ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 10278–10280

www.rsc.org/chemcomm

COMMUNICATION

An efficient synthesis of hydropyrido[1,2-*a*]indole-6(7*H*)-ones *via* an In(III)-catalyzed tandem cyclopropane ring-opening/Friedel–Crafts alkylation sequence†

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Received 9th July 2011, Accepted 28th July 2011
DOI: 10.1039/c1cc14131g

An efficient Lewis acid-catalyzed cyclopropane ring-opening/Friedel–Crafts alkylation sequence of methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates is reported. The protocol affords functionalized hydropyrido[1,2-*a*]indole-6(7*H*)-ones in up to 99% yield.

The hydropyrido[1,2-*a*]indole skeleton (**1**) and, more specifically, its C(*6*)-oxidized cogeners (**2**) are key structural motifs that appear in the core structures of an impressive number of naturally-occurring indole alkaloids and pharmaceutically-relevant compounds (Fig. 1).[1] Many approaches have been reported to construct the hydropyrido[1,2-*a*]indole skeleton.[2] Unfortunately, many of these strategies involve extensive multi-step sequences to construct the *N*-fused bicyclic ring system or do not allow for a large range of functionality to be accessed. Therefore, the development of a more general and efficient method for the facile construction of this polycyclic core remains a formidable goal for organic chemists.

In this communication, we describe an efficient and modular approach to hydropyrido[1,2-*a*]indole-6(7*H*)-ones **2** *via* the Lewis acid-catalyzed intramolecular cyclizations of methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates (Scheme 1). Mechanistically, the protocol involves cyclopropane ring-opening in the presence of a Lewis acid catalyst, followed by an intramolecular Friedel–Crafts alkylation[3] of the indole.[4,5] The cyclization proceeds through the aza-cationic intermediate **B**

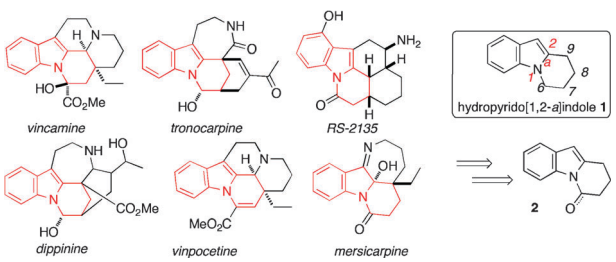

Fig. 1 Compounds containing the hydropyrido-[1,2-*a*]indole core.

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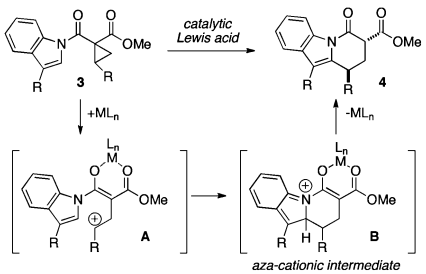
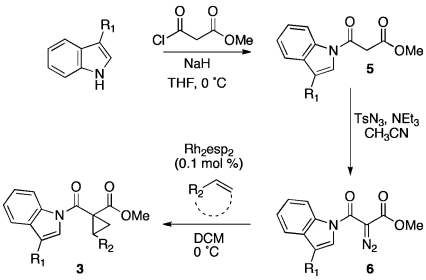
† Electronic supplementary information (ESI) available: full experimental details and ^{1}H and ^{13}C spectra for all new compounds. See DOI: 10.1039/c1cc14131g



Scheme 1 Tandem cyclopropane ring-opening/Friedel–Crafts alkylation.



Scheme 2 Modular preparation of cyclization precursors.

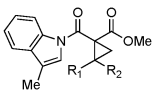
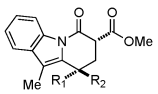
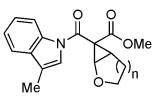
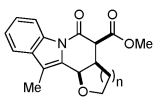
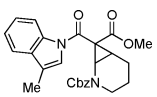
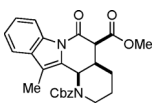
and, thus, incorporates a nitrogen atom into the newly formed ring. This transformation specifically generates the lactam ring portion of the hydropyrido[1,2-*a*]indole-6(7*H*)-ones.

We began our study by outlining a modular sequence for the preparation of the precursors required for cyclization. Cyclopropanes **3** were synthesized in three steps according to Scheme 2. *N*-Acylation of an indole with commercially-available methyl malonyl chloride afforded the 1,3-dicarbonyl compound **5**. Next, diazo transfer provided α-diazoester **6**. Lastly, cyclopropanation[6] with Rh_2esp_2 (bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]) in the presence of a requisite alkene provided the desired methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates **3** with yields up to 70% over the three steps.

With a diverse set of substrates in hand, we first examined the effects of various donor groups on the cyclopropane by changing the alkene used during cyclopropanation. Based on our recent success with $In(OTf)_3$ as an effective catalyst for six membered-ring formation,[7] cyclopropanes **3a–3q** (derived from 3-methyl indole) were treated with 30 mol% $In(OTf)_3$ in either dichloromethane at room temperature or 1,2-dichloroethane at reflux (Table 1).[8]

Cyclopropane **3a** rapidly cyclized to afford the hydropyrido-[1,2-*a*]indole based product **4a** in near quantitative yield with 2.6 : 1 *trans* : *cis dr* (entry 1). Likewise, 2-methoxy phenyl cyclopropane **3b** provided product **4b** in 95% with 3.2 : 1 *dr* (entry 2). Next, in order to examine the electronic effects of the *para*-substituent on the aromatic cyclopropane donor group, the phenyl, 4-fluorophenyl, 4-chlorophenyl and the 4-nitrophenyl cyclopropanes were synthesized. When the phenyl derivative **3c** was subjected to the same reaction conditions, no reaction occurred (only starting material was recovered). Upon heating to reflux in 1,2-dichloroethane, **3c** gave 52% yield of the desired hydropyrido[1,2-*a*]indole **4c** with 2.6 : 1 *dr* (entry 3).

Table 1 Substrate scope[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]	dr (*trans* : *cis*)[c]
					
1	**3a** (R_1 = H; R_2 = 4-MeOPh)	**4a**	2.0	99	2.6 : 1
2	**3b** (R_1 = H; R_2 = 2-MeOPh)	**4b**	3.0	95	3.2 : 1
3[d]	**3c** (R_1 = H; R_2 = Ph)	**4c**	8.0	52	2.6 : 1
4[d]	**3d** (R_1 = H; R_2 = 4-F-Ph)	**4d**	8.0	48	2.6 : 1
5[d]	**3e** (R_1 = H; R_2 = 4-Cl-Ph)	**4e**	12.0	50	1.9 : 1
6[d]	**3f** (R_1 = H; R_2 = 4-NO_2-Ph)	**4f**	20.0	*trace*	—
7	**3g** (R_1 = H; R_2 = 2-furyl)	**4g**	2.0	99	4.5 : 1
8	**3h** (R_1 = Me; R_2 = Ph)	**4h**	2.0	94	1.1 : 1[e]
9[d]	**3i** (R_1, R_2 = Et)	**4i**	6.0	85	—
10[d]	**3j** (R_1, R_2 = –$(CH_2)_4$–)	**4j**	6.0	88	—
11[d]	**3k** (R_1, R_2 = –$(CH_2)_5$–)	**4k**	6.0	79	—
12[d]	**3l** (R_1 = H; R_2 = CH_2TBDPS)	**4l**	16.0	82	—[f]
13[d]	**3m** (R_1 = H; R_2 = NPhth)	**4m**	8.0	55	4.8 : 1
14[d]	**3n** (R_1 = H; R_2 = SPh)	**4n**	7.0	81	6.3 : 1
					
15	**3o** (n = 1)	**4o**	2.5	97	—[f,g]
16	**3p** (n = 2)	**4p**	2.5	93	—[f,g]
	3q	**4q**			
17			2.0	97	7.1 : 1[h]

[a] Reactions run with 1 equiv. substrate **3** and 30 mol% $In(OTf)_3$ in CH_2Cl_2 at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^{1}H NMR of the crude reaction mixture and represent *trans* : *cis* diastereomeric ratios. [d] Reaction performed in 1,2-dichloroethane at 80 °C. [e] Relative configurational assignment not determined. [f] Only one diastereomer visible by ^{1}H NMR. [g] All-*cis* diastereomer. [h] Major component is the all-*cis* diastereomer, minor component is its C(7) epimer.

Similarly, for each of the other cyclization precursors bearing electron-withdrawing groups **3d–3f**, no reaction was observed at room temperature, whereas cyclized products were observed in 1,2-dichloroethane at reflux. The 4-chlorophenyl and 4-fluorophenyl derivatives furnished cyclized products **4d** and **4e** in 48% and 50% yield, respectively (entries 4 and 5). We were pleased with these results because the aromatic halogen may serve as a chemical handle for further synthetic functionalization. However, the 4-nitro derivative **3f** only afforded trace amounts of the desired product **4f** as indicated by crude ^{1}H NMR (entry 6). These observations can be rationalized based on an increasing cation destabilizing effect as the substituents are varied from the electron-donating 4-methoxy group to the electron-withdrawing 4-nitro group. These observations correlate well with known Hammett substituent values for benzylic cations.[9]

Similar reactivity was observed when a heteroaromatic group was employed as the donor substituent. For example, with furan as the donor group, cyclized product **4g** is readily obtained in 99% yield with 4.5 : 1 *dr* (entry 7). This result is noteworthy in that furyl donor groups of this type have previously been shown to be prone to polymerization.[10a]

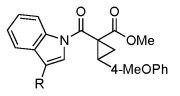
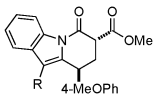
Placing another cation stabilizing donor substituent on the cyclopropane, as in **3h** (derived from α-methyl styrene), resulted in a dramatic accelerating effect. This effect can be seen in that **3h** readily cyclizes at room temperature to afford **4h** in high yield (94%) with 1.1 : 1 *dr* (entry 8), whereas **3c** does not cyclize at room temperature. The enhanced reactivity of **3h** is presumably attributed to faster ring-opening of the cyclopropane due to a release of steric ring strain and the formation of the more stable 3° benzylic carbocation. This is also important due to the formation of a quaternary stereocenter.

Since tertiary carbocations are very close in energy to benzylic carbocations[11] and a 3° carbocation will be formed upon cyclopropane ring-opening, we envisioned that cyclization would occur when two alkyl groups are placed geminally at the donor position of the cyclopropane. To explore this premise, **3i** (derived from 3-methylene pentane), **3j** (derived from methylene cyclopentane) and **3k** (derived from methylene cyclohexane) were synthesized. When subjected to heating in DCE with $In(OTf)_3$, each cyclopropane **3i**, **3j** and **3k** provided their respective hydropyrido[1,2-*a*]indole products **4i**, **4j** and **4k** in 85, 88 and 79% yield (entries 9–11). These results are particularly notable for several reasons: (1) spirocyclic compounds (as in **4j** and **4k**) can be readily accessed from an appropriate 1,1-disubstituted alkene; (2) the successful use of alkyl groups as donors has been limited to Tsuge's seminal report;[10d] and (3) a number of hydropyrido[1,2-*a*]indole natural products have *gem*-dialkyl substituents at C(*9*).

Activated alkyl donor substituents, such as the 2-trialkylsilylmethyl group,[10b] cyclized under similar reaction conditions. In one representative example, the 2-silylmethyl cyclopropane **3l** was synthesized and reacted to give **4l** in 82% yield, with only one observable diastereomer (entry 12). This silyl group not only stabilizes the carbocation (upon cyclopropane ring-opening) through the β-silyl effect, but, more importantly, acts as a point of further functionalization.

Next, the influence of a heteroatom-donating group on the cyclopropane was examined. In particular, oxygen, sulfur and

Table 2 Varying the indole moiety[a]

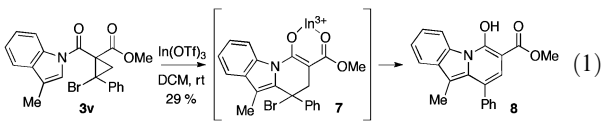
Entry	Substrate	Product	Time (h)	Yield (%)[b]	dr (*trans* : *cis*)[c]
					
1	**3r** (R = H)	**4r**	0.75	99	1.1 : 1
2	**3s** (R = CH_2CH_2Br)	**4s**	1.0	99	2.7 : 1
3	**3t** (R = CH_2CH_2NPhth)	**4t**	2.0	76	2.8 : 1
4	**3u** (R = CH_2CO_2Me)	**4u**	3.0	88	2.0 : 1

[a] Reactions run with 1 equiv substrate **3** and 30 mol% $In(OTf)_3$ in CH_2Cl_2 at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans* : *cis* diastereomeric ratios.

nitrogen groups were employed due to their established success for donor–acceptor cyclopropanes.[2c,10b] When a phthalimido group was the substituent, the desired cyclized product **4m** was obtained in 55% yield and 4.8 : 1 *dr* (entry 13). Phenyl thioether **3n** provided its cyclization product **4n** in 81% yield with 6.3 : 1 *dr* (entry 14). Cyclopropanes **3o** and **3p** (derived from dihydrofuran or dihydropyran) efficiently cyclized to give **4o** and **4p** in 97 and 93% yield, respectively (entries 15 and 16). In both cases, the major diastereomers have the all-*cis* configuration, as determined by NMR spectroscopy. Likewise, the Cbz-protected ring-fused piperidinyl cyclopropane **3q** afforded **4q** in 97% with a 7.1 : 1 *dr* (entry 17).

To further demonstrate the modular nature of our protocol, the indole moiety was changed from 3-methyl indole (Table 2). **3r** (derived from indole) was used to affirm that a substituent in the 3-position is not required for cyclization. Cyclization readily occurred to give **4r** in 99% yield with 1.1 : 1 *dr* (entry 1). Next, the 3-(2-bromoethyl)-1*H*-indole derived cyclopropane **3s** provided its cyclization product **4s** in near quantitative yield with 2.7 : 1 *dr* (entry 2). The bromide remains intact throughout the cyclization and, thus, is available for further functionalization. Similarly, when the phthalimide-protected tryptamine derivative **3t** was subjected to the reaction conditions, hydropyrido-[1,2-*a*]indole product **4t** was generated in 76% yield with 2.8 : 1 *dr* (entry 3). **4t** can then be readily deprotected under standard conditions to provide the free amine. Lastly, the methyl acetate substituted indole derivative **3u** provided the cyclized product **4u** in 88% yield with 2.0 : 1 *dr* (entry 4).

This method is also applicable to the direct synthesis of pyrido[1,2-*a*]indoles. In one representative example, when cyclopropane **3v** (from α-bromostyrene) was subjected to the reaction conditions, pyrido[1,2-*a*]indole **8** was observed in 29% yield (eqn (1)). This product seemingly arises from the rapid elimination of HBr from the cyclized intermediate **7** to generate the new aromatic ring.



(1)

In summary, we report an efficient catalytic cyclopropane ring-opening/Friedel–Crafts alkylation sequence for the facile construction of hydropyrido[1,2-*a*]indole based derivatives in good to excellent yields (48–99%) in four steps from readily-available indoles and alkenes. The methodology is highly modular, operationally simple and amenable to a large variety of functional groups and substitution patterns. Additional studies towards the application of this method for the synthesis of complex, biologically-active molecules are currently underway in our laboratories and will be discussed in due course.

S. F. thanks the NSF FACES Program for a Career Initiation Grant and ORAU for the Ralph E. Powe Junior Faculty Enhancement Award. M. A. C. thanks the Ford Foundation (Diversity Fellowship), the NSF (Graduate Research Fellowship), and Georgia Tech (Presidential Fellowship) for generous support.

Notes and references

1 For some selected examples, see: (*a*) D. L. Taylor, P. S. Ahmed, P. Chambers, A. S. Tyms, J. Bedard, J. Duchaine, G. Falardeau, J. F. Lavallee, W. Brown, R. F. Rando and T. Bowlin, *Antiviral Chem. Chemother.*, 1999, **10**, 79; (*b*) X. Li and R. Vince, *Bioorg. Med. Chem.*, 2006, **14**, 294; (*c*) O. Khdour and E. B. Skibo, *J. Org. Chem.*, 2007, **72**, 8636; (*d*) J. Magolan, C. A. Carson and M. A. Kerr, *Org. Lett.*, 2008, **10**, 1437; (*e*) R. A. Bunce and B. Nammalwar, *J. Heterocycl. Chem.*, 2009, **46**, 172.

2 For recent representative syntheses, see: (*a*) H. Zhu, J. Stockigt, Y. Yu and H. Zou, *Org. Lett.*, 2011, **13**, 2792; (*b*) M. Mizutani, F. Inagaki, T. Nakanishi, C. Yanagihara, I. Tamai and C. Mukai, *Org. Lett.*, 2011, **13**, 1796; (*c*) F. De Simone, J. Gertsch and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 5767; (*d*) A. Biechy and S. Z. Zard, *Org. Lett.*, 2009, **11**, 2800; (*e*) D. Facoetti, G. Abbiati and E. Rossi, *Eur. J. Org. Chem.*, 2009, 2872.

3 For a recent example of Friedel–Crafts alkylations using donor–acceptor-acceptor cyclopropanes, see: A. O. Chagarovskiy, E. M. Budynina, O. A. Ivanova, Y. K. Grishin, I. V. Trushkov and P. V. Verteletskii, *Tetrahedron*, 2009, **65**, 5385.

4 For a mechanistically similar reaction, see: T. Vaidya, G. F. Manbeck, S. Chen, A. J. Frontier and R. Eisenberg, *J. Am. Chem. Soc.*, 2011, **133**, 3300.

5 In the literature, this type of transformation has fallen under the term "homo-Nazarov" cyclization. The term "homo-Nazarov" cyclization has been used either to describe the type of reaction intermediate (a six-membered oxyallyl cation) or the type of product formed (a six-membered ring) in direct comparison to the classic Nazarov cyclization. Hence, the use of the prefix "homo" to describe the six-membered ring homo-Nazarov products when compared to the standard Nazarov products. While we have previously published reports under this name, however, as one reviewer pointed out, this terminology can be misleading based on mechanistic considerations, since the Nazarov cyclization is an electrocyclization, whereas the homo-Nazarov cyclization is not. To alleviate further confusion, we will refer to our reactions as a tandem cyclopropane ring-opening/Friedel–Crafts alkylation sequence. For literature on the homo-Nazarov cyclization, see ref. 10.

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8 Lower catalyst loadings will also catalyze the cyclizations, albeit with longer reactions and/or less conversion.

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