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The Diels–Alder Reactions of Quinone Imine Ketals: A Versatile Synthesis of Highly Substituted 5-Methoxyindoles

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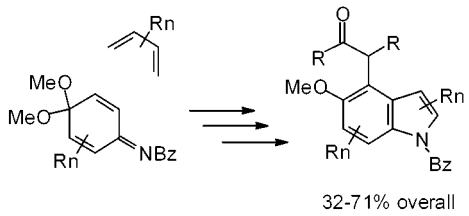
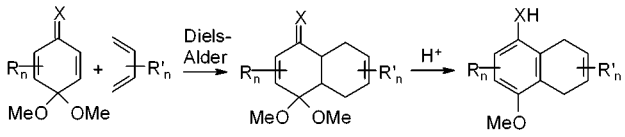
ABSTRACT



N-Benzoylated quinone imine ketals undergo smooth cycloadditions in a [4 + 2] sense to yield the expected cycloadducts. The crude cycloadducts, when subjected to a short series of simple transformations, produce synthetically useful quantities of 5-methoxyindoles in excellent overall yields.

Recently we reported that quinone mono ketals (QMK) **1** and quinone imine ketals (QIK) **2** undergo smooth cycloaddition at 13 kbar with 1,3-butadienes to yield the expected endo cycloadducts **3** and **4** in excellent yields with extremely high regiochemical and diastereofacial control (Scheme 1).[1]

Scheme 1. The Diels−Alder Reactions of Quinoid Mono Ketals



1: X = O
2: X = NBz
3: X = O
4 X = NBz
5: X = O
6: X = NBz

The source of the regiocontrol is the ketal moiety since it both sterically biases the dienophilic double bond and removes a carbonyl from conjugation with it. A steric model for this selectivity has been proposed by us previously.[1b] Although isolable and stable, the adducts undergo facile acid-catalyzed aromatization to produce the corresponding dihydronaphthalenes **5** and **6**. We have applied this chemistry to the synthesis of the seco-ergoline skeleton.[2] Although QMK's have received some attention as dienophiles in the Diels−Alder reaction,[3] we are aware of only one report other than ours of similar chemistry involving QIK's.[4] The preparation and rich chemistry of QIK's has been explored by Swenton and co-workers.[5]

Our interest in the synthesis and reactivity of the indole moiety, stemming from its position at the forefront of medicinal and alkaloid chemistry,[6] is ongoing. A strategy occurred to us, which envisioned 5-methoxyindoles being expeditiously accessible via the Diels−Alder reaction of QIK's. Scheme 2 illustrates such a strategy. Dihydronaph-

Scheme 2. Strategy for the Formation of 5-Methoxyindoles

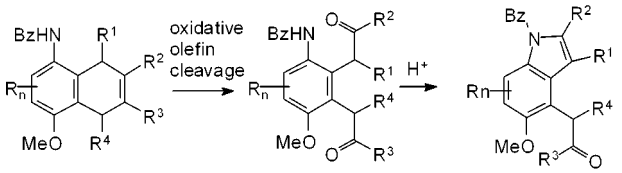


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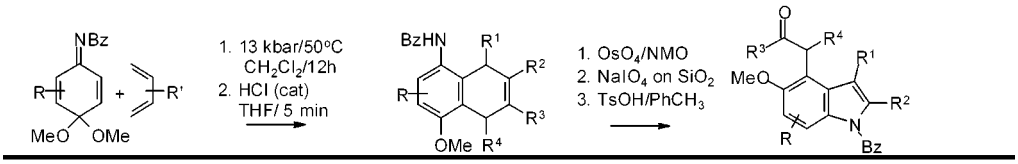
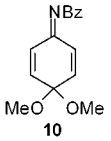
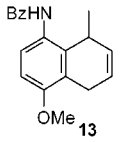
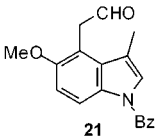
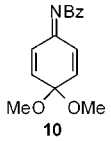
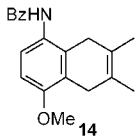
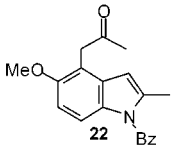
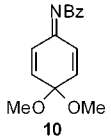
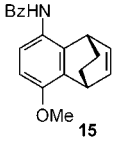
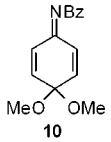
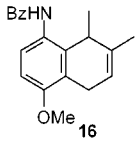
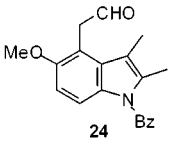
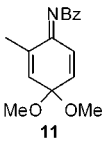
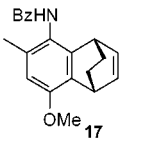
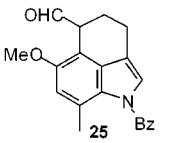
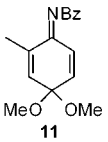
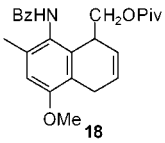
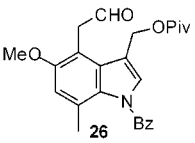
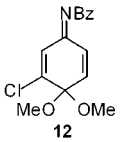
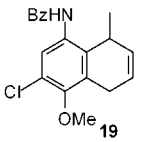
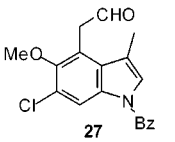
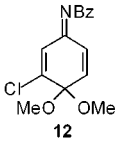
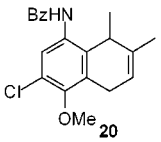
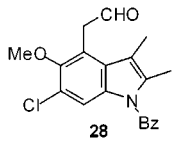
Table 1. The Synthesis of 5-Methoxyindoles from Quinone Imine Ketals



entry	dienophile	diene	dihydronaphthalene (yield from QIK)		indole (yield)	
1	 **10**		 **13**	97%	 **21**	73% from **13** 71% from **10**
2	 **10**		 **14**	87%	 **22**	37% from **14** 32% from **10**
3	 **10**		 **15**	92%	 **23**	71% from **15** 65% from **10**
4	 **10**		 **16**	81%	 **24**	80% from **16** 65% from **10**
5	 **11**		 **17**	92%	 **25**	69% from **17** 63% from **11**
6	 **11**		 **18**	70%	 **26**	46% from **18** 32% from **11**
7	 **12**		 **19**	85%	 **27**	77% from **19** 65% from **12**
8	 **12**		 **20**	90%	 **28**	70% from **20** 63% from **12**

thalenes **7** (available via the reaction sequence shown in Scheme 1) are subjected to oxidative cleavage of the olefinic moiety producing dicarbonyl compound **8**, which when treated with acid would produce indole **9**.[7] Judicious choice of the reactants allows access to a wide variety of 5-methoxyindoles. Herein we report our success in this regard and the development of an indole synthesis that complements the methods which exist for the formation of the benzopyrrole system.[8]

Table 1 shows the results of the high-pressure[9] Diels–Alder reactions of several QIK's (**10**–**12**) with a variety of dienes[10] and subsequent conversion to indoles by the strategy outlined in Scheme 2. QIK's **11** and **12** were chosen simply to illustrate the tolerability of substitution at the 2 and 3

(1) (a) Kerr, M. A.; Jarvo, E. R.; Boothroyd, S. R. *Synlett* **1996**, 897–899. (b) Kerr, M. A. *Synlett* **1995**, 1165–1167.

(2) Banfield, S. C.; Kerr, M. A. *Synlett* **2001**, 436–438.

(3) (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, 1559–1562. (b) Gerstenberger, I.; Hansen, M.; Mauvais, A.; Wartchow, R.; Winterfeldt, E. *Eur. J. Org. Chem.* **1998**, 643–650. (c) Russel, R. A.; Evans, D. A. C.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1699–1707. (d) Carreño, M. C.; Fariña, F.; Ruano, J. L. C.; Puebla, L. *J. Chem. Res., Synop.* **1984**, 288–289. (e) Carreño, M. C.; Fariña, F.; Galan, A.; Ruano, J. L. C. *J. Chem. Res., Synop.* **1979**, 296–297.

positions of the dienophile. We have been unsuccessful in promoting these reactions using ambient pressure conditions; however, on the basis of literature precedent with quinone mono ketals, the use of Lewis acids appears to hold some promise[3a] and work is in progress to explore this method of cycloaddition. Treatment of the crude isolated adduct in THF with a drop of concentrated HCl results in the rapid (<5 min) and quantitative conversion to the dihydronaphthalenes shown in Table 1. Previously[1b] we had used catalytic *p*-toluenesulfonic acid in toluene to effect the aromatization with yields of only 50−60%; the use of HCl in THF was a simple but exceedingly important modification of our protocol. Purification of the dihydronaphthalene is usually accomplished by simple trituration with hexanes. Although acid labile, the adducts (prior to aromatization) are otherwise stable and can be chromatographically purified and stored for extended periods of time in the freezer. It should be emphasized that a single regioisomer of the Diels−Alder adduct was formed in all cases.

With the adducts in hand, the oxidative cleavage of the olefin could be effected. While a variety of methods were investigated (ozonolysis, Johnson−Lemieux oxidation), dihydroxylation with catalytic OsO_4 in the presence of NMO[11] proved to be the method of choice. The diol was typically not isolated in pure form, the crude product being subjected to scission with $NaIO_4$ supported on silica gel.[12] The crude dicarbonyl compound was treated with acid (*p*-TsOH/toluene) to form the indoles shown in Table 1 in excellent overall yields (32−71% over the five steps).[13]

As expected, the tetrasubstituted olefin in **14** was the most difficult to cleave oxidatively. In the other cases this transformation proceeded in yields typical of previous literature examples. It should be noted that $NaIO_4$ supported on silica was key to the clean cleavage of the diol.

The dienes and dienophiles were selected to illustrate the generality of this method for the formation of 5-methoxyindoles with virtually any substitution pattern. Compound **28**, in fact, is a hexasubstituted indole. It is evident that by employing the appropriate dienes and dienophiles a wide variety of indoles may be prepared. Note that **23** and **25** represent the seco-ergoline system with the formyl group as a handle for elaboration into the side chain present in the ergot alkaloids.

In summary, we have reported a simple and high-yielding preparation of densely substituted 5-methoxyindoles. The key steps are the hyperbaric Diels−Alder reaction of the quinone imine ketal and the subsequent oxidative cleavage of the dihydronaphthalene. The overall synthesis of the indoles requires only two purifications, one of which is a final purification of the indole by flash column chromatography. Efforts are underway to examine more electron withdrawing nitrogen substituents as well as Lewis acids in order to make this an ambient pressure and truly scalable process.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC), the Ontario Ministry of Science and Technology, and MedMira Laboratories for generous financial support of this research. D.B.E. is the recipient of an OGSST scholarship.

Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR, ^{13}C NMR, IR, and MS analysis data for compounds **13**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Coutts, I. G. C.; Culbert, N. J.; Edwards, M.; Hadfield, J. A.; Musto, D. R.; Pavlidis, V. H.; Richards, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 9, 1829−1836.

(5) (a) Swenton, J. S.; Bonke, B. R.; Chen, C.-P.; Chou, C.-T. *J. Org. Chem.* **1989**, *54*, 51−58. (b) Swenton, J. S.; Shih, C.; Chen, C.-P.; Chou, C.-Y. *J. Org. Chem.* **1990**, *55*, 2019−2026. (c) Swenton, J. S.; Bonke, B. R.; Clarke, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027−2034.

(6) (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Pergammon Press: New York, 1996; Vol. 2, pp 203−257. (b) Snieckus V. A. In *The Alkaloids*; Academic Press: New York, 1968; Vol. 11, Chapter 1.

(7) Kraus and co-workers cleaved a 1,4-tosylamido dihydronaphthalene in an elegant synthesis of the pyrroloindole subunit of CC-1065. See: Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 284−286.

(8) (a) Gribble, G. W. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 1045−1075. (b) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (c) Brown, R. K. In *Heterocyclic Compounds*, Vol. 25 Part 1; Wiley: New York, 1972; Chapter 2.

(9) (a) Klarner, F.-G.; Diedrich, M. K.; Wigger, A. E. In *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 3. (b) Jurczak J.; Gryko, D. T. In *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 4. (c) Isaacs, N. S. In *High-Pressure Techniques in Chemistry and Physics*; Holzapfel, W. B., Isaacs, N. S., Oxford: New York, 1997; Chapter 7.

(10) Diels−Alder reactions were typically performed on a 2 to 3 mmol scale. See the Supporting Information for experimental details.

(11) Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, 65, 3346−3356.

(12) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.

(13) Although not isolated in practice, the crude diol resulting from osmylation and the crude dicarbonyl resulting from oxidative cleavage were characterized by NMR in one case to confirm that these were, in fact, synthetic intermediates.