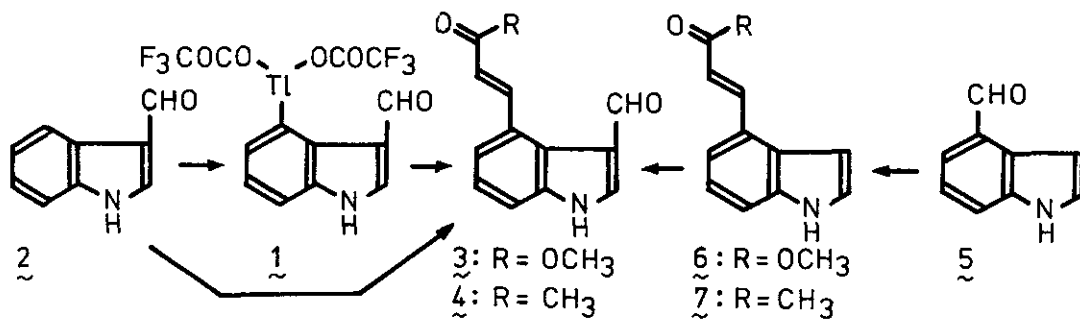


A FACILE SYNTHESIS OF 4-SUBSTITUTED 3-FORMYLINDOLES¹

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Abstract ——— A new synthetic method for 3-formylindoles having a carbon side chain at the 4-position was elaborated by means of thallation-palladation method.

Although the preparation of (3-formylindol-4-yl)thallium bis-trifluoroacetate (1) from 3-formylindole (2) was reported,² no attempt has been made to introduce carbon side chains into the C-Tl bond because of the lack of suitable method. Our interest in the synthesis of 4-substituted indoles prompted us to develop such method. Recently, Spencer and Thorpe³ reported the reaction of arylthallium compounds with olefins in methanol in the presence of stoichiometric amounts of lithium tetrachloropalladate, but the yields of arylated olefins were not satisfactory and biaryls⁴ were formed in significant amounts as side products. Now, we found solutions to overcome both of these problems. Simply by employing catalytic amount of palladium acetate and replacing the solvent by N,N-dimethylformamide (DMF), the compound (1) reacted successfully with olefins to give 3-formylindoles having a carbon side chain at the 4-position in excellent yields. Thus, treatment of 1 with methyl acrylate (3 mol eq.) in DMF for 0.5 h at 120°C in the presence of palladium acetate (0.07 mol eq.) was found to produce methyl 3-(3-formylindol-4-yl)acrylate (3)⁵ in 87% yield together with 2. The effect of the amount of palladium acetate on the yield of 3 is summarized in the Table. When methyl vinyl ketone was used as an olefin component in the above reaction, 4-(3-formylindol-4-yl)-3-buten-2-one (4)⁶ was obtained in 86% yield. Generally, isolation of organothallium compounds is not recommended due to their toxic nature.⁷ Therefore, direct syntheses of 3 and 4 from 2 were examined. Thus, the compound (2) was reacted with thallium trifluoroacetate in trifluoroacetic acid⁸ for 1 h at room temperature. After evaporation of the solvent *in vacuo*, the



residue was reacted with olefins as described above. By this procedure, 3 and 4 were obtained in 70% and 80% overall yields from 2, respectively, together with a minor amount of the starting material (2).

The structures of 3 and 4 were determined unequivocally by the following alternative syntheses. 4-Formylindole (5) was converted to 4-(indol-4-yl)-3-buten-2-one (7) in 98% yield as described before.⁹ Methyl 3-(indol-4-yl)acrylate (6)¹⁰ was produced in 97% yield by the reaction of 5 with methoxycarbonylmethylenetriphenylphosphorane. Subsequent Vilsmeier reaction of 6 and 7 afforded 3 (48%) and 4 (85%), respectively, which were identical with the samples prepared by the above thallation-palladation method.

It should be noted that our thallation-palladation method tolerate to air and moisture. Furthermore, the yields are high and none of the formation of biaryls⁴ was not detected. Since the compounds 3 and 4 are suitable synthetic intermediates for ergot alkaloid, we are currently investigating their total synthesis. We are also investigating the introduction of various other carbon side chains into the aromatic substrates by this thallation-palladation method.

Table. Effect of The Relative Ratio of Palladium Acetate to 1 in The Reaction with Methyl Acrylate

Reaction Time (h)	Palladium Acetate (mol eq. to 1)	Yield (%) of	
		<u>3</u>	<u>2</u>
4 a)	0.015	53	25
2 b)	0.03	70	20
2 b)	0.07	97	0
0.5 b)	0.07	87	trace

All reactions were carried out in DMF at 120°C. a) 1.5 Mol eq. of freshly distilled methyl acrylate was used. b) 3 Mol eq. of methyl acrylate was used.

REFERENCES AND NOTES

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5. Mp 187-188°C. IR (KBr): 3185 (br), 1710, 1648 cm^{-1} . $^1\text{H-NMR}$ (10% CD_3OD in CDCl_3) δ : 3.77 (3H, s), 6.32 (1H, d, $J=16$ Hz), 7.00-7.59 (3H, m), 7.92 (1H, s), 9.18 (1H, d, $J=16$ Hz), 9.64 (1H, s).
6. Mp 224-225°C. IR (KBr): 3060, 1654, 1624 cm^{-1} . $^1\text{H-NMR}$ (CD_3OD) δ : 2.50 (3H, s), 6.53 (1H, d, $J=16$ Hz), 7.21 (1H, t, $J=8$ Hz), 7.45 (1H, dd, $J=8$ and 2 Hz), 7.58 (1H, dd, $J=8$ and 2 Hz), 8.12 (1H, s), 9.45 (1H, d, $J=16$ Hz), 9.66 (1H, s).
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10. Mp 128.5-129°C. IR (KBr): 3360, 1689, 1620 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 3.73 (3H, s), 6.46 (1H, d, $J=16$ Hz), 6.68 (1H, br d, $J=3.2$ Hz), 6.87-7.43 (4H, m), 7.96 (1H, d, $J=16$ Hz), 8.33 (1H, br s, NH).

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