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Methodology for Regioselective Synthesis of Substituted Pyridines via Intramolecular Oximino Malonate Hetero Diels–Alder Reactions

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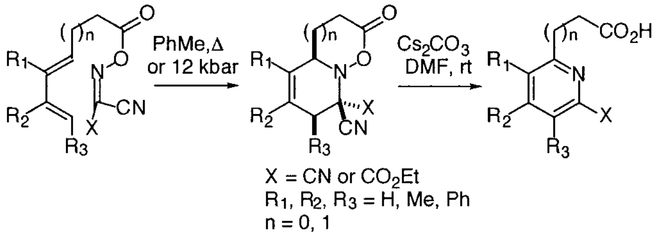
ABSTRACT

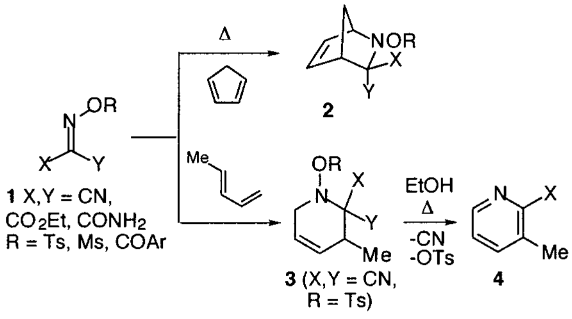


Various substituted pyridines can be prepared regioselectively by a sequence involving an intramolecular thermal or high-pressure Diels–Alder cycloaddition of an oximino malonate dienophile tethered to a dienic carboxylic acid, followed by mild aromatization of the resulting cycloadduct with cesium carbonate in DMF at room temperature.

In recent years, Diels−Alder cyclizations of imino dienophiles have provided powerful methodology for construction of a diverse array of nitrogen heterocycles and alkaloids.[1] In a series of papers commencing about 30 years ago, Fleury and co-workers found that various oximino malonate derivatives **1** undergo Diels−Alder cycloadditions with cyclopentadiene, as well as a few simple acyclic dienes, to afford adducts such as **2** and **3**, respectively (Scheme 1).[2]

In general, the degree of regioselectivity of this process appears to be good, although this aspect of the chemistry has not been extensively investigated. It does appear, however, that the regiochemistry with **1** is reversed relative to that found with simpler imino dienophiles.[1] Fleury found that solvolysis of adduct **3** in refluxing ethanol produced pyridine **4**. Subsequent work by Breitmaier involved using 1-oxygenated butadienes in the cycloaddition with **1** (X, Y = CN, R = Ts),[3] and it was demonstrated that these types

Scheme 1



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[1] For reviews and leading references to imino Diels−Alder reactions, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987; Chapter 2. (b) Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 401.

[2] (a) Biehler, J.-M.; Perchais, J.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2711. (b) Biehler, J.-M.; Fleury, J.-P. *J. Heterocycl. Chem.* **1971**, *8*, 431. (c) Perchais, J.; Fleury, J.-P. *Tetrahedron* **1972**, *28*, 2267. (d) Fleury, J.-P. *Chemia* **1977**, *31*, 143. (e) Fleury, J.-P.; Desbois, M.; See, J. *Bull Soc. Chim. Fr.* **1978**, II-147.

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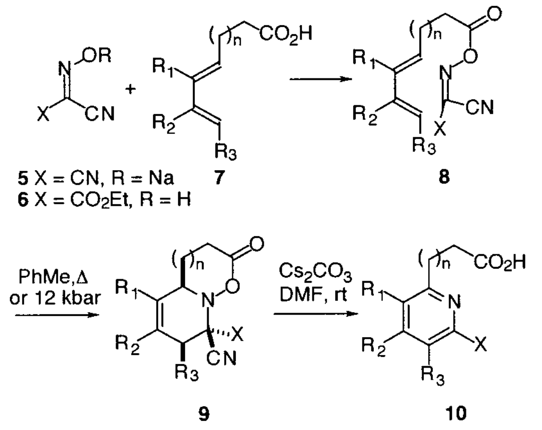
of cycloadducts could also be converted to pyridines by base-promoted elimination in low to modest yields. More recently, Katagiri[4] and Danheiser[5] have explored [4 + 2]-cycloadditions with Meldrum's acid analogues of dienophiles **1**. In addition, the latter group developed methodology for efficient conversion of these adducts to pyridines.[5]

One simple strategy for controlling regiochemistry of imino Diels–Alder reactions is to make the process intramolecular.[6] To our knowledge, however, intramolecular cycloadditions of oximino dienophiles have not previously been reported. Herein we demonstrate the feasibilty of this approach and also report good methodology for aromatization of the resulting cycloadducts to pyridines.

Various dinitrile substrates **8** (X = CN) for the cycloadditions were prepared by *O*-acylating commercially available sodium (hydroxyimino)malononitrile (**5**) with the acid chlorides derived from diene acids **7** (Scheme 2).[2]

Scheme 2

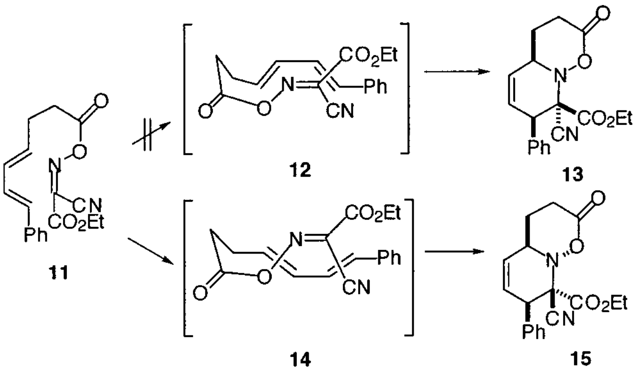


The corresponding ester nitrile precursors **8** (X = CO_2Et) were synthesized directly from oxime **6** and the diene acids using DCC as the coupling reagent (see Supporting Information). It was found that heating acyl oximes **8** in refluxing toluene overnight promoted [4 + 2]-cycloaddition to afford the desired cycloadducts **9**. The best yields of compounds **9** were obtained if the thermolyses were conducted in dilute solution (0.005 M) since at higher concentrations considerable amounts of tarry material were formed. Table 1 shows examples of these Diels–Alder reactions. In addition, the cycloadditions could be promoted by high pressure (12 Kbar, rt) in similar yields.

After screening a variety of bases, it was found that treatment of adducts **9** with cesium carbonate in DMF at room temperature effects aromatization to pyridines **10**. Other bases such as DBU, triethylamine, and Dowex 1X8-400 ion-exchange resin afforded the pyridines in irreproducible or considerably lower yields. Table 1 contains examples of these transformations in several systems.

It was observed that all intramolecular cycloadditions involving the unsymmetrical oximino dienophile **6** afforded products which were single stereoisomers. We have probed these interesting stereochemical issues with the help of X-ray crystallography.[8] Thus, it was found by crystallography that oxime **6** is in fact the *E*-geometrical isomer. X-ray analysis also demonstrated that the cycloadduct formed from diene ester **11** is the stereoisomer shown in **15** (Table 1 entry 2, and Scheme 3).

Scheme 3



Assuming that oxime isomerization of **6** does not occur during the esterification of the diene acid, and that Diels–Alder precursor **11** has the anticipated *E*-geometry, cycloaddition must occur via a transition state having the cyano group *endo*. Molecular mechanics calculations (PCModel, version 6) indicate that pseudo boat **14** is ~2.8 kcal/mol more stable than the *exo*-cyano pseudo boat conformation **12**, which would lead to the alternative stereoisomer **13**. The corresponding pseudo chairs related to **12** and **14** are both considerably higher in energy. Cyclization of conformer **14** leads initially to a *cis* azadecalin, which then inverts to the *trans* system as is evident from the X-ray data (see Supporting Information). Moreover, cyclization of **12** would lead directly to a *trans* azadecalin.

X-ray analysis of the cycloadduct in Table 1, entry 4 (X = CO_2Et) demonstrates that the same stereochemical preference for an *endo* cyano group applies in the 6,5-fused system. It might also be noted that Fleury et al. found that the *intermolecular* cycloaddition between the tosylate of oxime **6** and cyclopentadiene gave exclusively the product (cf. **2**) having the cyano group *exo*.[2b]

In summary, we have found that substituted pyridines can be produced regioselectively by a sequence utilizing an

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(3) Dormagen, W.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1988**, 636.

(4) Katagiri, N.; Nochi, H.; Kurimoto, A.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 1251.

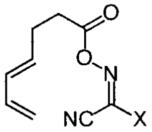
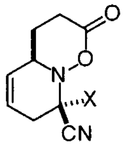
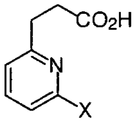
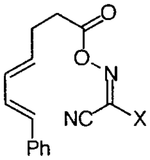
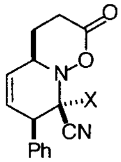
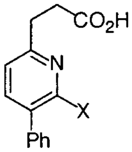
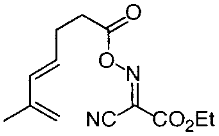
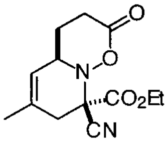
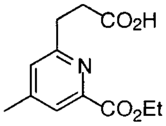
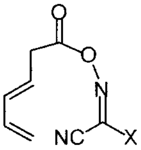
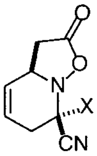
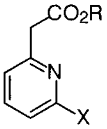
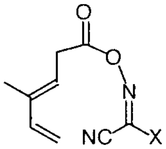
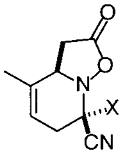
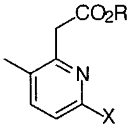
(5) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840.

(6) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.

(7) For preparation of these types of dienic acids, see inter alia: (a) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (b) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274. (c) Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335.

(8) We are grateful to Dr. M. Shang (University of Notre Dame) for conducting the X-ray analyses of compound **6** and the cycloadduct shown in entry 4, Table 1 (X = CO_2Et) and Dr. D. Powell (University of Wisconsin) for analysis of **15**.

Table 1. Intramolecular Diels–Alder Reactions of Oximino Malonates and Aromatization of the Resulting Cycloadducts

entry	Diels-Alder precursor	cycloadduct	yield method A[a]	yield method B[b]	pyridine[c]	yield
1			X = CN 68% X = CO_2Et 70%	X = CN 65% X = CO_2Et 76%		X = CN 72% X = CO_2Et 69%
2			X = CN 52% X = CO_2Et 74%	X = CO_2Et 63%		X = CN 79% X = CO_2Et 71%
3			35%			81%
4			X = CN 67% X = CO_2Et 63%			X = CN, R = H 67% X = CO_2Et, R = Et 53%[d]
5			X = CN 62% X = CO_2Et 67%			X = CN, R = H 67% X = CO_2Et, R = Et 38%[d]

[a] PhMe (0.005 M), reflux, 24–48 h. [b] 12 Kbar, CH_2Cl_2, rt, overnight. [c] Cs_2CO_3 in DMF, rt, overnight. [d] For ease of isolation in this case, the acid was converted to the ethyl ester (see Supporting Information for details).

intramolecular oximino malonate hetero Diels–Alder reaction, followed by mild base-catalyzed aromatization of the resulting cycloadduct. This methodology should be particularly useful in preparation of pyridines involving cases of functionally unsymmetrical but electronically symmetrical dienes. We are currently investigating extensions and applications of this chemistry.

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for generous financial support of this research and to Professor R. L. Funk for helpful discussions and assistance in performing the molecular mechanics calculations.

Supporting Information Available: Experimental details and spectral data for compounds in Table 1 and an ORTEP drawing of compound **15**. This material is free of charge via the Internet at http://pubs.acs.org.

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