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Potassium Hydroxide/Dimethyl Sulfoxide Promoted Intramolecular Cyclization for the Synthesis of Benzimidazol-2-ones

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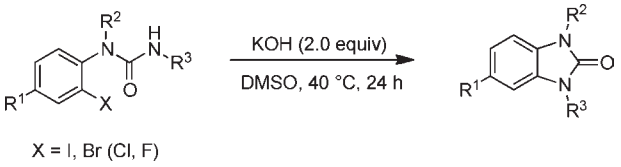
ABSTRACT



X = I, Br (Cl, F)

A new protocol for intramolecular N-arylations of ureas to form benzimidazol-2-ones has been developed. The cyclization reaction occurs in the presence of KOH and DMSO at close to ambient temperature. Under these conditions the yields are high and a wide range of functional groups are tolerated.

Benzimidazol-2-ones are important heterocycles with an embedded cyclic urea scaffold that is a core element of many pharmaceutically relevant compounds. They can exhibit a wide range of biological activities including, for example, inhibitions of the respiratory syncytial virus (RSV) fusion[1] and the non-nucleoside reverse transcriptase (NNRT).[2] Furthermore, benzimidazol-2-one derivatives play important roles as progesterone receptor antagonists,[3] in the selective inhibition of farnesyltransferase (FTase),[4] and the activation of K^+ channels.[5] Challenged by the demand, various synthetic approaches toward those interesting compounds have been developed, most of them using benzene-1,2-diamines as key intermediates. Their subsequent cyclization to form the imidazolone core then requires the use of phosgene,[6] triphosgene,[7] or carbonyldiimidazole (CDI).[8] To avoid the use of such toxic substances and the often harsh reaction conditions, alternative protocols have been introduced giving

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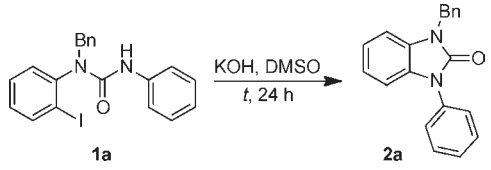
access to imidazo[4,5-*b*]pyridine-2-ones[9] or benzimidazol-2-ones[10] by palladium or copper catalysis.[11] In these reactions the formations of the cyclic urea units occur either by metal-catalyzed N-arylation or coupling of ammonia with 2-iodoacetanilides followed by acid-catalyzed cyclization.[12] Also here, elevated temperatures (> 80 °C) and additional activation modes such as microwave irradiation were required. We now developed a transition-metal-free base-promoted intramolecular N-arylation of ureas to form benzimidazol-2-ones.[13−16] Noteworthy, it utilizes simple KOH in DMSO, takes place at close to ambient temperature, and is applicable to a wide range of substrates. The results of our studies are described herein.

Initially, the reaction conditions were optimized by examining the conversion of 1-benzyl-1-(2-iodophenyl)-3- phenylurea (**1a**), synthesized by a transition-metal-free two-step procedure from 2-iodoaniline,[17] into 1-benzyl-3-phenyl-1,3-dihydro-benzoimidazole-2-one (**2a**) (Table 1).

Table 1. Optimization of the Reaction Conditions



1a **2a**

entry	KOH (equiv)	*t* °C, 24 h	yield %[a]
1	2.0	80	decomp.
2	2.0	40	89 (98)[b]
3	2.0	rt	67
4	2.0	rt	84[c]
5	2.0	40	88[d]
6	1.0	40	23

[a] After column chromatography; use of 0.234 mmol of **1a**. [b] In parentheses, yield from a reaction with 0.700 mmol of **1a**. [c] Reaction time: 44 h. [d] Reaction time: 6 h.

To our delight, the reaction proceeded well, and in the presence of 2 equiv of KOH in DMSO at 40 °C a smooth cyclization occurred providing the product in up to 98% yield (Table 1, entry 2). Attempts to perform the reaction at 80 °C resulted in complete decomposition of the starting material (entry 1). At room temperature the cyclization was slow, and after the standard 24 h reaction time product **2a** was isolated in only 67% yield. It required an additional 20 h to reach a yield of 84% (Table 1, entries 3 and 4, respectively). The use of 2 equiv of KOH proved essential. Decreasing the amount of the base to 1 equiv led to a significant reduction in yield (entry 6).

Encouraged by these results, various phenyl ureas were synthesized and submitted to the KOH−DMSO mixture to determine the scope and the limitations of the cyclization method. Table 2 shows the data.

Pleasingly, a wide variety of products were accessible under the optimized reaction conditions, and commonly good to excellent yields were achieved. As demonstrated for the synthesis of benzimidazol-2-one **2a** the product could be obtained not only by starting from iodo-substituted phenyl urea **1a** but also through cyclizations of the analogous bromo, chloro, and fluoro derivatives **1b**−**d**, respectively (Table 2, entries 1−3). Compared to the conversion of **1a** transformations of the latter halo phenyl ureas were less effective, but nevertheless yields of up to 79% were achieved here as well. Attempts to cyclize less substituted urea **1e** (where R^2 = H) remained unsuccessful, and after 24 h the entire amount of starting material was recovered (Table 2, entry 4).[18] This result showed that an *N*,*N*,*N*′-trisubstitution of the urea core in **2** was critical for the cyclization (Table 2, entry 4). With respect to the N-substituent R^2 we were pleased to find that both alkyl (methyl, entries 10 and 16) and benzyl groups were tolerated. The latter could have additional aryl substituents which appeared to have no significant influence on the cyclization toward the corresponding benzimidazol-2-ones **2** (entries 9, 11, 12). Substrates with additional chloro or bromo substituents (R^1) at the 4-position of the 2-halophenyl moiety showed reactivity differences, but in all cases the products were formed well reaching a yield of 93% in the synthesis of chloro-substituted **2i** (Table 2, entry 13). Comparing the cyclization results of 2-iodo derivatives **1a** (R^1 = H), **1n** (R^1 = Cl), and **1p** (R^1 = Br) revealed that the latter process was the most difficult one leading to product **2j** in only 78% yield (Table 2, entry 15). Variations of the N′-aryl (R^3) indicated that substituents in the *para* position had almost no effect on the product yield (Table 2, entries 5−8, 19). One exception is nothworthy: The cyclization of *p*-methoxy-substituted **1h** provided the corresponding product **2d** in

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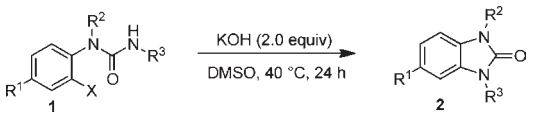
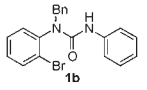
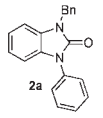
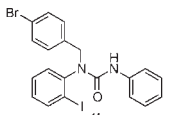
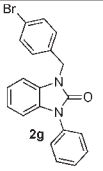
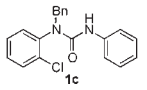
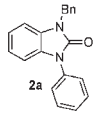
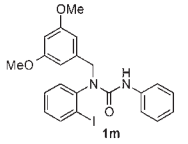
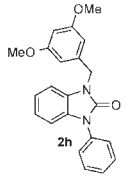
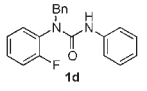
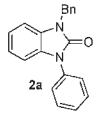
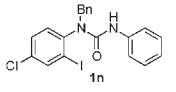
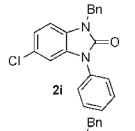
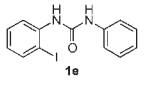
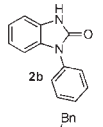
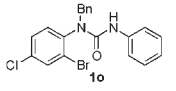
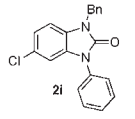
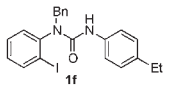
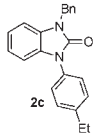
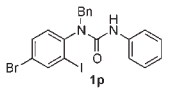
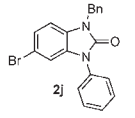
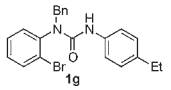
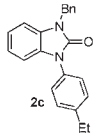
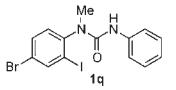
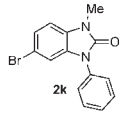
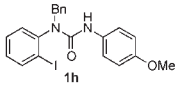
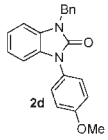
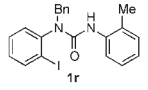
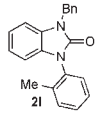
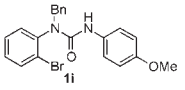
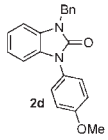
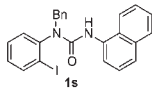
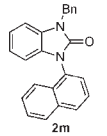
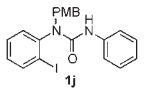
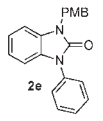
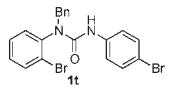
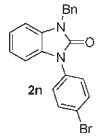
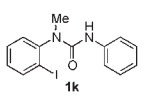
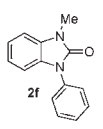
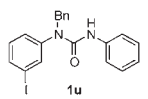
(18) Also attempted cyclizations of **1e** with 3 or 4 equiv of KOH (at 40 °C) remained unsuccessful. At 100 °C (using 2 equiv of KOH) only traces of **2b** were detected after 22.5 h.

Table 2. Scope of the Intramolecular N-Arylation of Phenyl Ureas



1 2

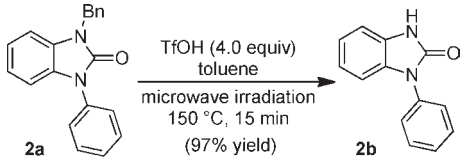
entry	substrate	product	yield %[a]	entry	substrate	product	yield %[a]
1	 1b	 2a	77	11	 1l	 2g	94
2	 1c	 2a	35[b]	12	 1m	 2h	97
3	 1d	 2a	79[b]	13	 1n	 2i	93
4	 1e	 2b	-	14	 1o	 2i	77
5	 1f	 2c	88	15	 1p	 2j	78
6	 1g	 2c	82[b]	16	 1q	 2k	61
7	 1h	 2d	99	17	 1r	 2l	66
8	 1i	 2d	70	18	 1s	 2m	79
9	 1j	 2e	87	19	 1t	 2n	49 (63)[b]
10	 1k	 2f	89	20	 1u	2a	-

[a] After column chromatography; using 0.234 mmol of starting material. [b] At 60 °C.

99% yield, which was the best result of the entire study. When R^3 had an *ortho* substituent, as in compounds **1r** and **1s** (entries 17 and 18), the yields were lower (66 and 79%, respectively). If R^3 was cyclohexyl, no cyclization occurred, and only hydrolysis of the starting material was observed.

To add synthetic value and demonstrate the usefullness of the obtained fully substituted benzimidazol-2-ones we decided to investigate debenzylation reactions. To our surprise, hydrogenation with $Pd(OH)_2/C$ proved inapplicable, and when **2a** was used as a test substrate only arene reduction of the benzyl group was observed.[19] After numerous attempts a recently described protocol by Rombouts[20] led to success. Thus, treatment of **2a** with triflourmethane sulfonic acid (TfOH) in toluene under microwave irradiation afforded debenzylated urea **2b** in almost quantitative yield (Scheme 1).

Scheme 1. Microwave-Promoted Debenzylation of **2a**



2a **2b**

Finally, we wondered about the cyclization mechanism. As indicated by the yields of **2a** starting from **1a**–**d** the aryl halide reactivity did not follow the expected order (F > Cl > Br) for a standard S_NAr mechanism.[21] A reaction via an aryne intermediate would require the generation of a carbanion.[22] In order to evaluate this reaction path, we attempted to obtain the identical species as for a reaction with **1a** starting from isomeric 1-benzyl-1-(3-iodophenyl)-3-phenylurea (**1u**) (Table 2, entry 20). When this compound was submitted to the KOH–DMSO mixture, however, no cyclization was observed and the starting material remained unreactive. Although not entirely conclusive, this result indicates that arynes do not play a central role in the cyclization. Currently, we assume that short-lived radical intermediates are formed,[22] and subsequent studies shall be directed toward their detection.

In summary, we have developed a new protocol for the synthesis of substituted benzimidazol-2-ones. The intramolecular cyclization is promoted by KOH in DMSO at nearly ambient temperature. Various aryl halides show satisfying reactivities, and the protocol proved promising for the formation of synthetically relevant nitrogen-containing heterocycles.

Acknowledgment. We are grateful to the Fonds der Chemischen Industrie for financial support.

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

(19) Even at 70 bar of hydrogen pressure (RT, 22 h) formation of **3a** was not observed, and the yield of 1-(cyclohexylmethyl)-3-phenyl-1,3-dihydrobenzoimidazol-2-one was only 32%.

(20) Rombouts, F.; Franken, D.; Martínez-Lamenca, C.; Braeken, M.; Zavattaro, C.; Chen, J.; Trabanco, A. A. *Tetrahedron Lett.* **2010**, *51*, 4815.

(21) For a review, see: Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

(22) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *3*, 91.

(23) (a) Bunnett, J. F. *Acc. Chem. Res.* **1987**, *11*, 413. (b) For a recent overview on metal-free arylations under basic conditions involving radical anions, see: Yanagisawa, S.; Itami, K. *ChemCatChem* **2011**, DOI: 10.1002/cctc.201000431.