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SYNTHESIS OF BENZO[*d*]PYRROLO[1,2-*a*]IMIDAZOLES BY IMINOCYCLOPROPANE REARRANGEMENT OF C-CYCLOPROPYL-BENZIMIDAZOLES

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Abstract – The MgI_2 or NH_4I mediated iminocyclopropane rearrangement of trisubstituted acrylonitrile benzimidazoles provides an attractive access to novel pyrrolo[1,2-*a*]imidazoles. The rearrangement precursors, C-cyclopropylbenzimidazoles, are obtained by a Corey-Chaykovsky cyclopropanation of the acrylonitrile. We determine the scope of the iminocyclopropane rearrangement to 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]-imidazole-3-carbonitrile and 2,4-dihydro-2,4-disubstituted as well as 1,2,4-trisubstituted 1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole-3-carbonitriles, and describe some of the limitations and side reactions, including the formation of aromatized 4*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole-3-carbonitriles.

In contrast to the well-established conversion of vinylcyclopropanes to cyclopentenes,[1,2] heteroatom variants of this rearrangement have in the past only sporadically been explored. For example, Wasserman and Dion noted that dicyclopropyl ketimines underwent an acid-catalyzed thermolysis to yield cyclopropyl 1-pyrrolines in the presence of ammonium halides, with a likely intermediate formed by cyclopropane ring opening with nucleophilic chloride halide anion (Scheme 1).[3,4] Schultz et al. quantitatively converted C-vinyl aziridines to 2-pyrrolines by heating at 150 °C,[5] and Wu and Wang found that phenyl and acyl substitutions at C-1 and C-2 of the cyclopropyl ring were critical for the successful thermal rearrangement of *N*-acylcyclopropylimines to 2-pyrrolines.[6] Campos et al. reported a photochemically driven rearrangement of *N*-cyclopropylimines to 1-pyrrolines.[7] This transformation is

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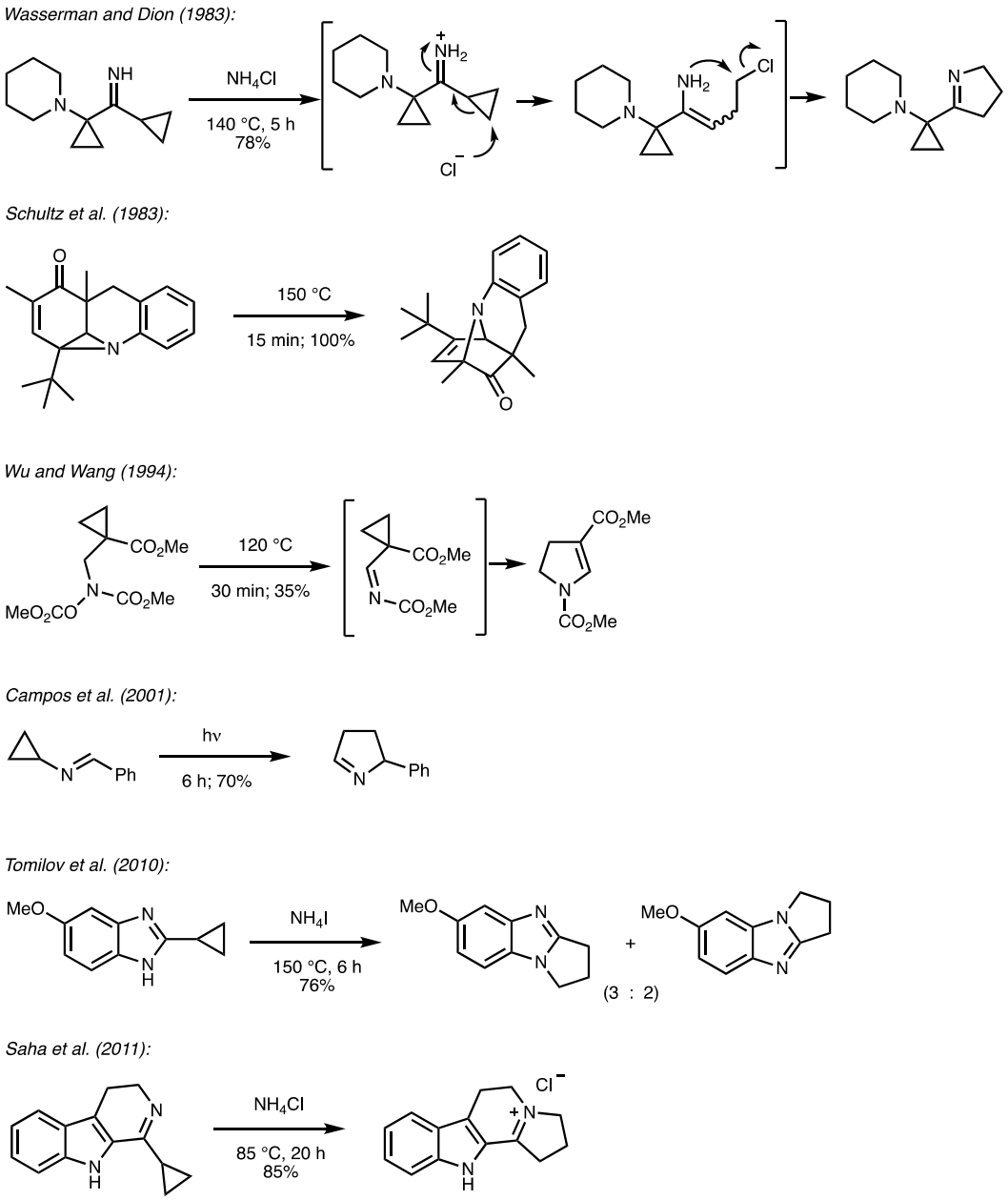
Dedicated with respect and friendship to Professor Somsak Ruchirawat on the occasion of his 80th birthday

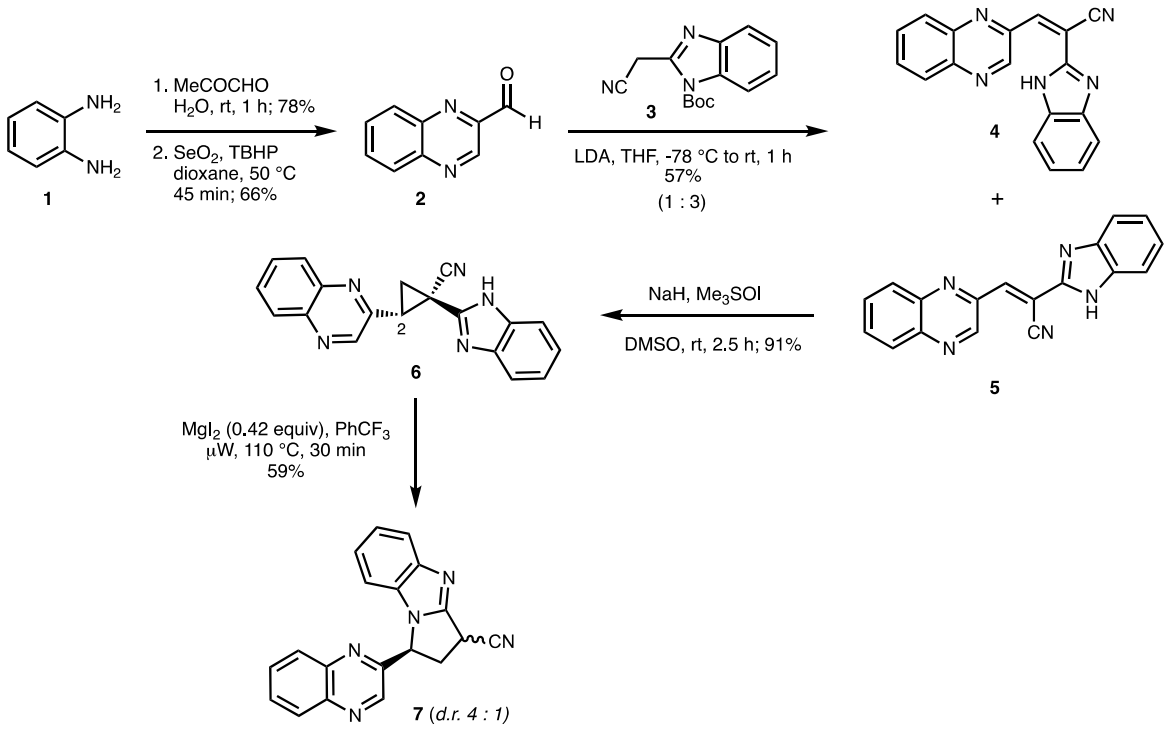
also suitable for the preparation of fused heterocycles, as demonstrated by Tomilov et al. in the thermal conversion of C-cyclopropylbenzimidazoles to 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazoles.[8-10] Furthermore, Saha et al. applied this method for a preparation of the alkaloids crispine and harmicine.[11]



Scheme 1. Overview of representative literature iminocyclopropane rearrangements

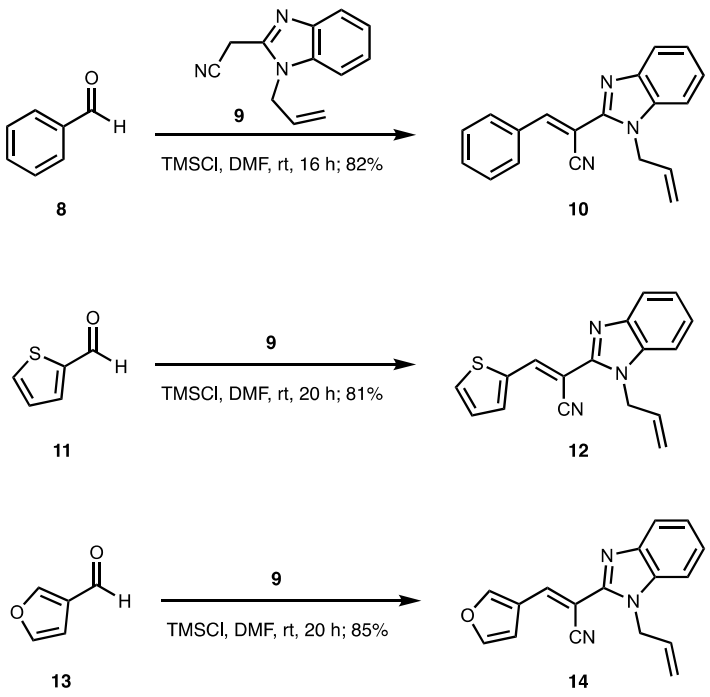
As part of our interest in generating cyclopropane bioisosteres of alkenes in biologically active compounds,[12-14] we recently prepared acrylonitrile **5** and the corresponding cyclopropane analog **6** from the condensation of diamine **1** with 2-oxopropanal,[15] followed by benzylic oxidation[16] and a Knoevenagel condensation with benzimidazole **3**[17,18] (Scheme 2). Acrylonitriles **4** and **5** were formed as a 3:1 ratio of

(*E*)- vs (*Z*)-stereoisomers, and after purification by precipitation from the reaction mixture, (*E*)-alkene **5** was subjected to a Corey-Chaykovsky cyclopropanation[19] to provide 2-cyclopropyl- imidazole **6**. Exposure of **6** to magnesium iodide in trifluorotoluene under microwave irradiation at 110 °C for 30 min triggered an iminocyclopropane rearrangement and generated the pyrrolo[1,2-*a*]imidazole **7** in 59% yield as a 4 : 1 ratio of diastereomers. We initially selected magnesium iodide for this rearrangement based on literature precedents,[20] as well as the unique combination of iodide nucleophilicity facilitating opening of the cyclopropane and the strong Lewis acid character of the magnesium(II) counterion toward nitrile and imidazole functional groups further activating the conjugated cyclopropane. Microwave irradiation in trifluorotoluene was used to allow for a fast heating and cooling process, since some of the products proved to be thermally labile (*vide infra*). Preferential opening of the cyclopropane was observed at the benzylic methine position C(2), possibly suggesting a Lewis acid induced weakening of the more substituted cyclopropane bond. However, we do not have any evidence for a mechanism involving a benzylic cation or iodide intermediate. We were intrigued by this facile preparation of the fused heterocyclic scaffold in **7** containing a highly functionalized pyrrolidine core, and therefore embarked on an investigation of the preparative scope of this process.

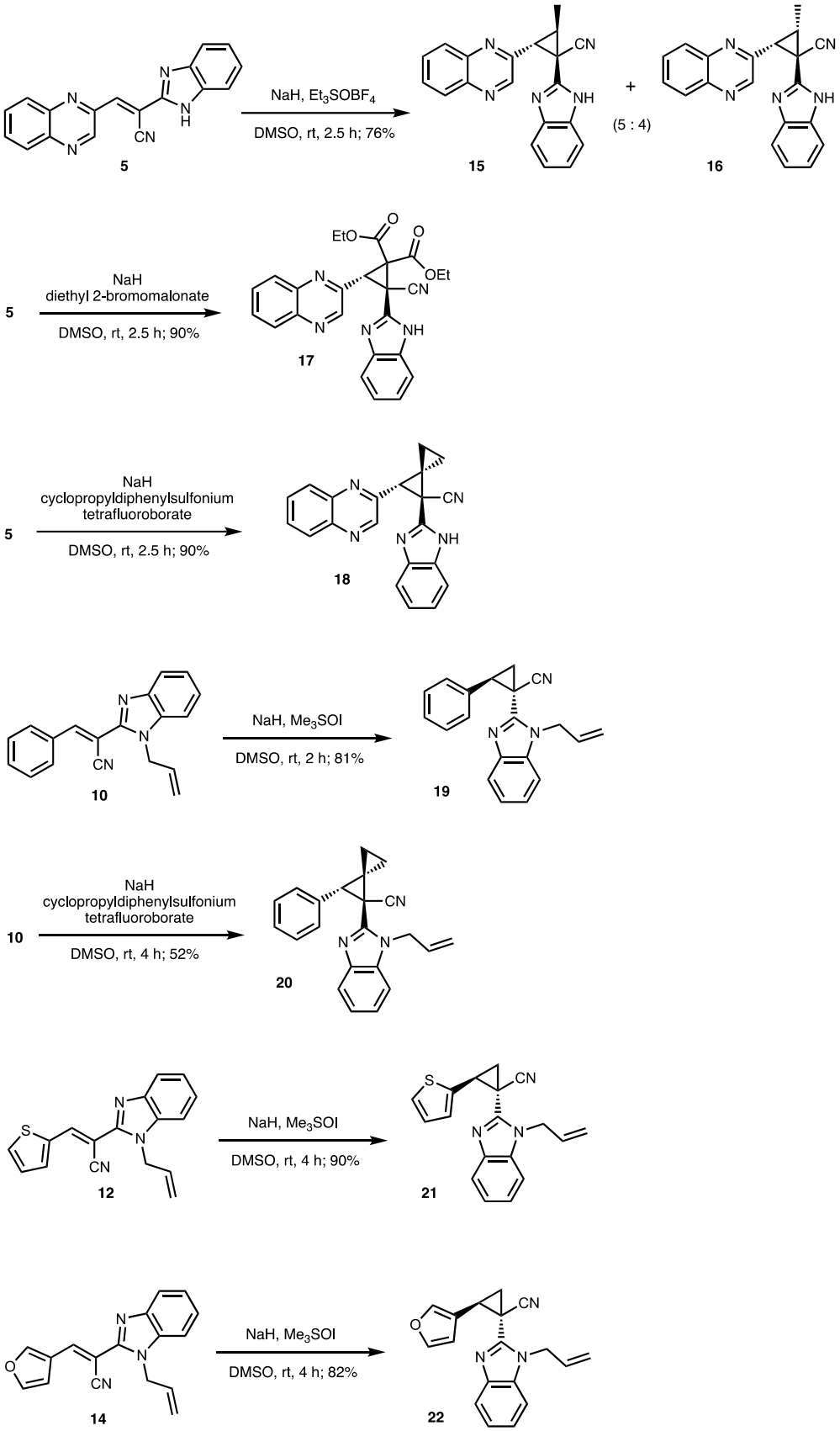


Scheme 2. Preparation of cyclopropane **6** and MgI_2-catalyzed rearrangement to give pyrroloimidazole **7**

Analogous to the preparation of acrylonitrile **5** but using a TMS-Cl mediated Knoevenagel condensation that provided greater *trans*-selectivity,[21] we generated nitriles **10**, **12**, and **14** from aldehydes **8**, **11**, and **13**, respectively, in 81-85% yield by condensation with *N*-allylated benzimidazole **9**[22,23] (Scheme 3). The *N*-allyl group was selected because of its ease of introduction and possibility for selective removal as a protective group.[24] While the kinetic control in the base-mediated addition of **3** to aldehyde **2** provided alkenes **4** and **5** as a mixture of stereoisomers, thermodynamic control under TMS-Cl conditions proved selective for the formation of *E*-alkenes **10**, **12**, and **14**. These nitriles were then subjected to a range of trialkylsulfonium ylides, generating the corresponding cyclopropanes in generally high yield (Scheme 4). Methyl-substituted diastereomers **15** and **16** were formed in a 5:4 ratio from acrylonitrile **5**, which also served as the precursor to the malonate derivative **17** and the unique *spiro*-biscyclopropane **18**. The phenyl analog **10** was converted to the cyclopropane **19** and the *spiro*-biscyclopropane **20** in 81% and 52% yield, respectively. The thiophene and furan analogs **12** and **14** were similarly readily converted to cyclopropanes **21** and **22**.



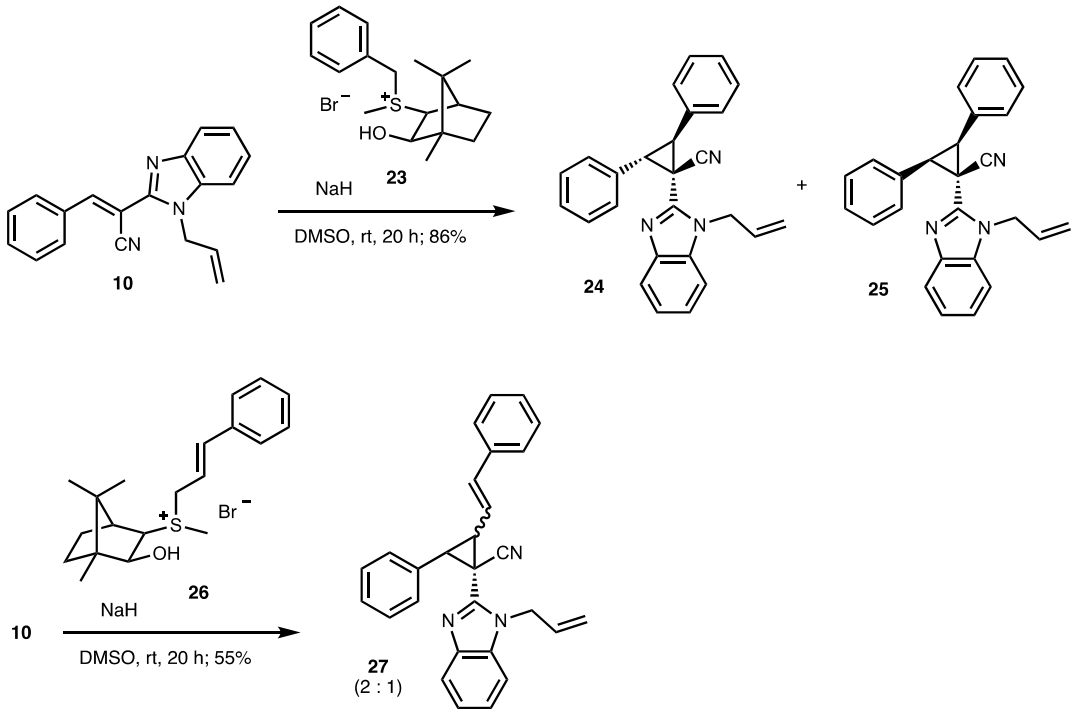
Scheme 3. Preparation of acrylonitriles **10**, **12**, and **14**



Scheme 4. Preparation of cyclopropylbenzimidazoles **15**-**22** with trialkylsulfonium ylides

We also prepared the camphor-derived chiral sulfonium bromides[25] **23** and **26** to access enantioenriched cyclopropanes, but both **24** and **27** were isolated as racemic mixtures (Scheme 5).

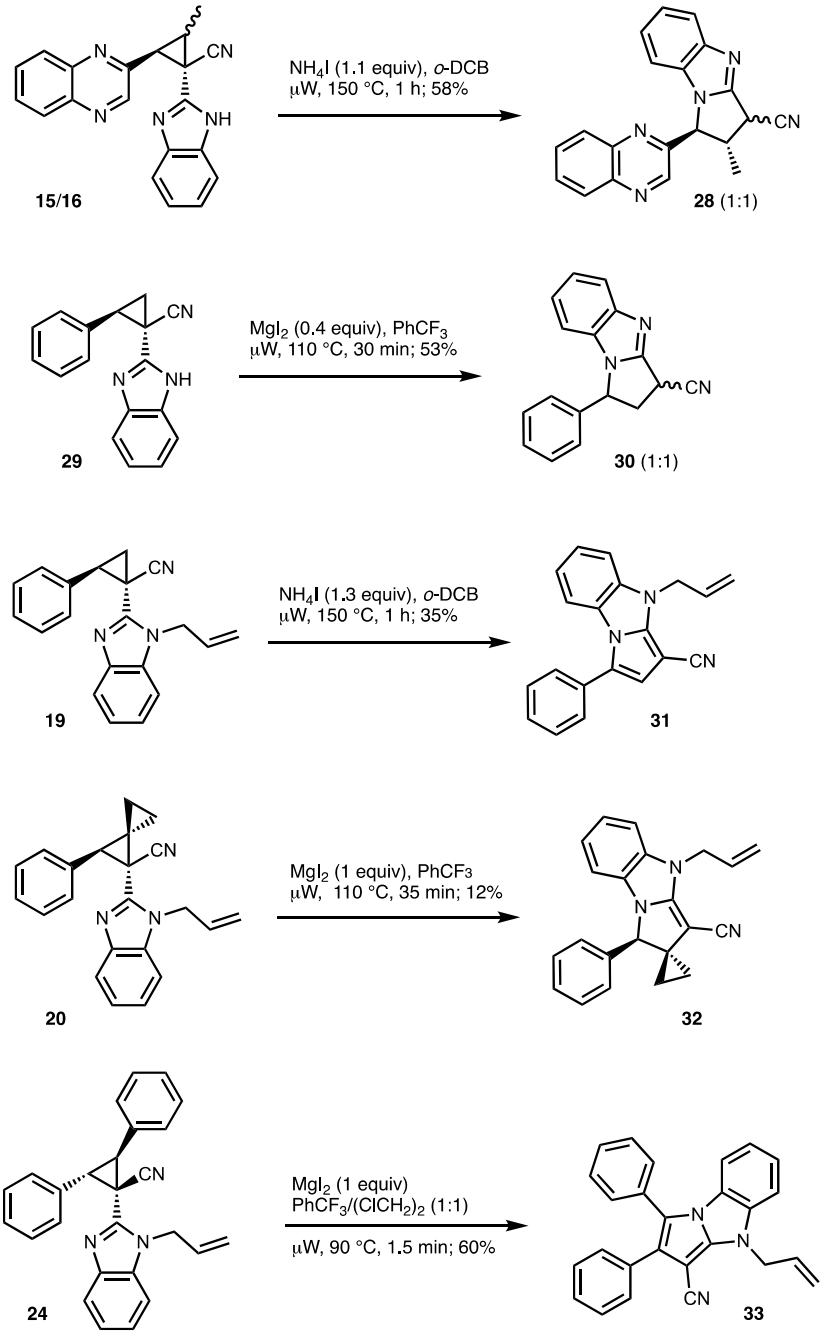
Cyclopropane **24** was formed as the major product in the addition of the sulfur ylide derived from **23**, accompanied by traces of a diastereomer that we assigned tentatively as the *cis*-isomer **25**. Cyclopropane **27** was obtained as an inseparable mixtures of diastereomers. We are continuing efforts to realize an enantioselective cyclopropanation in order to investigate the intrinsic stereoselectivity of this rearrangement.



Scheme 5. Attempted enantioselective preparation of cyclopropylbenzimidazoles **24** and **27** with camphor-derived trialkylsulfonium ylides

With the desired polysubstituted cyclopropane benzimidazoles in hand, we next explored the scope of the iminocyclopropane rearrangement (Scheme 6). The mixture of methylated cyclopropanes **15** and **16** remained unchanged under standard MgI_2 conditions, but in the presence of 1.1 equiv of NH_4I[10] at 150 °C in *ortho*-dichlorobenzene (*o*-DCB) a 1:1 mixture of pyrrolines **28** was isolated in 58% yield. In contrast, cyclopropane **29** formed pyrrolidine **30** with 0.4 equiv of MgI_2 in 53% yield as a chromatographically inseparable mixture of stereoisomers. While the exposure of the *N*-allylated benzimidazole **19** to MgI_2 conditions led to significant decomposition even at lower temperatures, the use of NH_4I at 150 °C in *o*-DCB delivered the aromatized pyrrole **31** in 35% yield. The *spiro*-biscyclopropane **20** provided the rearranged compound **32** in 12% yield, but the amount of MgI_2 Lewis acid had to be increased to 1 equiv

for this otherwise sluggish conversion. Finally, cyclopropane **24** also yielded a complete conversion to the aromatized pyrrole **33** in 60% yield when subjected to 1 equiv of MgI_2 in a mixture of trifluorotoluene and 1,2-dichloroethane (to improve solubility) at 90 °C for 1.5 min in the microwave reactor. Under a range of sampled reaction conditions at up to 110 °C, cyclopropanes **17**, **18**, **21**, **22** and **27** did not form any rearranged products and decomposed under harsher conditions. This observation suggests that aliphatic substitutions at the methylene group of the cyclopropane modify the activation barrier for the



Scheme 6. Successful iminocyclopropane rearrangements of cyclopropanes **15**/**16**, **19**, **20**, **24** and **29**

rearrangement; while monosubstitution is still tolerated (e.g. substrate **15**/**16**) and aromatic substituents, such as a phenyl group (e.g. substrate **24**) actually accelerate the reaction, disubstitution with electron-withdrawing esters such as in malonate **17**, or the *spiro*-biscyclopropane **18**, prevent the rearrangement or greatly reduce its efficiency (e.g. *spiro*-biscyclopropane **20**). It is possible that the styryl group in **27** triggers additional side reactions and rearrangements, thus preventing the isolation of the 5-membered iminocyclopropane rearrangement product. Furthermore, another current limitation of this transformation is the preference for electron-deficient heterocycles at the methine group C(2) of the cyclopropane. While the quinoxaline-substituted cyclopropanes **6** and **15**/**16** rearrange in 50-60% yield, the yield drops to 10-50% for the phenyl-substituted **20**, **24** and **29**, respectively, and the expected pyrroloimidazole is not obtained from thiophene **21** and furan **22**. It is also possible that the *N*-allyl group on the benzimidazole in the latter substrates interferes with the rearrangement process; in this context, the difference in reaction outcome for substrates **19** and **29** is quite instructive, and we plan to investigate these substituent effects further in future work. Finally, it is interesting but not completely unexpected that additional substitution with aryl groups on the cyclopropane and higher temperatures accelerate the aromatization to pyrroles **31** and **33**; likely through spontaneous air oxidation.

In conclusion, we have discovered a facile iminocyclopropane rearrangement of trisubstituted acrylonitrile benzimidazoles to give benzopyrrolo[1,2-*a*]imidazoles via the corresponding C-cyclopropylimidazoles obtained by Corey-Chaykovsky cyclopropanation of the acrylonitriles. While the scope of this transformation is still limited, it allows a convenient preparation of highly substituted fused heterocycles for the study of their biological effects as well as for building blocks for pharmaceutical, agricultural, and materials research. The heterocyclic core motif in these iminocyclopropane rearrangement products, e.g. aryl- and alkyl- as well as spiro-substituted 1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole-3-carbonitriles, is almost unprecedented in the literature, and to the best of our knowledge, only two unrelated approaches have been published to access the aromatic pyrrole product.[26,27] Therefore, this synthetic study represents a novel entry to attractive new heterocyclic scaffolds. We also plan to further investigate this transformation with the goal to develop an enantioselective variant and further broaden its substrate scope.[28]

SUPPORTING INFORMATION

Supplementary (synthesis of starting materials and products, IR, ^{1}H and ^{13}C NMR, MS spectral data, copies of ^{1}H and ^{13}C NMR spectra) data associated with this communication can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27639/105/1.

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REFERENCES AND NOTES

1. A. Thakur and J. Louie, 'Vinylcyclopropane–Cyclopentene Rearrangement. In Molecular Rearrangements in Organic Synthesis,' ed. by C. M. Rojas, John Wiley & Sons, Inc., 2015, pp. 323-362.
2. V. Ganesh and S. Chandrasekaran, *Synthesis*, 2016, **48**, 4347.
3. H. H. Wasserman and R. P. Dion, *Tetrahedron Lett.*, 1983, **24**, 3409.
4. R. V. Stevens, *Acc. Chem. Res.*, 1977, **10**, 193.
5. A. G. Schultz, J. P. Dittami, S. O. Myong, and C. K. Sha, *J. Am. Chem. Soc.*, 1983, **105**, 3273.
6. P.-L. Wu and W.-S. Wang, *J. Org. Chem.*, 1994, **59**, 622.
7. P. J. Campos, A. Soldevilla, D. Sampedro, and M. A. Rodríguez, *Org. Lett.*, 2001, **3**, 4087.
8. Y. V. Tomilov, D. N. Platonov, A. E. Frumkin, D. L. Lipilin, and R. F. Salikov, *Tetrahedron Lett.*, 2010, **51**, 5120.
9. Y. V. Tomilov, R. F. Salikov, D. N. Platonov, D. L. Lipilin, and A. E. Frumkin, *Mendeleev Commun.*, 2013, **23**, 22.
10. R. F. Salikov, D. N. Platonov, A. E. Frumkin, D. L. Lipilin, and Y. V. Tomilov, *Tetrahedron*, 2013, **69**, 3495.
11. S. Saha, C. Venkata Ramana Reddy, and B. Patro, *Tetrahedron Lett.*, 2011, **52**, 4014.
12. M. J. Sarachine, J. M. Janjic, P. Wipf, and B. W. Day, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2404.
13. C. D. Hopkins, J. C. Schmitz, E. Chu, and P. Wipf, *Org. Lett.*, 2011, **13**, 4088.
14. S. Wu, Z. Guo, C. D. Hopkins, N. Wei, E. Chu, P. Wipf, and J. C. Schmitz, *Oncotarget*, 2015, **6**, 40866.
15. C. Delpivo, G. Micheletti, and C. Boga, *Synthesis*, 2013, **45**, 1546.
16. Y. Tagawa, K. Yamashita, Y. Higuchi, and Y. Goto, *Heterocycles*, 2003, **60**, 953.
17. M. M. Sirim, V. S. Krishna, D. Sriram, and O. U. Tan, *Eur. J. Med. Chem.*, 2020, **188**, 112010.
18. A. K. Nadipuram, W. M. David, D. Kumar, and S. M. Kerwin, *Org. Lett.*, 2002, **4**, 4543.
19. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
20. (a) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, and E. M. Carreira, *Angew. Chem. Int. Ed.*, 1999, **38**, 3186; (b) R. W. Coscia and T. H. Lambert, *J. Am. Chem. Soc.*, 2009, **131**, 2496; (c) D. J. Mack and J. T. Njardarson, *ACS Catal.*, 2013, **3**, 272.

21. K. Wang, C. Chen, X. Liu, D. Li, T. Peng, X. Liu, D. Yang, and L. Wang, *Org. Lett.*, 2018, **20**, 5260.
22. P. Thapa, P. M. Palacios, T. Tran, B. S. Pierce, and F. W. Foss Jr., *J. Org. Chem.*, 2020, **85**, 1991.
23. R. M. Mohareb, A. E. M. Abdallah, and A. A. Mohamed, *Chem. Pharm. Bull.*, 2018, **66**, 309.
24. L. S. Lin, T. J. Lanza, L. A. Castonguay, T. Kamenecka, E. McCauley, G. Van Riper, L. A. Egger, R. A. Mumford, X. Tong, M. MacCoss, J. A. Schmidt, and W. K. Hagmann, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2331.
25. (a) K. Huang and Z.-Z. Huang, *Synlett*, 2005, 1621; (b) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu, and L.-X. Dai, *J. Am. Chem. Soc.*, 2006, **128**, 9730.
26. W.-S. Hsu, V. Paike, and C.-M. Sun, *Mol. Divers.*, 2013, **17**, 285.
27. B. D. Narhe, M.-H. Tsai, and C.-M. Sun, *ACS Comb. Sci.*, 2014, **16**, 421.
28. Aldehyde **2**,[15,16] benzimidazoles **3** and **9**,[17,18,21,22] and camphor-derived sulfonium salts **23** and **25**[25] were prepared by previously reported procedures. Experimental details and ^{1}H NMR and ^{13}C NMR spectra for new compounds are given in the Supplementary Material.