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Intramolecular Aromatic Nucleophilic Substitution of the Benzimidazole-Activated Nitro Group

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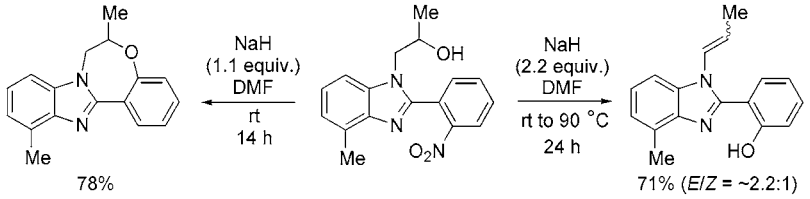
ABSTRACT

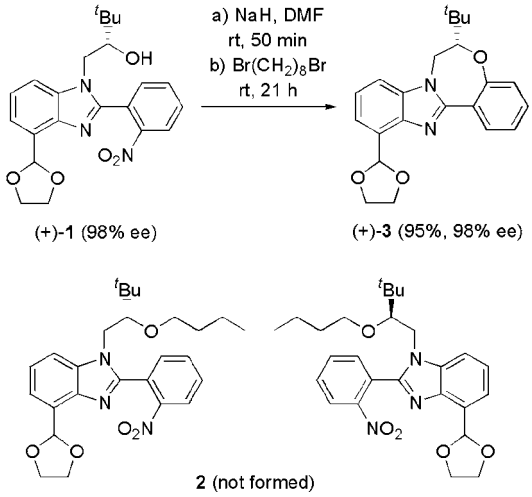


A wide range of 2-(2-nitrophenyl)-1*H*-benzimidazoles undergo high-yielding intramolecular S_NAr of nitrite with N-pendant alkoxides under mild conditions (DMF, rt). When this operationally simple process is carried out at elevated temperatures in the presence of excess NaH, the initially formed S_NAr products are converted to the corresponding *N*-vinyl-substituted 2-(2-hydroxyphenyl)-1*H*-benzimidazoles via base-catalyzed isomerization.

In the course of our ongoing studies on the synthesis of configurationally stable, highly ruffled, cyclic bis(benzimidazole) ligands,[1,2] we required etherification of alcohol **1** (Scheme 1). Somewhat unexpectedly, its treatment with NaH in DMF, followed by the addition of 1,8-dibromooctane, did not give the desired bis(ether) **2**. Instead, the seven-membered cyclic ether **3**, possessing a novel, tetracyclic 6,7-dihydro-5-oxa-7*a*,12-diazadibenzo[*a*,*e*]azulene skeleton, was formed in excellent yield as the only isolable product, apparently via an intramolecular S_NAr of the nitro group.

As benzimidazole is an important scaffold in drug discovery, with many of its analogues being used in the treatment of various viral, bacterial, and fungal infections,[3] we were surprised to find that the activating properties of benzimidazole for promoting S_NAr reactions have not been frequently utilized. To the best of our knowledge, the only examples of benzimidazole-activated S_NAr transformations have been reported by Hedrick and co-workers. These reactions involve the high-temperature intermolecular re-

Scheme 1. Attempted Etherification of Alcohol **1**



(1) (a) Payra, P.; Hung, S.-C.; Kwok, W.-H.; Johnston, D.; Gallucci, J.; Chan, M. K. *Inorg. Chem.* **2001**, *40*, 4036−4039. (b) Kwok, W.-H.; Zhang, H.; Payra, P.; Duan, M.; Hung, S.-C.; Johnston, D. H.; Gallucci, J.; Skrzypczak-Jankun, E.; Chan, M. K. *Inorg. Chem.* **2000**, *39*, 2367−2376. (c) Payra, P.; Zhang, H.; Kwok, W.-H.; Duan, M.; Gallucci, J.; Chan, M. K. *Inorg. Chem.* **2000**, *39*, 1076−1080.

(2) Fekner, T.; Gallucci, J.; Chan, M. K. *J. Am. Chem. Soc.*, in press.

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placement of fluoride by phenoxides in the preparation of thermally stable polymers.[4]

Although the nitro group is most frequently utilized to activate S_NAr reactions in fluoroarenes, a wide range of electron-withdrawing substituents[5,6] (e.g., $-CF_3$,[6a,b] $-NO_2$,[6c−e] $-CN$,[6f] $-COR$,[6e] $-CO_2R$,[6f] etc.) have been reported to facilitate its replacement.

Various electron-withdrawing heterocyclic functionalities[7] (e.g., oxadiazoles,[7a] benzoxazoles,[7b] benzothiazoles,[7c] triazoles,[7d] phenylquinoxalines,[7e,f] triazines,[7g] etc.), that are also capable of stabilizing the negative charge developed during S_NAr reactions (Meisenheimer complex), have been successfully used as activating groups (especially for fluoride).

The new transformation depicted in Scheme 1 proved to be quite general, and a series of structurally diverse analogues of alcohol **1**[8] were shown to be competent substrates (Table 1).[9] As can be noted, the steric hindrance on the nucleophilic arm is well tolerated, and both moderately (entries 1 and 2) and severely (entries 3−6) sterically hindered secondary alcohols undergo the cyclization in high yield. In addition, tertiary alcohol **14** (entry 7) undergoes a smooth nitro group displacement to give the cyclized product **15** in good yield. Substitution ortho to the nitro group, however, gives mixed results. Although the nitro group in benzimidazole **16** (entry 8) undergoes the displacement with high yield, replacement of the chloro substituent with a methyl group (entry 9) has a detrimental effect on the yield of the cyclized product **19**. This result can be attributed to both the unfavorable steric and electronic contributions of the methyl group that hinders formation of the intermediate Meisenheimer complex and also decreases its stability.

Table 1. Intramolecular Replacement of the Benzimidazole-Activated Nitro Group[a]

entry	substrate	product	yield (%)[b]
1	**4**: R = Me	**5**	78
2	**6**: R = *n*-Bu	**7**	75
3	**8**: R = H	**9**	86
4	**10**: R = Me	**11**	96
5	**12**: R = CO_2Et	**13**	89
6	**1**: R = [1,3]-dioxolane-1-yl	**3**	92
7	**14**	**15**	68
8	**16**: R = Cl	**17**	80
9	**18**: R = Me	**19**	7

[a] Reactions were performed in DMF in the presence of NaH (1.1 equiv). For details, see Supporting Information. [b] Isolated yield of spectroscopically (^{1}H NMR) pure products.

Single crystals of the cyclic ether **9** suitable for X-ray analysis were grown by slow evaporation of its CH_2Cl_2−petroleum ether solution. As anticipated (Figure 1), the three-atom bridge spanning the two aromatic subunits forces them into a nearly perfect coplanarity (the dihedral angle $N_2-C_7-C_8-C_9$: 1.4 and 10.9°, respectively, for the two enantiomeric molecules in the asymmetric unit). This conformational constraint, common to all the studied seven-membered cyclization products, has a marked effect on the ^{1}H NMR chemical shift of the aromatic proton located ortho to the aryl-heteroaryl axis.[10] As this proton is placed directly within

(3) (a) Pratt, W. B. *Chemotherapy of Infection*; Oxford University Press: New York, 1977. (b) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084−4097. (c) Bostock-Smith, C. E.; Searle, M. S. *Nucleic Acid Res.* **1999**, *27*, 1619−1624. (d) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, Jr., R. W.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199−4207.

(4) Twieg, R.; Matray, T.; Hedrick, J. L. *Macromolecules* **1996**, *29*, 7335−7341.

(5) For a review on S_NAr of the nitro group, see: Beck, J. R. *Tetrahedron* **1978**, *34*, 2057−2068.

(6) (a) Chung, I. S.; Kim, S. Y. *J. Am. Chem. Soc.* **2001**, *123*, 11071−11072. (b) Park, S. K.; Kim, S. Y. *Macromolecules* **1998**, *31*, 3385−3387. (c) Kornblum, N.; Cheng, L.; Kerber, R. C.; Kestner, M. M.; Newton, B. N.; Pinnick, H. W.; Smith, R. G.; Wade, P. A. *J. Org. Chem.* **1976**, *41*, 1560−1564. (d) Zlotin, S. G.; Kislitsin, P. G.; Samet, A. V.; Serebryakov, E. A.; Konyushkin, L. D.; Semenov, V. V.; Buchanan, A. C., III; Gakh, A. A. *J. Org. Chem.* **2000**, *65*, 8430−8438. (e) Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343−3346. (f) Beck, J. R. *J. Org. Chem.* **1973**, *38*, 4086−4087.

(7) (a) Hedrick, J. L.; Twieg, R. *Macromolecules* **1992**, *25*, 2021−2025. (b) Hilborn, J. G.; Labadie, J. W.; Hedrick, J. L. *Macromolecules* **1990**, *23*, 2854−2861. (c) Hedrick, J. L. *Macromolecules* **1991**, *24*, 6361−6364. (d) Carter, K. R.; Miller, R. D.; Hedrick, J. L. *Macromolecules* **1993**, *26*, 6, 2209−2215. (e) Hedrick, J.; Twieg, R, Matray, T.; Carter, K. *Macromolecules* **1993**, *26*, 4833−4839. (f) Hedrick, J. L.; Labadie, J. W. *Macromolecules* **1990**, *23*, 1561−1568. (g) Fink, R.; Frenz, C.; Thelakkat, M.; Schmidt, H.-W. *Macromolecules* **1997**, *30*, 8177−8181.

(8) Most of the alcohols used in these studies were prepared by the Cu(OTf)$_2$-catalyzed ring opening of epoxides with 1-unsubstituted benzimidazoles. This reaction had previously been successfully applied to the epoxide ring opening with poorly nucleophilic nitroanilines; see: Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287−289.

(9) **Typical Experimental Procedure** (Table 1, entry 3). To a solution of alcohol **8** (100 mg, 0.29 mmol) in anhydrous DMF (2 mL) was added NaH (60% w/w, 12.8 mg, 0.32 mmol) to give a dark-green solution. After 11 h at room temperature, the reaction mixture was quenched with water and diluted with EtOAc. The organic phase was washed repeatedly with water, dried ($MgSO_4$), and evaporated in vacuo to give a yellow solid. Purification by flash chromatography (silica gel, $CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc (10/1)) gave the title compound **9** (74 mg, 86%) as a white solid.

(10) For a recent controversy concerning the ring current effects on ^{1}H NMR chemical shifts, see: Wannere, C. S.; Schleyer, P. v. R. *Org. Lett.* **2003**, *5*, 605−608.

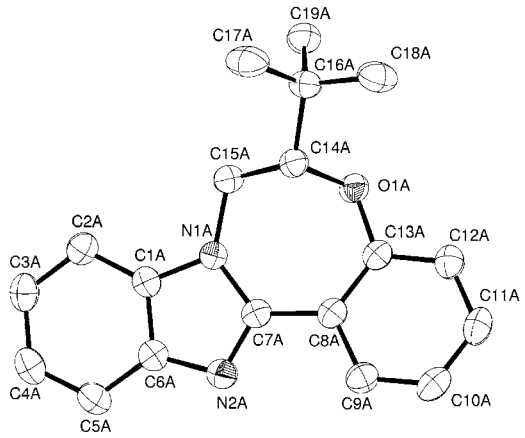
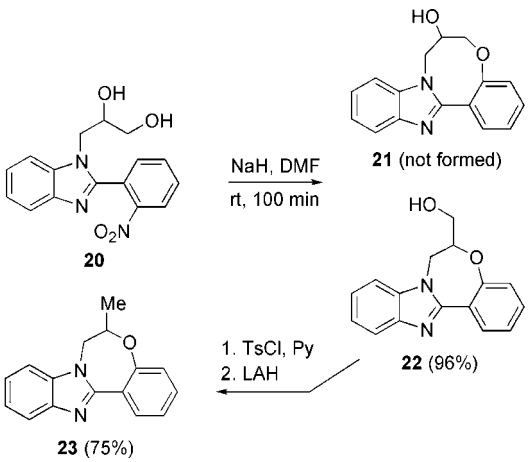


Figure 1. ORTEP view (50% probability thermal ellipsoids) of benzimidazole **9**. Oxygen and nitrogen atoms are hatched. Hydrogen atoms are omitted for clarity.

the deshielding region of the benzimidazole aromatic ring current, it is subject to a significant downfield shift compared to the remaining aromatic protons. Indeed, the presence of a significantly downshifted proton signal in the ^{1}H NMR spectrum can be used to confirm the intramolecular nitro replacement reaction.

To determine whether there is a preferred ring size for this S_NAr cyclization, diol **20** (Scheme 2) was studied.[11] For

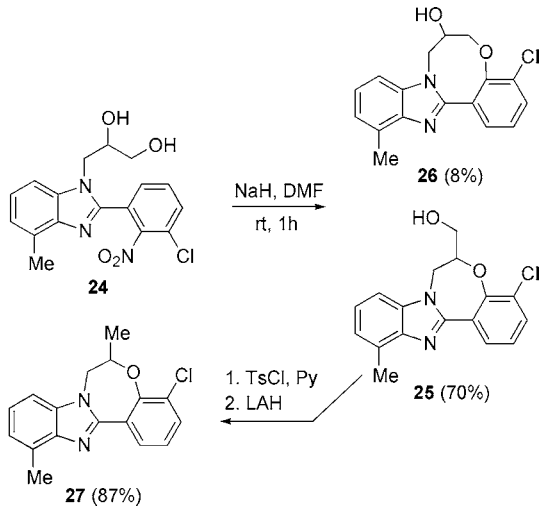
Scheme 2. Intramolecular S_NAr of the Sterically Unhindered Benzimidazole-Activated Nitro Group in Diol **20**



this compound, two modes of cyclization are plausible. One involves the displacement of the nitro group by the sterically less hindered primary alkoxide with the formation of the eight-membered cyclic ether **21**, whereas the other involves an analogous displacement by the sterically more encumbered secondary alkoxide leading to ether **22**. As the rotation about the aryl−heteroaryl axis in the latter compound is expected to be more severely restricted, it is presumably thermodynamically less favored than its eight-membered analogue **21**. It was subsequently experimentally demonstrated that diol **20**, when subjected to the standard reaction conditions, is converted exclusively to the seven-membered cyclic ether **22** in high yield. This result presumably reflects an overwhelming kinetic preference for the formation of the smaller of the two possible rings. The identity of the cyclized product **22** was unambiguously confirmed by its conversion, via the corresponding tosylate, into benzimidazole **23**. ^{1}H NMR analysis of compound **23** indicated the presence of an aliphatic methyl group at 1.46 ppm (d, J = 6.5 Hz) that corresponds to the hydroxymethyl group in benzimidazole **22**. This proved the involvement of the secondary alkoxide in the cyclization of diol **20**.

It was expected, however, that this strong preference for the seven-membered product could be altered by introduction of additional steric bulk ortho to the nitro group. When diol **24**[11] (Scheme 3) was subjected to the standard reaction

Scheme 3. Intramolecular S_NAr of the Sterically Hindered Benzimidazole-Activated Nitro Group in Diol **24**



conditions, the seven-membered cyclic ether **25** was the major product (70%), but a small amount (8%) of its eight-membered analogue **26** was also isolated.[12]

Although there is no universal scale of nucleofugicity for various leaving groups in S_NAr,[13] it is widely recognized that the nitro and fluoro groups frequently have similar

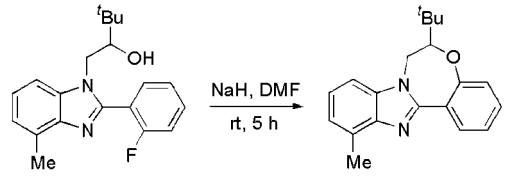
(11) Diols **20** and **24** were prepared by Sharpless asymmetric dihydroxylation of the corresponding *N*-allyl-substituted benzimidazoles. ^{1}H NMR analysis of their Mosher diesters (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549) indicated that the parent diols **20** and **24** were virtually racemic (ee < 5%).

(12) The identity of the two compounds **25** and **26** was elucidated by ^{1}H NMR analysis, as their D_2O-exchangeable primary and secondary hydroxyl groups, respectively, gave the anticipated splitting patterns. In addition, the aromatic proton located ortho to the aryl−heteroaryl axis in the seven-membered cyclic ether **25** experiences a far greater downfield shift than the analogous proton in the rotationally less restricted eight-membered cyclic ether **26** (8.44 and 7.74 ppm, respectively). The identity of the hydroxymethyl compound **25** was further confirmed by its conversion, via the corresponding tosylate, into its methyl analogue **27**.

(13) Bartoli, G.; Todesco, P. E. *Acc. Chem. Res.* **1977**, *10*, 125−132.

reactivity. Accordingly, when benzimidazole **28** was subjected to the standard reaction conditions (Scheme 4), the fluorine was efficiently displaced with the formation of the same cyclic ether **11** previously obtained by nitro displacement in alcohol **10** (Table 1, entry 4).

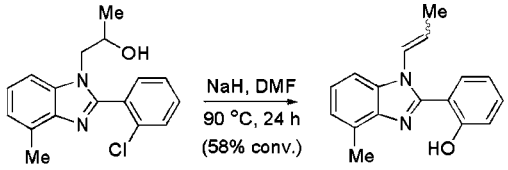
Scheme 4. Intramolecular S_NAr of the Benzimidazole-Activated Fluoro Group in Alcohol **28**



28 **11** (93%)

In contrast, the chloro group in alcohol **29** (Scheme 5) proved to be significantly less reactive, and no product of its displacement was detected when the reaction was carried out under standard conditions (NaH, DMF, rt, 24 h). When an analogous reaction was performed at elevated temperature, a mixture of isomeric alkenes **30** was isolated as the main product, and only traces (~2%) of the expected cyclic ether **5** were detected. Presumably, under forcing reaction conditions, the intermediate cyclic ether **5** undergoes base-catalyzed isomerization into alkenes **30**.[14]

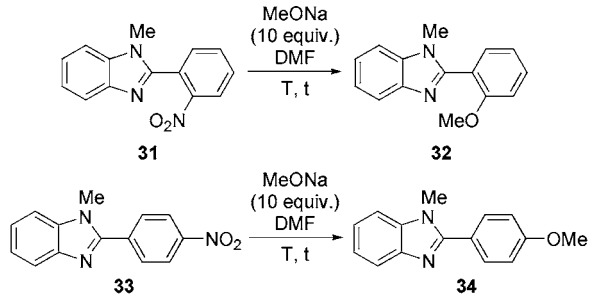
Scheme 5. Intramolecular S_NAr of the Benzimidazole-Activated Chloro Group in Alcohol **29**



29 **30** (35%, *E*/*Z* = ~2:1)

Intermolecular S_NAr of the benzimidazole-activated nitro group has also been examined. As anticipated, this process is significantly less efficient than its intramolecular counterpart (Scheme 6).[15]

Scheme 6. Intermolecular S_NAr of the Benzimidazole-Activated Nitro Group in **31** and **33**



substrate	product	T/°C	t/h	conversion/%
31	**32**	rt	25	23
31	**32**	100	20	34
33	**34**	rt	24	24
33	**34**	100	18	58

In conclusion, a synthetically useful and operationally simple method for the preparation of rotationally restricted 2-aryl-1*H*-benzimidazoles via intramolecular S_NAr of the nitro group by alkoxides has been developed. The scope of this transformation should be subject to structural variation with respect to substituent diversity on both the two aromatic subunits and the nucleophile-bearing arm. These methodologies should also be extendable beyond O-nucleophiles, thus providing a novel entry into various heterocyclic systems.

Acknowledgment. This work was supported by the National Science Foundation (CAREER Award No. 9984071).

Supporting Information Available: Synthetic procedures and copies of ^1H and ^{13}C NMR spectra for all the new compounds and crystallographic details for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) When **5** was treated with NaH in DMF for 18 h at 90 °C, alkenes **30** (*E*/*Z* ≈ 2:1) were formed in high yield (85%). Treatment of alcohol **4** with excess NaH (2.2 equiv) for 24 h at room temperature → 90 °C also gave alkenes **30** (71%, *E*/*Z* ≈ 2.2:1). For sterically more demanding secondary alcohols (e.g., **10**), the post-S_NAr isomerization step is much slower, requiring higher temperatures and more prolonged reaction times, and leads to formation of isomeric alkenes with a higher *E*/*Z* ratio.

(15) It is frequently observed in S_NAr processes that a nitro group located ortho to an activator is replaced more readily than a para-positioned group (Bendedetti, F.; Marshall, D. R.; Stirling, C. J. M.; Leng, J. L. *Chem. Commun*. **1982**, 918−919), as the former is more likely to be out-of-plane relative to the aromatic ring. Therefore, formation of an intermediate Meisenheimer complex is expected to disturb the aromaticity of the molecular system to a lesser degree. However, **33** is a superior substrate, especially at elevated temperatures, with respect to its analogue **31**.