THE OXIDATION REACTION OF INDOLES WITH THALLIUM(III) TRINITRATE

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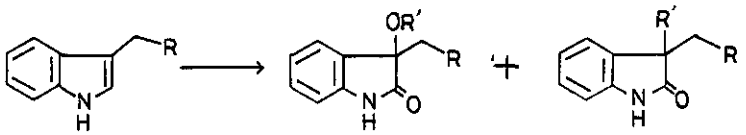
Dedicated to Professor *Kyosuke Tsuda* on the occasion of his 75th birthday

Abstract - Some indole derivatives were submitted to the oxidation with thallium(III) trinitrate[TTN] to give the corresponding oxindole and isatin derivatives. Indole-3-propionic acid derivatives were oxidized with TTN to afford the spiro-γ-lactones in good yields.

During the past decade, the investigation of oxidation reaction of olefinic compounds with thallium(III) reagents has been extensively made by McKillop and Taylor,[1] who clarified the unique useful properties of this reagent to be unattainable with any other oxidizing reagents for organic syntheses. Although oxidation reactions at C_2,C_3-double bond of indole derivatives for generation of the corresponding oxindoles with a variety of oxidizing agents have been known,[2] these methods are not always useful because of low overall yields accompanied by unfavored by-products under rather drastic conditions.

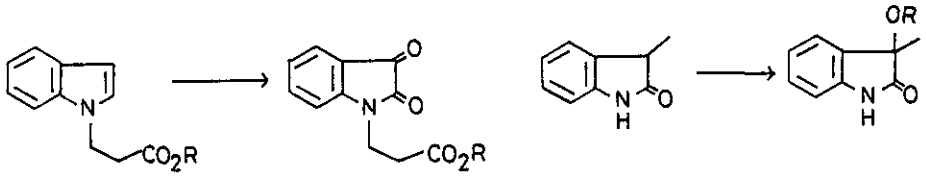
We describe here the new oxidation method of some indole derivatives with thallium(III) trinitrate[TTN][3] giving the notable results. Table I summarizes the conversion of indoles(1, 2, 7, and 8) with TTN into the corresponding C_3-disubstituted oxindoles(3,[4] 4,[5] 5, and 6) and isatin derivatives(9 and 10),[6] while oxidations of the same compounds performed with $Tl(OAc)_3$ and $Tl(OCOCF_3)_3$ were not satisfactory. In the cases of 5 and 6, it was presumed that the nitro group was introduced to C_3-position of the oxindoles based on their spectral data[5, mp 149-151°, IR($CHCl_3$) 1745 and 1550 cm^{-1}; MS m/e 192(M^+) and 146(M^+- NO_2, base peak): 6, IR($CHCl_3$) 1730 and 1555 cm^{-1}; MS m/e 278(M^+) and 232(M^+-NO_2, base peak)] and the elemental analyses. The oxidation of oxindole 11 with TTN in methanol at 25° afforded 3 in a high yield. When this oxidation was conducted in dry acetonitrile and then treated with water,[7] a nitrate group was introduced to give the 3-nitroxyoxindole 13[mp 110°, IR($CHCl_3$) 3200, 1735, and 1640 cm^{-1}; MS m/e 208(M^+) and 162 (M^+-NO_2, base peak)], and 12[mp 155-157°(lit[8] 161-162°)] as its hydrolyzed product



1, R = H
2, R = CH_2CO_2Et

3, R = H, R' = Me
4, R = CH_2CO_2Et, R = H

5, R = H, R' = NO_2
6, R = CH_2CO_2Et, R' = NO_2



7, R = H
8, R = Me

9, R = H
10, R = Me

11

3, R = Me
12, R = H
13, R = NO_2

Table I

Compd	TTN(eq Mol)	Solvent	Reaction Temp(°C)	Product(% yield)[a]
1	1.4	MeOH	10	5(27)
	1.4	MeOH	-60	3(11), 5(10)
2	2.0	5% aq CH_3CN	-10	4(19), 6(16)
7	2.8	5% aq CH_3CN	0	9(57)
8	2.5	5% aq CH_3CN	0	10(33)
11	1.0	MeOH	25	3(92)
	1.5	CH_3CN	25	12(20), 13(11)

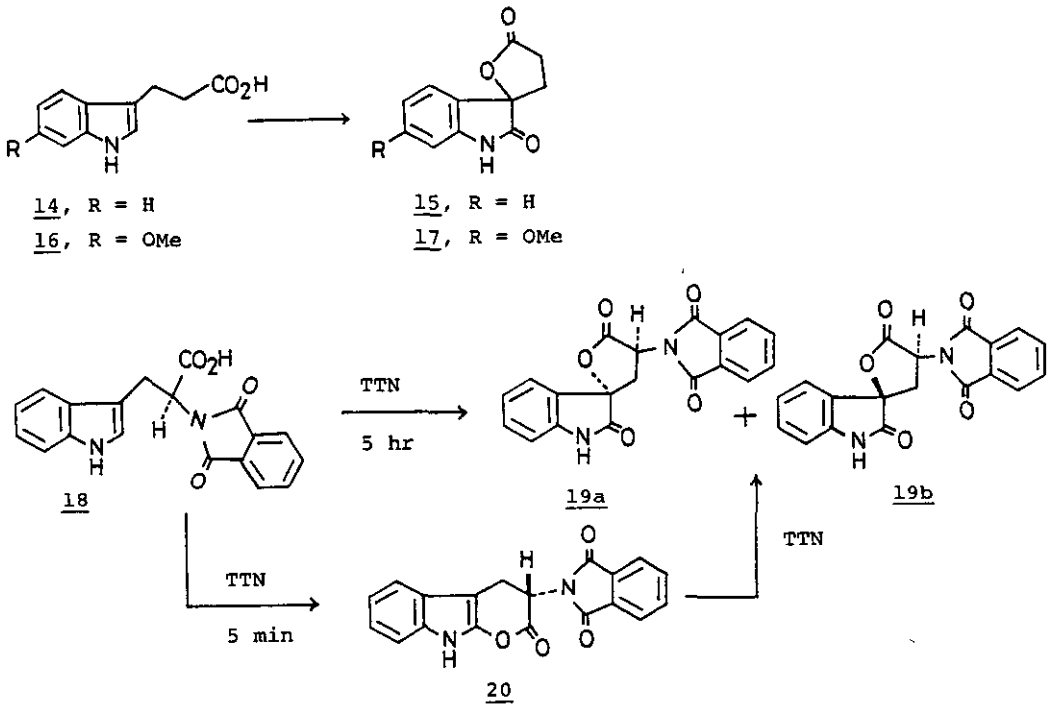
[a]All products show isolated yields after purification of silica gel chromatography.

(Scheme 1).

This new oxidation method of indoles was further applied to the other indole systems having a nucleophilic site such as carboxyl group in the molecules, which afforded the corresponding spirolactone-oxindoles in better yields than by NBS oxidation method[9] (Scheme 2). Oxidative lactonization of the acid 14 with TTN has been already reported to give 15.[10] In a similar manner, 16 was submitted to the oxidation [TTN(2.0 equiv), MeOH, -10°, 15 min] to furnish 17 (56%) [mp 160-161°, IR($CHCl_3$) 3200, 1780, and 1730 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.3-3.5(m, 4), 3.81(s, 3), 6.5-7.3(m, 3) and 8.56(broad, 1, D_2O exchange); MS m/e 233(M^+)]. Also, the oxidation of N-phthalimide-L-tryptophan(18) with TTN(2.5 equiv)(10% aq

CH_3CN, 0°→rt, 5 h) gave two diastereomeric lactones, 19a (34%)[mp 271-273°, $[\alpha]_D^{20}$ -163°(c 0.5, acetone)][11] and 19b (16%)[mp 261-263°, $[\alpha]_D^{20}$ -220°(c 0.5, acetone)],[12] whose stereochemistry at the spiro position was determined by comparison with the known optical rotations.[13] In this oxidation reaction, if the reaction time was limited to 5 min under a similar condition (0°), there was readily trapped the intermediate 20 (80%) [mp 239-243°(decomp), $[\alpha]_D^{20}$ -38°(c 0.5, acetone); IR(Nujol) 3300, 1780, 1750, and 1720 cm^{-1}; ^1H NMR(DMSO-d_6) δ 5.73(t, 1, J=10Hz), 7.0-7.4(m, 4), 7.96(s, 4), and 11.65(s, 1); MS m/e332(M^+)], which was further treated with TTN in 5% aq CH_3CN to give a mixture of 19a and 19b in 62% yield.[14] Further studies are in progress.

Scheme 2



14, R = H
16, R = OMe

15, R = H
17, R = OMe

18

19a

19b

20

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4. The compound 3, mp 120-122°(lit[8] 121-123°), IR(Nujol) 1745 and 1715 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.60(s, 3), 3.09(s, 3), 6.9-7.3(m, 4), and 9.11(broad, 1, D_2O exchange); MS m/e 177(M^+).

5. The compound 4, IR($CHCl_3$) 3250 and 1720 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.20(t, 3, J=7Hz), 2.3(m, 4), 4.09(q, 2, J=7Hz), 4.2(broad, 1, D_2O exchange), 7.2(m, 4), and 8.81(broad, 1, D_2O exchange); MS m/e 249(M^+).

6. The compounds, 9[IR(Nujol) 1740, 1720, and 1700 cm^{-1}; ^1H NMR(acetone-d_6) δ 2.76 (t, 2, J=7Hz), 4.02(t, 2, J=7Hz) and 7.0-7.8(m, 4); MS m/e 219(M^+) and 132 (base peak)], and 10[mp 97.5°, IR(Nujol) 1740 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.71(t, 2, J=8Hz), 3.62(s, 3), 3.97(t, 2, J=8Hz), and 6.9-7.6(m, 4); MS m/e 233(M^+) and 132(base peak)]. Furthermore, the compound 10 was identical with the sample obtained through N-alkylation of isatine with methyl acrylate in the presence of sodium hydride in THF-DME at room temperature.

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11. The compound 19a, IR(Nujol) 3250, 1790, 1760, 1745, and 1700 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.11(dd, 2, J=3, 10Hz), 5.71(t, 1, J=10Hz), 7.0-7.6(m, 4) and 7.95(s, 4); MS m/e 348(M^+)].

12. The compound 19b, IR(Nujol) 3200, 1800, 1770, 1740, and 1710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.8-3.2(m, 2), 5.83(dd, 1, J=10, 13Hz), 6.9-7.8(m, 4) and 7.92 (s, 4); MS m/e 348(M^+).

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