in Scheme 1. The copper catalyst reacts with the alkyne to form the copper acetylide. The in situ formed imine is attacked by the copper acetylide (transitions state **A**), resulting in the copper-complexed intermediate **B**. Decomplexation produces the free propargylamine **4** and regenerates the Cu(I) catalyst.

In conclusion, we have developed a novel Cu(I)-catalyzed, microwave-assisted, three-component coupling of a ketone, an alkyne, and a primary amine, called a KA^2-coupling reaction. The replacement of an aldehyde for a ketone in the A^3 coupling is unprecedented. Moreover, the application of primary amines, known to be difficult reaction partners for A^3-coupling reactions compared to secondary amines, results in the formation of synthetically useful secondary alkylpropargylamines. Therefore, this KA^2 coupling can be

Scheme 1. Proposed Mechanism for the KA^2 Coupling



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(13) For the addition of lithium acetylides and *n*-BuLi to six-membered ketimines, see: Ma, Y.; Lobkovsky, E.; Collum, D. B. *J. Org. Chem.* **2005**, *70*, 2335.

regarded as a welcome additional method for the generally applied A^3-coupling reaction.

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Supporting Information Available: Representative experimental procedure and characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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