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Microwave-Accelerated Coupling-Isomerization Reaction (MACIR) – A General Coupling-Isomerization Synthesis of 1,3-Diarylprop-2-en-1-ones

Oana G. Schramm (née Dediu)[a] and Thomas J. J. Müller[a,b,*]

[a] Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax: (+49)-6221-546-579; e-mail: Thomas.J.J.Mueller@oci.uni-heidelberg.de
[b] Present address: Institut für Organische Chemie und Makromolekulare Chemie der Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany
Fax: (+49)-211-84-14324; e-mail: ThomasJJ.Mueller@uni-duesseldorf.de

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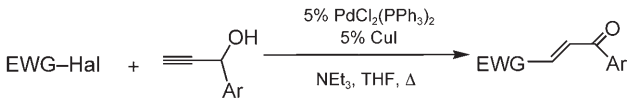
Abstract: The microwave-accelerated coupling-isomerization reaction (MACIR) of (hetero)aryl halides and propargyl alcohols represents a general Pd/Cu and base-catalyzed process for the synthesis of 3-arylprop-2-en-1-ones in good yields.

Keywords: alkynes; copper; cross-coupling; isomerization; palladium

The coupling-isomerization reaction[1] (CIR) of electron-deficient (hetero)aryl halides and (hetero)aryl propargyl alcohols under the conditions of the Sonogashira coupling[2] is a domino process[3] and furnishes 1,3-di(hetero)arylpropenones in good yields (Scheme 1). In recent years, this new chalcone synthesis has been elaborated into an entry to novel consecutive one-pot syntheses of pharmaceutically relevant heterocycles.[1,4] Mechanistically, the CIR proceeds as a rapid palladium/copper-catalyzed alkyne coupling followed by a rate-determining base-catalyzed propargyl alcohol to enone isomerization. Kinetic studies of the isomerization step show that the reaction proceeds fastest at a more than five-fold excess of amine base and in a dipolar aprotic medium.[5]

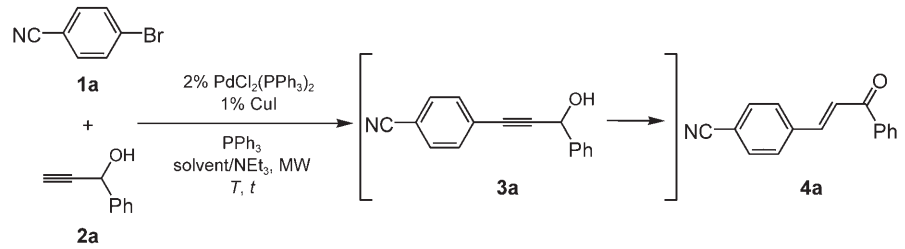


Scheme 1. Synthesis of electron-deficient chalcones by CIR.

Although the CIR is a mild and versatile synthesis of chalcones it has some inherent scope limitations and shortcomings under the conditions of conductive heating. Besides a limited choice of the reaction media, a relatively large excess of base, and long reaction times (16–24 h), most strikingly, the demand for an activating electron-deficient (hetero)aryl halide as a coupling partner is less advantageous. However, the advent of microwave acceleration of organic reactions has drastically reduced reaction times and has considerably improved and facilitated transformations classically performed by conductive heating.[6] Since Sonogashira alkynylations can be significantly accelerated by dielectric heating, i.e., under microwave irradiation,[6a,e,7] the inevitable of probing microwave-accelerated CIR (MACIR) should lead to an improved process. Here, we communicate the optimization and generalization of the CIR under microwave irradiation leading to the general MACIR synthesis of 3-arylprop-2-en-1-ones.

A suitable model reaction to optimize the MACIR is the reaction of *p*-bromobenzonitrile (**1a**) and 1-phenylpropyn-1-ol (**2a**) that has been thoroughly studied under conductive heating (Scheme 2).[5] After Sonogashira alkynylation, the intermediate propargyl alcohol **3a** is isomerized by triethylamine to furnish the chalcone **4a**. Therefore, parameters such as solvent, effective temperature in the reaction vessel, irradiation time, triphenylphosphane, triethylamine and substrates concentrations were varied and optimized (Table 1).

Kinetics of the model reaction under conventional heating revealed that, for the rate-limiting isomerization step, dipolar aprotic solvents such as acetonitrile and DMF give rise to fastest conversions and almost quantitative yields.[5] However, under dielectric heat-



Scheme 2. MACIR of *p*-bromobenzonitrile (**1a**) and 1-phenylpropyn-1-ol (**2a**).

Table 1. MACIR optimization experiments for the reaction of **1a** and **2a** with NEt_3 as a base.

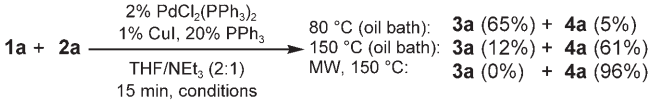
Entry	Solvent	PPh_3	c_0(**1a**) [mol/L][a]	$c(NEt_3)$ [mol/L][a]	T [°C]	t [min]	Yield of **4a**[b]
1	CH_3CN	none	0.5	1.5	120	60	63%
2	CH_3CN	none	1.4	4.3	120	60	61%
3	CH_3CN	none	0.5	2.5	150	60	52%
4	CH_3CN	none	0.77	3.8	150	60	44%
5	CH_3CN	none	0.5	2.5	150	20	58%
6	CH_3CN	none	0.5	2.5	120	40	52%
7	CH_3CN	none	0.33	1.7	120	60	66%
8	CH_3CN	none	0.33	3.3	120	60	67%
9	DMF	none	2.0	20.0	120	10	70%
10	DMF	none	2.0	20.0	120	20	73%
11	DMF	0.2 equivs.	1.0	2.6	150	10	87%
12	DMF	0.2 equivs.	0.5	2.6	150	5	87%
13	THF	none	1.0	2.5	150	30	62%
14	THF	none	1.0	5.0	150	30	84%
15	THF	0.2 equivs.	1.0	2.5	150	15	96%
16	THF	0.2 equivs.	1.0	2.5	150	20	92%
17	THF	0.2 equivs.	1.0	2.5	150	30	88%
18	THF	0.2 equivs.	1.0	2.5	150	45	79%
19	THF	0.2 equivs.	1.0	1.05[c]	150	5	85%

[a] Concentration in THF.
[b] Based upon isolated yields after standardized chromatography on silica gel.
[c] DBU as a base.

ing the yields in acetonitrile never exceeded 67% (entries 1–8). Increasing the effective temperature inside the reaction vessel from 120 to 150 °C led to decreased yields of **4a** (entries 3 and 4), whereas, a shorter reaction time at higher temperature gave comparable yields (entry 5). Interestingly, switching from acetonitrile to DMF and increasing the triethylamine concentration caused a considerable reduction of the reaction times to obtain slightly higher yields (entries 9 and 10). Upon adding 20 mol% of triphenylphosphane for stabilizing the palladium and copper species at the higher effective temperature[8] not only the triethylamine concentration was lowered by one order of magnitude but also the reaction times for complete conversion were reduced to 5 and 10 min resulting in significantly higher yields of **4a** (entries 11 and 12). Changing the solvent from a dipolar aprotic one to the weak microwave absorber THF gave rise to higher yields at 150 °C and 5.0 M triethylamine concentration (entry 14). However, as before the addition of 20 mol% of triphenylphosphane not only reduced the base concentration and the reaction times but also complete conversion and almost quantitative yields of **4a** were obtained (entry 15). Entries 15 to 18 also clearly show that prolonged reaction times at an effective temperature of 150 °C led to a decrease in the yields of **4a**. Further increases in the rate were achieved by increasing the base strength from triethylamine ($pK_b = 3.35$) to DBU ($pK_b = 1.1$) where not only the base concentration could be reduced to the stoichiometrically necessary amount of 1.05 equivs., but also a reaction time of 5 min for full conversion with 85% yield of **4a** was obtained (entry 19).

Although increased substrate concentration (by reduction of the solvent volume) generally enhance the reaction rates, it should be noted that, at higher concentrations, the chance for explosion of the reaction mixture rises. Since Pd and Cu catalysts are very strong microwave absorbers, higher catalyst concentrations might be critical.

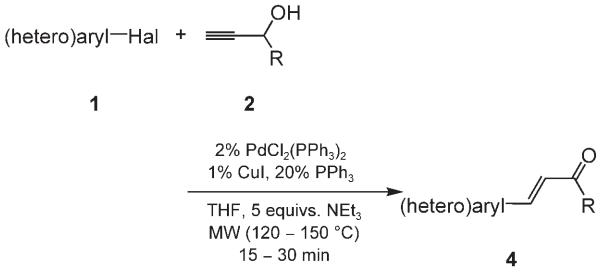
In comparison to conductive heating, MACIR shortens the reaction time for full conversion from 14 h to 15 min. The question arises of whether the reaction might have been affected by any kind of peculiar rate enhancing microwave effect. Such non-thermal effects were for a long time discussed in the literature.[9] Therefore, CIR were conducted for the model reaction (Scheme 3) under exactly similar conditions (15 min, THF/NEt_3 = 2:1, substrate concentrations of 1.0 M) using both conventional (reflux temperature at



Scheme 3. Conductive *vs.* dielectric heating for the reaction of **1a** and **2a**.

80 °C and 150 °C oil bath temperature) and microwave heating (effective temperature inside the vessel of 150 °C). As expected, the classical conventional CIR at 80 °C gives the predominant formation of the propargyl alcohol **3a** with only a minor amount of the chalcone **4a**. The direct comparison at 150 °C between conductive heating CIR and MACIR furnishes in the former case only 61 % of **4a** along with 12 % of **3a**, yet with incomplete conversion of **1a** and **2a**, whereas the latter microwave-accelerated process furnishes exclusively the chalcone **4a** in excellent yield. Therefore, the significant difference of the isolated yields can be attributed to the entirely thermal microwave effect[10] as a consequence of more efficient gradient-less energy transfer to the medium and the reactants, the so-called "molecular heating".

Based upon these findings the MACIR for electron-deficient (hetero)aryl halides **1** was probed for some representative examples (Scheme 4, Table 2).[11] For comparison, the results of CIR under conductive heating were included in Table 2.



Scheme 4. MACIR of (hetero)aryl halides **1** and propargyl alcohols **2**.

With the combination of high effective internal temperatures and short reaction times good to excellent yields (62–96 %) were obtained in 15 min. The yields of MACIR are comparable to those of conductive heating for 16–24 h in the most cases. Interesting-

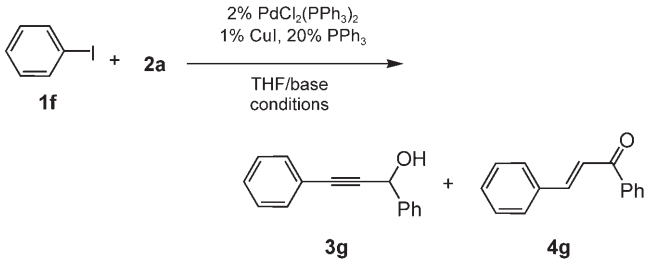
Table 2. MACIR of (hetero)aryl halides **1** and propargyl alcohols **2** (at an effective internal temperature of 150 °C, 15 min, 5 equivs. of NEt_3).

Entry	(Hetero)aryl halide **1**	Propargyl alcohol **2**	*T* [°C]	Product	Yield of **4**[a,b]
1	*p*-NCC_6H_4Br (**1a**)	R = Ph (**2a**)	150	**4a**	96 % (95 %)
2	2-pyrimidylBr (**1b**)	**2a**	120	**4b**	84 % (91 %)
3	2-pyridylBr (**1c**)	**2a**	150	**4c**	78 % (79 %)
4	*p*-$H_2NSO_2C_6H_4Br$ (**1d**)	**2a**	150	**4d**	62 % (31 %)
5	**1a**	R = 3-thienyl (**2b**)	150	**4e**	70 % (–)
6[c]	*p*-NCC_6H_4I (**1e**)	R = *n*-propyl (**2c**)	150	**4f**	62 % (0 %)

[a] Based upon isolated yields after chromatography on silica gel.
[b] The yields for conductive heating CIR (80 °C, 16-24 h) are given in parentheses.
[c] DBU as a base.

ly, the results are significantly better for sulfonamides under microwave irradiation (entry 5). An alkyl propargyl alcohol like 1-hexyn-3-ol (**2c**) is transformed to the enone in reasonable yield (entry 6). It is noteworthy that under conventional heating **2c** only gives rise to the formation of the coupling product but the isomerization does not occur.

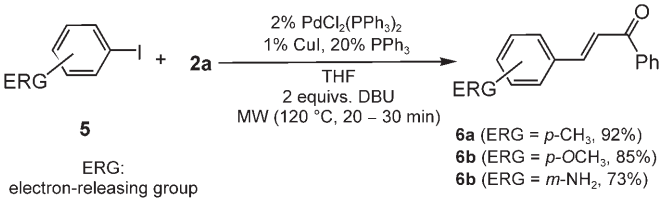
Encouraged by the general acceleration of CIR by dielectric heating we next scouted the possibility of applying electroneutral aryl halides such as iodobenzene (**1f**) under MACIR conditions (Scheme 5, Table 3). It is interesting to mention in advance that, under prolonged conventional heating at 80 °C, the reaction of **1f** and **2a** exclusively gives rise to the formation of the coupling product **3g** without any trace of the isomerization product **4g**.[1]



Scheme 5. CIR of iodobenzene (**1f**) and **2a** under dielectric and conductive heating.

Since the isomerization step is a base-catalyzed process, several amine bases of various pK_b were tested. For triethylamine as a base (pK_b = 3.35) the isolated yields were poor both for the coupling product **3g** and for the enone **4g** (entries 1 and 2). In the case of piperidine, a slightly stronger base (pK_b = 3.2) than triethylamine, the coupling product **3g** was formed at 100 °C in higher yield (entry 3). However, increasing the temperature led to extensive side reactions and only 9% of coupling product **3g** was obtained (entry 4). Using only 1.05 equivs. of DBU as a much stronger amine base (pK_b = 1.1), the reaction furnished 70% of **3g** and 8% of **4g** (entry 5). Therefore, increasing the amount of DBU to 2 equivs. gave rise to complete conversion of **1f** and **2a** to give a yield of 92% of the chalcone **4g** in 30 min at an effective internal temperature of 100 °C (entry 6). Applying the same parameters, however, under conductive heating in an oil bath, only 71% of **4g** were obtained (entry 7). As before, the difference in the isolated yields can be accounted to heating by gradient-less, efficient energy transfer to the reactants and the reaction medium.

Finally, we wanted to probe the generality of MACIR for even electron-rich aryl iodides. In three examples, iodobenzenes **5** bearing electron-releasing substituents were reacted with **2a** under MACIR conditions giving rise to the formation of the corresponding chalcones **6** in good to excellent yields (Scheme 6).



Scheme 6. MACIR of electron-rich iodobenzenes **5** and **2a**.

In conclusion, we have developed a general, rapid and efficient synthesis of enones based upon the microwave-assisted coupling-isomerization reaction (MACIR) of (hetero)aryl halides and propargyl alcohols. The enones were generally obtained in good to excellent yields and within 8–30 min. For electron-rich aryl iodides DBU is the most favorable base both for the coupling and the isomerization steps. This protocol under dielectric heating overcomes the limitation of CIR under conductive heating to use only electron-deficient (hetero)aryl halides. Further studies addressing the development of MACIR-based sequential and consecutive processes and the scope and limitations in the propargyl substrates are currently underway.

Table 3. MACIR and conductive CIR of iodobenzene (**1f**) and **2a**.

Entry	Base	Conditions	T [°C]	t [min]	Yield of **3g**[b]	Yield of **4g**[b]
1	NEt_3 (5 equivs.)	microwave	100	30	0%	35%
2	NEt_3 (5 equivs.)	microwave	120	20	30%	0%
3	piperidine (5 equivs.)	microwave	100	30	80%	0%
4	piperidine (5 equivs.)	microwave	150	30	9%	0%
5	DBU (1.05 equivs.)	microwave	100	60	70%	8%
6	**DBU (2 equivs.)**	**microwave**	**100**	**30**	**0%**	**92%**
7	DBU (2 equivs.)	oil bath	120	30	0%	71%

[a] Based upon isolated yields after standardized chromatography on silica gel.

Experimental Section

General Considerations

All reactions involving palladium-copper catalysis were performed in degassed oxygen-free solvents under a nitrogen atmosphere in sealed reaction vessels. All reactions involving microwave irradiation were conducted under nitrogen in heavy-walled glass Smith process vials sealed with aluminium crimp caps fitted with a silicon septum. The inner diameter of the vial filled to the height of 2 cm was 1.3 cm. The microwave heating was performed in a Smith Synthesizer single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden). Reaction mixtures were stirred with a magnetic stir bar during the irradiation. The temperature, pressure and irradiation power were monitored during the course of the reaction. The average pressure during the reaction was 3–4 bar. After completed irradiation, the reaction tube was cooled with high pressure air until the temperature had fallen below 39 °C (*ca.* 2 min). Halogen compounds **1**, $(Ph_3P)_2PdCl_2$, and CuI were purchased as reagent grade from ACROS, Aldrich, Fluka or Merck and used without further purification. Triethylamine, acetonitrile, DMF, and THF were dried and distilled according to standard procedures.[12] Propargyl alcohols **2** were prepared in analogy to literature procedures[13] by addition of ethynylmagnesium bromide to the corresponding aldehydes.

Column chromatography: silica gel 60 (Merck, Darmstadt), mesh 70–230. TLC: silica gel plates (60 F_{254} Merck, Darmstadt). Melting points (uncorrected values): Büchi Melting Point B-540. ^1H and ^{13}C NMR spectra: Bruker ARX 300, Varian VXR 400S $CDCl_3$, C_2D_6O and DMSO-d_6. The assignments of quaternary C, CH, CH_2 and CH_3 have been made by using DEPT spectra. IR: Perkin–Elmer Lambda 3. UV/vis: Perkin–Elmer Model Lambda 16. Fluorescence: Perkin–Elmer LS-55. MS: Finnigan MAT 90 and MAT 95 Q. Elemental analyses were carried out in the Microanalytical Laboratories of the Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg.

General Procedure for the CIR of Aryl Halides 1 with Propargyl Alcohols 2

A solution of 1.00 mmol of halogen compound **1** (or **5**), 1.05 mmol of propargyl alcohol **2**, 20 mg (0.02 mmol) of $(PPh_3)_2PdCl_2$, and 2 mg (0.01 mmol) of CuI in 2–5 equivs. of degassed base and 1.5 mL of THF under nitrogen was magnetically stirred in a heavy-walled SmithCreator process vial at the microwave generated temperature and for the time indicated (for experimental details see Table 3) in the microwave cavity. After cooling to room, aqueous work-up and extraction with ethyl acetate (4×15 mL), the combined organic phases were dried with magnesium sulfate. After filtration the solvents were removed under vacuum and the residue was chromatographed on silica gel (hexane/ethyl acetate, 4:1 or 1:1) and crystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure enones **4** or **6**, respectively.

Characterization data of the isolated compounds are given in the Supporting Information.

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