

Communications to the Editor

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TIN-THALL REACTION, A VERSATILE METHOD FOR CROSS COUPLING
TIN COMPOUNDS WITH THALLIUM COMPOUNDS¹⁾

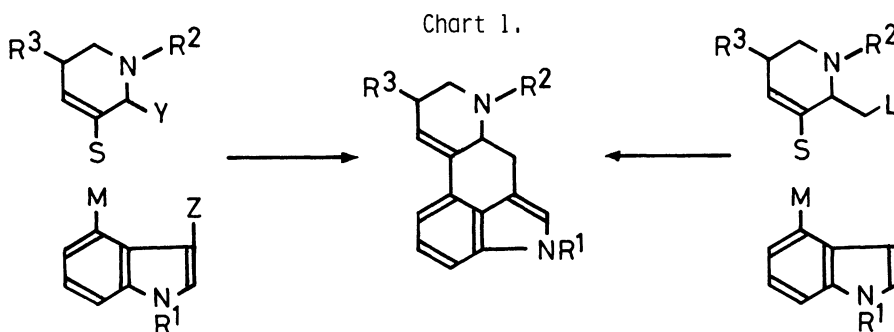
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A new cross coupling reaction between tin compounds and thallium compounds is developed and its versatility is demonstrated by the convenient synthesis of various 4-substituted indoles.

KEYWORDS ——— tin-thall reaction; thallation-palladation; cross coupling; 4-substituted indole; thallium compound; tin compound; palladium acetate; 4-(3-pyridyl)-3-indolecarbaldehyde

Our short step synthesis strategy for ergot alkaloids shown in Chart 1 led us to examine various known cross coupling reactions that have possibilities for incorporating pyridine derivatives²⁾ and cyclic compounds²⁾ into the 4-position of the indole nucleus. This survey resulted in the successful development of thallation-palladation³⁾ and boronation-thallation methods.^{2,3)} In our continuing work in search of an effective cross coupling reaction working directly at the 4-position of the indole nucleus, we have now found a new palladium-catalyzed reaction between tin and thallium compounds, designated the tin-thall reaction, as a version of the thallation-palladation method.³⁾ It has the advantage of being carried out in the presence of air and moisture.



The reaction of (3-formylindol-4-yl)thallium bis-trifluoroacetate⁴⁾ (2), prepared in 72% yield from 3-indolecarbaldehyde (1), with (3-pyridyl)trimethyltin⁵⁾ in the presence of a catalytic amount of palladium acetate in refluxing *N,N*-dimethylformamide produced 57% yield of 4-(3-pyridyl)-3-indolecarbaldehyde (3)^{2,6)} together with 1 and 4-methyl-3-indolecarbaldehyde (4) in 28% and 3% yields, respectively (Chart 2). Under similar reaction conditions, 4 was produced in 33% yield, together with 48% yield of 1, by treating 2 with tetramethyltin. 4-Phenyl-3-indolecarbaldehyde²⁾ (5) was also prepared in 54% yield in addition to 36% yield of 1 by

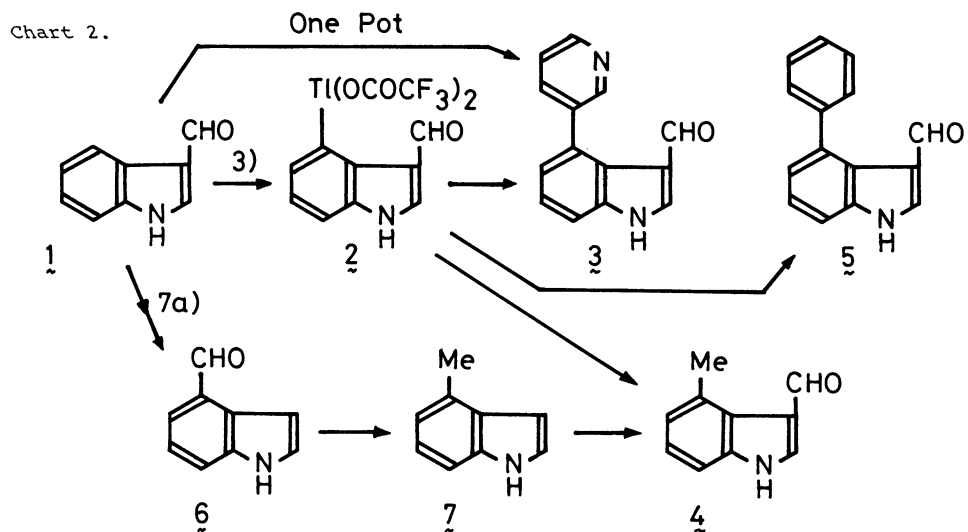
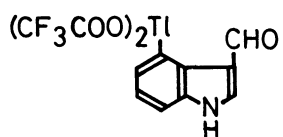
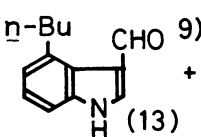
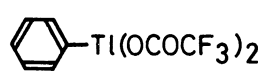
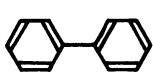
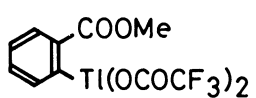
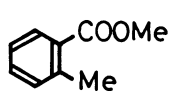
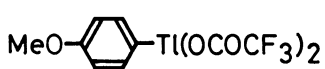
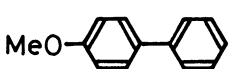
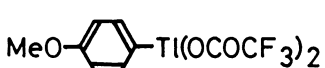
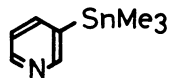
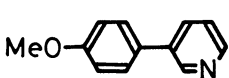


Table. The Palladium-Catalyzed Tin-Thall Reaction

Run	Thallium Compounds	Tin Compounds	Products (%)
1		$(n\text{-Bu})_4\text{Sn}$	 9 + 1 (13) (53)
2		Ph_4Sn	 10 (84)
3		Me_4Sn	 10 (38)
4		Ph_4Sn	 10 (49)
5			 11 (40)

treating 2 with tetraphenyltin.

The tin-thall reaction can be carried out in a one-pot procedure and the desired compounds are obtained directly from the starting materials. For example, after thallation of 1 with thallium tris-trifluoroacetate in trifluoroacetic acid, the solvent was removed under reduced pressure to give crude 2, which was treated without purification with (3-pyridyl)trimethyltin to afford 3, 1, and 4 in 45, 25, and 6% yields, respectively. The one-pot procedure and recycling of the recovered starting material make the present reaction profitable.

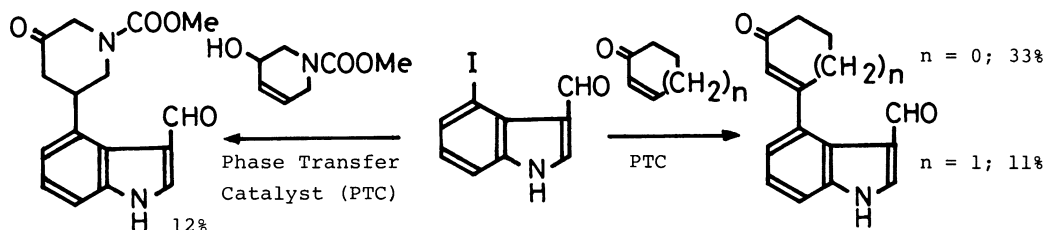
The structures of 3 and 5 were verified by direct comparison with authentic samples, prepared according to our reported procedure.²⁾ The structure of 4 was unequivocally proved by the following alternative synthesis. 4-Indolecarbaldehyde⁷⁾ (6) was converted to 4-methylindole⁸⁾ (7) in 90% yield by the Wolff-Kishner reduction using hydrazine, potassium hydroxide, and ethylene glycol. The subsequent Vilsmeier reaction applied to 7 afforded 4 in 66% yield.

Further applications of the tin-thall reaction and their results are summarized in the Table. As can be seen, variation of the substituent on both the tin and thallium compounds seems to have significant effect on the reaction, although the yields have not been optimized.

Investigations for establishing optimum reaction conditions such as changing solvents, reaction temperatures, catalysts, species of tin compounds, etc., are currently in progress.

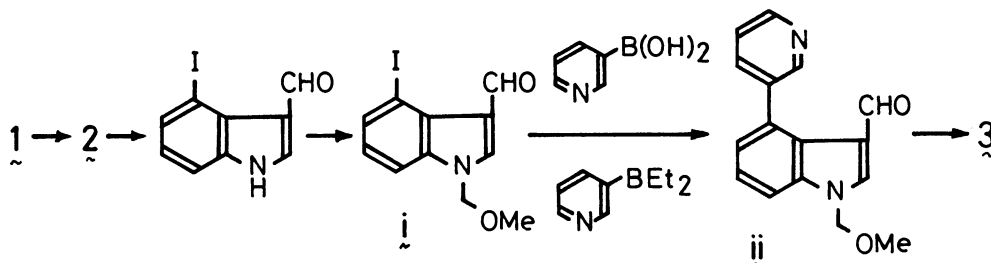
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methods work well if the indole nitrogen is protected in advance. Thus, the 4-iodo-1-methoxymethyl-3-indolecarbaldehyde (i) reacted with 3-pyridylboronic acid or (3-pyridyl)diethylborane in the presence of a catalytic amount of palladium acetate to give 1-methoxymethyl-4-(3-pyridyl)-3-indolecarbaldehyde (ii) in 68% and 78% yields, respectively. However, the overall yield of 3 from 1 became insufficient to warrant further studies of total synthesis because of the inevitable extra three steps, iodination, protection, and deprotection. Therefore, we believe that the present tin-thall reaction is adequate to meet our end. Detailed results will be presented in due course.



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