ORGANIC LETTERS

2006
Vol. 8, No. 6
1081−1084

Tandem Photocycloaddition–Retro-Mannich Fragmentation of Enaminones. A Route to Spiropyrrolines and the Tetracyclic Core of Koumine

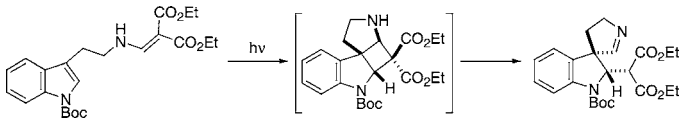
James D. White* and David C. Ihle

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@oregonstate.edu

Received December 6, 2005

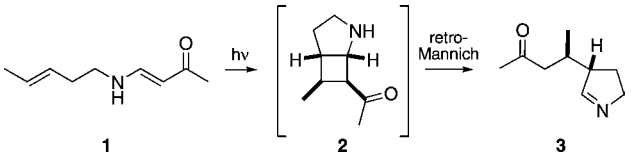
ABSTRACT



Intramolecular [2 + 2] photocycloaddition of β-aminoalkylidene malonates gives transiently a cyclobutane which undergoes retro-Mannich fragmentation to a Δ¹-pyrroline. The tandem sequence, exemplified in two series based on tryptamine and aminoethyl-1,4-cyclohexadiene, leads to a spiroindolopyrroline skeleton and to the nonindolenine portion of koumine.

Enaminones (vinylogous amides) are photochemically reactive, and when irradiated they undergo [2 + 2] cycloaddition with an alkene to generate a cyclobutane.[1,2] The intramolecular variant of this photocycloaddition (Scheme 1) is also known.[3−5] Ring strain generated in the conversion of **1** to **2** can lead to fragmentation of the cyclobutane via a retro-Mannich reaction, with the result that a Δ¹-pyrroline (**3**) is formed in a stereodefined manner.

Scheme 1

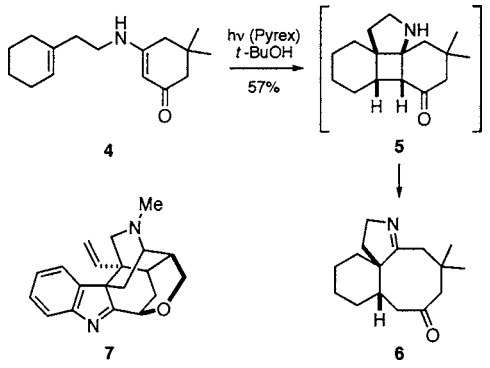


The overall conversion **1** → **3** is the intramolecular nitrogen counterpart of a process first described by De Mayo, in which an enolic β-diketone undergoes [2 + 2] photocycloaddition with an alkene followed by retro-aldol fragmentation of the intermediate cyclobutane to produce a 1,5-diketone.[6] An early example of the process shown in Scheme 1 was reported by Schell, who showed that irradiation of **4** through Corex glass led initially to tetracycle **5** and then to the cyclooctanone **6** (Scheme 2).[7] Application of this tandem sequence has been made by Winkler in syntheses of several alkaloids, including mesembrine,[8] perhydrohistrionicotoxin,[9] vindorozine,[10] and manzamine A,[11] and Swindell has used the method for construction of the taxane BC subunit.[12]

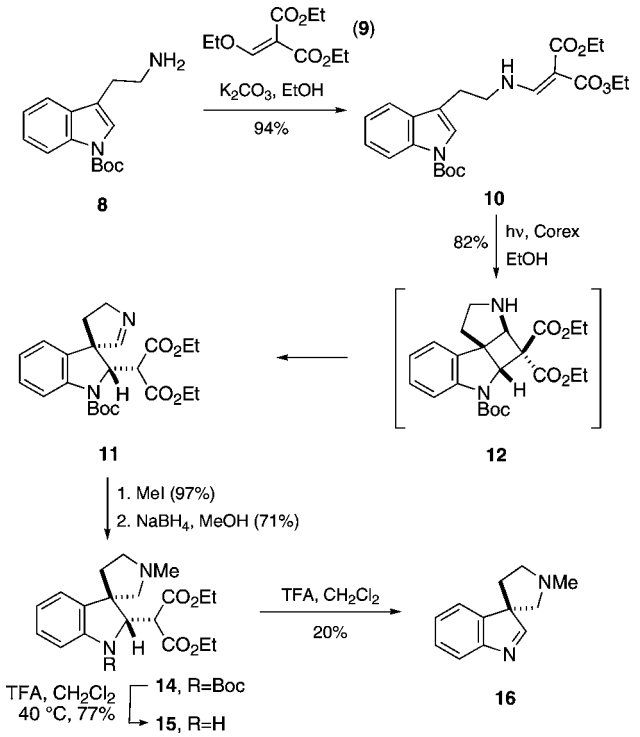
(1) Bohme, E. H.; Valenta, Z,; Wiesner, K. *Tetrahedron Lett.* **1965**, 2441.
(2) Cantrell, T. S. *Tetrahedron* **1971**, *27*, 1227.
(3) Wiesner, K.; Musil, V.; Wiesner, K. J. *Tetrahedron Lett.* **1968**, 5643.
(4) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702.
(5) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 1380.
(6) De Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.
(7) Schell, F. M.; Cook, P. M. *J. Org. Chem.* **1984**, *49*, 4067.
(8) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831.
(9) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
(10) Winkler, J. D.; Scott, R. D.; Williard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 8971.
(11) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.

10.1021/ol052955y CCC: $33.50
Published on Web 02/21/2006

Scheme 2



Scheme 3

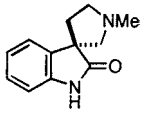


However, the scope of the intramolecular photocycloaddition−retro-Mannich process has received less attention than the De Mayo reaction despite the opportunities it presents for preparing a diverse set of nitrogen heterocycles with good stereocontrol.

We now report the results of a study which demonstrate that the intramolecular [2 + 2] photocycloaddition−retro-Mannich construct can be applied to substrates based on tryptamine and β-phenethylamine templates. Among other attributes, this chemistry has provided entry to the core structure of the indolenine alkaloid koumine (**7**).[13]

Our initial studies focused on the intramolecular photocycloaddition of β-amino-substituted alkylidene malonates on the premise that a sequence akin to that in Scheme 1 would yield a product in which the ester groups could be differentiated and therefore modified in selective fashion. The protected tryptamine **8** was condensed with diethyl β-ethoxymethylidene malonate (**9**) under basic conditions to afford **10**,[14] which was irradiated through Corex glass with a 450 W Hanovia mercury lamp (Scheme 3). After 7 h, reaction was complete and the spiropyrroline **11** was isolated in high yield. The intermediate tetracycle **12** could not be detected in this reaction, presumably because retro-Mannich fragmentation occurred as soon as **12** was formed, but a subsequent experiment provided circumstantial evidence that **12** was indeed the initial product from **10** (vide infra). Only a single stereoisomer of **11** was produced from **10**, reflecting the uniquely defined configuration around the tetrasubstituted cyclobutane of **12**. This result appears to eliminate a stepwise radical mechanism initiated by attack of the photoexcited alkylidene malonate at the indole 3-position.

Alkaloids of the spiroindolopyrrolidine family,[15] such as the oxindole coerulescine **13**,[16] generally bear a methyl substituent on the pyrrolidine nitrogen. Introduction of this methyl substituent into **11** was accomplished by N-alkylation with methyl iodide followed by reduction of the resulting iminium iodide with sodium borohydride to furnish **14**.



13

Removal of the Boc protection from **14** with trifluoroacetic acid afforded a good yield of **15**, but also led to a minor amount of spiroimine **16** in which the malonate residue was absent. The latter product is apparently the result of a further retro-Mannich fragmentation of **15**.

A useful extension of the sequence shown in Scheme 3 would be incorporation of an alkyl substituent at C2 of the spiropyrrolidine **15** since this could potentially offer a new route to the family of Strychnos alkaloids[17] that includes, for example, akuammicine (**17**).[18] To that end, protected tryptamine **8** was condensed with alkylidene malonate **18** to give **19** (Scheme 4). Irradiation of **19** through Pyrex again afforded a single spiroimine **20**, presumably via cyclobutane **21**. Reduction of **20** with sodium cyanoborohydride yielded **22** as a single epimer resulting from delivery of hydride to the less hindered face of the imine.

Our strategy for assembling the nonindolenine portion **23** of koumine (**7**) envisioned cyclization of octahydroisoquino-

(12) Swindell, C. S.; Patel, B. P.; DeSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346.

(13) (a) Liu, C.; Wang, Q.; Wang, C. *J. Am. Chem. Soc.* **1981**, *103*, 4634. (b) Khuong-huu, F.; Chiaroni, A.; Riche, C. *Tetrahedron Lett.* **1981**, *22*, 733. (c) Zhujin, L.; Qianshong, Y. *Youji Huaxu* **1986**, *1*, 36.

(14) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 2224.

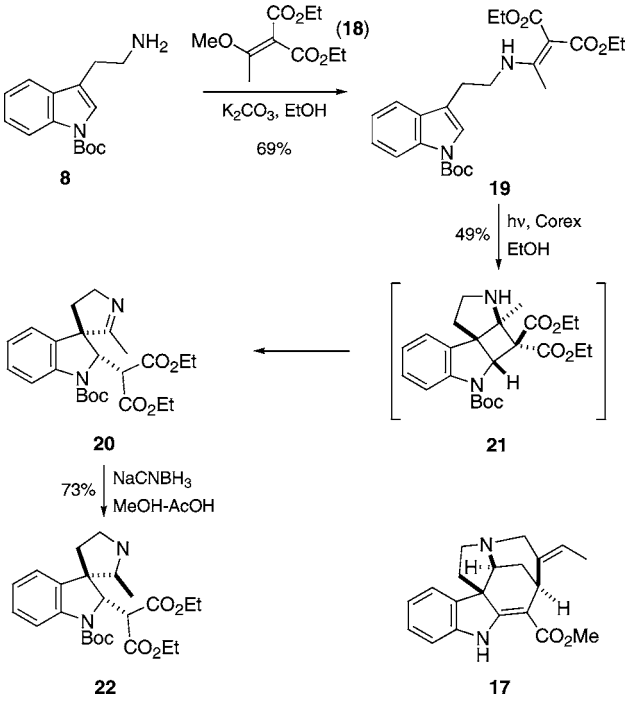
(15) For a review, see: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(16) Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, *48*, 437.

(17) For a review of Strychnos alkaloids: Bosch, J.; Bonjoch, J.; Amat, M. *The Strychnos Alkaloids*; Academic: New York, 1996; pp 75−189.

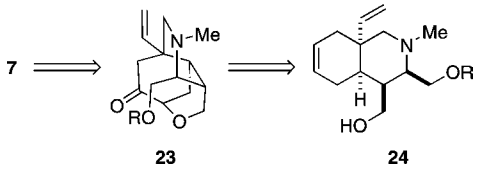
(18) (a) Millson, P.; Robinson, R.; Thomas, A. F. *Experientia* **1953**, *9*, 89. (b) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152.

Scheme 4



line **24**, which we believed could be constructed via a photocycloaddition−retro-Mannich approach similar to that developed with tryptamine (Scheme 5). In this case, our

Scheme 5

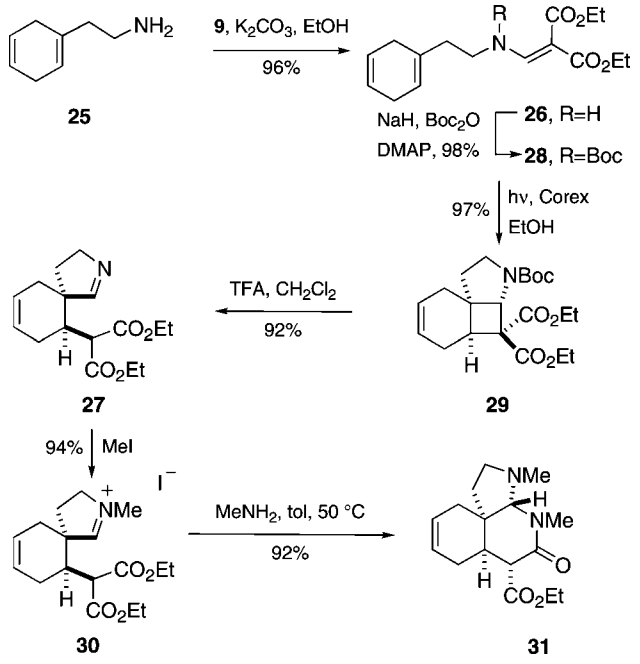


starting point was the Birch reduction product **25**[19] of *β*-phenethylamine, which was condensed with **9** to furnish **26** (Scheme 6). Irradiation of **26**, as expected, produced spiroimine **27** (61% yield), but it was found that the yield of this process could be improved if **26** was first converted to its Boc derivative **28**. When the latter was irradiated through Corex rather than Pyrex glass, the cyclobutane **29** could be isolated in nearly quantitative yield. Subsequent removal of the Boc protection from **29** caused spontaneous retro-Mannich fragmentation to **27**. To activate **27** for cyclization to a precursor for **24**, the imine nitrogen was first methylated and the resultant methiodide **30** was treated with methylamine in warm toluene. The product **31**, obtained in high yield, was the result of initial formation of an aminal followed by intramolecular acylation by one of the two ethyl esters to give a *δ*-lactam.

With **31**, there was now an opportunity to employ the fused pyrrolidine of this tricycle as the progenitor of the angular

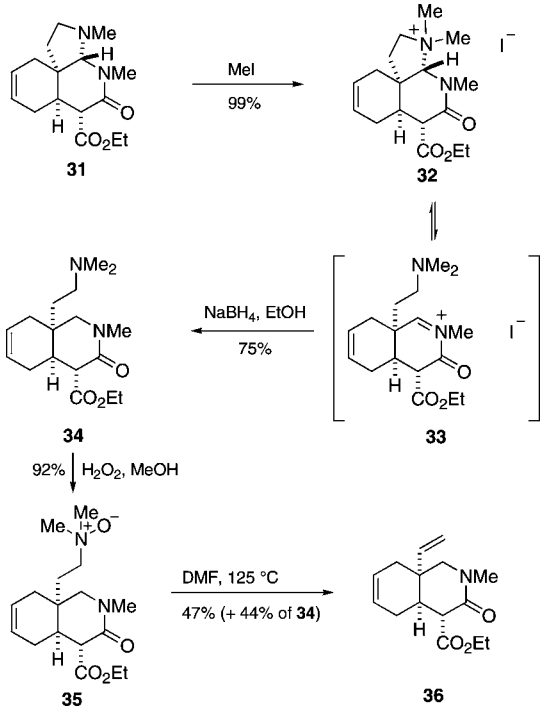
(19) Wimalasena, K.; Alliston, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 1220.

Scheme 6

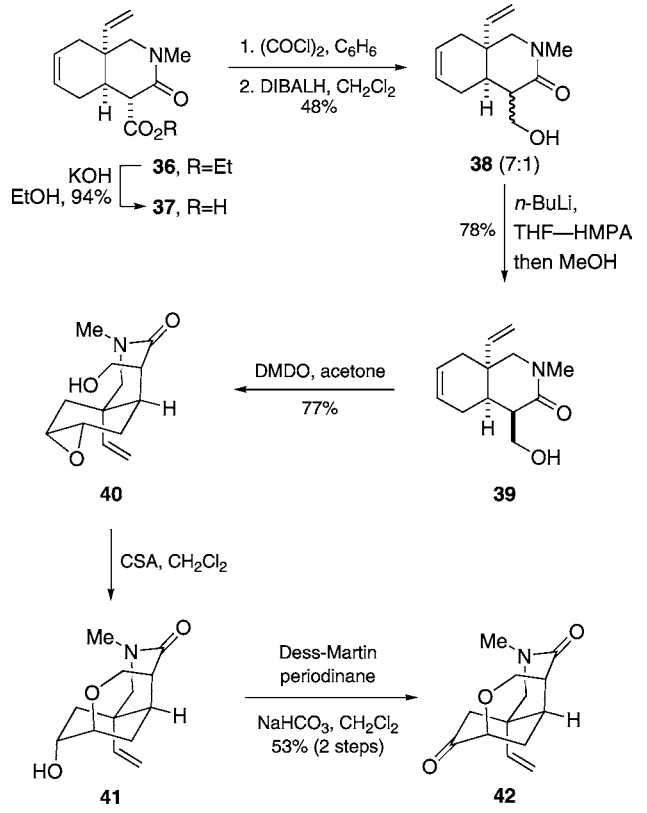


vinyl substituent needed for **24**. The basic pyrrolidine nitrogen of **31** was alkylated with methyl iodide in the expectation that the resultant quaternary iodide **32** would exist in equilibrium with acyliminium iodide **33** (Scheme 7). In practice, reduction with sodium borohydride in situ after treatment of **31** with methyl iodide afforded tertiary amine **34** in excellent yield. Conversion of **34** to its *N*-oxide

Scheme 7



Scheme 8



35 was straightforward, but Cope elimination[20] of **35** in hot DMF yielded isoquinoline **36** accompanied by a significant quantity of **34** resulting from deoxygenation.[21] The latter was recycled through **35** to augment the yield of **36**.

(20) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.
(21) Crabb, T. A.; Wilkinson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1465.

It was now necessary to invert the configuration of the ester carbon of **36** in order to set in place an endo primary alcohol that could be used to construct the tricyclic ether **23**. This was accomplished by saponification of **36**, conversion of the resulting carboxylic acid to its acyl chloride, and reduction with diisobutylaluminum hydride, a sequence that avoided unwanted reduction of the lactam carbonyl (Scheme 8). The mixture of primary alcohols **38** produced in this manner[22] was isomerized to endo alcohol **39** via its dianion followed by reprotonation at low temperature. Treatment of **39** with dimethyldioxirane[23] afforded exo epoxide **40** with only a trace of product resulting from epoxidation of the vinyl group, and exposure of **40** to camphorsulfonic acid resulted in clean cyclization to cylic ether **41**. This alcohol was oxidized[24] in situ to ketone **42**, which now stands ready for homologation of the lactam carbonyl, Fischer indolization, and final intramolecular alkylation at the indole β carbon to reach koumine.[25,26]

Acknowledgment. Financial support from the National Institute of General Medical Sciences through Grant No. GM058889 is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and representative ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052955Y

(22) The stereochemistry of the resulting alcohols was determined by cyclization with mercury(II) acetate. The exo primary alcohol underwent intramolecular oxymercuration exlusively at the vinyl group, whereas **39** yielded the product of oxymercuration at the cyclohexene double bond.
(23) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, 91.
(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(25) For a total synthesis of (+)-koumine, see: (a) Magnus, P.; Mugrage, B.; Deluca, M.; Cain, G. A. *J. Am Chem.* Soc. **1989**, *111*, 786. (b) Magnus, P.; Mugrage, B.; Deluca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220.
(26) For a formal synthesis of (+)-koumine, see: (a) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895. (b) Bailey, P. D.; McLay, N. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 441.