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Synthesis of Benzo[c]-2,7-naphthyridines by Palladium-catalyzed Coupling of Pyridine Methylstannanes with ortho Bromoacetanilides in the Presence of Copper(II)oxide

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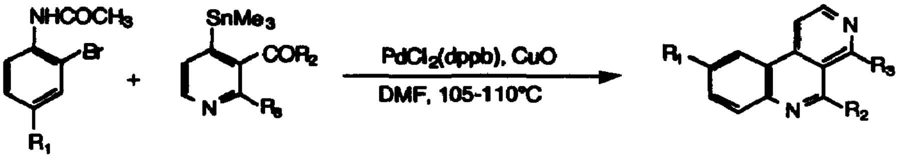
Abstract: Derivatives of benzo[c]-2,7-naphthyridine have been prepared in fair to excellent yields and in one step by the Pd(0)-catalyzed cross-coupling of pyridine methylstannanes with ortho bromoacetanilides. The coupling is greatly promoted by the addition of copper(II)oxide.

The benzo[c]-2,7-naphthyridine ring system has during the last decade been identified in a number of marine natural products.[1] In connection with projects aimed at the total synthesis of some of these compounds, we wished to prepare some derivatives of benzo[c]-2,7-naphthyridine.

In 1986 we reported a convenient one-pot reaction for the synthesis of phenanthridine,[2] which was followed by the assembly of several other tricycles.[3] The strategy followed uses the Pd(0)-catalyzed cross-coupling of *o*-formylarylboronic acids or *o*-formylaryltin trialkyl derivatives with *o*-amino- or protected *o*-aminoaryl halides. A recent synthesis of 4-oxo-dihydrobenzo[c]-2,7-naphthyridine (perlolidine),[4] using a similar technique as our method, prompted us to publish some preliminary results from our investigation.

The results are given in the Table and utilizes the Pd(0)-catalyzed cross-coupling of 4-trimethylstannyl-3-pyridinecarboxaldehyde,[5] 2-methoxy-4-trimethylstannyl-3-pyridinecarboxaldehyde[6] and 4-trimethylstannyl-3-pyridinemethylketone[7] with 2-bromoacetanilides (Scheme). The benefit of using copper(II)oxide as *co-reagent* in Pd(0)-catalyzed cross-coupling reactions could clearly be demonstrated in this work.[8] Upon adding copper(II)oxide, benzo[c]-2,7-naphthyridine,[9] 9-methyl-,[10] 9-methoxy-,[10] 5-methyl-[11] and 4-methoxybenzo[c]-2,7-naphthyridine[12] were all obtained in good yields and within two hours of reaction.[13] It may also be noted that $PdCl_2(dppb)$ was found to be a more effective catalyst than $Pd(PPh_3)_4$ and that negligible coupling occurred below 105°C.



Scheme

Table

R_1	R_2	R_3	Yield(%)[a]
H	H	H	78 (43)
Me	H	H	87
OMe	H	H	91 (65)
H	Me	H	80 (10)
H	H	OMe	68 (17)

[a] All yields are isolated yields. Yields within parenthesis refers to runs without copper(II)oxide.

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6. This compound was prepared in 53% yield from 2-methoxy-3-pyridinecarboxaldehyde according to the procedure in reference 5. IR(film): ν CH 2950,2910,2870, ν CO1730 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 10.44(d,1H,CHO), 8.29(d,1H,H_6), 7.21(dd,1H,H_5), 4.06(s,3H,OCH_3), 0.27(s,9H,CH_3), $J_{CHO,5}$ = 0.9, J_{56}=4.7 Hz. Exact mass calculated for $C_{10}H_{15}NOSn(M+H)^+$: 302.0203, found 302.0205.
7. This compound was prepared in 46% yield from 3-acetylpyridine according to the procedure in reference 5. IR(film): ν CH 2910,2950, ν CO 1740 cm^{-1}; ^1H-NMR($CDCl_3$): δ 9.20(d,1H,H_2), 8.67 (d, 1H,H_6), 7.66 (dd,H1,H_5), 2.71(s,3H,$COCH_3$), 0.28(s,9H,CH_3), J_{25}=0.9, J_{56}= 4.6 Hz. Exact mass calculated for $C_{10}H_{15}NOSn$ $(M+H)^+$: 286.0253, found 286.0247.
8. For the use of copper(II)oxide in a previous paper, see: Gronowitz, S.; Björk, P; Malm, J.; Hörnfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127-129.
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12. Mp 139-141°C; ^1H-NMR($CDCl_3$): δ 9.67(s, 1H,H_5), 8.49(dd,1H,H_7), 8.43(d,1H,H_2), 8.23(dd, 1H, H_{10}), 7.93(d,1H,H_1), 7.85(m,1H,H_8), 7.72(m,1H,H_9), J_{15}=0.9, J_{12}= 5.9 Hz; MS: m/z 210(100,M^+), 209(56,M^+-1), 181(33), 180(27), 179(28). Exact mass calculated for $C_{13}H_{10}N_2O$: 210.0793, found 210.0793.
13. *General procedure for the Pd-catalyzed coupling:* A mixture of the appropriate halogen compound (1.0 mmol), $PdCl_2$(dppb) (0.05 mmol) and copper(II)oxide (1.0 mmol) in 4 ml dimethylformamide was stirred at 105-110°C. After 1 min the appropriate tin compound (1.5 mmol) dissolved in 1 ml of dimethylformamide was added. After the halogen compound was consumed, the reaction mixture was allowed to attain room temperature, the precipitate was filtered off and the filtrate evaporated. The residue was subjected to chromatography.

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