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Transition-Metal-Free Synthesis of Benzimidazoles Mediated by KOH/DMSO

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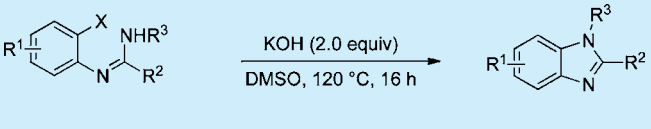
Supporting Information

ABSTRACT: Benzimidazoles are prepared by intramolecular N-arylations of amidines mediated by potassium hydroxide in DMSO at 120 °C. In this manner, diversely substituted products have been obtained in moderate to very good yields.



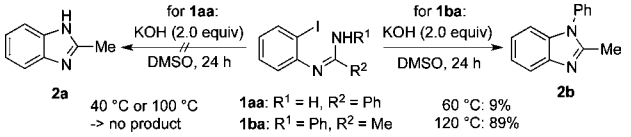
X = F, Cl, Br, I
R^1 = F, Cl, Br, Me, CF_3
R^2 = Me, Ph, *o*-tol, *o*-Br-C_6H_4, *p*-F-C_6H_4, thiophen-2-yl
R^3 = Ph, Me, Bn, PMP

Cross-coupling reactions are important transformations in organic synthesis, which are commonly catalyzed by metals such as Pd, Cu, Fe, or Ni.[1] Recently, we reported analogous C−N, C−O, C−S, and C−C bond-forming processes that occurred in the absence of transition metals.[2,3] In general, such protocols are of great synthetic interest because they allow trace-metal impurities to be avoided in the final products.

Benzimidazoles can reveal important bioactivities,[4] and several strategies for their synthesis have been developed. Commonly, they are prepared from 1,2-diaminoarenes by condensations with carboxylic acids under harsh dehydrating conditions[5] or oxidative couplings with aldehydes.[6] Under milder reaction conditions benzimidazoles can be accessed from amidines by metal-catalyzed intramolecular C−N cross-couplings.[7] Considering our previous findings,[2] we hypothesized that the latter transformations could also be promoted by a strong base under transition metal-free conditions.[8] Here, we report on the realization of this concept.

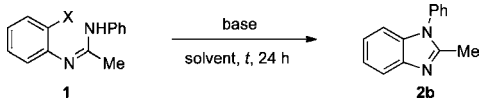
At the outset, amidine **1aa** with a free NH_2 group was chosen as substrate, and we attempted to cyclize it in the superbasic medium consisting of KOH and DMSO (Scheme 1).[9−11]

Scheme 1. First Attempts for the Intramolecular N-Arylation of Amidines



Unfortunately, however, no conversion of **1aa** was observed, at 40 °C or 100 °C after 24 h. Assuming that the nucleophilicity of the resulting anion was too low for the cyclization to occur, *N*-phenyl-substituted amidine **1ba** was subjected to the KOH/DMSO mixture next. As expected, **1ba** showed a higher reactivity, affording benzimidazole **2b** in 9% yield at 60 °C (Scheme 1 and Table 1, entry 1). To our delight, increasing the reaction temperature had a positive effect on the cyclization

Table 1. Optimization of the Reaction Conditions



entry	X	1	base (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	I	**ba**	KOH (2.0)	DMSO	60	24	9
2	I	**ba**	KOH (2.0)	DMSO	80	24	61
3	I	**ba**	KOH (2.0)	DMSO	100	24	82
4	I	**ba**	KOH (2.0)	DMSO	120	24	89
5	Br	**bb**	KOH (2.0)	DMSO	120	24	96
6	Cl	**bc**	KOH (2.0)	DMSO	120	24	67
7	F	**bd**	KOH (2.0)	DMSO	120	24	97
8	Br	**bb**	KOH (2.0)	DMSO	120	16	93
9	Br	**bb**	KOH (2.0)	DMSO	120	2	86
10	Br	**bb**	KOH (1.0)	DMSO	120	16	70
11	Br	**bb**	KOH (2.0)[b]	DMSO	120	16	96
12	Br	**bb**	K_2CO_3 (2.0)/ DMEDA (0.1)	toluene	120	24	s.m.
13	Br	**bb**	K_2CO_3 (2.0)/ DMEDA (0.1)	MeCN	120	24	s.m.

[a]After column chromatography. [b]Use of KOH with a purity of >99.99%; s.m. = starting material.

(Table 1, entries 1−4), and performing the same transformation at 120 °C led to **2b** in 89% yield. The product formation was also affected when the iodo substituent of **1ba** was changed to a bromo, chloro, or fluoro group (Table 1, entries 5−7). While chloro-substituted **1bc** gave **2b** in a lower yield (67%, Table 1, entry 6), bromo- and fluoro-substituted amidines **1bb** and **1bd** performed better leading to **2b** in 96%

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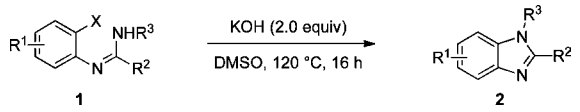
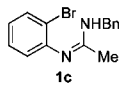
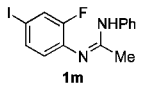
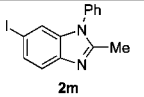
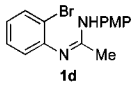
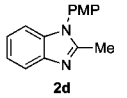
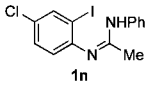
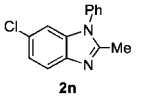
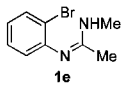
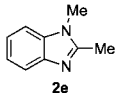
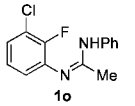
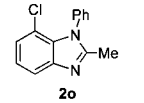
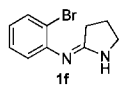
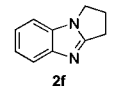
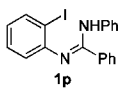
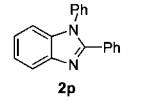
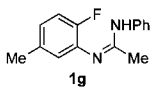
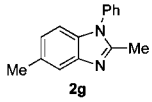
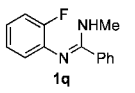
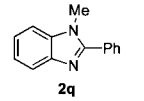
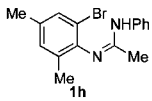
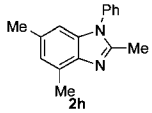
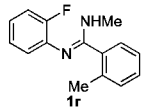
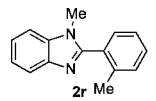
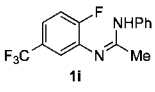
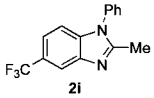
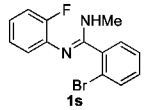
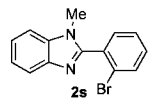
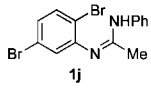
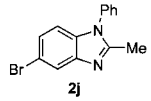
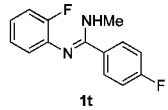
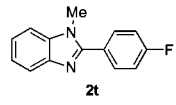
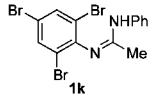
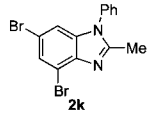
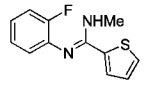
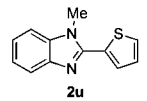
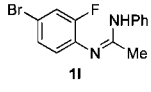
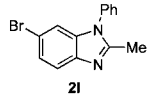
Table 2. Scope of the Intramolecular N-Arylation for the Synthesis of Benzimidazoles



1 2

entry	substrate	product	yield (%)[a]	entry	substrate	product	yield (%)[a]
1	 1c	 2c	28	11	 1m	 2m	58
2	 1d	 2d	89	12	 1n	 2n	87
3	 1e	 2e	73	13	 1o	 2o	69
4	 1f	 2f	65	14	 1p	 2p	90
5	 1g	 2g	90	15	 1q	 2q	86
6	 1h	 2h	89	16	 1r	 2r	87
7	 1i	 2i	79	17	 1s	 2s	36
8	 1j	 2j	79	18	 1t	 2t	27
9	 1k	 2k	79	19	 1u	 2u	91
10	 1l	 2l	83				

[a]After column chromatography.

and 97% yield, respectively. These observations are important with respect to the mechanism (see discussion below) because the results are inconsistent with a typical nucleophilic substitution reaction where the leaving group ability of the halide commonly shows a clear trend (F > Cl > Br > I).[12]

Further optimization studies revealed that the reaction time could be shortened from 24 to 16 h and even 2 h providing product **2b** in 93% and 86%, respectively (Table 1, entries 8 and 9). The use of 2 equiv of KOH was crucial for complete conversion. When only 1 equiv was used, the product yield was lower (70%, Table 1, entry 10). To ensure that the base quality did not affect the cyclization yield, the commonly used KOH (Grüssing, 85%) was substituted by a sample with a purity of >99.99% (from Acros Organics). Also in this case, the yield of **2b** was 96% (Table 1, entry 11) indicating that this factor was irrelevant here.

Finally, as we have recently found a mild cyclization of *N*-tosyl hydrazones upon treatment with K_2CO_3/DMEDA providing indazoles,[2e] this protocol was applied here using **1bb** as starting material. Unfortunately, no conversion occurred, and the attempt was unsuccessful in both toluene and acetonitrile (Table 1, entries 12 and 13).

Next, the substrate scope was investigated (Table 2). Varying the substituent on the amidine nitrogen had a significant effect on the product yield. While benzyl-substituted **1c** gave benzimidazole **2c** in only 28% yield (Table 2, entry 1), *p*-methoxyphenyl-bearing **1d** cyclized well to provide **2d** in 89% yield (Table 2, entry 2). Reactions of alkyl-substituted amidines **1e** and **1f** proved to be less efficient leading to the corresponding products **2e** and **2f** in 73% and 65% yield, respectively (Table 2, entries 3 and 4). Using amidine with electron-donating substituents on the arene core afforded benzimidazoles in high yields (Table 2, entries 5 and 6). The presence of an additional halo substituent slightly decreased the amidine conversion giving products with yields ranging from 58% to 83% (Table 2, entries 7−13). The moderate yield of **2m**

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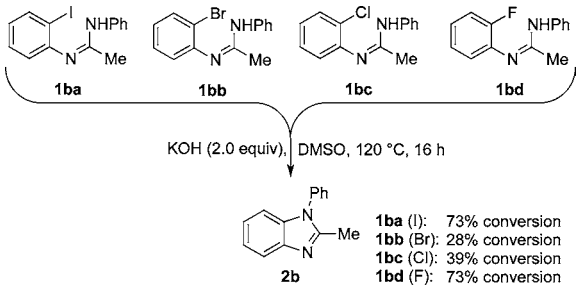
(58%, Table 2, entry 11) might be due to side reactions taking place at the iodo-substituted sites of both substrate **1m** and product **2m**. The steric hindrance induced by the *o*-chloro group of amidine **1o** can be responsible for the relatively low yield of **2o** (69%, Table 2, entry 13).

Finally, R^2 of the amidine was varied from methyl and cycloalkyl to aryl. In general, those substrates (**1p**−**u**) cyclized well, providing the corresponding benzimidazoles in high yields (Table 2, entries 14−19). Three points are noteworthy in the context: First, steric bulk did not significantly affect the reaction as revealed by the high yield in the formation of **2r** (Table 2, entry 16). Second, for unknown reasons, halo-substituted amidines **1s** and **1t** gave the corresponding products in only 36% and 27% yield, respectively (Table 2, entries 17 and 18). Third, also hetaryl **1u** cyclized well to provide thiophenyl-substituted benzimidazole in remarkable 91% yield (Table 2, entry 19).

To gain a deeper mechanistic understanding, inter- and intramolecular competition experiments were performed. Using a mixture of halo-substituted amidines **1ba-bd** in "one pot" (Scheme 2) confirmed the aforementioned observation that the

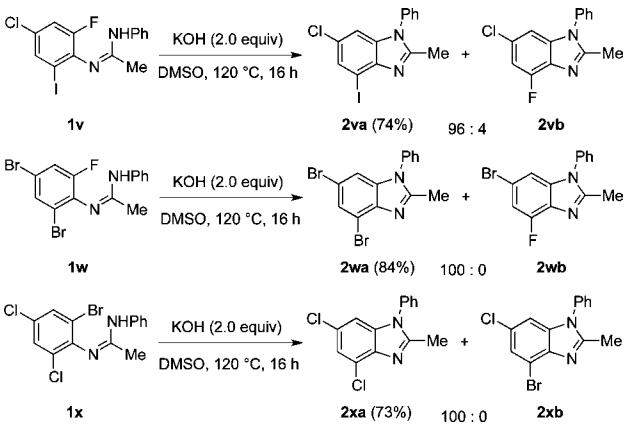
Scheme 2. Intermolecular Competition Experiments



reactivity order was inconsistent with a typical S_NAr mechanism.[13] While iodo- and fluoro-substituted amidines **1ba** and **1bd** showed the same level of conversion, bromo-substituted amidine **1bb** reacted surprisingly slow under these conditions, and its conversion was even lower than that of chloro-substituted **1bc.**

Intramolecular competition experiments were performed with substrates **1v**−**x** having two different halo groups in the *ortho*-positions of the reacting moiety (Scheme 3). Interestingly, in all three cases high product ratios were observed (as determined by GC−MS). In both F/I-substituted **1v** and F/Br-

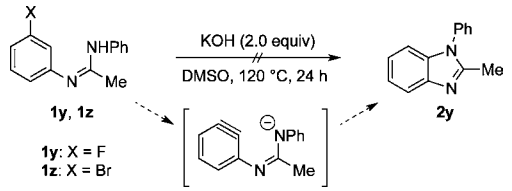
Scheme 3. Intramolecular Competition Experiments



bearing **1w** the fluoro group was substituted. In Br/Cl-containing **1x** the bromo moiety served as leaving group. From these data a reactivity order of F > I > Br > Cl can be deduced.

To evaluate if the reaction proceeded via an aryne intermediate as proposed by Xiang, Wang, and co-workers,[8] two substrates with halo substituents in the *meta*-position were examined (Scheme 4). For both fluoro-substituted compound

Scheme 4. Control Experiment: Aryne Mechanism



1y and bromo-bearing amidine **1z** no conversion was observed, which makes an aryne mechanism in these cases unlikely. The result with dihalo-substituted amidine **1o** can be interpreted in the same manner. There, cyclization to give **2o** occurred although aryne formation can be excluded (Table 2, entry 13).

Taking all results into account, we consider an $S_{RN}1$ mechanism and the involvement of short living radicals as most likely for the iodo-containing aryl halides.[3d,14,15] In contrast, the fluoro-, bromo-, and chloro-substituted compounds seem to react through a typical S_NAr mechanism.

In summary, a new protocol for the synthesis of benzimidazoles starting from amidines has been developed. The cyclization is mediated by KOH in DMSO at 120 °C. Various functional groups are tolerated giving access to a wide range of substituted benzimidazoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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