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Mn(III)-Catalyzed Synthesis of Pyrroles from Vinyl Azides and 1,3-Dicarbonyl Compounds

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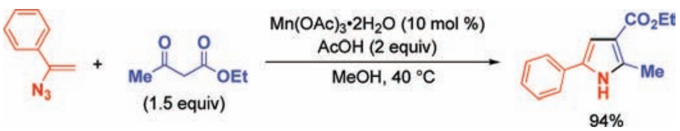
ABSTRACT



Polysubstituted *N*-H pyrroles with a wide variety of substituents were prepared from vinyl azides and 1,3-dicarbonyl compounds by using Mn(III) complexes as catalysts.

Pyrroles are one of the most prevalent heterocyclic compounds, being present as the basic cores in many natural products,[1] potent pharmaceutical compounds,[2] and various kinds of functional materials.[3] Despite numerous diverse approaches toward the synthesis of pyrroles developed so far,[4] it is still challenging to prepare polysubstituted pyrroles with various substituents from readily available building blocks. Recently, we have reported a synthetic method to prepare pyrroles by Cu(II)-catalyzed reactions of vinyl azides and ethyl acetoacetate.[5] In this reaction, however, introduction of an alkoxycarbonyl group at the α-position of vinyl azides is indispensable to realize high yield. It is probably because this transformation proceeds by 1,4-anionic addition of ethyl acetoacetate to vinyl azides.[6] Furthermore, 1,3-diketones such as acetylacetone could not be utilized for this Cu(II)-catalyzed method. Based on these backgrounds, we

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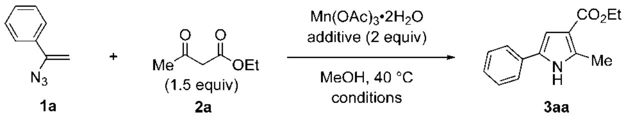
10.1021/ol802120u CCC: $40.75

have strived to develop a more general method for pyrrole synthesis by applying a radical mechanism. Herein, we report Mn(III)-catalyzed pyrrole formation from vinyl azides with a variety of substituents and various 1,3-dicarbonyl compounds such as β-keto esters and 1,3-diketones.

To achieve pyrrole formation from a wide range of vinyl azides, we turned our attention to a radical pathway in which α-carbonyl radicals generated from 1,3-dicarbonyl compounds add to vinyl azides to afford iminyl radicals.[7] The resulting iminyl radicals would cyclize with an intramoelcular carbonyl moiety to give pyrroles.[8]

At first, a stoichiometric amount (1.5 equiv) of Mn(III) acetate, which has been widely used for oxidative radical formations from carbonyl compounds,[9,10] was employed for the reaction of α-azidostyrene (**1a**) and ethyl acetoacetate (**2a**) in some solvents under N_2 atmosphere. It was found that the reaction proceeds smoothly in MeOH[11] at 40 °C to give pyrrole **3aa** in 84% yield (Table 1, entry 1). Interestingly, even with the use of a catalytic amount (20 mol %) of Mn(III) acetate, pyrrole **3aa** was obtained in 90% yield (entry 2). Addition of acetic acid (2 equiv) accelerated the reaction and reduced the catalyst loading to 10 mol % (entry 3).

Table 1. Reaction of Vinyl Azide **1a** with Ethyl Acetoacetate **2a** by the Use of $Mn(OAc)_3{\cdot}2H_2O$[a]

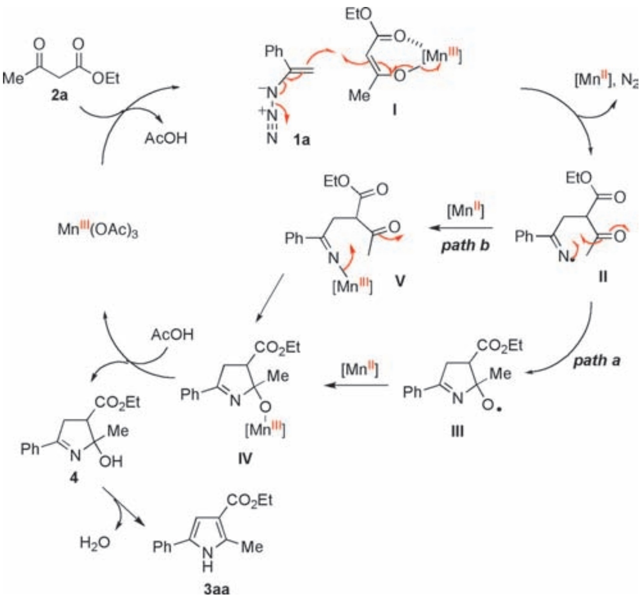


entry	$Mn(OAc)_3$ $2H_2O$ (equiv)	additive	time/h	yield[b]/%
1	1.5		2	84
2	0.2		8	90
3	0.1	AcOH	2	94 (90)[c]

[a] Reactions were performed under N_2 atomsphere using 0.3 mmol of **1a**. [b] Isolated yield. [c] Isolated yield using 1.0 mmol of **1a**.

This catalytic reaction may be initiated by addition of Mn(III) enolate **I** to vinyl azide **1a** via a radical pathway, giving iminyl radical **II** with release of Mn(II) species and dinitrogen (Scheme 1). The resulting iminyl radical **II** undergoes intramolecular additon to a carbonyl group to give alkoxyl radical **III**. Reduction of this alkoxyl radical **III** by Mn(II) species gives Mn(III) alkoxide **IV** (path a). Alternatively, reaction of iminyl radical **II** with Mn(II) species affords alkylideneaminomanganese(III) **V**, nucleophilic attack of which to a carbonyl group yields addition intermediate **IV** (path b).[12] Finally, protonation of **IV** with acetic acid followed by dehydration yields pyrrole **3aa** along with regeneration of Mn(III). Most of the reported radical reactions of 1,3-dicarbonyl compounds with alkenes using Mn(III) acetate are performed in a stoichiometric manner, although there are a few reports on catalytic usage of Mn(III) acetate in the presence of reoxidants.[13−16] Thus, this catalytic pyrrole formation prompted us to investigate the further potential for a synthetic method.

Scheme 1. Proposed Mechanisms



Using Mn(III) acetate as a catalyst, we next examined the scope of this pyrrole formation. First, the reactions of various vinyl azides **1** with ethyl acetoacetate (**2a**) were examined as shown in Table 2. α-Aryl vinyl azides reacted smoothly to afford pyrroles **3aa**−**ia** in good yield (entries 1−9).

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(6) For an example, the reaction of α-azidostyrene (**1a**) with ethyl acetoacetate (**2a**) gave the corresponding pyrrole **3aa** in only 9% yield; see ref 5.

(7) For prior studies on the iminyl radical formation from vinyl azides, see: (a) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5864. (b) Bamford, A. F.; Cook, M. D.; Roberts, B. P. *Tetrahedron Lett.* **1983**, *24*, 3779.

(8) For reviews of the synthesis of aza-heterocycles using iminyl radicals, see: (a) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 407. (b) Mikami, T., Narasaka, K. In *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; JAI: Stamford, 1999; Vol. 2, p 45. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (d) Zard, S. Z. *Synlett* **1996**, *n/a*, 1148.

(9) For reviews, see: (a) Melikyan, G. G. *Org. React.* **1997**, *49*, 427. (b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(10) The structure of Mn(III) acetate is actually an oxo-centered triangle of Mn(III) bridged by acetoxy ions. For the report on the crystal structure of anhydrous Mn(III) acetate, see: Hessel, L. W.; Romers, C. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 545.

(11) Other solvents such as DMF, CH_3CN, and EtOH were not so effective for this reaction.

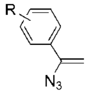
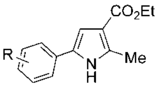
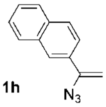
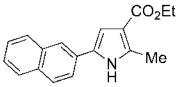
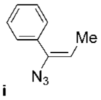
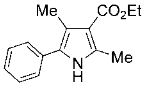
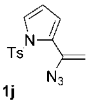
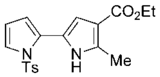
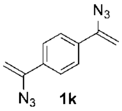
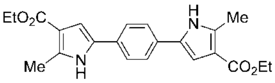
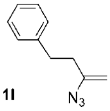
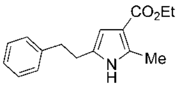
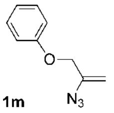
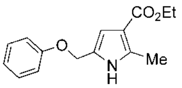
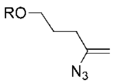
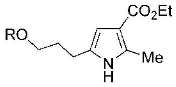
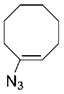
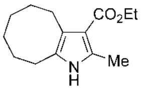
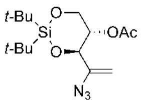
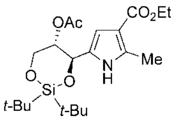
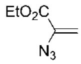
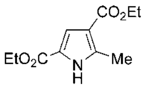
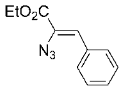
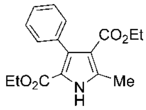
(12) For an example of addition of aminyl radicals to carbonyl groups, see: Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328.

(13) For the catalytic radical reactions using the Mn(II)/Co(II)/O_2 redox system, see: (a) Kagayama, T.; Fuke, T.; Sakaguchi, S.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1673. (b) Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970. (c) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, *n/a*, 2317.

(14) For peroxidation of alkenes with Mn(III) acetate under oxygen atomsphere, see: (a) Asahi, K.; Nishino, H. *Tetrahedron* **2005**, *61*, 11107. (b) Rahman, M. T.; Nishino, H. *Tetrahedron* **2003**, *59*, 8383.

(15) For the use of electrooxidation, see: (a) Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* **1991**, *47*, 831. (b) Coleman, J. P.; Hallcher, R. C.; McMackins, D. E.; Rogers, T. E.; Wagenknecht, J. H. *Tetrahedron* **1991**, *47*, 809. (c) Nédélec, J. Y.; Nohair, K. *Synlett* **1991**, 659.

Table 2. Mn(OAc)$_3$·2H$_2$O-Catalyzed Synthesis of Pyrroles **3** from Vinyl Azides **1** and Ethyl Acetoacetate (**2a**)[a]

entry	vinyl azides	[MnIII] / mol %	time / h	product (yield / %)[b]
				
1	**1a**: R = H	10	2	**3aa** (94)
2	**1b**: R = 2-Br	10	2	**3ba** (94)
3	**1c**: R = 4-Br	10	2	**3ca** (86)
4	**1d**: R = 4-CO$_2$Me	10	2	**3da** (88)
5	**1e**: R = 3-NO$_2$	10	2	**3ea** (95)
6	**1f**: R = 4-Me	10	4	**3fa** (78)
7	**1g**: R = 2-OMe	10	4	**3ga** (75)
8	 **1h**	20	2	 **3ha** (83)
9	 **1i**	20	2	 **3ia** (72)
10	 **1j**	20	24	 **3ja** (68)[c]
11	 **1k**	40	24	 **3ka** (48)
12	 **1l**	20	3	 **3la** (90)
13	 **1m**	20	2	 **3ma** (85)
				
14	**1n**: R = Ac	20	1	**3na** (94)
15	**1o**: R = Si(*t*-Bu)Ph$_2$	20	2	**3oa** (85)
16	 **1p**	40	1	 **3pa** (60)[d]
17	 **1q**	40	5	 **3qa** (74)
18	 **1r**	5	2	 **3ra** (98)
19	 **1s**	20	24	 **3sa** (78)[e]

[a] Reactions were performed in MeOH at 40 °C with 1.5 equiv of ethyl acetoacetate (**2a**) under N$_2$ atomsphere. [b] Isolated yield. [c] Vinyl azide **1j** was recovered in 25% yield. [d] Vinyl azide **1p** was recovered in 10% yield. [e] Vinyl azide **1s** was recovered in 15% yield.

Relatively longer reaction time or higher catalyst loading was necessary in the cases of vinyl azides bearing electron-rich aryl groups (entries 6−8). Trisubstituted vinyl azide β-methyl-α-azidostyrene (**1i**) also reacted with ethyl acetoacetate to give tetrasubstituted pyrrole **3ia** in good yield (entry 9). The reaction of α-pyrrolyl vinyl azide **1j** proceeded to give the corresponding dipyrrole **3ja** in 68% yield in spite of the slower reaction rate (24 h) (entry 10). 1,4-Dipyrroylbenzene **3ka** could be obtained in 48% yield[17] by treatment of bis(α-azidovinyl)benzene **1k** with 40 mol % of Mn(III) acetate (entry 11). The reaction of α-alkyl vinyl azides with some functional groups also gave the corresponding pyrroles **3la**−**qa** in good yield (entries 12−17). From 1-azidocyclooctene (**1p**), bicyclic pyrrole **3pa** was obtained in 60% yield (entry 16). Vinyl azide **1q** with a chiral polyol function prepared from D-glucal derivatives[18] could be transformed to pyrrole **3qa** in 74% yield without cleavage of silyloxy moieties by employing 40 mol % of Mn(III) acetate (entry 17). Vinyl azides having an ethoxycarbonyl group at the α-position could also be employed in this pyrrole synthesis (entries 18 and 19). In the case of the reaction of ethyl 2-azidoacrylate (**1r**), the use of only 5 mol % of Mn(III) acetate was sufficient to complete the reaction within 2 h, affording pyrrole **3ra** almost quantitatively (entry 18). Although tetrasubstituted pyrrole **3sa** were obtained in good yield, the reaction of β-aryl vinyl azides **1s** required a longer reaction time (24 h) even by the use of 20 mol % of Mn(III) acetate, probably due to steric hindrance (entry 19).

Next, the generality of 1,3-dicarbonyl compounds was examined using α-azidostyrene (**1a**) and ethyl 2-azidoacrylate (**1r**) as shown in Table 3. By employing β-keto esters **2b**−**d**, phenyl, ethoxymethyl, and cyclopropyl groups were successfully installed at the C2-position of pyrroles **3** (entries 1−6). A slow reaction rate was observed when acetylacetone (**2e**) was employed (entry 7), and the yield of the obtained pyrrole **3ae** was low (21%) along with recovery of **1a** (63%) even after 24 h. The formation of pyrrole **3ae**, however, encouraged us to improve the product yield by modification of Mn(III) complexes because the previous Cu(II)-catalyzed

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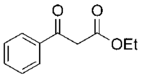
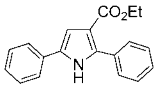
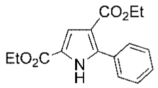
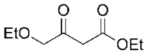
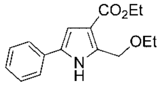
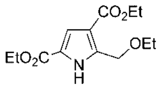
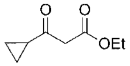
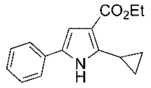
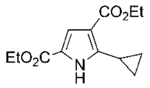
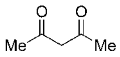
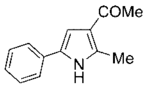
(16) For the use of sonochemical conditions, see: (a) Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron* **1994**, *50*, 13847. (b) Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* **1993**, *49*, 10705.

(17) The low yield of pyrrole **3ka** is probably due to instability of **3ka** in the present reaction conditions.

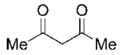
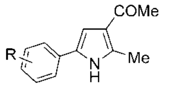
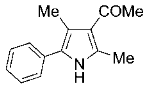
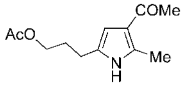
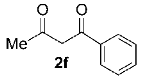
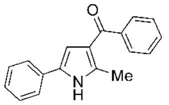
(18) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *Org. Lett.* **2003**, *5*, 3729.

Table 3. Mn(OAc)$_3$·2H$_2$O-Catalyzed Synthesis of Pyrroles **3** from Vinyl Azides **1** and 1,3-Dicarbonyl Compounds **2**[a]

entry	vinyl azides	1,3-dicarbonyl compounds	[MnIII] / mol %	time / h	pyrrole 3 (yield / %)[b]
1	**1a**	 **2b**	40	4	 **3ab** (63)
2	**1r**		40	2	 **3rb** (72)
3	**1a**	 **2c**	20	3	 **3ac** (55)
4	**1r**		20	5	 **3rc** (77)
5	**1a**	 **2d**	40	8	 **3ad** (56)
6	**1r**		40	2	 **3rd** (72)
7	**1a**	 **2e**	20	24	 **3ae** (21)[c]

[a] Reactions were performed in MeOH at 40 °C with 1.5 equiv of 1,3-dicarbonyl compounds under N$_2$ atomsphere. [b] Isolated yield. [c] Vinyl azide **1a** was recovered in 63% yield.

Table 4. Mn(pic)$_3$-Catalyzed Pyrrole Formation from Vinyl Azides **1** and 1,3-Diketones **2**[a]

entry	vinyl azides 1	1,3-diketones 2	time / h	pyrrole 3 (yield / %)[b]
				
1	**1a**	**2e**	20	R = H **3ae** (76)
2	**1e**	**2e**	36	R = 3-NO$_2$ **3ee** (80)
3	**1f**	**2e**	46	R = 4-Me **3fe** (52)
4	**1i**	**2e**	24	 **3ie** (41)[c]
5	**1n**	**2e**	48	 **3ne** (71)
6	**1a**	 **2f**	24	 **3af** (61)[d]

[a] Reactions were performed in MeOH at 40 °C using 20 mol % of Mn(pic)$_3$ with 1.5 equiv of 1,3-diketones under N$_2$ atomsphere. [b] Isolated yield. [c] Vinyl azide **1i** was recovered in 21% yield. [d] Vinyl azide **1a** was recovered in 17% yield.

reaction[5] with any 1,3-diketone did not give the corresponding pyrrole at all.

Interestingly, when the reaction of acetylacetone (**2e**) with **1a** was tried using 20 mol % of Mn(III) tris(2-pyridinecarboxylate) [Mn(pic)$_3$],[19,20] pyrrole **3ae** was afforded in 76% yield after 20 h (Table 4, entry 1).[21] Treatment of some vinyl azides **1e**, **1f**, **1i**, and **1n** with acetylacetone (**2e**) under the same reaction conditions led to the formation of pyrroles **3** in good to moderate yield (entries 2−5). The reaction of unsymmetrical 1,3-diketone benzoylacetone (**2f**) with vinyl azide **1a** proceeded to afford pyrrole **3af** in 61% yield as a sole product via C−N bond formation with a less hindered acetyl group (entry 6).

In summary, a Mn(III)-catalyzed method has been developed for synthesis of tri- and tetrasubstituted *N*-H pyrroles from readily available vinyl azides and 1,3-dicarbonyl compounds. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

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Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Mn(III) tris(2-pyridinecarboxylate) has a monomeric octahedral structure; see: Figgis, B. N.; Raston, C. L.; Sharma, R. P.; White, A. H. *Aust. J. Chem.* **1978**, *31*, 2545.

(20) For the oxidative radical reaction by using Mn(III) tris(2-pyridinecarboxylate) as an oxidant, see: (a) Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Ikeno, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 85. (b) Narasaka, K. *Pure Appl. Chem.* **1997**, *69*, 601. (c) Vo, N. H.; Snider, B. B. *J. Org. Chem.* **1994**, *59*, 5419. (d) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217, and references therein.

(21) The reaction of vinyl azide **1a** with ethyl acetoacetate (**2a**) using 10 mol % of Mn(III) tris(2-pyridinecarboxylate) proceeded at 40 °C more slowly than using Mn(III) acetate, giving 28% yield of pyrrole **3aa** along with recovery of **1a** (55%) after 22 h.