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Doubly Activated Cyclopropanes as Synthetic Precursors for the Preparation of 4-Nitro- and 4-Cyano-dihydropyrroles and Pyrroles

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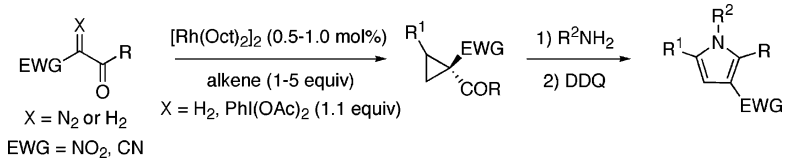
ABSTRACT



1-Nitro- and 1-cyano-cyclopropyl ketones have been prepared in an expedient manner from cyclopropanation reactions of alkenes by diazo compounds or in situ-generated phenyliodonium ylides catalyzed by Rh(II) carboxylates. The doubly activated cyclopropanes were used as synthetic precursors for the regiospecific synthesis of 4-nitro- and 4-cyano-dihydropyrroles upon treatment with primary amines. Oxidation of the dihydropyrroles with DDQ allows rapid access to densely functionalized pyrroles.

Pyrrole and its derivatives are ubiquitous in nature. As such, the pyrrole subunit has found widespread applications in therapeutically active compounds, including fungicides, antibiotics (**1**),[1] nonsteroidal antiinflammatory drugs (NSAIDS) (**2**),[2] cholesterol-reducing drugs (**3**),[3] and antitumor agents[4] (Figure 1). The pyrrole subunit also plays an important role in material science[5] as it is found in organic conducting polymers,[6] indigoid dyes, and porphyrins.[7]

The abundance of the pyrrole motif in biologically active compounds and potential drug candidates has resulted in the development of many methods for their synthesis. Classical methods for pyrrole synthesis include the Paal−Knorr synthesis[8] and the Hantzsch synthesis.[9] These methods are

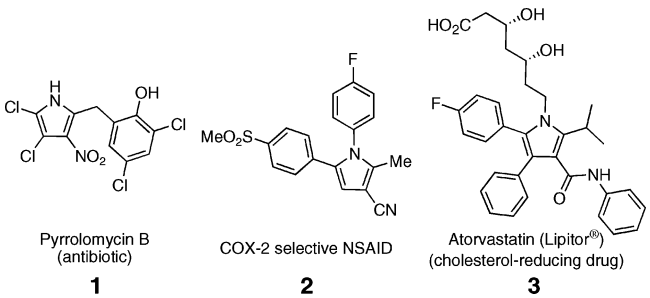


Figure 1. Examples of biologically active pyrroles.

(1) For examples of biologically active 4-nitropyrroles, see: (a) Ono, N.; Muratani, E.; Ogawa, T. *J. Heterocycl. Chem.* **1991**, *28*, 2053−2055. (b) Nishiwaki, N.; Nakanishi, M.; Hida, T.; Miwa, Y.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *J. Org. Chem.* **2001**, *66*, 7535−7538. (c) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiotics* **1981**, *34*, 1366−1368. (d) Koyama, M.; Kodama, Y.; Tsuruoka, T.; Ezaki, N.; Niwa, T.; Inouye, S. *J. Antibiotics* **1981**, *34*, 1569−1576. (e) Koyama, M.; Ezaki, N.; Tsuruoka, T.; Inouye, S. *J. Antibiotics* **1983**, *36*, 1483−1489. (f) Koyama, M.; Ohtani, N.; Kai, F.; Moriguchi, I.; Inouye, S. *J. Med. Chem.* **1987**, *30*, 552−562.

(2) See for example: (a) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619−1633. (b) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.* **1995**, *38*, 3895−3901. (c) Wilkerson, W. W.; Galbraith, W.; Gans-Brangs, K.; Grubb, M.; Hewes, W. E.; Jaffee, B.; Kenney, J. P.; Kerr, J.; Wong, N. *J. Med. Chem.* **1994**, *37*, 988−998.

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very useful when the appropriate starting materials are available. However, there exist limitations that make certain classes of pyrroles difficult to prepare or inaccessible using these methods.

Cyclopropanes have been shown to be useful synthetic precursors in organic synthesis.[10] Depending on the functionalities present on the cyclopropane ring, fragmentation of these three-membered carbocycles represents a useful method for the construction of a wide variety of carbon skeletons. We recently reported a cyclopropanation reaction involving in situ generation of phenyliodonium ylides for the preparation of nitro cyclopropanecarboxylates using hypervalent iodine(III) reagents.[11] Reduction of the nitro group using Zn−HCl affords a structurally diverse series of cyclopropane α-amino acids.[12]

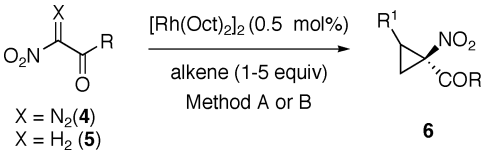
To extend the synthetic utility of 1-nitro-cyclopropylcarbonyls further,[13] a strategy to access dihydropyrroles[14] and pyrroles was envisaged. Herein, we describe the preparation of these compounds from nitro- and cyano-containing doubly activated cyclopropyl ketones.

Preparation of 1-nitro-cyclopropyl ketones began by cyclopropanation of alkene substrates either with α-nitro-α-diazoketones[15] or with phenyliodonium ylides derived from α-nitroketones. Ylide intermediates are presumably generated in situ upon treatment of α-nitroketones with $PhI(OAc)_2$ (Table 1).

The chemical yields of the desired cyclopropanes were similar in most cases using the two different cyclopropanation protocols. However, when the alkene substrate is expensive or lacks α-stabilization (i.e., 4-Ph-1-butene), cyclopropanation with the diazo substrate gives higher chemical yields of the desired cyclopropane.

Müller and Ghanem have recently extended the in situ protocol to include Meldrum's acid[16] and dimethyl malonate[17] as substrates, and we now wish to report that

Table 1. Preparation of 1-Nitro-1-cyclopropyl Ketones



X = N_2(**4**)
X = H_2 (**5**)

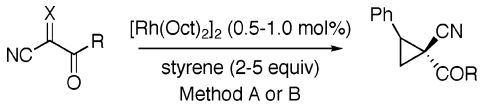
6

product	R	R^1	method[a]	yield of **6** (%)[b]	*E*:*Z* ratio
6a	Me	Ph	A	77	78:22
6a	Me	Ph	B	59[c]	78:22
6b	*n*-propyl	Ph	A	74	81:19
6b	*n*-propyl	Ph	B	62[c]	88:12
6c	Ph	Ph	A	74	16:84
6c	Ph	Ph	B	75	10:90
6d	*c*-C_3H_5	Ph	A	69	76:24
6d	*c*-C_3H_5	Ph	B	73	74:26
6e	Me	4-F-Ph	A	63[d]	73:27
6f	Me	1-naphthyl	A	52[d]	79:21
6g	Me	phenethyl	A	36	53:47

[a] Method A: **4** (1.0 M in CH_2Cl_2) was added dropwise to the alkene (2−3 equiv) and $[Rh(Oct)_2]_2$ (0.5 mol %). Method B: **5**, $PhI(OAc)_2$ (1.1 equiv), alkene (5.0 equiv), and $[Rh(Oct)_2]_2$ (0.5 mol %) stirred at 40 °C for 3 h. [b] Isolated yields after column chromatography. [c] Stirred at room temperature for 20 h. [d] Performed with 1.0 equiv of alkene.

α-cyanoketones are also viable substrates. Accordingly, a variety of additives, including 4 Å MS, Al_2O_3, Na_2CO_3, and MgO, were screened in the cyclopropanation reaction involving benzoylacetonitrile (**8a**) and $PhI(OAc)_2$ as the iodine(III) source.[18] The reaction was also performed in organic solvents, solventless, and under aqueous reaction conditions (Table 2). The optimal reaction conditions for the benzoylacetonitrile (**8a**) involved use of Na_2CO_3 (2.3 equiv) and 4

Table 2. Cyclopropanation of Alkenes with α-Cyanoketones and α-Cyano-α-diazoketones



X = N_2(**7**)
X = H_2 (**8**)

9

product (R)	method[a]	additive	yield of **9** (%)[b]	*E*:*Z* ratio
9a (Ph)	A		95	88:12
9a (Ph)	B	none	63[c]	86:14
9a (Ph)	B	Na_2CO_3 + 4 Å MS	88	86:14
9a (Ph)	B	H_2O	52	87:13
9b (Bn)	A		83	77:23
9b (Bn)	B	Na_2CO_3 + 4 Å MS	64	78:22
9c (4-MeO-Ph)	A		97	94:6
9c (4-MeO-Ph)	B	Na_2CO_3 + 4 Å MS	72	89:11
9d (styryl)	A		96	57:43
9d (styryl)	B	none	67[c]	56:44

[a] Method A: **7** (1.0 M in CH_2Cl_2) was added dropwise to styrene (2.0 equiv) and $[Rh(Oct)_2]_2$ (0.5 mol %). Method B: **8**, $PhI(OAc)_2$ (1.1 equiv), $[Rh(Oct)_2]_2$ (1.0 mol %), and styrene (5.0 equiv), and the additive was stirred in CH_2Cl_2 (1.0 M) for 18 h at room temperature. [b]Isolated yields after column chromatography. [c] Reaction performed without solvent.

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(14) For an example of a related dihydropyrrole synthesis, see: (a) Jacoby, D.; Celerier, J. P.; Haviari, G.; Petit, H.; Lhommet, G. *Synthesis* **1992**, 884−887. (b) Celerier, J. P.; Haddad, M.; Jacoby, D.; Lhommet, G. *Tetrahedron Lett.* **1987**, *28*, 6597−6600.

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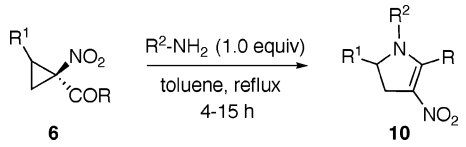
Table 3. Preparation of 4-Nitro-dihydropyrroles from 1-Nitro-1-cyclopropyl Ketones and Primary Amines



product	R	R^1	R^2	yield of **10** (%)
10a	Me	Ph	Ph	91
10b	*n*-propyl	Ph	Ph	78
10c	Ph	Ph	Ph	91
10d	*c*-C_3H_5	Ph	Ph	79
10e	*c*-C_3H_5	Ph	4-MeO-Ph	97
10f	Me	Ph	allyl	48[a]
10g	Me	Ph	benzyl	35
10h	Me	Ph	(*R*)-(+)-α-methylbenzyl	84[b]
10i	Me	Ph	*t*-Bu	47[a]
10j	Me	Ph	4-Cl-Ph	95
10k	Ph	Ph	4-MeO-Ph	96
10l	Me	4-F-Ph	Ph	99
10m	Me	1-naphthyl	Ph	84
10n	Me	phenethyl	Ph	18[c]

[a] Reaction performed in a sealed tube. [b] 55:45 mixture of the two diastereomers isolated. [c] Mass balance was unreacted cyclopropane **6g**.

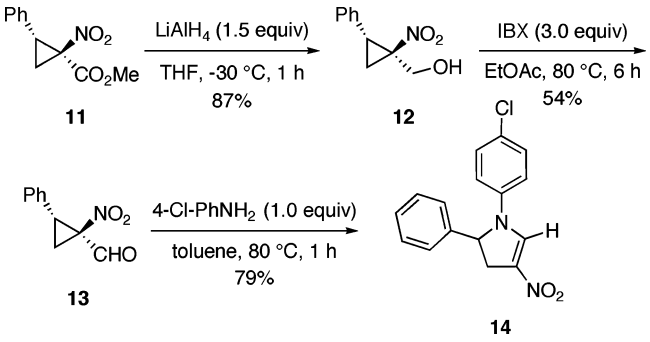
Å MS, resulting in isolation of the desired cyclopropane **9a** in 88% yield (Table 2). Somewhat inferior yields were possible when the reaction was performed under solventless or biphasic aqueous conditions. For comparison, the cyclopropanation reaction was performed with the corresponding diazo compound **7a**[19] (method A), affording cyclopropane **9a** in 95% yield (Table 2).

Other α-cyanoketone substrates were also found to undergo cyclopropanation reactions in modest yields ranging from 64 to 72% (Table 2). The pK_a values of these substrates are somewhat higher than that of benzoylacetonitrile, which likely accounts for the observed decline in reaction yields.

With the doubly activated cyclopropanes in hand, dihydropyrroles could be prepared by treatment of the *E*:*Z* mixtures with a variety of primary amines in refluxing toluene.[20] In this manner, the corresponding 4-nitro-dihydropyrroles **10** could be isolated in modest to excellent yields from 1-nitro-1-cyclopropyl ketones **6** (Table 3).

Modification of the ketone (R) had little influence on the reaction yields when aniline was used (**10a**−**d**, Table 3). Interestingly, when R was a cyclopropyl group, dihydropyrroles **10d**−**e** were obtained exclusively, resulting from reaction with only the doubly activated cyclopropane (Table 3). Variation of the primary amine (R^2) demonstrated that

Scheme 1



the rearrangement proved to be most facile with aromatic amines (Table 3). Less nucleophilic amines such as carbamates did not result in dihydropyrrole formation under these reaction conditions, and the starting materials were recovered.

The 2-substituent on the cyclopropane ring (R^1) was also examined and found to lead to efficient dihydropyrrole formation when aromatic groups were directly attached to the cyclopropane ring (**10l**,**m**). However, the cyclopropane derived from 4-phenyl-1-butene **6g** exhibited greatly reduced rates of reaction.

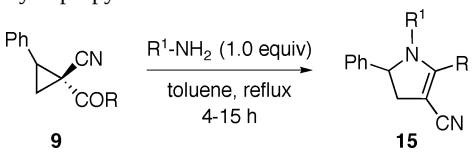
If desired, trisubstituted 4-nitro-dihydropyrroles can also be accessed. Cyclopropylcarboxaldehyde **13** was prepared by $LiAlH_4$ reduction of cyclopropylester **11** followed by IBX oxidation of the resulting cyclopropylmethanol **12**. Treatment of aldehyde **13** with 4-chloroaniline afforded the desired 4-nitro-1-(4-chlorophenyl)-2-phenyl-2,3-dihydro-1*H*-pyrrole (**14**) in 79% yield (Scheme 1).

1-Cyano-cyclopropyl ketones **9** rearranged with various primary amines in an analogous fashion to those observed with 1-nitro-cyclopropyl ketones. The desired 4-cyano-dihydropyrroles **15** could be isolated in excellent yields (Table 4).

The regiospecific nature of the dihydropyrrole formation was confirmed by X-ray crystallography of dihydropyrrole **10b**, illustrating the expected connectivity.[21]

The mechanism of the dihydropyrrole formation is thought to proceed by initial nucleophilic ring opening of the

Table 4. Preparation of 4-Cyano-dihydropyrroles from 1-Cyano-cyclopropyl Ketones and Amines



product	R	R^1	R^2	yield of **15** (%)
15a	styryl	Ph	4-Cl-Ph	82
15b	Bn	Ph	4-Cl-Ph	91
15c	Ph	Ph	Ph	97
15d	Ph	Ph	4-Cl-Ph	99
15e	4-MeO-Ph	Ph	Ph	77

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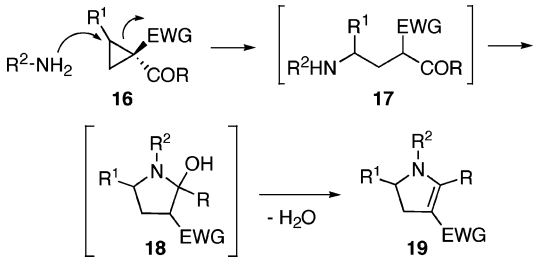
(19) For the synthesis of α-cyano-α-diazocarbonyls, see: Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett.* **2003**, *44*, 8845−8848.

(20) For examples of Lewis acid-catalyzed ring opening of cyclopropanes, see: (a) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139−141. (b) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554−8557. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057−1059.

Scheme 2

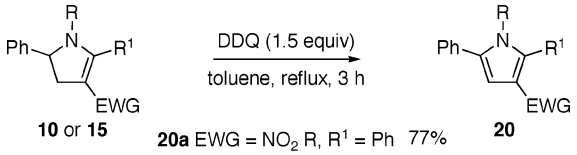


activated cyclopropane **16** at the 2-position, followed by intramolecular condensation of intermediate **17** to yield the dihydropyrrole **19** (Scheme 2). This would suggest that aromatic substituents serve to make the 2-position more electrophilic.[14b] Following this logic, the phenethyl-derived cyclopropane **6g** activates the cyclopropane to a lesser extent, and the rates of dihydropyrrole formation decrease, leading to reduced yields along with unreacted **6g** (Table 3).

Alternatively, the mechanism could involve imine formation between the ketone and amine followed by ring opening. ^{1}H NMR experiments show that the rate of consumption of the *E*- and *Z*-diastereomers is similar, suggesting the former mechanism. Moreover, only starting materials and products can be observed during the reaction.

Oxidation of the 4-nitro- and 4-cyano-dihydropyrroles to pyrroles **20** could be successfully accomplished using DDQ in refluxing toluene (Scheme 3).[22] These pyrroles can also serve as precursors to 4-amino pyrroles[23] via reduction of the nitro group through known literature methods.[24]

Scheme 3



20a EWG = NO_2 R, R^1 = Ph 77%
20b EWG = CN R,R^1 = Ph 94%
20c EWG = CN, R = 4-Cl-Ph, R^1 = styryl 91%

In summary, the in situ-generated phenyliodonium ylide cyclopropanation protocol was extended to include α-cyanoketone substrates. The doubly activated cyclopropanes were then applied to the preparation of a series of highly functionalized dihydropyrroles and pyrroles. The synthesis is modular, allowing the preparation of a variety of analogues in an efficient and expedient manner.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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