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The High Pressure Reaction of Cyclopropanes with Indoles Catalyzed by Ytterbium Triflate

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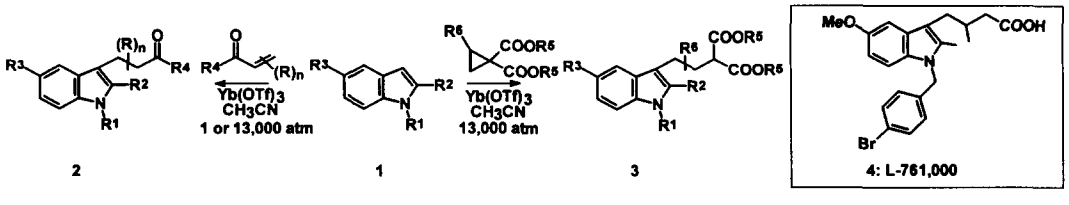
Abstract: *A variety of 1,1-cyclopropane dicarboxylic acid esters were reacted with a selection of indoles under hyperbarric conditions. In the presence of $Yb(OTf)_3 3H_2O$, smooth ring opening resulted in the formation of 4-indolyl dicarboxylic acid esters. Hydrolysis and decarboxylation resulted in the formation of the mono-acids. Nucleophilic attack occurred specifically at the more hindered position of the substituted cyclopropanes.*

Recently as part of our efforts toward the synthesis of the hapalindole marine alkaloids, we have been interested in methods for the mild alkylation of indoles at the 3-position with suitable Michael acceptors. We have since reported[1] that the use of catalytic ytterbium triflate[2] results in the addition of indoles **1** (via the electron rich 3-position)to α,β-unsaturated ketones, affording the 3-indolyl ketones **2** in excellent yields (Scheme 1). The use of ultra high pressures facilitates this process. This exploitation of the natural enamine character of the indole system avoids the need for generation of a discrete carbanionic species at this position (i.e. an organometallic compound). It occurred to us that this methodology would be complimented by a homologous process, that is, a homo-Michael addition to afford the 4-indolyl carbonyl compounds of type **3**. Naturally, the nucleophilic ring opening of an activated cyclopropane occurred to us as a way of accomplishing this. This endeavor seemed all the more worthwhile in light of the recent report that compounds such as **4** are potent and promising nonsteroidal antiinflammatory drugs (NSAIDS).[3] In this letter we report the intial results of our work in which we have shown that under ultra high pressures, alkylation of indoles with cyclopropane-1,1-dicarboxylic acid esters proceeds smoothly to give good yields of the adducts.

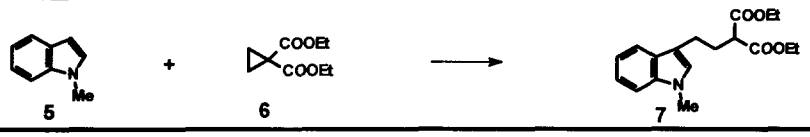


2 **1** **3** **4: L-761,000**

In order to determine the ideal reaction conditions for the opening of activated cyclopropanes under hyperbarric conditions, a systematic optimization study was undertaken using 1-methylindole and diethyl 1,1-cyclopropanedicarboxylate as the substrates.[4] The results are shown in table 1. Although it is difficult to

generalize, it is clear from these data that there is a pronounced solvent dependence with acetonitrile being the solvent of choice. The use of an extremely polar solvent such as DMF resulted in the complete suppression of the desired process. Although no unusual byproducts were isolated, it is possible that under the high pressure reaction conditions, the solvent acted as the nucleophile in the opening of the cyclopropane ring. Alternatively the solvent may have buffered the Lewis acid catalyst, thereby inhibiting the reaction. This could explain the complete failure of the reaction when a small amount of water was added to acetonitrile, an otherwise excellent solvent. Note that the fact that water suppresses the reaction stands in contrast to the results of Jenner that water is a good co-solvent for acetonitrile in high pressure reactions involving ytterbium triflate as a catalyst.[5] This is also contradictory to the fact that ytterbium triflate has been shown to retain its Lewis acidity in aqueous media.[6] Finally note that in the absence of solvent, the reaction does proceed, albeit at a reduced efficiency.

Table 1. Optimization of reaction conditions



5 + 6 → 7

Entry	Time	Pressure	5:6 ratio	Mole % catalyst	Solvent	Yield[a]
1	5d	13 kbar	1:2	2.5	acetonitrile	20
2	5d	13 kbar	1:2	2.5	dichloromethane	8
3	5d	13 kbar	1:2	2.5	acetonitrile/water	0
4	5d	13 kbar	1:2	2.5	nitromethane	12
5	5d	13 kbar	1:2	2.5	toluene	2
6	5d	13 kbar	1:2	2.5	THF	7
7	5d	13 kbar	1:2	2.5	DMF	0
8	5d	13 kbar	1:2	0	acetonitrile	0
9	5d	13 kbar	1:2	5	acetonitrile	23
10	5d	13 kbar	1:2	10	acetonitrile	44
11	5d	13 kbar	1:2	5(anh)	acetonitrile	36
12	5d	13 kbar	1:5	5	acetonitrile	16
13	**5d**	**13 kbar**	**5:1**	**5**	**acetonitrile**	**70**
14	4d	13 kbar	1:2	5	neat	11
15	1d	13 kbar	1:2	5	acetonitrile	22
16	2d	13 kbar	1:2	5	acetonitrile	22
17	3d	13 kbar	1:2	5	acetonitrile	26
18	4d	13 kbar	1:2	5	acetonitrile	34
19	5d	1 atm	1:2	5	acetonitrile	3
20	1d	13 kbar	5:1	10	acetonitrile	67
21	1d	13 kbar	5:1	5	acetonitrile	35
22	5d	13 kbar	1:2	2/day	acetonitrile	42

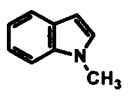
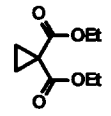
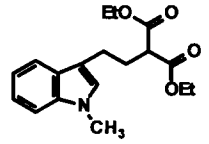
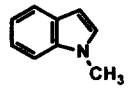
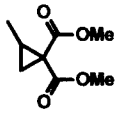
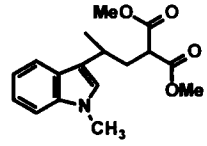
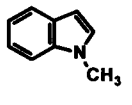
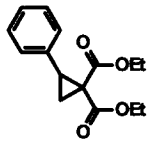
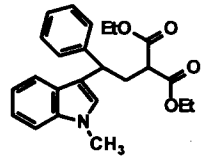
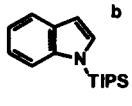
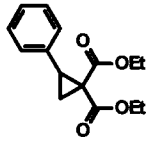
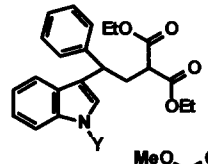
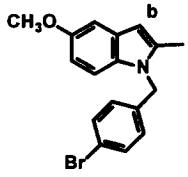
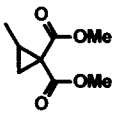
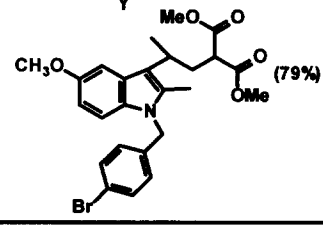
a) yields refer to isolated, pure material

Although the presence of some catalyst is necessary (entry 8), variation of the amounts from 2.5-10 mole percent had little effect on yields (entries 1,9,10). Use of anhydrous catalyst did little to improve the yield (entry 11). A reaction time of five days was generally used, however the reaction was essentially complete after one day (entries 15-18). Finally, note that the ideal stoicheometry involes an excess of the indole; our best results were with a five-fold excess (entry 13). Beyond this ratio, purification was difficult.

In order to explore the general utility of this reaction, a series of substituted cyclopropanes were prepared by standard methods[7] and were then subjected to the optimum conditions as determined from Table 1 (entry 13). Table 2 illustrates the results.[8] Most worthy of note is the fact that the attack on the cyclopropane

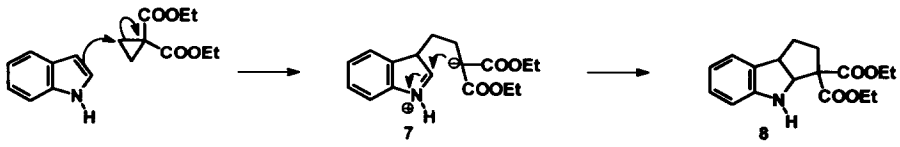
ring takes place exclusively at the more substituted carbon. Furthermore, the best yield by far was obtained with a phenyl substituted cyclopropane. These results would seem to indicate that there is significant cationic character on the carbon under attack in the transition state (in the extreme case, a high pressure induced ring opening of the cyclopropane in the presence of the Lewis acid, followed by attack of the nucleophilic indole).

Table 2. Reactions of indoles with activated cyclopropanes [a]

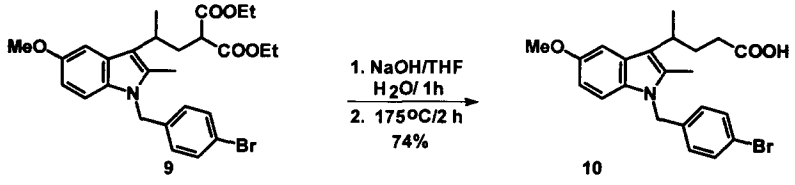
Entry	Indole	Cyclopropane	Product (yield) [c]	
1				(75%) [d]
2				(55%)
3				(97%)
4	 [b]			Y = TIPS (49%) Y = H (27%)
5	 [b]			(79%)

[a] All reactions were performed using 5 mole % of Yb(OTf)3 under a pressure of 13 kbar using acetonitrile as the solvent and an indole to cyclopropane molar ratio of 5:1 unless otherwise indicated. [b] 2:1 indole to cyclopropane molar ratio. [c] Isolated yield unless otherwise indicated. [d] Yield based on 75% conversion.

The use of a silyl protecting group on the indole nitrogen was problematic in that the addition reaction proceeds with partial desilylation. In the cases where there is no substituent on the indole nitrogen, the yield was dramatically lowered and the formation of an interesting byproduct **8** was observed, presumably via a tandem attack of the putative malonic enolate on the intermediate iminium ion **7**.



The fact that attack on the cyclopropane ring takes place on the more highly substituted carbon is unfortunate from the point of view of accessing compounds such as **4**. In fact note that addition of the appropriate indole to a suitable cyclopropane (entry 5) yields **9** which was hydrolyzed and decarboxylated to give the constitutionally isomeric 4-indolyl carboxylic acid **10**.



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References and Notes

1. Harrington, P.E.; Kerr, M.A. *Synlett* **1996**, 1047.

2. For a review see: Marshman, R.W. *Aldrichimica Acta* **1995**, 28, 77

3. **a)** Black, W.C., Bayly, C.; Belley, M.; Chan, C.-C.; Charleson, S.; Denis, D.; Gauthier, J.Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C.K.; Leblanc, Y.; Mancini, J.; Ouellet, M.; Percival, D.; Roy, P.; Skorey, K.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, 725. **b)** Leblanc, Y.; Black, W.C., Chan, C.-C.; Charleson, Delorme, D.; Denis, D.; Gauthier, J.Y.; Grimm, E.L.; Gordon, R.; Guay, D.; Hamel, P.; Kargman, S.; Lau, C.K.; Mancini, J.; Ouellet, M.; Percival, D.; Roy, P.; Skorey, K.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, 731.

4. General procedure: The indole and the cyclopropane (about 1 mmol of limiting reagent) were measured into a length of heat shrinkable Teflon tubing closed at one end with a brass clamp. The solvent (1 mL/mmol of limiting reagent) was added followed by the catalyst. The tube was sealed with another brass clamp and placed in a LECO Tempres high-pressure chemical reactor and the reactor pressurized. After a period of time the mixture was depressurized and the solvent removed. The residue was subjected to flash chromatography on silica gel and the product isolated as a pure oil.

5. Jenner, G. *Tetrahedron Lett.* **1995**, 233.

6. **a)** Chen, D.; Yu, L.; Wang, P.G. *Tetrahedron Lett.* **1996**, 4467. **b)** Yu, L.; Chen, D.; Wang, P.G. *Tetrahedron Lett.* **1996**, 2169. **c)** Kobayashi, S. *Synlett*, **1994**, 689.

7. **a)** Magnus, P.; Schultz, J.; Gallagher, T. *J. Am. Chem. Soc.* **1985**, *107*, 1984. **b)** Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1965.

8. All compounds exhibited satisfactory ^{1}H NMR, ^{13}C NMR, IR, and mass spectra.

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