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Rapid and General Protocol towards Catalyst-Free Friedel–Crafts *C*-Alkylation of Indoles in Water Assisted by Microwave Irradiation

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An efficient and simplified protocol for uncatalyzed Friedel–Crafts alkylation of indoles using microwave irradiation in water is described. A series of functionalized indole derivatives has been synthesized in very short times with moderate to good yields. The combination of microwave irradiation and superheated water offers significant advantages over conventional methods, such as higher selectivities, simplicity, shorter reaction times, and no need for a catalyst.

Introduction

The indole framework, identified as *privileged structure*,[1] is a structural motif observed in various natural products possessing different biological activities and in complex molecules with numerous applications, such as pharmaceuticals and agrochemicals.[2] Among the various methods for the introduction of functionalized alkyl frameworks at the 3-position of the indolyl core, Lewis and Brønsted acid promoted Friedel–Crafts reactions (FC)[3] play a prominent role. The classical Friedel–Crafts reaction suffers from relevant drawbacks, such as chemical aspects (reactivity and selectivity), environmental concerns associated with the use of poorly manageable catalysts and the release of large amounts of environmentally hazardous wastes, this also combined with indole's susceptibility to strong acid catalysts. These disadvantages have encouraged the development of numerous reaction variants with an ever increasing attention to cleaner and environmentally more friendly strategies.[4]

Water-mediated reactions have attracted much attention in organic synthesis in recent years,[5] not only because water offers practical advantages over organic solvents from economical, environmental and safety standpoints, but also because reactions in aqueous media display reactivities and selectivities different from those in conventional organic solvents, and in many cases they exceed those in organic solvents. Historically, the inability to perform the Friedel–Crafts reaction under basic and even neutral aqueous conditions is reported,[3,6d] since water, as a strong nucleophile, could immediately trap the S_N1 reaction intermediate and thus annihilate the chance of π nucleophiles to intercept the transient carbocation.

Interesting advances in this field were made by Mayr et al.[6] It was found that the alkylation reactions between alkyl halides and π nucleophiles, such as indole, are possible in water, a solvent considered prohibitive for such reactions, without the use of any catalyst. The indole can compete with the solvent system by trapping the intermediate carbocation, provided that the nucleophilicity of the reaction intermediate is higher than that of the solvent system.[6] However, the method is not general and is limited by the ionization rates of the corresponding alkyl halides – this has been often reported for benzhydrylium and 4-methoxybenzyl cations (classical carbocations present in the Mayr's list).[6]

Over the past years, the combination of water as reaction medium with microwave irradiation as a nonclassical energy source has been recognized as a viable environmentally friendly alternative. The interest in this field is evidenced by the increasing number of related publications and reviews, which emerged in recent years.[7] The efficiency of microwave irradiation with dramatically reduced reaction times and increased product yields as well as selectivity improvement is one of the key features of this approach, in addition to the advantages of conducting organic reactions in water. Furthermore, under microwave (M.W.) irradiation water is rapidly heated to high temperatures (>100 °C, "superheated conditions") enabling its behavior as a pseudo-organic solvent with favorable physical and chemical property changes.

Based on the above reports and expecting beneficial microwave effects according to the reaction mechanism and the polarity change of the system during the reaction progress, we envisioned the possibility of using a combination of microwave irradiation and superheated water as an op-

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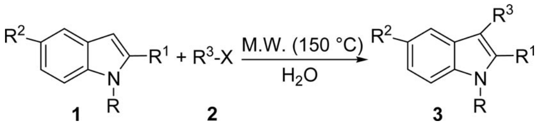
portunity to improve the Friedel–Crafts alkylation reaction of indoles with different S_N1-reactive benzyl halides, both in terms of generality and efficiency (Scheme 1).



Scheme 1. Catalyst-free microwave-promoted Friedel–Crafts alkylation of indoles with benzyl halides in water.

Bringing these two areas (chemistry in water and microwave irradiation) together offers several advantages such as higher selectivities, simplicity, shorter reaction times, and no need to use a catalyst.

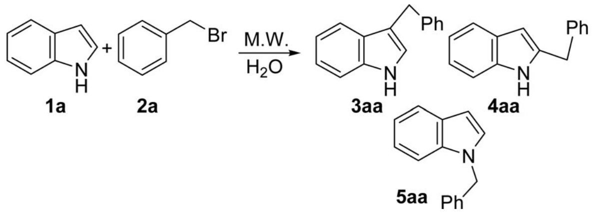
Results and Discussion

Initially, we examined the Friedel–Crafts alkylation of indole (**1a**) with benzyl bromide (**2a**) in water without any catalyst. Preliminary experiments were carried out both under microwave irradiation and under conventional conditions. When the reaction was run at room temperature (Mayr's conditions),[6f] it provided no conversion of starting material, even after prolonged time (12 h), but instead yielded side products, such as benzyl alcohol as a result of alkyl halide hydrolysis in aqueous medium (Table 1, Entry 1). However, upon increasing the reaction temperature to reflux conditions (Table 1, Entry 2), we were able to obtain the product in moderate yield, but with a low discrimination between the *N*-alkylated product (25% yield) and the *C*-alkylated product (37% yield). Interestingly, improved yields and selectivities were obtained by the microwave-assisted procedure within only a few minutes. The reaction was performed in sealed microwave tubes under microwave irradiation by using a CEM Discover single mode reactor (Table 1, Entry 3). Moreover, under microwave irradiation the reaction was clean and proceeded with increased regioselectivity: the *N*-alkylation product was detected in the crude mixture only in very low yield, and the *C*-alkylation occurred with high selectivity at position 3 of the indole.

Prompted by this result, a series of experiments was performed under microwave irradiation at various reaction times, temperatures and power settings aimed to optimize the reaction conditions. Raising the reaction temperature from 150 °C to 170 °C had no effect on the yield (Table 1, Entry 4), whereas temperatures below 150 °C decreased noticeably the reaction efficiency (Table 1, Entries 5, 6). Similarly, running the reaction for a shorter time led to a lower conversion (Table 1, Entries 3, 7, 8). As shown in Table 1, the best yield of adduct **3aa** was achieved at 150 °C in 8 min (Table 1, Entry 3) with an irradiation power of $P = 200$ W.

In order to investigate the role of water, the reaction was performed neat under the optimized reaction conditions. Under these conditions, only a trace amount of product **3aa** was found with many side products. The influence of different molar ratios of substrate/alkyl halide and reaction

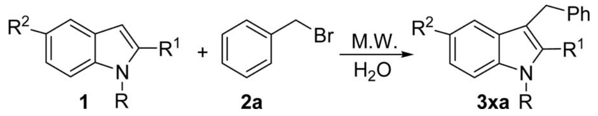
Table 1. Microwave-enhanced Friedel–Crafts alkylation of indole (**1a**) with benzyl bromide (**2a**).



Entry[a]	Time [min]	T [°C]	Yield of **3aa** + **4aa** (%)[b]	Selectivity C-3/C-2	Yield of **5aa** (%)[b]
1[c]	720	r.t.	–	–	–
2[d]	720	reflux	37	98:2	25
3	8	150	68	94:6	10
4	8	170	67	87:13	10
5	8	130	51	94:6	9
6	8	110	28	100:0	8
7	4	150	32	94:6	2
8	6	150	52	90:10	2
9	10	150	62	94:6	6
10[e]	10	150	59	92:8	5
11[d]	16	150	15	98:2	5

[a] Reaction conditions: indole (0.6 mmol) and benzyl chloride (0.5 mmol) in water (1 mL) were irradiated in a monomode microwave reactor ($P = 200$ W). [b] Based on the isolated yield of pure product **3aa** after column chromatography. [c] Reaction performed under Mayr's conditions as reported in ref.[6f] [d] Reaction performed using conventional heating with an oil bath. [e] The reaction mixture was irradiated at $P = 125$ W.

Table 2. Microwave-enhanced Friedel–Crafts alkylation reactions of indoles **1** with benzyl bromide (**2a**).



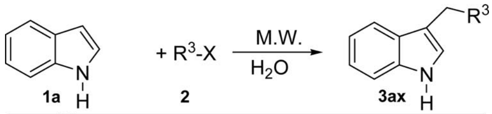
Entry[a]	R	R¹	R²	Product	Yield (%)[b,d]	Ratio C-3/C-2[c]
1	H	H	H	**3aa**	68	94:6
2	H	Me	H	**3ba**	88	–
3	Me	H	H	**3ca**	61	–
4	Me	Me	H	**3da**	78	–
5	H	H	Me	**3ea**	55	98:2
6	H	H	OMe	**3fa**	69	100:0
7	H	Me	OMe	**3ga**	72	–
8	H	H	Br	**3ha**	65	95:5
9	H	Me	Cl	**3ia**	81	–
10	H	H	CN	**3ja**	46	93:7
11 (3-Me-indole)	H	–	H	**3ka**	62	–

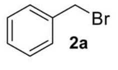
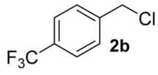
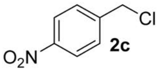
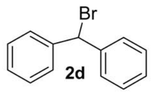
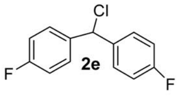
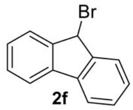
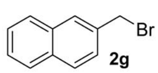
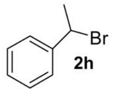
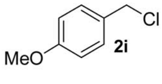
[a] All the reactions were conducted on a 0.5 mmol scale under microwave-irradiation conditions: $P = 200$ W, $T = 150$ °C, reaction time = 8 min. [b] Isolated yield after column chromatography. [c] The ratio was determined by ^{1}H NMR peak integration of the crude products. [d] All products were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (see Supporting Information). The NMR spectra of the products **3aa**,[8] **3ba**,[8] **3ca**,[9] **3da**,[10] **3fa**,[11] **3ha**,[12] **3ja**[11] and **3ka**[13] are in accordance with those in the literature.

concentration were screened, and it was found that only a 1.2:1.0 ratio of indole/benzyl bromide was required for an efficient conversion, thereby preventing the use of a large excess of reagents without any concentration influence.

Since we wanted to determine whether our reaction could be equally well carried out by using conventional heating, we performed the reaction in a pre-heated oil bath at 150 °C under exactly the same set of conditions as in the M.W.-assisted reaction (sealed 10 mL microwave tube, same quantities of reagents and water). After 16 min, the reaction mixture was cooled to afford the adduct in only 15% together with a considerable amount of starting material (Table 1, Entry 11).

Table 3. Microwave-enhanced Friedel–Crafts alkylation reactions of indole **1a** with different alkyl halides **2**.



Entry[a]	Alkyl halide **2**	Product **3**	Yield (%)[b,c]	Ratio C3/C2[c]
1	 **2a**	**3aa**[d]	68	94/6
2	 **2b**	**3ab**[d]	56	100/0
3	 **2c**	**3ac**	48	100/0
4	 **2d**	**3ad**[d]	77	100/0
5	 **2e**	**3ae**	60	100/0
6	 **2f**	**3af**	76	100/0
7	 **2g**	**3ag**	50	100/0
8	 **2h**	**3ah**[d]	60	93/7
9	 **2i**	**3ai**	80	100/0

[a] All the reactions were conducted on a 0.5 mmol scale under microwave-irradiation conditions: P = 200 W, T = 150 °C, reaction time = 8 min. [b] Isolated yield after column chromatography. [c] All products were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (see Supporting Information). [d] The NMR spectra of the products **3aa**,[8] **3ab**,[14] **3ad**,[15] and **3ah**[8] are in accordance with those in the literature.

Encouraged by these results, we explored the general validity of the procedure. The optimized procedure was used for the reaction of substituted indoles **1** with benzyl bromide (**2a**) (Table 2).

As can be seen from the Table 2, preferential or exclusive 3-attack generally occurred with some *N*-attack (5–12% yield) in the case of 2-unsubstituted indoles. The presence of *N*-alkylated indole adducts can be reasonably attributed to the absence of steric hindrance in the position adjacent to the site of electrophilic attack. Introduction of electron-donating and -withdrawing groups was tolerated as was substitution in the 3-position. When the C-3 position of the indole was blocked by a substituent (Table 2, Entry 11), the nucleophilic attack occurred at the C-2 position, known to be very difficult, to afford the adduct **3ka** in moderate yield under our conditions. In the same way, the reaction efficiencies proved to follow the established order of nucleophilic reactivity from the weakest nucleophile, 5-cyanoindole (**1j**), to the strongest ones, such as 2-methylindole (**1b**) and 2-methyl-5-methoxyindole (**1g**).

Finally, we probed the feasibility of the reaction with various S_N1-reactive benzyl halides **2a**–**2i** by using the optimized conditions (Table 3).

In all cases, moderate to good yields were achieved with high degrees of selectivity. Since the 3-position is the preferred site for electrophilic substitution reactions, C-3-substituted indoles were formed almost exclusively with small amounts of *N*-alkylated adduct (<10%). In general, alkyl halides with more stabilized carbocations gave better yields.

In order to contribute to energy savings and therefore to the sustainability of the microwave-heated experiments compared to conventionally heated ones, we monitored the energy consumption (kWh) during the course of the reaction using a commercially available domestic electricity meter (Table 4).[16]

Table 4. Comparison of the energy consumed by microwave irradiation (M.W.) and oil bath (Δ) for the Friedel–Crafts reaction between indole **1a** and benzyl bromide **2a**.

Entry	Heating method	Scale [mmol]	T [°C]	t [min][a]	Yield (%)[b]	E [kWh][c]	E [kWh mol^{-1}][d]
1	oil bath	0.5	100	180	21	0.27	2571
2	oil bath	0.5	100	720	37	1.02	5513
3[e]	oil bath	0.5	150	16	15	0.1	1333
4	M.W.	0.5	150	8	68	0.03	88.23
5	M.W.	1.0	150	8	65	0.03	46.15

[a] Reaction time (t) is defined as the total heating time. For oil-bath experiments, this includes the time required for heating the bath to the desired temperature. [b] Isolated yield of pure product. [c] Energy consumption as measured by the Watt meter for the total heating time (t) specified. [d] Energy consumption calculated on the basis of mol of product formed. [e] Run performed in a sealed vessel.

The collected data point out that conventional heating consumes a large amount of energy (with longer reaction times and lower product yields), whereas the microwave-assisted process under sealed-vessel conditions led to significant savings in energy (with shorter reaction times and much improved product yields), thus demonstrating the superiority of our procedure.

Conclusions

We have reported an efficient and green alternative protocol for the Friedel–Crafts alkylation of indoles with different benzyl halides in water with moderate to good yields. In contrast to the classical conditions for Friedel–Crafts reactions, the notable features of this procedure are the use of water as green solvent, the efficiency by reducing reaction times, the increase of adduct yields and selectivities, the easy workup and last but not least that no catalyst or additives are needed. This method demonstrates the potential benefits on the reaction resulting from the combination of microwave irradiation and superheated water, and it could be a convenient synthetic way to obtain functionalized indoles avoiding the use of catalysts and organic solvents.

Experimental Section

Typical Microwave-Assisted Experimental Procedure: A sealed 10 mL glass tube containing a solution of the benzyl halide (0.5 mmol) and indole derivative (0.6 mmol) in distilled water (1 mL) was introduced in the cavity of a microwave reactor (CEM Co., Discover System, single-mode reactor) and irradiated for an appropriate time and temperature under magnetic stirring. After air-flow cooling to room temperature, the tube was removed from the rotor, the reaction mixture was diluted with a small amount of ethyl acetate and poured into a separating funnel. Water was added and the organic material was extracted with ethyl acetate (3 × 4 mL). The combined extracts were dried with $MgSO_4$, and – after removal of the solvent – the mixture was purified by column chromatography (hexane/AcOEt as eluent) to yield the expected products. The identity and purity of the compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization of the products.

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