

NEW REACTIONS OF THALLIUM COMPOUNDS: A SIMPLE SYNTHESIS OF 4-
AND 7-SUBSTITUTED INDOLES BEARING A NITRO OR AN AZIDO GROUP¹

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Abstract ————— New reactions for converting thallium compounds to nitro and azido compounds are elaborated. Applying these reactions, 4-nitroindole-3-carboxaldehyde and 1-acetyl-2,3-dihydro-7-nitroindole are now readily available in one pot reaction from indole-3-carboxaldehyde and 1-acetyl-2,3-dihydroindole, respectively. 4-Azidoindole-3-carboxaldehyde and 1-acetyl-7-azido-2,3-dihydroindole are similarly produced. Preparation of methyl 4-nitroindole-3-carboxylate is also reported.

Recently, indoles bearing nitrogen containing functional group, such as 4-nitro-,²⁻⁵ 4-amino-,^{4,5} and 4-azidoindoles,⁶ have been much interested because they are suitable building blocks for biologically interesting teleocidines⁷ and 4-azidoindole-3-acetic acid,^{6d} which is a plant growth regulator and an important tool for the study of active site of auxin.^{6d} Various reactions have been developed for the syntheses of 4-amino- and 4-nitroindole derivatives and they are classified into three categories: direct nitration method of indoles,² construction method of indoles from an appropriately substituted benzene derivatives,³⁻⁵ and ring transformation method.⁵ However, these reactions are still not satisfactory due to the lack of regioselectivity and low overall yield.

Thus far we have engaged in the regioselective syntheses of 4-^{4,8} and 7-substituted indoles,⁹ and developed a three step synthetic method of 4-nitroindole^{4,5} (7) in 67% overall yield from 2,6-dinitrotoluene (6). In this report, we describe a new convenient two step or one pot synthesis of 4-nitro- (3) and 4-azidoindole-3-carboxaldehyde (13). Syntheses of 7-nitro-^{9d} (11a), 7-azido-1-acetyl-2,3-dihydroindole (5), and methyl 4-nitroindole-3-carboxylate (8) are also reported.

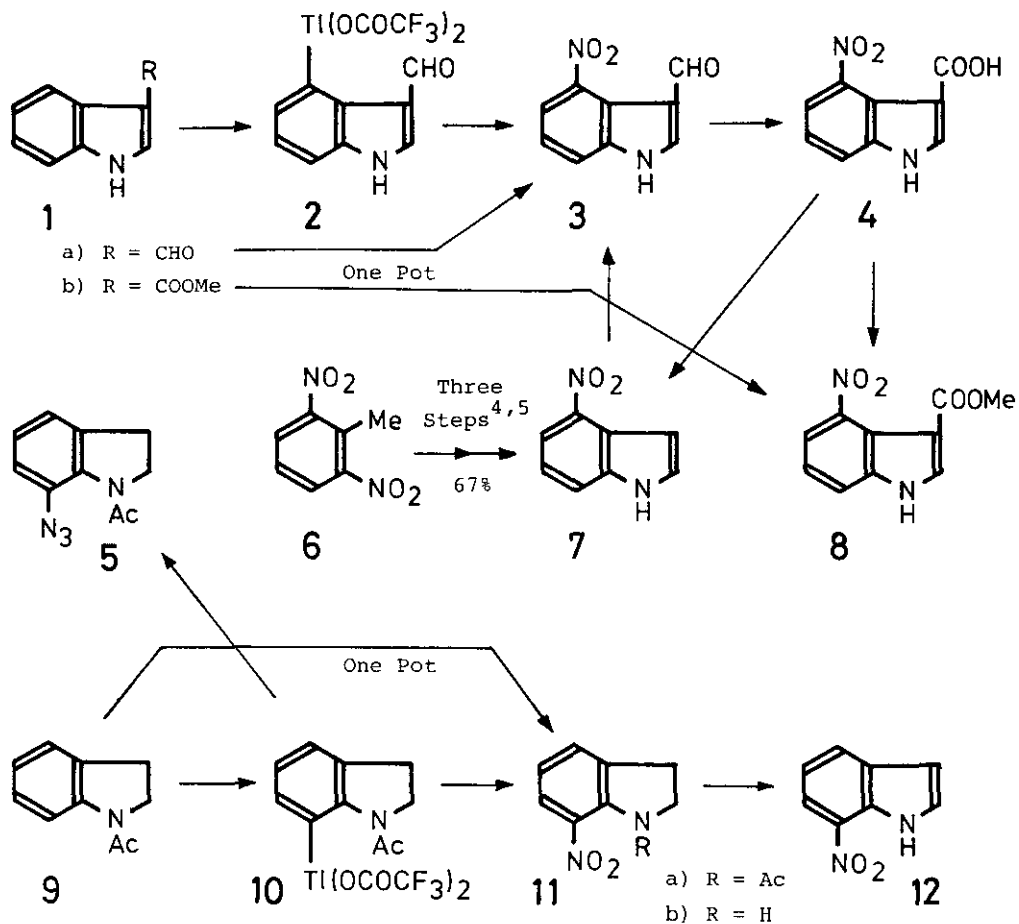


Table I. Synthesis of 4-Nitroindole-3-carboxaldehyde (3)

2 $\xrightarrow{\text{DMF, 100}^\circ\text{C}}$ 3 + 7 + 1a

Run	CuSO ₄ ·5H ₂ O (mol eq.)	NaNO ₂ (mol eq.)	Yield (%) of		
			3	7	1a
1	1	4	13	0	5
2	1	5	33	0	4
3	1	7	64	4	6
4	2	6	38	2	4
5	2	9	59	1	4
6	2	10	68	2	4
7	3	8	48	2	0
8	3	15	63	0	3
9	6	16.5	66	4	0
10	9	24	72	2	5

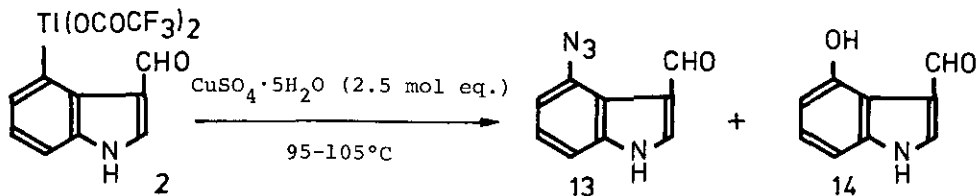
First, we tried to synthesize 4-nitroindole-3-carboxaldehyde (3). Although 3 could be prepared in 89% yield from 7 by Vilsmeier reaction, four steps are needed from the expensive starting material (6). Therefore, we next attempted a simple one pot synthesis of 3 from indole-3-carboxaldehyde (1a), utilizing readily available (3-formylindol-4-yl)thallium bis(trifluoroacetate) (2).¹⁰ Based upon our working hypothesis that cupric ion can activate aromatic thallium compounds by forming π -complex¹¹ and, in both electrophilic^{9d} and nucleophilic¹² ways, the ligand coordinated to cupric ion can form a bond with the carbon of carbon-thallium bond, we examined the reaction of 2 with sodium nitrite (NaNO_2) in the presence of cupric sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$). After various trials, we found a new and simple desired reaction. Typical results are summarized in Table I. As can be seen from the Table, we can now obtain 3 (mp 196-198°C) in 72% yield together with 7 (2%) and 1a (5%) only by heating 2 with NaNO_2 (24 mol eq.) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (9 mol eq.) in N,N-dimethylformamide (DMF) at 100°C for 24h (run 10). The same reaction conditions are successfully applied to (1-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate)⁹ (10) and 1-acetyl-2,3-dihydro-7-nitroindole^{9d} (11a, mp 163-164°C) could be prepared in 86% yield.

Since the isolation of thallium compounds is not necessary, we next tried a one pot synthesis. Thus, thallation of 1a, 1-acetyl-2,3-dihydroindole (9), or methyl indole-3-carboxylate (1b) with 1.2-1.5 molar equivalents of thallium tris(trifluoroacetate) in trifluoroacetic acid¹³ and subsequent nitration of the residue, obtained after evaporation of the solvent, under the same reaction conditions as described in the run 10 in Table I, afforded 3, 11a, or methyl 4-nitroindole-3-carboxylate^{2e} (8, mp 186-187°C) in 65%, 58%, or 54% yields, respectively.

On the other hand, the reaction of 2 with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and sodium azide in DMF and H_2O was newly found to produce 4-azidoindole-3-carboxaldehyde (13, mp 180-182°C) in addition to 4-hydroxyindole-3-carboxaldehyde¹² (14) and an unknown compound.¹⁴ The results are summarized in Table II. Under the similar reaction conditions, 10 afforded 1-acetyl-7-azido-2,3-dihydroindole (5, mp 77.5-79.5°C) in 90% yield. It is interesting to note that the compounds, (5) and (13), are relatively stable.

Structural determination of 3 and 11a was unambiguously carried out as follows. Thus, 3 was oxidized with sodium chlorite¹⁵ in the presence of 2-methyl-2-butene to 4-nitroindole-3-carboxylic acid (4). Subsequent treatment of crude 4 with ethereal diazomethane produced 8 in 92% overall yield. Since the compound (4) is sensitive to heat, decarboxylation¹⁶ of crude 4 was carried out in pyridine by heating at 100°C

Table II. Synthesis of 4-Azidoindole-3-carboxaldehyde (13)



Run	Solvent	NaN_3 (mol eq.)	Reaction Time (h)	Yield (%) of	
				13	14
1	DMF-H ₂ O (1:1)	6	8	28	1
2	"	6	12	31	0
3	"	6	17	10	9
4	DMF only	8	12	3	1
5	"	12	12	24	3

In all cases, formation of an unknown compound¹⁴ was observed.

to give 77% overall yield of 4-nitroindole (7), which was identical with the authentic sample.³⁻⁵ While the compound (11a) was hydrolyzed by aqueous sodium hydroxide to give 2,3-dihydro-7-nitroindole (11b, mp $85-86^\circ\text{C}$) in 96% yield. Salcomine catalyzed oxidation¹⁷ of 11b with dioxygen afforded 92% yield of 7-nitroindole (12, mp $97-98^\circ\text{C}$), whose spectral data and melting point were identical with the reported ones.¹⁸ In conclusion, we can now produce indoles and 2,3-dihydroindoles bearing an azido or a nitro group at the 4- or 7-position. These new and simple synthetic methods should find wide application in synthetic organic chemistry.

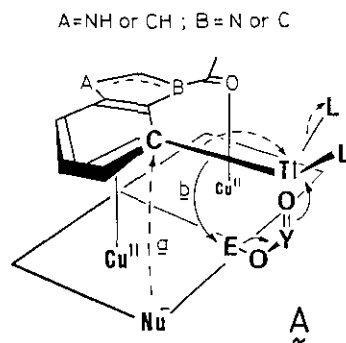
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 11. We are speculating the formation of the following π -complex (A), where coordinated nucleophiles (Nu^-) and electrophiles (E) exist in the vicinity of the carbon of the carbon-thallium bond and they can react intramolecularly. In the case of the present report, E, Y, and Nu^- are incidentally $\text{N}=\text{O}$, N, and N_3^- , respectively. We have already reported novel reactions, which correspond to the cases where Nu^- is X^- ,^{4c,9} CN^- ,^{9d,16} RO^- ,¹⁹ and H_2O .^{9d,12} This working hypothesis would be fruitful for further developing new reactions of thallium compounds.



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