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Unprecedented $InCl_3$-catalyzed formation of *cis*-fused perhydrofuro[2,3-*b*]oxepines

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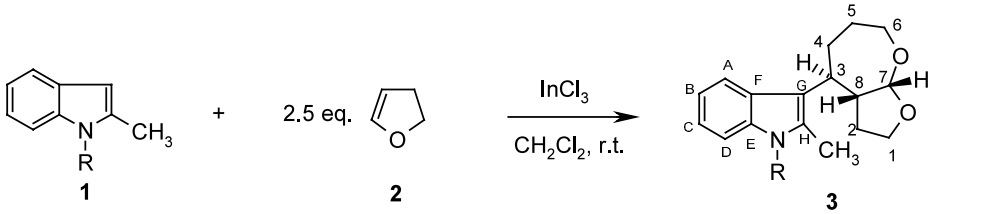
Abstract—2-Methylindole and its *N*-substituted derivatives react smoothly with 2,3-dihydrofuran (DHF) in the presence of a catalytic amount of $InCl_3$ under mild conditions to afford the corresponding 2-methyl-3-perhydrofuro[2,3-*b*]oxepin-4-yl-1*H*-indole derivatives in fairly good yields with high diastereoselectivity, while 3,4-dihydro-2*H*-pyran (DHP) affords exclusively 5,5-di(1*H*-3-indolyl)-1-pentanol derivatives in high yields under similar reaction conditions.

The seven-membered azepine and oxepine ring systems are important core units in a variety of biologically interesting natural products such as balanol, a potent protein kinase C inhibitor and isolaurepinnacin and many others.[1] In addition to this, indole and its derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[2] Consequently, the synthesis and reactions of indole and its derivatives have attracted great prominence in organic synthesis. However, there are no examples of the *C*-alkylation of indoles with cyclic enol ethers.

In our ongoing program on the utilization of indium halides for novel synthetic methodology,[3] we observed for the first time the unusual formation of 2-methyl-3-perhydrofuro[2,3-*b*]oxepin-4-yl-1*H*-indole **3a** from 2-methylindole and 2,3-dihydrofuran employing a catalytic amount of indium trichloride under mild conditions (Scheme 1).

The assignment of the structure and stereochemistry of the product **3a** was achieved by incisive and detailed NMR studies including DQF-COSY, HSQC and HMBC experiments. The HSQC and ^{13}C spectra clearly showed the presence of 17 carbons, with 1-methyl, 5-methylene, 7-methines and 4-quaternary carbons. The heterocyclic five- and seven-membered rings are *cis* fused so generating a [2,3]-oxepine moiety as evidenced by the coupling constant ($J_{7,8}=5.1$ Hz) and the presence of a strong cross peak between H7–H8 in the



1a : R = H; **1b** : R= methyl;
1c : R = *t*-butoxycarbonyl;
1d : R = ethyl; **1e** : R= benzyl;
1f : R= allyl;

3a : R = H; **3b** : R= methyl;
3c : R = *t*-butoxycarbonyl;
3d : R = ethyl; **3e** : R= benzyl;
3f : R= allyl;

Scheme 1.

Keywords: indium reagents; indoles; cyclic enol ethers; perhydrofuro[2,3-*b*]oxepines.
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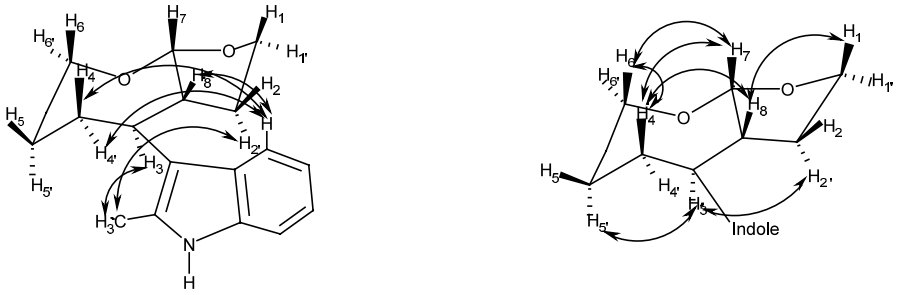

Figure 1. Important NOEs present in compound **3a**.

NOESY spectrum. The proton at $\delta = 5.28$ is attached to a carbon ($\delta = 108.72$) which in turn is connected to two oxygen atoms in the five- and seven-membered rings. The seven-membered ring takes a twist conformation which is characterized by the following cross peaks H7–H6, H7–H4, H6–H4, H5′–H3 and H4–H8 in the NOESY spectrum. Further support came from the large diaxial couplings $^{3}J_{H6-H5'} = 12.5$ Hz, $^{3}J_{H5'-H4} = 12.9$ Hz, $^{3}J_{H4-3} = 10.3$ Hz, $J_{H3-H8} = 10.3$ Hz, and the long range ω coupling $^{4}J_{H6'-H4'} = 1.6$ Hz.

The detailed information on the five-membered ring conformation could not be obtained because of severe overlap of the H2, H2′, H1 and H1′ resonances. However, NOESY cross peaks of significant intensity between H1–H8 and H2′–H3 indicated a twist conformation with C8 *endo* to H7 and C2 *endo* to H3. A strong NOE between H2′–H3 was consistent with a puckering for the five-membered ring (Fig. 1). Having fixed the structure and relative stereochemistry of the bicyclic ring, it was crucial to fix the position of the C–C bond between the oxepine and the indole ring. The presence of cross peaks between H3 and carbons F, G and H in the HMBC spectra, showed that the C–C linkage is between C3–CG. Further conclusive support of the structure came from other NOESY cross peaks HA–H4, HA–H4′, HA–H8, CH_3–H3, CH_3–H2′ between the indole ring and the oxepine moiety (Fig. 2). Characteristic NOE peaks showed that the molecule predominantly exists with the planes of the two rings approximately perpendicular to each other, with the six-membered ring proton A close to H4 and H8 and the methyl group in the proximity of H3.

These unexpected results prompted us to extend this reaction to other 2-methylindole derivatives. Interestingly, *N*-protected 2-methyl indole derivatives reacted smoothly with 2,3-dihydrofuran under these reaction conditions to afford the corresponding 2-methyl-3-perhydrofuro[2,3-*b*]oxepin-4-yl-1*H*-indole derivatives in fairly good yields with high selectivity. However, indole and 5-substituted indoles such as 5-bromo- and 5-methoxy derivatives with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of 10 mol% $InCl_3$ for 3.0–5.0 h in dichloromethane afforded the corresponding 5,5-di(1*H*-3-indolyl)-1-pentanol and di(1*H*-3-indolyl)-1-butanol derivatives respectively in 70–80% yields (Scheme 2).

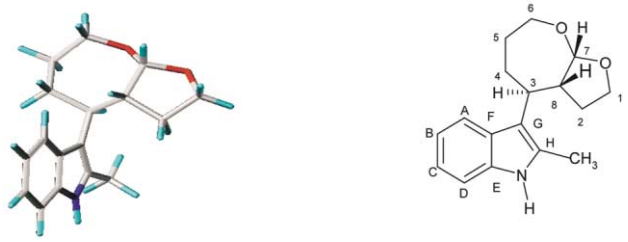

Figure 2. Energy-minimized structure and chemical structure of **3a**.

In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. The reactions are clean and complete within a short period. The reaction may proceed through the formation of a 1-aza-diene in situ from the enol ether and the indole followed by attack of a second molecule of the enol ether or indole resulting in the formation of product **3** or **4** as shown in Scheme 3.

Since indium trichloride is a mild and water-tolerant Lewis acid, this method does not require anhydrous solvents or stringent reaction conditions whilst no precautions need to be taken to exclude moisture from the reaction media. This method is equally effective for both electron-rich as well as electron-withdrawing functionalities on the ring nitrogen and the results are presented in Table 1. Among various catalysts such as $InBr_3$, $CeCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$, indium trichloride was found to be superior in terms of conversion and selectivity.

In summary, this paper describes a novel method for the synthesis of *cis*-fused perhydrofuro[2,3-*b*]oxepinyl indole derivatives through a 2:1 coupling of 2,3-dihydrofuran and 2-methylindoles employing a catalytic amount of indium trichloride. This paper also describes a method for the synthesis of di(1*H*-3-indolyl)-1-pentanol and di(1*H*-3-indolyl)-1-butanol derivatives under similar reaction conditions.

Acknowledgements

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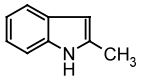
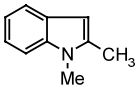
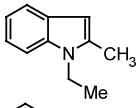
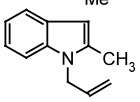
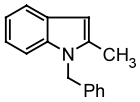
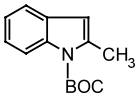
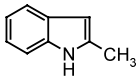
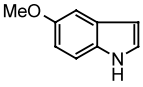
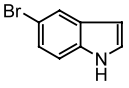
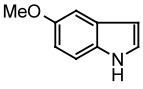
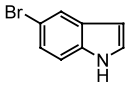
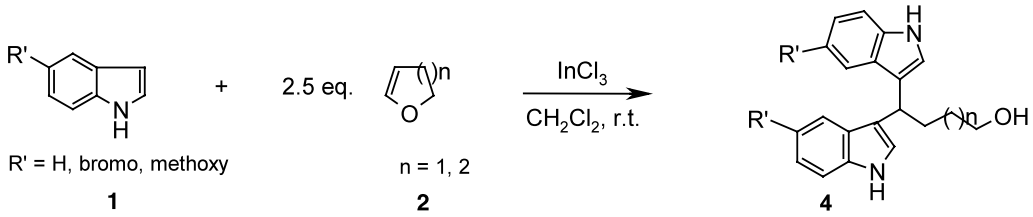
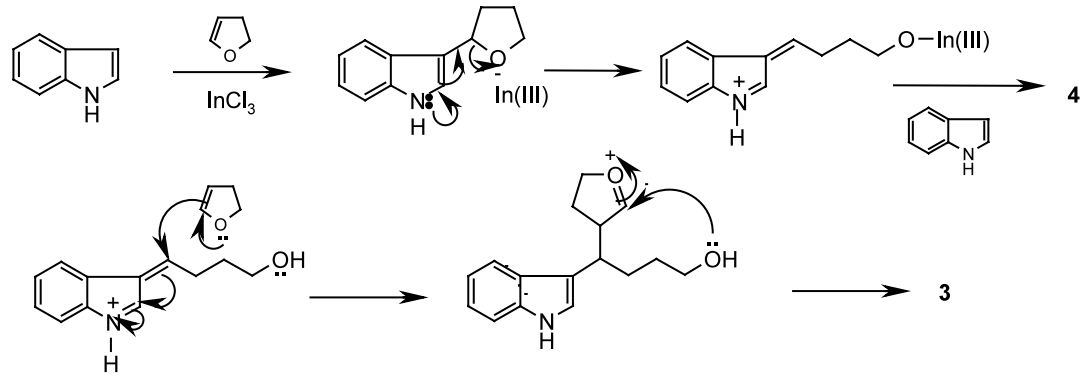
Table 1. $InCl_3$-catalyzed *C*-alkylation of indoles with cyclic enol ethers[4]

Entry	Indole	Enol ether	Product[a]	Time(h)	Yield(%)[b]
a			**3a**	3.5	87
b			**3b**	3.0	83
c			**3c**	3.5	85
d			**3d**	4.0	81
e			**3e**	4.0	78
f			**3f**	4.5	75
g			**4g**	3.5	84
h			**4h**	4.0	87
i			**4i**	3.0	85
j			**4j**	4.0	82
k			**4k**	5.5	77
l			**4l**	5.5	80
m			**4m**	5.5	72

a: All products were characterized by ^1H NMR, IR and mass spectroscopy
b: Isolated and unoptimized yields



Scheme 2.



Scheme 3.

References

1. (a) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc*. **1994**, *116*, 8402; (b) Suzuki, T.; Matsumura, R.; Oku, K.; Taguchi, K.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett*. **2001**, *42*, 65.
2. (a) Faulkner, D. J. *Nat. Prod. Rep*. **2001**, *18*, 1; (b) Ninomiya, I. *J. Nat. Prod*. **1992**, *55*, 541.
3. (a) Yadav, J. S.; Reddy, B. V. S.; Raman, J. V.; Niranjan, N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett*. **2002**, *43*, 2095; (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1417; (c) Yadav, J. S.; Sunny, A.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett*. **2001**, *42*, 8063.
4. *Typical procedure*: a mixture of indole (1 mmol), enol ether (2.5 mol) and indium trichloride 5 mol% in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure 3-alkylated indole derivative. The aqueous layer was concentrated under reduced pressure to recover the catalyst. Spectroscopic data for **3a**: Liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.74 (m, 2H, H2 and H2′), 1.81 (m, 1H, $J_{5',6}=12.9$ Hz, $H_{5'}$), 1.89 (m, 1H, H_5), 1.92 (m, 1H, H_4), 2.33 (m, 1H, $J_{4,3,}=10.3$ Hz, $J_{4,4'}=14.7$ Hz, $J_{5,4}=2.1$ Hz, $J_{5',4}=12.9$ Hz, H_4), 2.41 (s, 3H, CH_3), 2.78 (ddt, 1H, $J_{7,8}=5.1$ Hz, $J_{3,8}=10.3$ Hz, $J_{2,8}/J_{2',8}=10.3$ or 8.0 Hz, $J_{2',8}=8.0$ Hz, H_8), 3.01(t, 1H, $J_{4,3}=10.3$ Hz, $J_{3,8}=10.3$ Hz, H_3), 3.59 (dt, 1H, $J_{6,6'}=12.5$ Hz, $J_{6',5'}=12.5$ Hz, $J_{6,5}=3.0$ Hz, H_6), 3.63 (ddd, 1H, $J_{2',1}=6.9$ Hz, $J_{1,2}=10.1$ Hz, $J_{1,1}=8.0$ Hz, H_1), 4.14 (dt, 1H, $J_{2',1'}=8.0$ Hz, $J_{1,1'}=8.0$ Hz, $J_{2,1'}=2.7$ Hz, $H_{1'}$), 4.23 (ddt, 1H, $J_{6,6'}=12.5$ Hz, $J_{6',5}=5.0$ Hz, $J_{6',5'}=1.6$ Hz, $J_{6,4'}=1.6$ Hz, $H_{6'}$), 5.28 (d, 1H, $J_{7,8}=5.1$ Hz, H_7), 7.05 (dt, 1H, $J=7.7$ Hz, $J=0.7$ Hz, H_B), 7.10 (dt, 1H, $J=7.9$ Hz, $J=0.8$ Hz, H_C), 7.28 (dd, 1H, $J=7.9$ Hz, $J=0.7$ Hz, H_D), 7.60 (dd, 1H, $J=7.7$ Hz, $J=0.8$ Hz, H_A), 7.70 (brs, NH). ^{13}C (75 MHz, $CDCl_3$): δ 12.1 (CH_3), 31.1 (C-1), 33.3 (C-5), 34.1 (C-6), 40.0 (C-7) 51.5 (C-8), 68.5 (C-4), 70.3 (C-2), 108.7 (C-3), 110.4 (C–D), 116.8 (C–G), 118.8 (C–B), 119.1 (C–A), 120.8 (C–C), 126.9 (C–F), 129.4 (C–H), 135.5 (C–E). EIMS: m/z: 271, 198, 185, 155, 141, 91, 85, 71, 43.