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Expanding the Scope of $Mn(OAc)_3$-Mediated Cyclizations: Synthesis of the Tetracyclic Core of Tronocarpine

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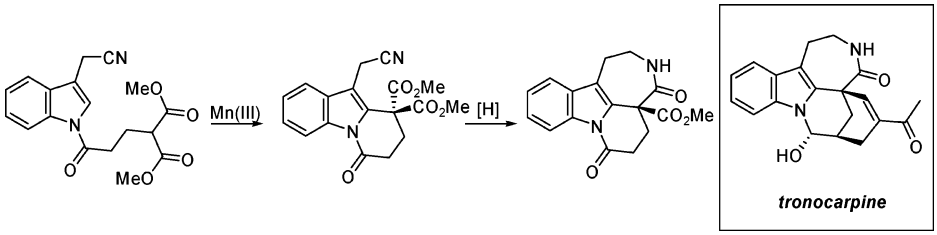
ABSTRACT



Pyrroles, indoles, and surprisingly, indolines, when equipped with a pendant malonyl group on the nitrogen atom, were effective substrates in a Mn(III)-mediated oxidative cyclization reaction, yielding the 1,2-annulated products in good to excellent yields. When indole acetonitrile was used as a substrate this method provided a rapid synthesis of a tetracyclic tronocarpine subunit.

Among the vast numbers of indole and pyrrole alkaloids[1] there exists a small number which bear a six-membered ring fused to the 1,2-positions and which have an all-carbon quaternary center attachment at the heterocyclic 2-position. Several of these alkaloids are shown in Figure 1.[2] While

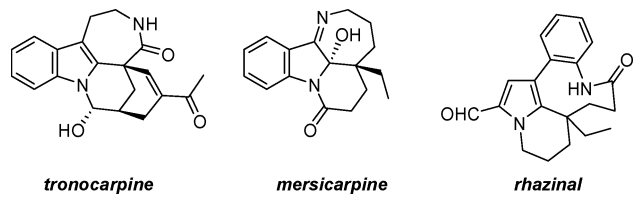
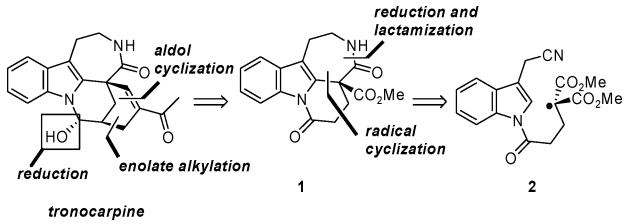


Figure 1. Tronocarpine, mersicarpine. and rhazinal.

rhazinal has succumbed to total synthesis by Banwell and co-workers,[3] tronocarpine and mersicarpine await their first chemical preparation.

A brief retrosynthesis of tronocarpine is shown in Scheme 1. Deconstruction of the bridging enone moiety via an aldol

Scheme 1. Retrosynthesis of Tronocarpine



and an enolate alkylation leads to precursor **1**. Lactam formation would occur in a traditional manner, whereas the key bond between the quaternary center and the indole

(1) (a) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442. (b) Cordell, G G. A. *The Alkaloids: Chemistry and Biology*; Elsevier Science: San Diego, 2003; Vol. 60.

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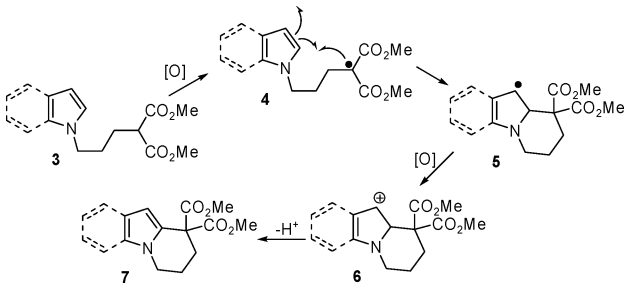
2-position would be formed via a malonic radical cyclization of **2**. The choice of this disconnection was inspired by the seminal work of Snider[4] and others.[5]

Notwithstanding the excellent contributions of Chuang and co-workers,[5] who have demonstrated the viability of malonic radical additions to indoles, a survey of the literature revealed that the cyclization of malonic radicals onto aromatics and especially heteroaromatics is an underdeveloped and underexploited synthetic method. In this paper, we report an expansion of the scope of this reaction *with the significant advance that indolines (rather than indoles) may be employed as substrates since they are oxidized to indoles under the radical cyclization conditions*.

These $Mn(OAc)_3$-mediated cyclizations are postulated[6] to proceed through the oxidation of a malonic enolate derived from **3** to yield a malonic radical **4** (Scheme 2). Cyclization

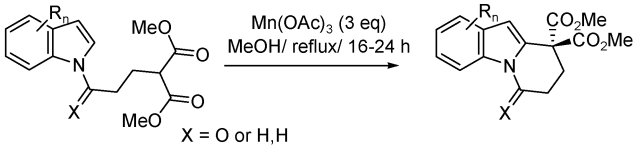
Scheme 2. Mechanism of Malonic Radical Cyclizations

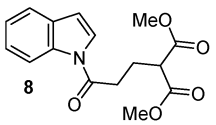
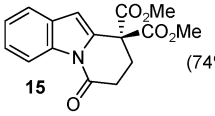
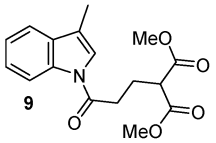
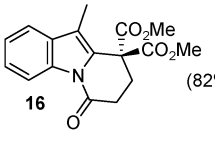
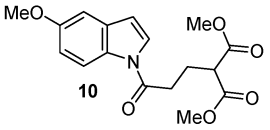
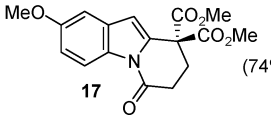
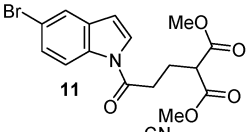
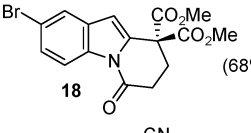
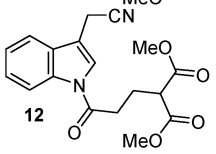
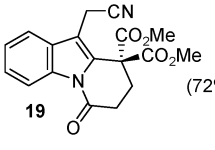
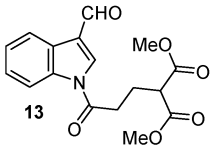
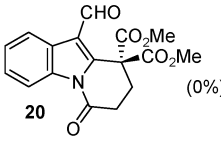
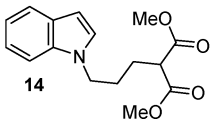
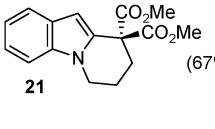


onto the 2-position of an indole or pyrrole yields a resonance stabilized radical **5** which may undergo further oxidation to carbonium ion **6**. Aromatization via proton loss gives the product **7**.

A variety of commercially available indoles and pyrroles were acylated or alkylated with malonyl-containing chains and subjected to oxidative cyclization with $Mn(OAc)_3$ in methanol. Table 1 shows the oxidative radical cyclization of *N*-acyl indoles **8**−**13** and the *N*-alkyl derivative **14**. While methanol was our preferred solvent for this transformation, acetic acid, the most common solvent for $Mn(OAc)_3$ chemistry, also yielded satisfactory results. It is likely that sensitive functionality in more complicated substrates will be more tolerant of methanol than acetic acid.

Table 1. Cyclizations of Malonyl Radicals to Indoles



entry	substrate	product (yield)
1		 (74%)
2		 (82%)
3		 (74%)
4		 (68%)
5		 (72%)
6		 (0%)
7		 (67%)

The yields in Table 1 are uniformly good with the exception of the indole-3-carboxaldehyde **13,** which decomposed under the reaction conditions with only trace amounts of **13** recovered. This surprised us since we were expecting the additional conjugation to make this substrate a better radical acceptor. Substitution at the indole 3-position did not appear to be a problem. In fact, the improved yield is consistent with the expected improved ease of formation of the radical of type **5** and subsequent oxidation of this radical by $Mn(OAc)_3$.[3a] The *N*-alkyl substrate **14** was also a willing participant in the radical cyclization yielding **21** in 67% yield. Compounds such as **14**, however, were more tedious to prepare than the *N*-acyl counterparts.

The analogous cyclizations onto pyrroles also proceeded as expected. Substrates **22**−**24** were prepared and subjected to typical cyclization conditions. Cyclization of the *N*-alkyl

(2) (a) Tronocarpine: Kam, T.-S.; Sim, K.-M.; Lim, T.-M. *Tetrahedron Lett.* **2000**, *41*, 2733. (b) Mersicarpine: Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995. (c) Rhazinal: Kam, T.-S.; Tee, Y.-M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307.

(3) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296

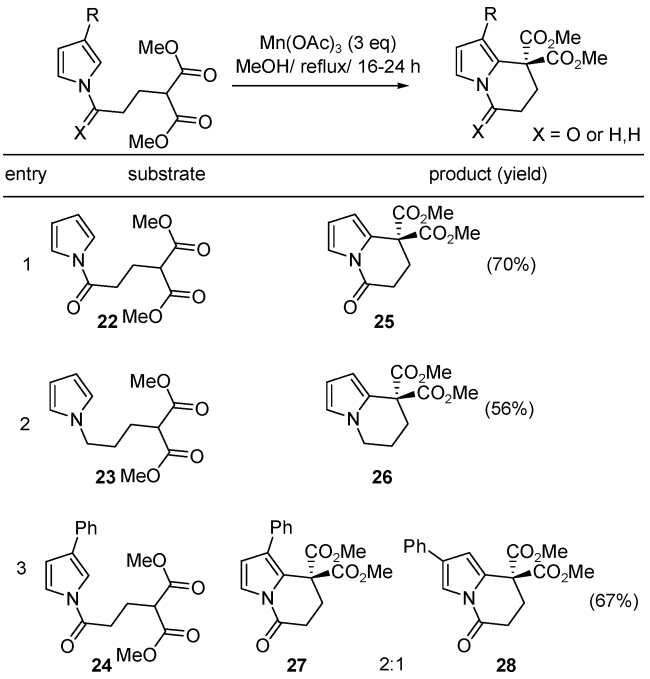
(4) For comprehensive reviews of $Mn(OAc)_3$ chemistry, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Snider, Barry B. Manganese(III)-based oxidative free-radical cyclizations. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vol. 1, pp 483−490.

(5) (a) Tsai, A.-I.; Lin, C.-H.; Chuang, C. P. *Heterocycles* **2005**, *65*, 2381. (b) Chuang, C. P.; Wang, S. F. *Tetrahedron Lett.* **1994**, *35*, 1283. (c) Artis D. R.; Cho I.-S.; Muchowski, J. M. *Can. J. Chem.* **1992**, *70*, 1838.

(6) (a) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **l985**, *50*, 10. (b) Fristad, W. E.; Hershberger, S. S. *J. Org. Chem.* **1985**, *50*, 1026. (c) Fristad, W. E.; Peterson, J. R.; Ernst, A. B. *J. Org. Chem.* **1985**, *50*, 3143. (d) Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493.

derivative of pyrrole itself **23** was slightly lower yielding than that of the *N*-acyl derivative of pyrrole **22**. The presence of a phenyl substituent at the 3-position of pyrrole **26** set up regiochemical considerations. The 3-phenyl group would be expected to stabilize the putative intermediate radical favoring cyclization proximal and not distal to the 3-phenyl substituent. This was in fact borne out and **24** yielded a 2:1 mixture of isomers **27** and **28** which were inseparable but could be easily differentiated in the proton NMR spectrum (Table 2).

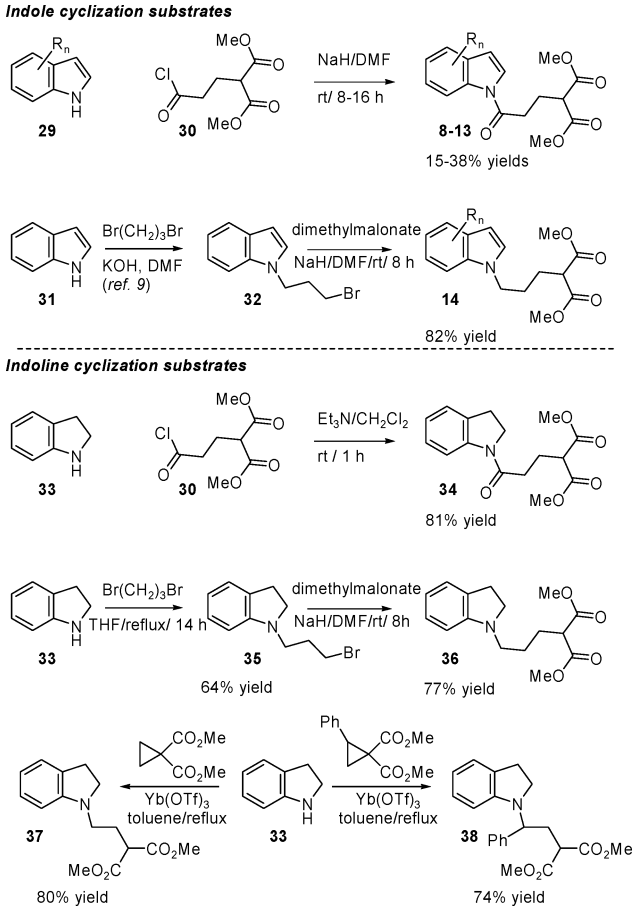
Table 2. Cyclizations of Malonyl Radicals to Pyrroles



One of the challenges with this synthetic method for the formation of complex indole scaffolds was, oddly enough, the preparation of the substrates. Scheme 3 summarizes their preparation. Substrates **8**−**13** were prepared by treatment of the deprotonated indole with a rather sensitive acid chloride **30**.[7] Although this was a reasonable method for preparing enough of the *N*-acyl indoles for this study the method was less than ideal. The *N*-alkyl substrates were prepared by first alkylating the indolate with 1,3-dibromopropane[8] and treatment of the resulting monobromide with sodium malonate.

In an effort to improve the overall efficiency of this synthetic methodology, we turned to acylation and alkylation of indolines rather than indoles. It was reasoned that the increased nucleophilicity of the indoline nitrogen would lead to improved reactivity in the acylation and alkylation chemistry. The indoline could then be dehydrogenated to the indole using traditional methods. We were pleased to realize

Scheme 3. Synthesis of Cyclization Substrates



excellent yields of the *N*-acyl species **34** when indoline **33** was treated with acid chloride **30** in the presence of triethylamine, while the *N*-alkyl compound **36** was accessed in a manner similar to the preparation of **14**. Moreover, we found that we could access the related compounds with a one-carbon shorter tether by employing indoline in a ring opening reaction with cyclopropane diesters. To this end, indoline **33** was treated with either the commercially available 1,1-carbomethoxycyclopropane or its phenyl-substituted counterpart[9] under the influence of $Yb(OTf)_3$ to effect the synthesis of the substrates **37** and **38** in good yields.

When surveying dehydrogenation methods for conversion of indolines to indoles we quickly realized that $Mn(OAc)_3$ could also be used to this end.[10] We then reasoned that both the dehydrogenation and cyclization may occur in one pot. We subjected **34**, **36**−**38** to the standard cyclization conditions (now with 5 equiv of $Mn(OAc)_3$ and were pleased to observe clean conversion to the 1,2-cyclized compounds. Table 3 illustrates the results. Indolines **36**−**38** underwent smooth reaction in methanol whereas the anilide **34** required refluxing acetic acid. In the case of anilide **34**, the methanolic conditions were insufficient to affect dehydrogenation in good yields, only trace amounts of the desired product **15**

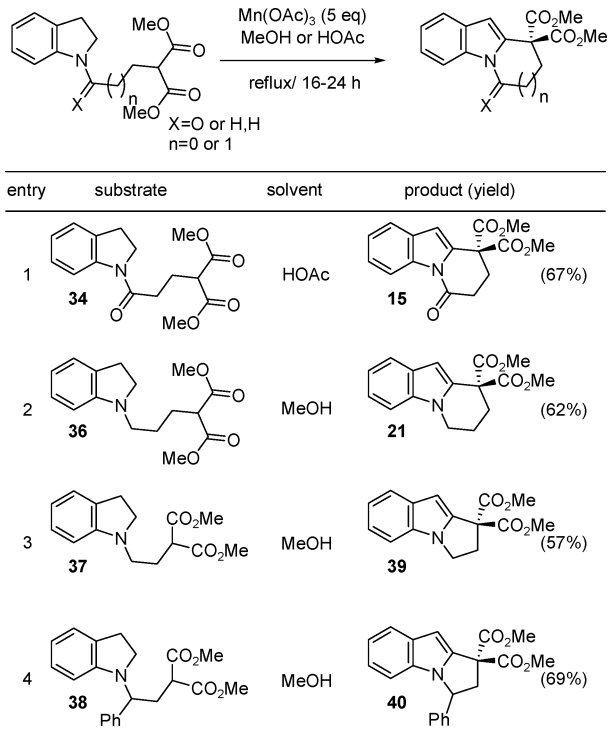
(7) Compound **30** was prepared from the corresponding carboxylic acid: Prabhu, K. R.; Pillarsetty, N.; Gali, H.; Katti, K. V. *J. Am. Chem. Soc.* **2000**, *122*, 1554.

(8) Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896.

(9) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(10) Ketcha, D. M. *Tetrahedron Lett.* **1988**, *29*, 2151.

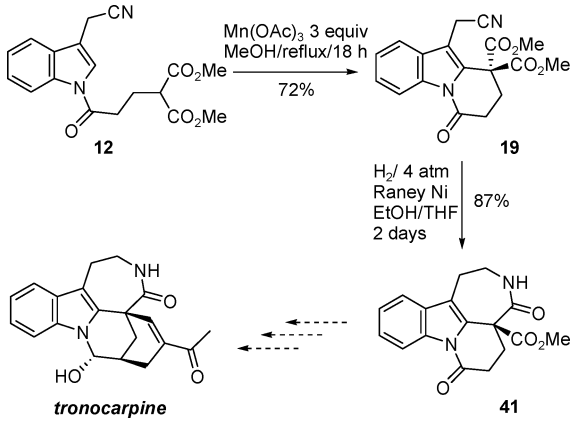
Table 3. Cyclizations of Malonyl Radicals to Indolines



were obtained until acetic acid was used. For the aniline substrates **36**−**38**, the milder methanolic conditions were ideal for both conversion to the indole and subsequent cyclization. That this was indeed two sequential oxidations and not some sort of C−H activation was indicated by the fact that at incomplete conversion the dehydrogenated but uncyclized indole could be isolated. If refluxing acetic acid was used as the medium in the cases of **36**−**38** only decomposition was observed. It is likely that the aniline was protonated leading to a species resistant to oxidation.

The application of the above methodology to the synthesis of a tetracyclic subunit of tronocarpine is illustrated in Scheme 4. As indicated in Table 1, indole-3-acetonitrile was acylated with acid chloride **30** to yield **12** which was treated with $Mn(OAc)_3$ in methanol to effect cyclization and produce **19** in 72% yield. Treatment of nitrile **19** with H_2 (4 atm) over Raney nickel resulted in reduction to the tryptamine derivative which spontaneously cyclized to **41** under the reaction conditions. Amide **41** contains four of the five rings of tronocarpine as well as suitable functionality for conversion to the natural product.[11]

Scheme 4. Synthesis of a Tronocarpine Substructure



In conclusion, we have demonstrated that the intramolecular cyclization of a malonic radical, generated with $Mn(OAc)_3$, onto the 2-position of indoles and pyrroles is an effective method for the generation of annulated heterocycles. Indoline substrates can also be employed as they are oxidized to indoles under the reaction conditions. The application of this method to the synthesis of the tetracyclic core of the natural product tronocarpine has also been illustrated. Efforts are underway to employ this synthetic methodology to the preparation of both tronocarpine and mersicarpine.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061698+

(11) Compound **41** has been reported in the literature (Mahboobi, v. S.; Burgemeister, T.; Kastner, F. *Arch. Pharm. Weinheim, Ger.* **1995**, *328*, 29). For a comparison of spectral data, see the Supporting Information.