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Fischer indole synthesis of 3-benzyl-1*H*-indole *via* conductive and dielectric heating

Jesco Panther[1], Julian Rechmann[1], Thomas J. J. Müller[1]*

[1] *Institute of Organic and Macromolecular Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany; e-mail: ThomasJJ.Mueller@hhu.de*

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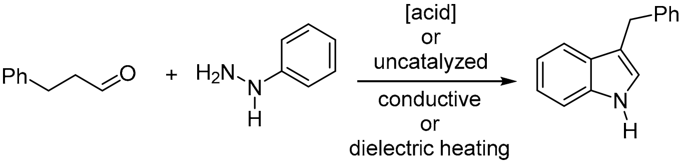


Fisher indole synthesis of 3-benzylindole

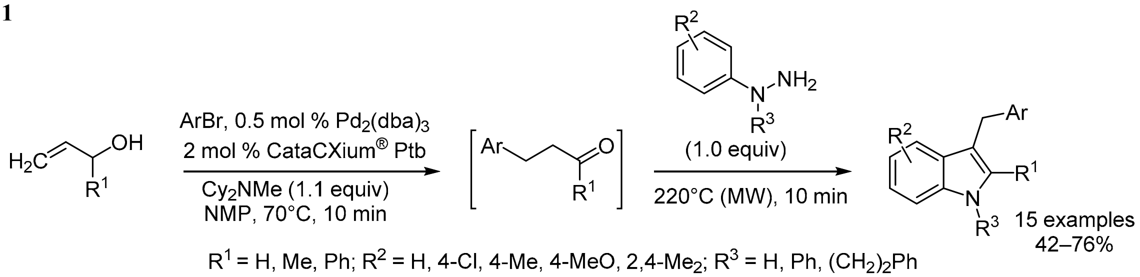
As a part of designing one-pot synthesis conditions for a combination of Heck isomerization and Fischer indolization (HIFI sequence), a model reaction was studied using 3-phenylpropanal and phenylhydrazine to furnish 3-benzyl-1*H*-indole under conductive and dielectric heating. While Amberlyst® 15 as an acidic catalyst or T3P® (propylphosphonic acid cyclic anhydride) as a condensation agent gave high yields of 3-benzyl-1*H*-indole under both conductive and dielectric heating, these agents were not compatible with the conditions of the initial Heck isomerization. However, the catalyst-free thermal process for the indolization step proceeded with good yields in conjunction with the preceding Heck isomerization in a one-pot process under dielectric heating in *N*-methylpyrrolidone as a solvent.

Keywords: indole, acid catalysis, condensation, Fischer indole synthesis, Heck isomerization, microwave-assisted reactions, one-pot reactions, thermal reactions.

The indole core is omnipresent in numerous naturally occurring and synthetic biologically active compounds, pharmaceutical ingredients,[1–6] and also in natural and synthetic dyes.[7] As a consequence, the development of indole syntheses has always remained an interesting synthetic task.[8–13] Undoubtedly, the classical Fischer indole synthesis[14–17] offers universal access to indoles by virtue of directly transforming ethanones as immediate structural precursors. The advent of transition metal catalysis within the concept of multicomponent syntheses of heterocycles, enabling modular, diversity-oriented synthetic strategies, has increasingly attracted attention over the past two decades.[18–20] Besides the pronounced practicability and efficiency, such domino, sequential, and consecutive multicomponent reactions (MCR) represent a reactivity-based concept[21] where reactive functionalities are created and transformed most efficiently in a one-pot fashion.[22–26] Eventually, MCR syntheses of indoles have become particularly interesting.[27]

In the course of our studies to develop novel MCR syntheses of heterocycles initiated by transition metal catalysis, using carbonyl derivatives as reactive intermediates,[28–31] and driven by our interest to develop diversity-oriented syntheses of functional chromophores,[32–35] we have discovered a novel consecutive three-component synthesis of intensively blue emissive 5-(3-indolyl)-oxazoles based on a one-pot concatenation of Sonogashira coupling, cycloisomerization, and concluding Fischer indole synthesis.[36] Just recently we reported a novel consecutive three-component one-pot synthesis of 3-arylmethyl-substituted indoles by a Heck isomerization–Fischer indolization (HIFI) sequence, starting from aryl bromides, allyl alcohols, and aryl hydrazines (Scheme 1).[37]

Scheme 1



The relevant intermediate enabling the terminal Fischer indolization step was a 3-aryl-1-oxopropyl derivative. Here we report in detail on the optimization of the Fischer indolization step with 3-benzyl-1*H*-indole as the model target compound. Our primary focus within this study is the comparative use of conductive and dielectric heating.

For the conception of the consecutive HIFI synthesis, we had to identify compatible conditions for all individual steps intended for the final one-pot procedure. Therefore, we reasoned that the terminal Fischer indole formation step could be studied by using the model reaction of 3-phenylpropanal (**1**) and phenylhydrazine (**2**) furnishing 3-benzyl-1*H*-indole (**3**) (Scheme 2).

First we set out to screen the conditions for acid catalysis. Brønsted and Lewis acids were previously identified to efficiently catalyze the Fischer indole synthesis, giving high yields of the desired indoles.[15] Brønsted acids that were successful in Fischer indolizations have ranged from strong acids (*p*-toluenesulfonic acid (PTSA),[38] polyphosphoric acid (PPA),[39] HCl,[40] H_2SO_4[41]), weak acids (acetic acid,[42] pyridinium chloride[43]), and acids on solid support (alumosilicates, such as bentonite clay K-10,[44] zeolite Y,[45] ion exchange resins, such as Amberlyst resins[46]). The Lewis acids previously used in these reactions include PCl_3,[47] $POCl_3$,[48] trimethylsilyl polyphosphate (PPSE),[49] $ZnCl_2$,[50] $Sc(OTf)_3$,[51] $Al(OTf)_3$,[51] $Y(OTf)_3$,[51] $Mg(OTf)_2$,[51] NaOTf,[51] Me_3OBF_4.[51] The reactions were monitored by TLC and the yields of 3-benzyl-1*H*-indole (**3**) were determined by gas chromatography with *n*-dodecane as a standard (Table 1). The screening was performed in closed vessels both for conductive heating in a preheated oil bath (Fig. 1, Table 2), as well as for dielectric heating in a microwave reactor (Fig. 2, Table 3), using THF and 1,4-dioxane as solvents. While the temperature range was screened between room temperature and 115°C for reactions in THF, higher temperatures could be used for 1,4-dioxane solutions under conductive heating. Under dielectric heating it was possible to perform superheating for both solvents uneventfully.

At the reaction temperature of 115°C in THF solution, Amberlyst® 15 as an acid catalyst on solid support gave the highest yields of 75% (conductive heating for 240 min) and 74% (dielectric heating for 30 min). Alumosilicates, such as bentonite clay K10 and zeolite Y, were not effective catalysts and, surprisingly, Lewis acidic catalysts also did not provide comparable yields neither in conductive nor dielectric heating experiments. Although Amberlyst® 15 turned out to be a superior catalyst system for Fischer indolization, the acidic conditions were not quite compatible with the preceding basic Heck reaction and only provided a 35–39% overall yield of 3-benzyl-1*H*-indole (**3**) in the one-pot sequence.[37]

Scheme 2

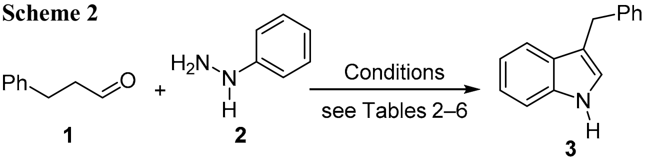


Table 1. Details of the calibration line for 3-benzyl-1*H*-indole (**3**)

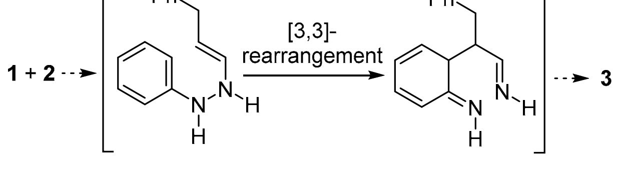
Integral for indole **3** (the average value)	Integral for *n*-dodecane (the average value)	Integral for indole **3** / integral for *n*-dodecane
0	502877	0.00
226674	503211	0.4504
465647	478737	0.9725
674866	471305	1.4322
938588	488278	1.9224
1107699	467122	2.3713

Recently, T3P® (propylphosphonic acid cyclic anhydride) was identified as a multifunctional agent in Fischer indolization, i.e., as a water scavenger in the hydrazone formation and then forming an acid to catalyze the [3,3]-sigmatropic diaza-Cope rearrangement.[52] Therefore, we screened T3P® as a condensation agent in conductive (Fig. 3, Table 4) and dielectric heating (Fig. 4, Table 5) experiments performed in THF and 1,4-dioxane.

For conductive heating experiments, the reaction temperature of 150°C and reaction time of 180 min in 1,4-dioxane turned out to give the highest yield of 3-benzyl-1*H*-indole (**3**). The presence of $Cy_2NMe{\cdot}HBr$ as a cocatalyst obviously slowed down the indole formation. Under dielectric heating conditions in both THF and 1,4-dioxane, the reaction temperature of 150°C and reaction times of 30 and 20 min were found to give almost identical high yields of 3-benzyl-1*H*-indole (**3**). Interestingly, neither a decrease nor increase of T3P® concentration could improve the yield of the indole under dielectric heating conditions. Also, increasing the concentration of aldehyde **1** and hydrazine **2** could not raise the yield of the indole **3**.

When probing the optimal conditions of indolization (150°C, microwave heating, 180 min) in the one-pot sequence,[37] only an 8% yield of 3-benzyl-1*H*-indole (**3**) was obtained. The general mechanism of the Fischer indolization suggested a [3,3]-sigmatropic rearrangement of an ene-hydrazinyl intermediate forming the carbon–carbon bond between the *ortho*-phenyl position and position 3 of the prospective indole in the sense of a diaza-Cope rearrangement (Scheme 3).[53] The purely thermal rearrangement of hydrazones to indoles[54,55] and aza-indoles[56] was shown to proceed at elevated temperatures (>170°C). Therefore, we rather preferred to switch to the uncatalyzed thermal process than to battle with the incompatibility of acidic catalysts with the ingredients of the preceding Heck reaction.

Scheme 3



Among higher-boiling solvents suitable for this reaction we quickly identified ethylene glycol and *N*-methyl-2-pyrrolidone (NMP). While the former only furnished

Table 2. Acid catalyst screening for conductive heating

Acid catalyst	Solvent	Temperature, °C	Time, min	Yield* of indole **3**, %
Glacial acetic acid (1.00 ml)	THF	100	465	1
0.5 M HCl (1.00 ml)	THF	100	960	46
1.0 M H_2SO_4 (0.76 mmol)	THF	70	180	34
$Cy_2NMe·HBr$ (553 mg, 2.00 mmol)	THF	100	65	–
Pyridinium chloride (115.6 mg, 1.00 mmol)	THF	70	1200	2
$POCl_3$ (277 mg, 1.81 mmol)	THF	rt	1020	20
PCl_3 (275 mg, 2.00 mmol)	THF	rt	60	18
$Sc(OTf)_3$ (50.7 mg, 0.10 mmol)	THF	85	1320	14
$Al(OTf)_3$ (48.4 mg, 0.10 mmol)	THF	85	1320	12
$Y(OTf)_3$ (63.9 mg, 0.10 mmol)	THF	85	1320	6
$Mg(OTf)_2$ (32.9 mg, 0.10 mmol)	THF	85	1320	2
NaOTf (17.6 mg, 0.10 mmol)	THF	85	1320	–
Bentonite clay K-10 (200 mg)	THF	70	1440	2
Amberlyst® 15 (300 mg)	THF	115	210	56
Amberlyst® 15 (300 mg)	THF	115	240	75
Amberlyst® 36 (300 mg)	THF	115	270	70
Amberlyst® 16 wet (300 mg)	THF	115	240	66
Amberlyst® 16 wet (300 mg)	THF	115	1260	70
PPSE (565 mg)	THF	85	20	51
Zeolite Y (300 mg)	THF	115	1200	34
Concd H_3PO_4 (1.50 ml)	1,4-Dioxane	100	210	16
PPA (870 mg)	1,4-Dioxane	130	120	68
PTSA (285 mg, 1.25 mmol)	1,4-Dioxane	150	60	32
$ZnCl_2$ (200 mg, 1.47 mmol)	1,4-Dioxane	130	90	36
Amberlyst® 15 (300 mg)	1,4-Dioxane	150	180	64
Amberlyst® 16 wet (300 mg)	1,4-Dioxane	150	180	42
Amberlyst® 15 (300 mg)	DMF	115	240	29

* The yield of product **3** was determined by GC analysis.

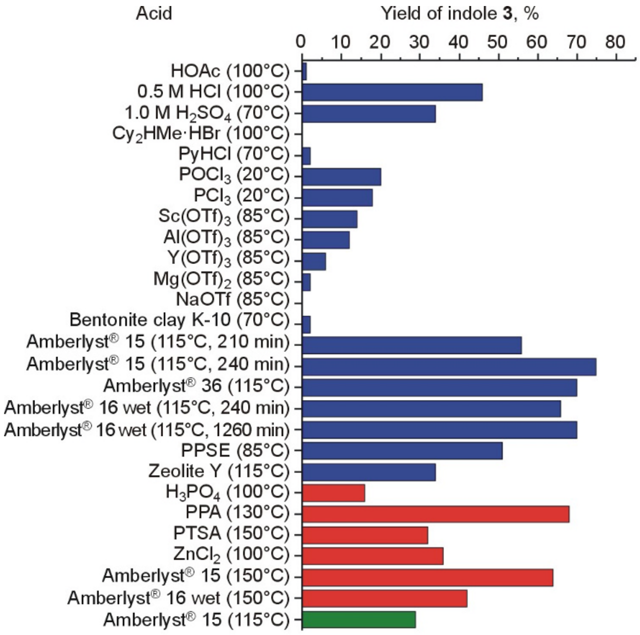


Figure 1. Acid catalyst screening in the synthesis of 3-benzyl-1*H*-indole (**3**) by conductive heating in THF (blue), 1,4-dioxane (red), or DMF (green) (c_0(**1**) = c_0(**2**) = 0.5 M).

Table 3. Acid catalyst screening for dielectric heating method

Acid catalyst	Solvent	Temperature, °C	Time, min	Yield* of indole **3**, %
1.0 M H_2SO_4 (0.76 mmol)	THF	100	15	41
$POCl_3$ (277 mg, 1.81 mmol)	THF	100	20	30
PCl_3 (280 mg, 2.00 mmol)	THF	100	10	42
$Me_3O·BF_4$ (152.5 mg, 1.00 mmol)	THF	150	30	35
Amberlyst® 15 (300 mg)	THF	115	30	74
Amberlyst® 15 (300 mg)	THF	150	57	28
Bentonite clay K-10 (200 mg)	THF	100	120	11
PTSA (285 mg, 1.25 mmol)	1,4-Dioxane	150	30	46

* The yield of product **3** was determined by GC analysis.

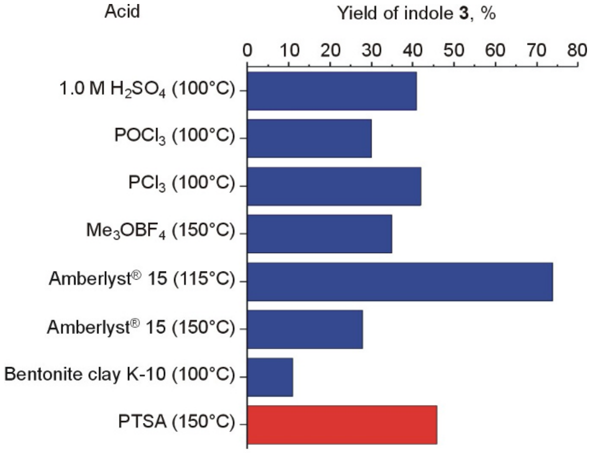


Figure 2. Acid catalyst screening in the synthesis of 3-benzyl-1*H*-indole (**3**) by dielectric heating in THF (blue) or 1,4-dioxane (red) (c_0(**1**) = c_0(**2**) = 0.5 M).

Table 4. Solvent screening for synthesis under conductive heating conditions, using T3P® as a condensation agent

Solvent	Temperature, °C	Time, min	Yield* of indole **3**, %
THF**	100	30	35
THF**	150	180	30
DMF***	150	180	24
1,4-Dioxane***	150	180	74
1,4-Dioxane***^{,*4}	150	180	43

* The yield of compound **3** was determined by GC analysis.
** T3P® was employed as 50 wt% solution in THF.
*** T3P® was employed as 50 wt% solution in toluene.
*⁴ $Cy_2NMe{\cdot}HBr$ (276 mg, 1.00 mmol) was added.

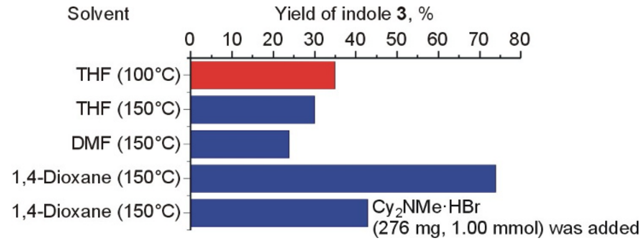


Figure 3. The temperature and solvent screening results in the synthesis of 3-benzyl-1*H*-indole (**3**) with T3P® as the condensation agent, using conductive heating in THF, 1,4-dioxane, and DMF after the reaction time of 30 min (red) and 180 min (blue) (c_0(**1**) = c_0(**2**) = 0.5 M).

Table 5. Screening the reaction conditions using dielectric heating with T3P® as a condensation agent

T3P®, mg (mmol)	Solvent	Temperature, °C	Time, min	Yield* of indole **3**, %
795 (1.25)**	THF	150	30	80
795 (1.25l)**	THF	150	60	28
636 (1.00)**	THF	150	30	59
955 (1.50)**	THF	150	30	75
1590 (2.50)**	THF	150	30	57
795 (1.25)**	THF***	150	30	14
795 (1.25)**^{,*4}	THF	150	30	55
795 (1.25)**^{,*5}	THF	150	10	46
795 (1.25)**^{,*5}	THF	150	20	53
795 (1.25)**^{,*5}	THF	150	30	56
795 (1.25)**^{,*5}	THF	150	60	57
795 (1.25)**^{,*6}	THF	150	10	73
795 (1.25)**^{,*6}	THF	150	20	75
795 (1.25)**^{,*6}	THF	150	30	44
795 (1.25)**	THF	165	10	62
795 (1.25)*⁷	1,4-Dioxane	180	10	79
795 (1.25)*⁷	1,4-Dioxane	180	20	82
795 (1.25)*⁷	1,4-Dioxane	180	30	50

* The yield of product **3** was determined by GC analysis.
** T3P® was employed as 50 wt% solution in THF.
*** Ethanol (1 ml) was added.
*⁴ The amount of phenylhydrazine (**2**) was 135 mg (1.25 mmol).
*⁵ The amount of phenylhydrazine (**2**) was 216 mg (2.00 mmol).
*⁶ The amount of 3-phenylpropanal (**1**) was 268 mg (2.00 mmol) and the amount of phenylhydrazine (**2**) was 216 mg (2.00 mmol).
*⁷ T3P® was employed as 50 wt% solution in PhMe.

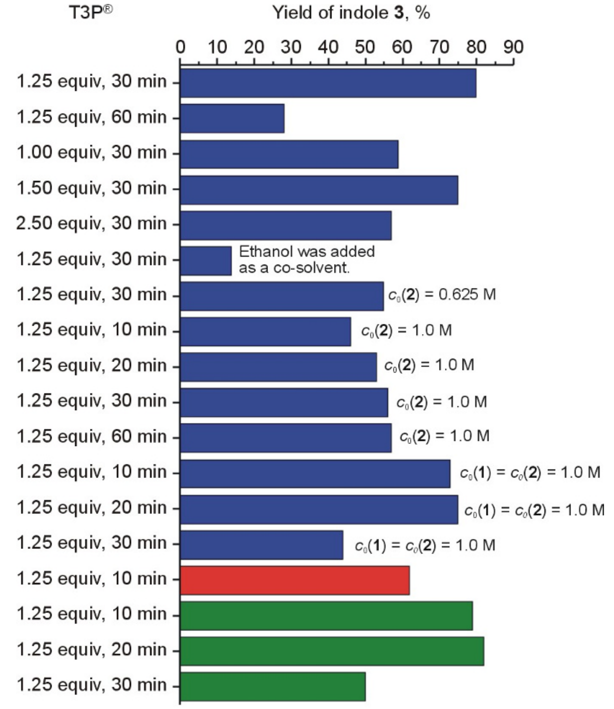


Figure 4. Screening the conditions for the synthesis of 3-benzyl-1*H*-indole (**3**) with T3P® as a condensation agent using dielectric heating at 150°C in THF (blue), 165°C in THF (red), and at 180°C in 1,4-dioxane (green) (c_0(**1**) = c_0(**2**) = 0.5 M).

31% yield of aldehyde **1** in the separate Heck reaction at 70°C in the microwave reactor, the latter turned out to be an excellent solvent giving 92% yield of aldehyde **1** with a minimum amount of NMP, so that the reaction could be performed at substrate concentrations of 2.0 M. Upon optimization of all parameters of the Heck step in NMP, 96% yield of the aldehyde **1** was obtained after 10 min microwave irradiation at 70°C, setting the stage for concatenating the indolization under thermal conditions with dielectric heating.

Therefore, as a model reaction for optimizing the terminal Fischer indolization step in the HIFI sequence,[37] bromobenzene (**4**) and allyl alcohol (**5**) were reacted in the presence of a palladium catalyst and Cy_2NMe in NMP in the microwave reactor at 70°C for 10 min, furnishing 3-phenylpropanal (**1**) that was subsequently treated with phenylhydrazine (**2**) in the microwave reactor for various duration at various temperatures to furnish 3-benzyl-1*H*-indole (**3**) (Scheme 4, Fig. 5, Table 6).

While a reaction temperature of 180°C did not prove to be sufficient for the indolization and only the hydrazone could be detected, maintaining the reaction mixture at temperatures between 200 and 240°C caused the formation of indole **3**. Performing the reaction at the maximum power of the microwave reactor (300 W), however, caused an automatic shutdown after 24 s due to rapid pressure increase in the vial. The optimal reaction temperature was identified to be 220°C for the duration of 15 min. With these parameters, the HIFI sequence was ultimately methodologically developed.

The optimization of Fischer indolization conditions for efficient concatenation into a one-pot sequence was started

Scheme 4

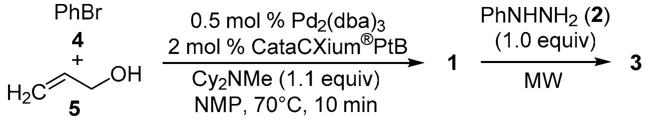


Table 6. Optimization of dielectric heating temperature and duration in the indolization step

Temperature, °C	Time, min	Yield* of indole **3**, %
180	15	0**
200	15	37
200	30	28
220	5	50
220	10	49
220	10	50***
220	15	53
220	30	43
240	15	46
P_{max}	(5)	35*4

* The yield of product **3** was determined by GC analysis.

** Only the hydrazone was formed.

*** Phenylhydrazine hydrochloride (**2·HCl**) was employed (145 mg, 1.00 mmol).

*4 The reaction was performed at the maximum power of the microwave reactor (300 W), however, the experiment was automatically shut down after 24 s due to a rapid increase of pressure in the vial.

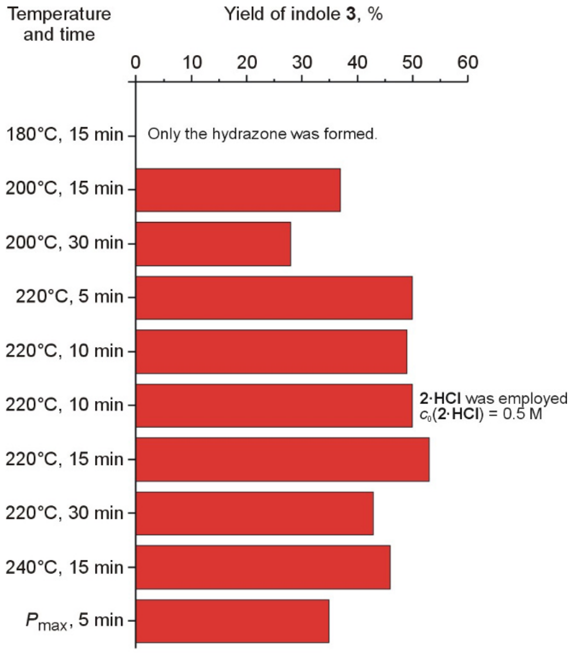


Figure 5. Optimization of the microwave-assisted Fischer indolization step in the one-pot HIFI synthesis of 3-benzyl-1*H*-indole (**3**) (c_0(**4**) = c_0(**5**) = c_0(**2**) = 0.5 M).

by testing acid-catalyzed (Amberlyst® 15) and condensation agent-mediated (T3P®) procedures, using THF and 1,4-dioxane as solvents, both under conductive and dielectric heating. The immediate advantages of dielectric heating are considerably shorter reaction times at comparable temperatures, presumably due to the more efficient gradientless energy transfer into the reaction vessel. However these conditions failed in the context of the rather basic conditions of the preceding Heck isomerization step. Nevertheless, switching to NMP as a high-boiling solvent enabled higher reaction temperatures under microwave heating and thereby circumvented the problems caused by acid catalysts used for triggering the [3,3]-sigmatropic diaza-Cope rearrangement. Again, the advantage of dielectric heating was in the rapid energy input, thereby overcoming high activation barriers.

Experimental

IR spectrum was recorded on a Shimadzu IRAffinity-1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra (300 and 75 MHz, respectively) were acquired on a Bruker Avance III-300 instrument in $CDCl_3$. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer. Elemental analysis was performed on a Perkin Elmer Series II Analyzer 2400. The melting point of indole **3** was determined on a Reichert Thermovar apparatus.

3-Phenylpropanal (**1**) was obtained by a modified Heck reaction[37] of bromobenzene (**4**) and allyl alcohol (**5**) as yellowish oil, with ^1H NMR spectra in full agreement with the literature.[57] 3-Benzyl-1*H*-indole (**3**) was isolated from the reaction mixtures by chromatography and purified by sublimation to give a colorless solid with spectroscopic data in full agreement with the literature.[58] Phenylhydrazine (**2**) and phenylhydrazine hydrochloride (**2·HCl**) were purchased from Sigma-Aldrich and used without further purification.

3-Phenylpropanal (1). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.66–2.74 (2H, m, 2-CH_2); 2.88 (2H, t, *J* = 7.3, 3-CH_2); 7.09–7.25 (5H, m, H Ph); 9.74 (1H, t, *J* = 1.4, CHO).

3-Benzyl-1*H*-indole (3). Colorless solid, mp 102°C (mp 101–102°C[59]). IR spectrum (film), ν, cm^{-1}: 692, 748, 808, 853, 907, 935, 974, 1036, 1088, 1109, 1148, 1179, 1192, 1227, 1265, 1314, 1368, 1391, 1454, 1497, 1603, 1653, 1717, 2858, 2905, 2934, 2980, 3026. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.04 (2H, s, CH_2); 6.81 (1H, m, CH); 6.97–7.29 (9H, m, H Ph, H Ar); 7.83 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 31.7 (CH_2); 111.2 (CH); 115.9 (C_{quat}); 119.3 (CH); 119.5 (CH); 122.3 (CH); 122.5 (CH); 126.0 (CH); 127.6 (C_{quat}); 128.4 (CH); 128.5 (CH); 128.8 (CH); 129.1 (CH); 136.6 (C_{quat}); 141.3 (C_{quat}). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 207 $[M]^+$ (100), 206 $[M–H]^+$ (78), 130 $[M–C_6H_5]^+$ (90), 91 $[C_7H_7]^+$ (24), 77 $[C_6H_5]^+$ (13). Found, %: C 86.66; H 6.43; N 6.99. $C_{15}H_{13}N$. Calculated, %: C 86.92; H 6.32; N 7.76.

Gas chromatographic calibration of the yields of 3-benzyl-1*H*-indole (3). Gas chromatography was performed on a Shimadzu GC-2012 instrument, using a DB-5 column. 3-Benzyl-1*H*-indole (**3**) was identified by its retention time (RT) and its content was quantified by a calibration line determined from the integrals of various defined amounts of 3-benzyl-1*H*-indole (**3**) relative to *n*-dodecane as a standard (Table 1, Fig. 6).

The conditions were as follows:

Complete measurement time: 25 min, initial temperature: 50°C (0 min), end temperature 250°C (25 min, linear slope);

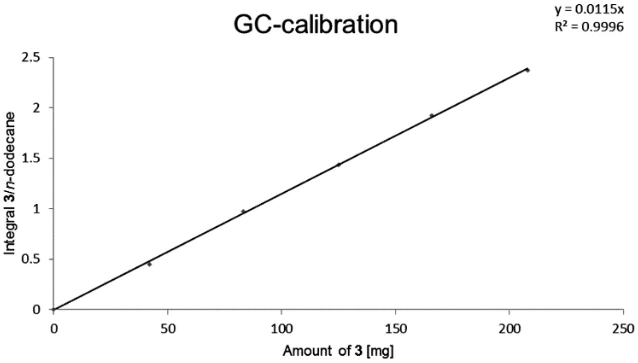


Figure 6. Calibration line for determining the yield of 3-benzyl-1*H*-indole (**3**).

RT (**1**) = 9.08 min, RT (**2**) = 9.40 min, RT (*n*-dodecane) = = 9.57 min, RT (**3**) = 20.43 min, RT (hydrazone) = = 20.59 min.

Acid catalyst screening for the synthesis of 3-benzyl-1*H*-indole (3) under conductive heating conditions.

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{\text{THF, 1,4-dioxane, or DMF}\\ \text{rt–150°C, 20–1440 min}}]{\text{[acid catalyst]}} \mathbf{3}$$

In a flame-dried Schlenk tube, the acid catalyst was placed in the solvent (2 ml) under nitrogen (Table 2). Then 3-phenylpropanal (**1**) (134 mg, 1.00 mmol) and phenylhydrazine (**2**) (108 mg, 1.00 mmol) were added. The reaction vessel was placed in a preheated oil bath at various temperatures for the time indicated, until the hydrazone formed from starting materials **1** and **2** was completely consumed or no further reaction could be detected (monitored by TLC, hexane–ethyl acetate, 5:1). For determining the yield after the end of reaction, *n*-dodecane (100 μl) was added as a standard. A 20 μl aliquot of the reaction mixture was filtered with THF (1.5 ml) through a short plug of silica gel (ca. 4×15 mm) into a GC vial and subjected to gas chromatography to determine the yield of 3-benzyl-1*H*-indole (**3**).

Acid catalyst screening for the synthesis of 3-benzyl-1*H*-indole (3) under dielectric heating conditions.

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{\text{THF or 1,4-dioxane}\\ \text{MW, 100–150°C, 10–120 min}}]{\text{[acid catalyst]}} \mathbf{3}$$

In a microwave vial (10 ml), the acid catalyst was placed in the solvent (2 ml) under nitrogen atmosphere (Table 3). Then 3-phenylpropanal (**1**) (134 mg, 1.00 mmol) and phenylhydrazine (**2**) (108 mg, 1.00 mmol) were added. The microwave vial was placed in the microwave reactor at various temperatures for the times indicated until the hydrazone formed from starting materials **1** and **2** was completely consumed or no further reaction could be detected (monitored by TLC, hexane–ethyl acetate, 5:1). For determining the yield after the end of reaction, *n*-dodecane (100 μl) was added as a standard. A 20 μl aliquot of the reaction mixture was filtered with THF (1.5 ml) through a short plug of silica gel (ca. 4×15 mm) into a GC vial and subjected to gas chromatography to determine the yield of 3-benzyl-1*H*-indole (**3**).

Temperature and solvent screening for the synthesis of 3-benzyl-1*H*-indole (3) with T3P® as a condensation agent under conductive heating conditions.

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{\text{THF, DMF, or 1,4-dioxane}\\ \text{100–150°C, 30–180 min}}]{\text{T3P® (1.25 equiv)}} \mathbf{3}$$

In a flame-dried Schlenk tube, solution of T3P® (795 mg, 1.25 mmol) in the appropriate solvent and a portion of pure solvent (2 ml) were placed under nitrogen atmosphere (Table 4). Then 3-phenylpropanal (**1**) (134 mg, 1.00 mmol) and phenylhydrazine (**2**) (108 mg, 1.00 mmol) were added. The reaction vessel was placed in a preheated oil bath at various temperatures for the time indicated, until the hydrazone formed from starting materials **1** and **2** was completely consumed or no further reaction could be detected (monitored by TLC, hexane–ethyl acetate, 5:1). For determining the yield after the end of the reaction, *n*-dodecane (100 μl) was added as a standard. A 20-μl aliquot of the reaction mixture was filtered with THF (1.5 ml) through a short plug of silica gel (ca. 4×15 mm) into a GC vial and subjected to gas chromatography to determine the yield of 3-benzyl-1*H*-indole (**3**).

Screening the conditions of 3-benzyl-1*H*-indole (3) synthesis with T3P® as a condensation agent under dielectric heating conditions.

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{\text{THF or 1,4-dioxane}\\ \text{MW, 150–180°C, 10–60 min}}]{\text{T3P® (1.00–2.50 equiv)}} \mathbf{3}$$

In a microwave vial (10 ml), a solution of T3P® in the appropriate solvent and a portion of pure solvent (2 ml) were placed under nitrogen atmosphere (for experimental details see Table 5). Then, 3-phenylpropanal (**1**) (134 mg, 1.00 mmol) and phenylhydrazine (**2**) (108 mg, 1.00 mmol) were added. The microwave vial was placed in the microwave reactor at various temperatures for the times indicated until the hydrazone formed from starting materials **1** and **2** was completely consumed or no further reaction could be detected (monitored by TLC, hexane–ethyl acetate, 5:1). For determining the yield after end of reaction, *n*-dodecane (100 μl) was added as a standard. A 20-μl aliquot of the reaction mixture was filtered with THF (1.5 ml) through a short plug of silica gel (ca. 4×15 mm) into a GC vial and analyzed by gas chromatography to determine the yield of 3-benzyl-1*H*-indole (**3**).

The optimization of dielectric heating temperature and duration in the indolization step.

$$\mathbf{4} + \mathbf{5} \xrightarrow[\substack{\text{Cy}_2\text{NMe (1.10 equiv)}\\ \text{NMP, 70°C, 10 min}}]{\substack{\text{0.5 mol \% Pd}_2\text{(dba)}_3\\ \text{2 mol \% CataCXium®PtB}}} \mathbf{1} \xrightarrow[\substack{\text{MW, 180–240°C}\\ \text{5–30 min}}]{\mathbf{2}\text{ (1.00 equiv)}} \mathbf{3}$$

A microwave vial (10 ml) was charged with $Pd_2(dba)_3$ (4.58 mg, 0.05 mmol), CataCXium®PtB (5.80 mg, 0.02 mmol), bromobenzene (**4**) (158 mg, 1.00 mmol), allyl alcohol (**5**) (65 mg, 1.1 mmol), Cy_2NMe (215 mg, 1.10 mmol), and NMP (0.5 ml) and filled with nitrogen.

The microwave vial was placed in the microwave reactor and the vial was irradiated at 70°C temperature for 10 min. After cooling to room temperature, phenylhydrazine (**2**) (216 mg, 1.00 mmol) was added, the microwave vial was placed again in the microwave reactor at various temperatures for the times indicated (Table 6). For determining the yield after cooling to room temperature, *n*-dodecane (100 μl) was added as a GC standard. A 20 μl of the reaction mixture was filtered with THF (1.5 ml) through a short plug of silica gel (ca. 4 × 15 mm) into a GC vial and analyzed by gas chromatography to determine the yield of 3-benzyl-1*H*-indole (**3**).

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References

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. Netz, N.; Opatz, T. *Mar. Drugs* **2015**, *13*, 4814.
3. Aygün, A.; Pindur, U. *Curr. Med. Chem.* **2003**, *10*, 1113.
4. Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442.
5. Schmidt, A. M.; Eilbracht, P. *J. Org. Chem.* **2005**, *70*, 5528.
6. Johansson, H.; Bøgeløv Jørgensen, T.; Gloriam, D. E.; Bräuner-Osborne, H.; Pedersen, D. S. *RSC Adv.* **2013**, *3*, 945.
7. Meredith, P.; Riesz, J. *Photochem. Photobiol.* **2004**, *79*, 211.
8. Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153.
9. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
10. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.
11. Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.
12. Gribble, G. W. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 1045.
13. Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195.
14. Robinson, B. *Chem. Rev.* **1969**, *69*, 227.
15. Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.
16. Przheval'skii, N. M.; Kostromina, L. Yu.; Grandberg, I. I. *Chem. Heterocycl. Compd.* **1988**, *24*, 709. [*Khim. Geterotsikl. Soedin.* **1988**, 867.]
17. Simoneau, C. A.; Ganem, B. *Tetrahedron* **2005**, *61*, 11374.
18. D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.
19. Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.
20. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.
21. Müller, T. J. J. In *Multicomponent Reactions 1. General Discussion and Reactions Involving a Carbonyl Compound as Electrophilic Component*, *Science of Synthesis Series*; Müller, T. J. J., Ed.; Georg Thieme Verlag KG: Stuttgart, 2014, p. 5.
22. Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.
23. Tietze, L. F.; Beifuss, U. *Angew. Chem.*, *Int. Ed. Engl.* **1993**, *32*, 131.
24. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
25. Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
26. Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948.
27. Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.
28. Müller, T. J. J. *Top. Heterocycl. Chem.* **2010**, *25*, 25.
29. Willy, B.; Müller, T. J. J. *Curr. Org. Chem.* **2009**, *13*, 1777.
30. Willy, B.; Müller, T. J. J. *ARKIVOC* **2008**, (i), 195.
31. Müller, T. J. J. *Targets Heterocycl. Syst.* **2006**, *10*, 54.
32. Levi, L.; Müller, T. J. J. *Eur. J. Org. Chem.* **2016**, 2902.
33. Levi, L.; Müller, T. J. J. *Chem. Soc. Rev.* **2016**, *45*, 2825.
34. Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609.
35. Müller, T. J. J. In *Functional Organic Materials. Syntheses*, *Strategies*, *and Applications*; Müller, T. J. J.; Bunz, U. H. F., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2007, p. 179.
36. Grotkopp, O.; Ahmad, A.; Frank, W.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 8130.
37. Panther, J.; Müller, T. J. J. *Synthesis* **2016**, *48*, 974.
38. Murakami, Y.; Yokoyama, Y.; Miura, T.; Hirasawa, H.; Kamimura, Y.; Izaki, M. *Heterocycles* **1984**, *22*, 1211.
39. Guy, A.; Guette, J. P. *Synthesis* **1980**, 222.
40. Ishii, H.; Murakami, Y.; Watanabe, T.; Suzuki, H.; Maejima, H. *Chem. Pharm. Bull.* **1983**, *31*, 4401.
41. Chen, C.-Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738.
42. Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215.
43. Welch, W. M. *Synthesis* **1977**, 645.
44. Penieres, G.; Miranda, R.; García, J.; Aceves, J.; Delgado, F. *Heterocycl. Commun.* **1996**, *2*, 401.
45. Kunkeler, P. J.; Rigutto, M. S.; Downing, R. S.; de Vries, H. J. A.; van Bekkum, H. In *Progress in Zeolite and Microporous Materials Studies in Surface Science and Catalysis*; Chon, H.; Ihm, S.-K.; Uh, Y. S., Eds.; Elsevier Science B. V., 1997, Vol. 105, p. 1269.
46. Duvala, R. A.; Lever, J. R. *Green Chem.* **2010**, *12*, 304.
47. Baccolini, G.; Marotta, E. *Tetrahedron* **1985**, *41*, 4615.
48. Baccolini, G.; Todesco, P. E. *J. Chem. Soc.*, *Perkin Trans. 1* **1983**, 535.
49. Yamamoto, K.; Watanabe, H. *Chem. Lett.* **1982**, 1225.
50. Hernández Franco, L.; Palermo, J. A. *Chem. Pharm. Bull.* **2003**, *51*, 975.
51. Prochazka, M. P.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 651.
52. Desroses, M.; Wieckowski, K.; Stevens, M.; Odell, L. R. *Tetrahedron Lett.* **2011**, *52*, 4417.
53. Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 827.
54. Fitzpatrick, J. T.; Hiser, R. D. *J. Org. Chem.* **1957**, *22*, 1703.
55. Kelly, A. H.; McLeod, D. H.; Parrick, J. *Can. J. Chem.* **1965**, *43*, 296.
56. Crooks, P. A.; Robinson, B. *Can. J. Chem.* **1969**, *47*, 2061.
57. Jeffery, T. *J. Chem. Soc.*, *Chem. Commun.* **1984**, 1287.
58. Angelovski, G.; Keränen, M. D.; Linnepe, P.; Grudzielanek, S.; Eilbracht, P. *Adv. Synth. Catal.* **2006**, *348*, 1193.