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# Synthesis of Indolizines and Benzoindolizines by Annulation of Donor-Acceptor Cyclopropanes with Electron Deficient Pyridines and Quinolines

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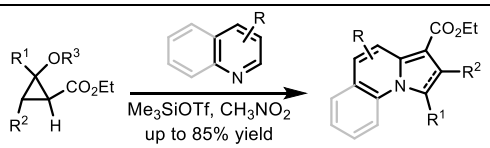
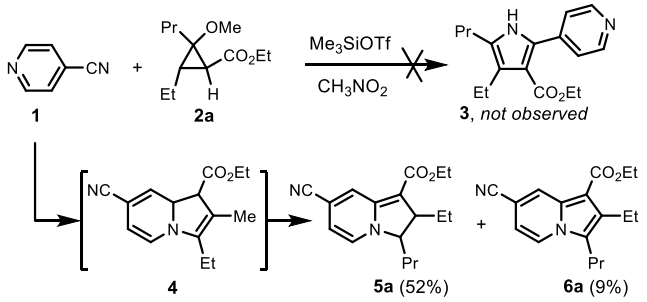
## Abstract




The formal [3+2] dipolar cycloaddition (or annulation) of donor-acceptor cyclopropanoate esters with pyridines and 5-nitroquinoline is reported. Electron deficient pyridine dipolarophiles (R = CN, $CO_2Et$, COMe) participate in the annulation whereas electron rich species do not. The product 2,3-dihydroindolizines undergo rapid autooxidation, and the X-ray structures for two of the aromatic products are reported.

Donor-acceptor alkoxy substituted cyclopropanoate esters are important synthetic intermediates that when suitably activated by Lewis acids can undergo fruitful annulation or [3+2] dipolar cycloaddition processes with electron rich aldehydes, imines and related pi systems.[1] We recently found success with nitrile dipolarophiles in such reactions,[2] and subsequently developed a general pyrrole synthesis.[3,4] While investigating the scope of the pyrrole synthesis with heteroaromatic nitriles[4] we examined the reaction between 4-cyano pyridine **1** and cyclopropane **2a** (Scheme 1) under the standard reaction conditions ($Me_3SiOTf$, $MeNO_2$ solvent, 0 °C → rt).[3] However, the anticipated pyrrole **3** was not observed, and instead the intensely purple 2,3-dihydroindolizine **5a** and the pale yellow indolizine **6a** were obtained by flash chromatography on silica gel in 52% and 9% isolated yield, respectively. The product **5a** is apparently tautomerized from the initial alkene **4**, and the fully aromatic indolizine **6a** is formed by autooxidation during workup and isolation.

## Scheme 1



This report describes our results from an exploration of this new synthetic pathway for preparing indolizines, the skeleton of which appears in biologically active natural products,[5] medicinal chemistry,[6] dyes[7] and agrochemicals.[8] Many creative methods have been devised for their synthesis.[9,10,11,12] Annulations between pyridines and cyclopropenones are known,[11,12] as are formal [3+2] dipolar cycloadditions of pyridines with certain 1,3-dipoles, such as nitrile ylides[13] and nitrile imines.[14]

The reaction of more electron rich pyridines, including pyridine itself and 4-methoxypyridine, with cyclopropane **2a** under the above conditions gave complex reaction mixtures. A trace amount of product was found from reaction with pyridine (3%), and nothing identifiable from 4-methoxypyridine. The original Lewis acid and solvent system for the reaction appear somewhat incompatible with pyridines. For example, reaction of $Me_3SiOTf$ and pryidine with the nitromethane solvent might lead to formation of the silylnitronate, or the interaction of the nucleophilic pyridine and electrophilic triflate might sequester them as their pyridinium salt. Therefore, efforts to optimize the reaction were undertaken that included adjusting stoichiometry and surveying various solvents ($PhNO_2$, $CH_2Cl_2$, $CCl_4$, EtOAc, PhMe) and Lewis acids ($Yb(OTf)_3$,[15] TBSOTf, $Me_3SiOMs$, $^iPr_3SiOTf$, $BF_3$•$OEt_2$, $ZnCl_2$). Additionally, different workup procedures that were tested ranged from strongly acid to basic and both aqueous and anhydrous. Unfortunately, none of these modifications proved generally more useful than the original combination of $Me_3SiOTf$ in $MeNO_2$.

The reaction scope was then evaluated by combining 4-cyanopyridine with additional cyclopropanes offering different substitution patterns (Figure 1), including those with: the $R^1$ and $R^2$ substituents tied back as a fused cyclohexane ring (**2b**), a phenyl ring at the alkoxy carbon (**2c**), a methyl at the alkoxy carbon (**2d**), no substituents (**2e**) and a fused pyranose structure (**2f**).[16] The fused cyclohexane proved compatible and gave the annulation highly air sensitive 2,3-dihydroindolizine along with some aromatic product (Table 1, entry b). Therefore to facilitate isolation and characterization the annulation products were immediately subjected to oxidizing conditions ($MnO_2$ or DDQ),[17] and the yields reported in Table 1 are for the two step sequence. The substrate bearing a phenyl group at the alkoxy carbon provided an additional class of compatible cyclopropanes (entry c), and the oxidized annulation product was obtained in a modest 35% yield (over two steps). With a methyl in the same position the yield dropped to 29% (entry d). No identifiable products could be isolated from complex decomposition residues after reaction with cyclopropanes **2e** and **2f**.

**Figure 1**. Representative Cyclopropanes

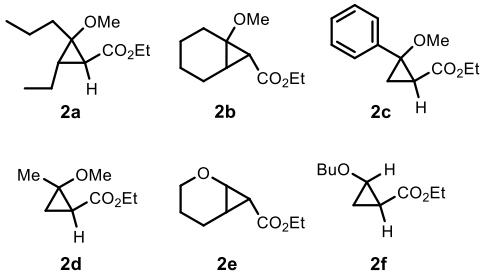
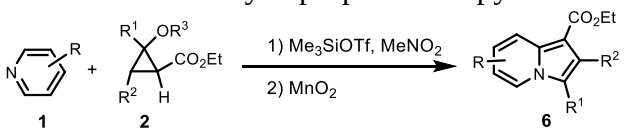
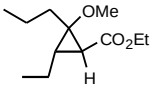
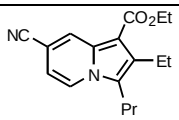
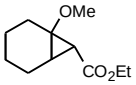
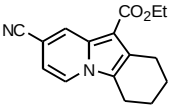
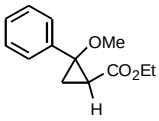
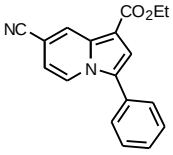
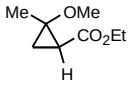
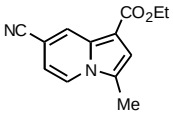
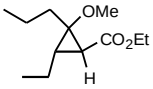
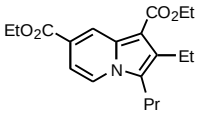
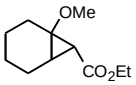
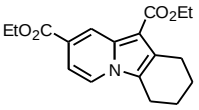
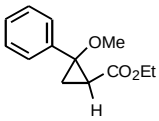
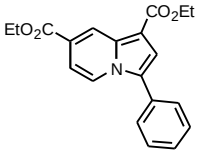
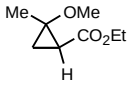
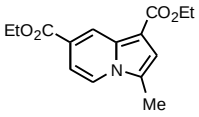
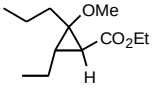
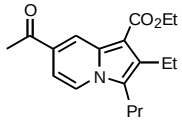
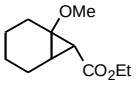
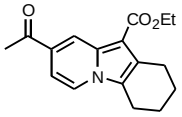
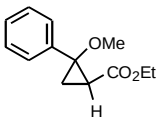
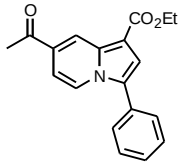
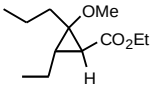
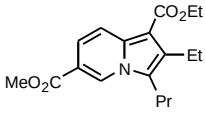
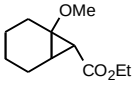
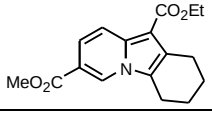



**Table 1**. Annulation and oxidation of DA cyclopropanes and pyridines



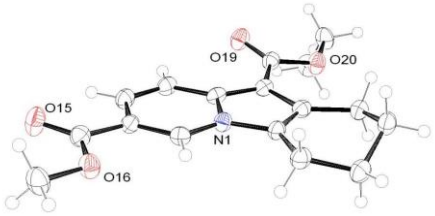
| Entry | Cyclopropane | Pyridine | Product | Yield[a] |
|---|---|---|---|---|
| a |  | 4-CN |  | 61% |
| b |  | 4-CN |  | 43% |
| c |  | 4-CN |  | 35% |
| d |  | 4-CN |  | 29% |
| e |  | 4-$CO_2$Et |  | 57% |
| f |  | 4-$CO_2$Et |  | 46% |
| g |  | 4-$CO_2$Et |  | 42% |
| h |  | 4-$CO_2$Et |  | 18% |
| i |  | 4-COMe |  | 8% |
| j |  | 4-COMe |  | 15% |
| k |  | 4-COMe |  | 33% |
| l |  | 3-$CO_2$Me |  | 10% |
| m |  | 3-$CO_2$Me |  | 12%[b] |

[a] Isolated yield over two steps. [b] $PhNO_2$ used as solvent.

Other electron deficient pyridines were examined, and ethyl isonicotinate performed comparably well with members of the representative set of cyclopropanes bearing untethered aliphatic substituents (entry e, 57%), a fused cyclohexyl ring (entry f, 46%), an aromatic substituent (entry g, 42%) and a methyl group (entry h, 18%). A 4-acylpyridine participates, but with test cyclopropanes **2a** and **2b** the yield was markedly lower at 8% and 15% (entries i and j). The 33% yield from reaction with aryl substituted cyclopropane **2c** (entry k) is, however, comparable to results with the other pyridines.

Reactions with non-symmetric methyl nicotinate took about five hours longer for complete consumption of cyclopropane (TLC), and yields were disappointing (entries l and m). Only the regioisomer shown with the pyridine substituent distal to the newly formed carbon-carbon bond was detected in these reactions. In the case of entry m a 6% yield was improved to 12% by replacing the $MeNO_2$ solvent with $PhNO_2$, and the oxidized product gave crystals of quality suitable for X-ray analysis (Figure 2).[18]

**Figure 2**. ORTEP of **6m**.[18]




Among all of the pyridines examined the best yields were obtained with cyclopropane **2a**, whereas only intractable mixtures were encountered with cyclopropanes **2e** and **2f**. One structural feature that appears necessary from this set of examples is the requirement that the alkoxy substituent be bonded to a quaternary carbon. It is noteworthy that the cyclopropanes that fail here excel in annulation reactions with nitriles.[3]

Quinolines were evaluated as annulation partners and quinoline, like the electron rich pyridines, gave complex reaction mixtures under the standard conditions.[12,19] Therefore commercially available 5-nitroquinoline was chosen as an electron deficient substrate, and with cyclopropane **2b** a more satisfying 85% isolated yield of the oxidized product **8** was obtained (Scheme 2). The structure was confirmed by single crystal X-ray analysis (Figure 3).

**Scheme 2**

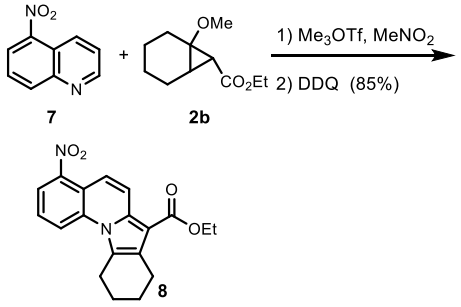
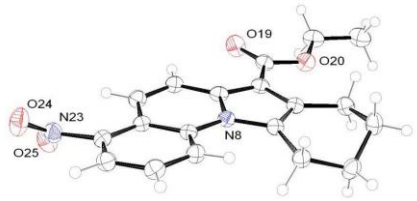
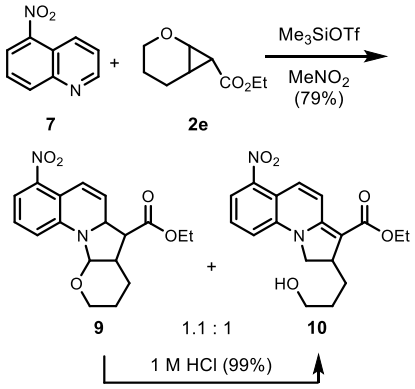


**Figure 3**. ORTEP of **8**.[18]

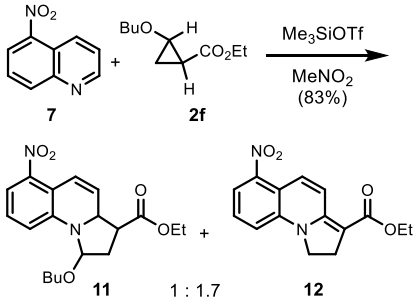



The improved reaction efficiency with 5-nitroquinoline fortunately extends to those cyclopropanes that proved incompatible in the pyridine series. For example, cyclopropanes **2e** and **2f** both failed to give any identifiable products with the pyridines in Table 1, whereas they were successful here. Specifically, reaction with **2e** furnished the aminal **9** and the non-oxidized elimination product **10** in a 1.1 to 1 ratio and 79% combined isolated yield (Scheme 3). The aminal **9** was cleanly converted to the dihydrobenzoindolizine **10** by treatment with dilute aqueous HCl. Reaction with cyclopropane **2f** was equally successful, and afforded the aminal **11** and the elimination product **12** in a 1 to 1.7 ratio and 83% yield (Scheme 4). No aminal products were detected during work with the pyridines.

**Scheme 3**



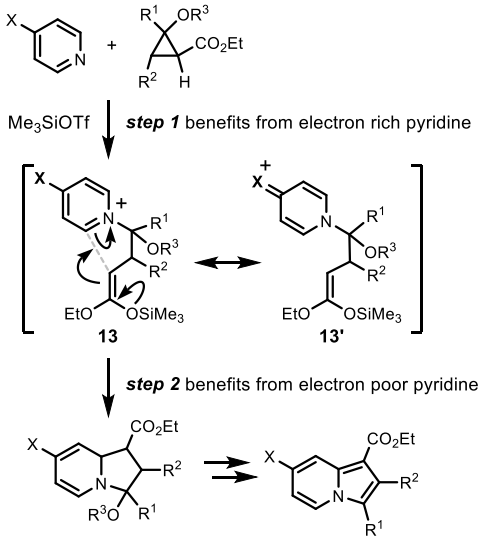

**Scheme 4**




It is clear from these results that reaction efficiency increases with electron deficient pyridines, a trend that is opposite to that observed with nitriles.[2-4] A mechanistic hypothesis that is consistent with these observations is provided in Scheme 5. Activation of the cyclopropane by $Me_3SiOTf$ generates an electrophilic oxocarbenium ion (or equivalent) that, in a stepwise mechanism, is intercepted by a nucleophilic pyridine (step 1) to give **13**. Electron donating groups (X) will improve nucleophilicity and facilitate step 1. However, the same group's stabilization of **13'** will critically render the pyridinium ion less susceptible to attack by

the ester enolate (step 2), and the reaction will fail. This mechanistic speculation implies that pyridines of a particular electronic disposition (i.e., an electron deficient X) are required to balance the opposing demands of the two bond forming steps. Quizzically, the observed electronic trends may be an unfortunate artifact resulting from complications due to the incompatibility of the $Me_3SiOTf$ and other reagents as discussed in an introductory paragraph. Furthermore, a dipolar cycloaddition mechanism is plausible.

**Scheme 5**




In summary, a new operationally simple annulation between DA-cyclopropanes with pyridines and quinolines for the synthesis of indolizines and benzoindolizines has been described. Electron poor pyridines and quinolines are superior substrates for this reaction at its current state of development. Despite some limitations in substrate scope, this methodology provides convenient new pathways that access a variety of indolizine scaffolds. It is hoped that future catalyst systems will result in greater substrate diversity and improved yields.

## Experimental Section

General annulation procedure. A degassed solution of cyclopropane (1.0 mmol) and pyridine (2.0 mmol) in $MeNO_2$ (0.6 mL) at 0 °C was treated with $Me_3SiOTf$ (1.1 mmol) and the resulting mixture was allowed to warm to room temperature. After two hours the solution was diluted with EtOAc (8 mL) and then poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (40 mL). The heterogeneous mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine and dried ($Na_2SO_4$). After filtration through a thin pad of celite the solution was divided into two equal portions. One was used for the (attempted) isolation and characterization of **5**. The other portion was concentrated under reduced pressure, dissolved in $CH_2Cl_2$ (10 mL) and treated with a mixture of powdered molecular sieves (4 Å, 1.2 g) and $MnO_2$ (5 mmol, 0.43 g, 10 equivalents). The reaction was heated to reflux and monitored periodically by TLC (ca. 3 h). The cooled reaction mixture was filtered through a pad of silica gel and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc-hexanes for elution provided the indolizine.

**Key words**: annulation, autooxidation, donor-acceptor systems, cyclopropanes, cycloadditions, zwitterions.

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