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Diastereoselective Intramolecular Friedel–Crafts Cyclizations of Substituted Methyl 2-(1*H*-indole-1-carbonyl)acrylates: Efficient Access to Functionalized 1*H*-Pyrrolo[1,2-*a*]indoles

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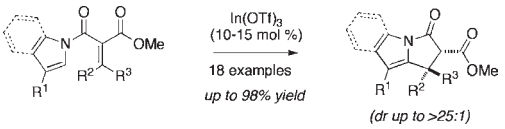
ABSTRACT



A general, catalytic method for the diastereoselective synthesis of functionalized 1*H*-pyrrolo[1,2-*a*]indoles via an intramolecular Friedel–Crafts alkylation of *N*-acyl indoles is reported. Products were obtained in excellent yields (up to 98%) with high diastereoselectivities (up to >25:1 *dr*).

[*a*]-Annelated indoles are unique structural features present in a wide range of heterocyclic compounds that play important roles in medicinal chemistry and organic synthesis.[1] Among [*a*]-annelated systems, the pyrrolo[1,2-*a*]-indole scaffold is a primary target for synthetic chemists due to its structural diversity (Figure 1).[2] For example, pyrrolo[1,2-*a*]indoles are primarily characterized by three isomeric structures (the 9*H*-pyrrolo[1,2-*a*]indoles **1**, the 3*H*-pyrrolo[1,2-*a*]indoles **2**, and the 1*H*-pyrrolo[1,2-*a*]-indoles **3**) or by the two reduced forms **4** and **5**. Moreover, compounds specifically containing a 1*H*-pyrrolo[1,2-*a*]-indole core demonstrate interesting physiological and therapeutic properties.[3] For example, mitomycin C (**6**)[4] exhibits strong antitumor activity; yuremamine (**7**)[5] shows hallucinogenic and psychoactive effects; isatisine A (**8**)[6] possesses antiviral activity; and flinderole C (**9**)[7] acts as a selective antimalarial agent (Figure 2).

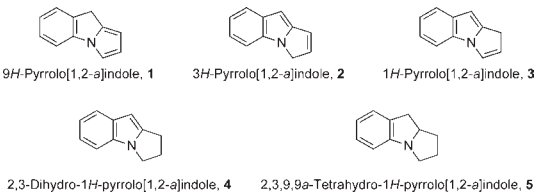


Figure 1. Representative pyrrolo[1,2-*a*]indole frameworks.

Numerous routes to the pyrrolo[1,2-*a*]indoles have been reported in recent years,[8] underlining the continued importance of this framework to the synthetic community.

(1) (a) Aygun, A.; Pindur, U. *Curr. Med. Chem.* **2003**, *10*, 1113. (b) Pindur, U.; Lemster, T. *Curr. Med. Chem.* **2001**, *8*, 1681. (c) Ishikura, M.; Terashima, M. *Tetrahedron Lett.* **1992**, *33*, 6849. (d) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317.

(2) For a representative example, see: Hao, L.; Pan, Y.; Wang, T.; Lin, M.; Chen, L.; Zhan, Z.-p. *Adv. Synth. Catal.* **2010**, *352*, 3215.

(3) (a) Kakadiya, R.; Dong, H.; Lee, P.-C.; Kapuriya, N.; Zhang, X.; Chou, T.-C.; Lee, T.-C.; Kapuriya, K.; Shah, A.; Su, T.-L. *Bioorg. Med. Chem.* **2009**, *17*, 5614. (b) Tanaka, M.; Sagawa, S.; Hoshi, J.-I.; Shimoma, F.; Yasue, K.; Ubukata, M.; Ikemoto, T.; Hase, Y.; Takahashi, M.; Sasase, T.; Ueda, N.; Matsushita, M.; Inaba, T. *Bioorg. Med. Chem.* **2006**, *14*, 5781.

(4) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.

(5) Vepsalainen, J. J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. C. *Planta Med.* **2005**, *71*, 1053.

(6) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.

(7) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329.

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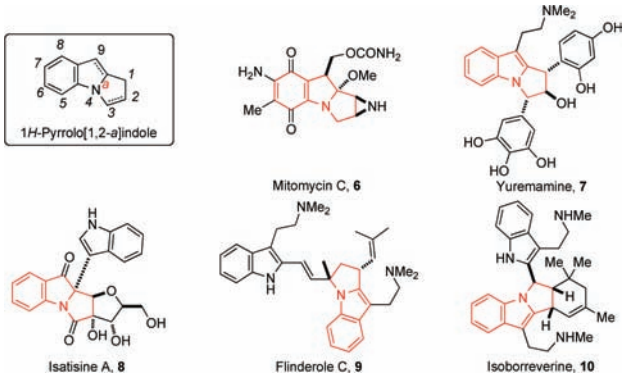
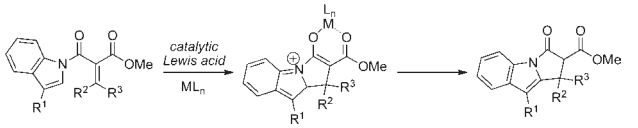


Figure 2. Representative examples of biologically active 1*H*-pyrrolo[1,2-*a*]indole-based natural products.

However, a general and efficient method that allows for a variety of functionality to be incorporated about the 1*H*-pyrrolo[1,2-*a*]indole skeleton has yet to be achieved.[9]

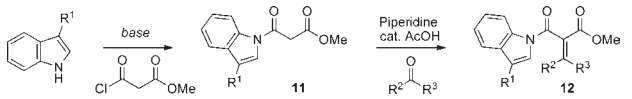
Scheme 1. Intramolecular Friedel–Crafts Alkylations of Methyl 2-(1*H*-Indole-1-carbonyl)acrylates



Toward this end, we report an efficient and diastereoselective approach to functionalized 1*H*-pyrrolo[1,2-*a*]-indole-3(2*H*)-ones via an In(OTf)$_3$-catalyzed intramolecular Friedel–Crafts (FC) alkylations of methyl 2-(1*H*-indole-1-carbonyl)acrylates (Scheme 1). The Michael-type FC reaction of indoles with α,β-unsaturated carbonyl compounds is a powerful strategy in the total synthesis of complex products.[10] While intermolecular examples of these reactions are prevalent in the literature,[11] the lesser studied intramolecular variants offer tremendous utility for the synthesis of complex indole-containing polycycles.[12] We recently reported an efficient synthesis of hydropyrido-[1,2-*a*]indole-6(7*H*)-ones via an In(III)-catalyzed tandem cyclopropane ring-opening/intramolecular FC alkylation sequence.[13] Encouraged by this previous work, we reasoned that an intramolecular FC reaction should occur if the corresponding methyl 2-(1*H*-indole-1-carbonyl)acrylates **12** were employed as the cyclization precursors.

Adding credence to this hypothesis, Hadjipavlou-Litina and Papaioannou recently reported the unexpected formation of a 1*H*-pyrrolo[1,2-*a*]indole-3(2*H*)-one from treatment of a *N*-cinnamoyl indole derivative with an excess of TFA in dichloromethane.[14] This reaction only occurred when the aryl portion of the cinnamate had electron-donating *ortho*- and *para*-methoxy substituents. When no methoxy group was present or if the aryl ring had only one methoxy group in the *ortho*- or *para*-position, no cyclization occurred.[15] In hopes of circumventing this limitation and given that alkylidene malonates have been shown to offer enhanced reactivity as Michael acceptors in comparison to simple α,β-unsaturated alkenes,[16] we synthesized *N*-acylated indoles **12** according to Scheme 2. Treatment of an indole with methyl malonyl chloride afforded the β-ester-amide **11**, and Knovenagel condensation with a suitable aldehyde/ketone furnished the desired acrylates **12**.

Scheme 2. Substrate Synthesis



With a facile method in hand to prepare the acrylates, we chose the 4-methoxyphenyl derivative **12a** (from *p*-anisaldehyde) as the test substrate to develop and optimize the reaction conditions. After several experimental iterations, the conditions for efficient and timely conversion were determined to be 10 mol % In(OTf)$_3$ in 1, 2-dichloroethane at reflux.[17]

Table 1 shows the scope and limitations of the cyclization when aromatic groups are present on the acrylate. Using the optimized conditions, the 1*H*-pyrrolo[1,2-*a*]indole product **13a** (derived from our test substrate **12a**) was formed in 95% yield with a 15:1 *trans*/*cis dr*[18] (entry 1).[19]

(8) For a seminal review on pyrrolo[1,2-*a*]indoles, see: Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199.

(9) For recent syntheses of pyrrolo[1,2-*a*]indoles, see: (a) Li, L.; Du, D.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2011**, 614. (b) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440. (c) Wood, K.; Black, D. S.; Kumar, N. *Aust. J. Chem.* **2010**, *63*, 761. (d) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028. (e) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626. (f) Huang, X.; Zhu, S.; Shen, R. *Adv. Synth. Catal.* **2009**, *351*, 3118. (g) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119. (h) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (i) Wood, K.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2009**, *50*, 574.

(10) For a seminal reference, see: Zhuang, W.; Hansen, T.; Jorgensen, K. A. *Chem. Commun.* **2001**, 347.

(11) For recent reviews, see: (a) Blay, G.; Pedro, J. R.; Vila, C. *Catal. Asymmetric Friedel-Crafts Alkylations* **2009**, 223. (b) Poulsen, T. B.; Jorgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903.

(12) For some representative examples of intramolecular Friedel–Crafts alkylations with indoles, see: (a) Medeiros, M. R.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2011**, *13*, 4012. (b) Zhou, J.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2009**, *65*, 6877. (c) Cincinelli, R.; Dallavalle, S.; Merlini, L.; Nannei, R.; Scaglioni, L. *Tetrahedron* **2009**, *65*, 3465. (d) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (e) Bergman, J.; Venemalm, L.; Gogoll, A. *Tetrahedron* **1990**, *46*, 6067.

(13) Patil, D. V.; Cavitt, M. A.; France, S. *Chem. Commun.* **2011**, *47*, 10278.

(14) Hadjipavlou-Litina, D.; Magoulas, G. E.; Krokidis, M.; Papaioannou, D. *Eur. J. Med. Chem.* **2010**, *45*, 298.

(15) The corresponding *N*-cinnamoyl indoles were synthesized, but no cyclization was observed when heated in DCE or toluene in the presence of Lewis acid catalysts (10 to 30 mol %).

(16) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

(17) For reaction optimization details, see Supporting Information.

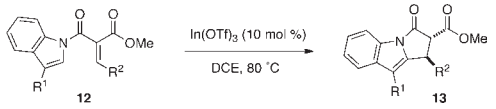
(18) For rationale behind *trans*/*cis dr* assignment, see Supporting Information.

(19) The high diastereoselectivity presumably arises from a postcyclization thermodynamic equilibration of the β-amidoester.

To determine whether the substituent on the aryl group conveys an effect upon product formation, the phenyl substrate **12b** and the electron-withdrawing 4-bromophenyl **12c**, 4-trifluoromethylphenyl **12d**, and the 4-nitrophenyl substrates **12e** were synthesized. The phenyl derivative cyclized to form **13b** in 97% yield with a 16:1 *dr* (entry 2). Similarly, the electron-deficient arenes **12c**−**e** also efficiently afforded products **13c**−**e** in high yields (84−93%) with > 16:1 *dr* (entries 3−5). Therefore, no discernible electronic effect of aryl substitution was observed.

Electron-rich heteroaromatics, such as the 2-substituted furanyl derivative **12f** and 2-thienyl derivative **12g**, proved to be suitable substrates, providing 1*H*-pyrrolo[1,2-*a*]indole products **13f** and **13g** in 97% and 98% yield, respectively, with high *dr* (entries 6 and 7). In contrast, the 2-pyridyl substrate **12h** did not undergo any appreciable cyclization (entry 8). This lack of reactivity may be attributed to inductive effects, given that the 2-pyridyl group prefers to serve as an electron acceptor. Moreover, the nitrogen of the pyridine could serve to deactivate the In catalyst by forming a stable complex.

Table 1. Friedel−Crafts Alkylation with Aromatic Acrylates[a]



entry	12	13	time (h)	yield (%)[b]	dr[c] (*trans*:*cis*)
1	**12a** (R^1 = Me; R^2 = 4-MeOPh)	**13a**	1.0	95	15:1
2	**12b** (R^1 = Me; R^2 = Ph)	**13b**	1.0	97	16:1
3	**12c** (R^1 = Me; R^2 = 4-BrPh)	**13c**	3.0	93	16:1
4	**12d** (R^1 = Me; R^2 = 4-CF_3Ph)	**13d**	3.0	92	20:1
5	**12e** (R^1 = Me; R^2 = 4-NO_2Ph)	**13e**	2.5	84	19:1
6	**12f** (R^1 = Me; R^2 = 2-furyl)	**13f**	2.0	97	18:1
7	**12g** (R^1 = Me; R^2 = 2-thienyl)	**13g**	2.0	98	24:1
8	**12h** (R^1 = Me; R^2 = 2-pyridyl)	--	24.0	NR	--
9	**12i** (R^1 = CH_2CH_2NPhth; R^2 = 4-MeOPh)	**13i**	4.0	96	14:1
10	**12j** (R^1 = CH_2CH_2Br; R^2 = 4-MeOPh)	**13j**	12.0	69	25:1
11	**12k** (R^1 = CH_2CO_2Me; R^2 = 4-MeOPh)	**13k**	3.0	93	13:1
12	**12l** (R^1 = H; R^2 = 4-MeOPh)	**13l**	1.0	98	10:1

[a] Reactions run with substrate (1 equiv) and $In(OTf)_3$ (10 mol %) in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^{1}H NMR of the crude reaction mixture and represent *trans*/*cis* diastereomeric ratio.

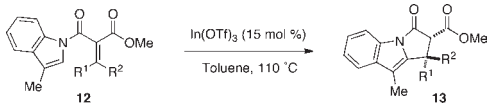
The cyclization is also amenable to substituent changes about the 3-position of the indole moiety. For example, when the phthalimide-protected tryptamine derivative **12i** was subjected to the reaction conditions, 1*H*-pyrrolo[1,2-*a*]-indole product **13i** was generated in 96% yield with 14:1 *dr* (entry 9). Moreover, **13i** can then be readily deprotected to provide the free amine, which is important for several natural product targets, such as the flinderoles **9**. The 3-(2-bromoethyl)-1*H*-indole derivative **12j** also provided its cyclization product **13j** in 69% yield with a 25:1 *dr* (entry 10). The methyl acetate substituted indole derivative **12k** generates its cyclized product **13k** in 93% yield with 13:1 *dr* (entry 11). Finally, when **12l** (derived from indole) was employed, cyclization readily occurred to afford **13l** in 98% yield and 10:1 *dr* (entry 12).

While pleased with the performance of the aromatic substrates, we were determined to expand the substrate scope to include nonaromatic substrates (Table 2). In particular, we were interested in systems derived from alkyl aldehydes and cinnamaldehyde. The ethyl substituted acrylate **12m** was the first nonaromatic substrate synthesized. Unfortunately, subjecting **12m** to the optimized reaction conditions only led to long reaction times (> 24 h) without any conversion to the desired 1*H*-pyrrolo-[1,2-*a*]indole. After some optimization, we found that the cyclization could be achieved more efficiently at a slightly higher catalyst loading (15%) in toluene at reflux. Under these new conditions, the cyclized product **13m** was furnished in 89% yield as the *trans* isomer (entry 1). Similar reactivity was observed for the corresponding propyl substituted derivative **12n** (entry 2). The parent compound, methyl 2-(1*H*-indole-1-carbonyl)acrylate **12o** (derived from formaldehyde), gave the 1*H*-pyrrolo[1,2-*a*]indole product **13o** in 47% yield. Cinnamate **12p** (from cinnamaldehyde) afforded its product **13p** in 71% yield with 8:1 *dr* (entry 4). We were extremely pleased to find that the 2,2-disubstituted acrylate **12q** (derived from 3-pentanone) cyclized to generate product **13q**, which now contains a quaternary carbon, in 98% yield (entry 5). Thus, this method is amenable to substrates derived from ketones and offers a powerful method to generate a functionalized quaternary carbon, particularly, if an unsymmetric ketone is used.

An interesting result was obtained when acrylate **12r** (derived from isobutyraldehyde) was subjected to the same conditions. While we formed the anticipated *trans*-1*H*-pyrrolo[1,2-*a*]indole product **13r** in 86% yield, we also observed a small amount of the hydropyrido[1,2-*a*]-indole product **14** (Scheme 3). This product seemingly arises from a putative carbocationic intermediate **I** that undergoes a 1,2-hydride shift to generate carbocation **II**, an intermediate observed in our tandem cyclopropane ring-opening/intramolecular FC cyclization.[13] **II** then undergoes an intramolecular FC reaction to generate the six-membered ring in **14**. Frontier recently noted this type of transformation for alkenyl 2-furyl and alkenyl 2-benzofuryl ketones in the presence of a highly Lewis acidic Ir^{III} catalyst.[20] Both examples highlight the existence of two possible pathways that depend

(20) Vaidya, T.; Manbeck, G. F.; Chen, S.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2011**, *133*, 3300.

Table 2. Reaction Scope with Nonaromatic Acrylates[a]

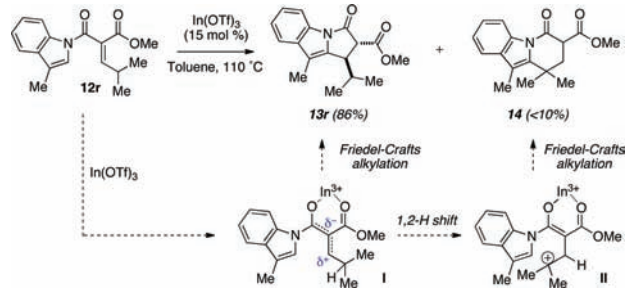


entry	12	13	time (h)	yield (%)[b]	dr[c] (*trans*:*cis*)
1	**12m** (R^1 = H; R^2 = Et)	**13m**	12.0	89	--[d]
2	**12n** (R^1 = H; R^2 = Pr)	**13n**	12.0	84	--[d]
3	**12o** (R^1 = H; R^2 = H)	**13o**	1.0	47	--
4	**12p** (R^1 = H; R^2 = β-styryl)	**13p**	12.0	71	8:1
5	**12q** (R^1 = Et; R^2 = Et)	**13q**	1.0	98	--

[a] Reactions run with substrate (1 equiv) and $In(OTf)_3$ (15 mol %) in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^{1}H NMR of the crude reaction mixture and represent *trans*/*cis* diastereomeric ratio. [d] Only one diastereomer observable by crude NMR.

on both the aromatic character of the heteroaryl moiety and the Lewis acid catalyst.

Scheme 3. An Alternative Reaction Pathway

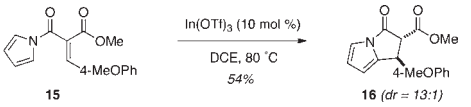


Finally, to expand the scope of this synthetic approach, we performed a preliminary test on a different substrate.

(21) Hall, G.; Sugden, J. K.; Waghela, M. B. *Synthesis* **1987**, 10.

Given that the cyclization readily occurs with indoles, we anticipated that pyrroles would behave similarly under the reaction conditions to form 1*H*-pyrrolizin-3(2*H*)-ones. Pyrrolizine derivatives, many of which are naturally occurring, have attracted considerable attention from both synthetic and medicinal chemists for their interesting biological activities and therapeutic potential.[21] To our satisfaction, when *N*-acyl pyrrole **15** was treated with $In(OTf)_3$ in 1,2-dichloroethane at reflux, the expected pyrrolizine product **16** was obtained in 54% yield[22] (unoptimized) with 13:1 *dr* (Scheme 4).

Scheme 4. Pyrrole as an Effective Substrate



In summary, we have developed a diastereoselective, Lewis acid-catalyzed intramolecular Friedel–Crafts reaction that efficiently generates functionalized 1*H*-pyrrolo-[1,2-*a*]indole-3(2*H*)-ones in high yields (up to 98%) with high diastereoselectivities (up to >25:1 *dr*) from simple, readily available starting materials. Efforts to employ chiral catalyst complexes to promote enantioselectivity as well as further examination of the cationic rearrangement pathway are currently underway. Future application of this reaction toward the synthesis of natural products will be reported in due course.

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

(22) Under the reaction conditions, some degradation of **15** was observed resulting in decreased isolated yields.