

PALLADIUM(0)-CATALYZED CONDENSATION OF BROMOPYRIDINES  
WITH  $\alpha$ -SUBSTITUTED ACETONITRILES

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Abstract—— The condensation of bromopyridines with the sodium salts of phenylsulfonylacetonitrile and diethyl cyanomethylphosphonate in the presence of tetrakis(triphenylphosphine)palladium in 1,2-dimethoxyethane gave the corresponding  $\alpha$ -substituted pyridineacetonitrile derivatives in good yields.

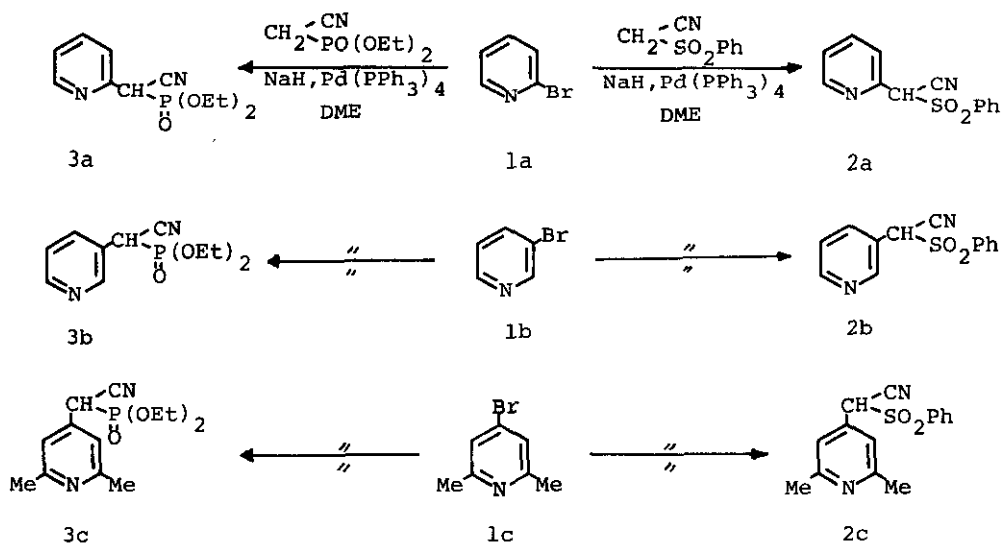
In the preceding paper,<sup>1</sup> we described that the condensation of aryl halides with sodium salts of malononitrile and ethyl cyanoacetate is well facilitated by catalytic amounts of tetrakis(triphenylphosphine)palladium. In order to expand the synthetic utility of the above reaction, we subsequently investigated the reaction of bromopyridines with some active methylene compounds. The present paper deals with the scope of the reaction together with the conversion of the side-chains introduced into pyridine rings to the other functional groups.

When 4-bromo-2,6-dimethylpyridine (**1c**)<sup>2</sup> was heated with sodium salt of phenylsulfonylacetonitrile, prepared with sodium hydride, in 1,2-dimethoxyethane under reflux in the presence of tetrakis(triphenylphosphine)palladium<sup>3</sup> as a catalyst,  $\alpha$ -phenylsulfonyl-2,6-dimethylpyridine-4-acetonitrile (**2c**)<sup>4</sup>, mp 275°C (dec.) (66 %) was obtained.

Similarly, 2-bromo- (**1a**) and 3-bromopyridine (**1b**) smoothly reacted with phenylsulfonylacetonitrile under the same conditions to give  $\alpha$ -phenylsulfonylpyridine-2-acetonitrile (**2a**),<sup>4</sup> mp 125-127°C (85 %) and  $\alpha$ -phenylsulfonylpyridine-3-acetonitrile (**2b**)<sup>4</sup>, mp 142-143°C (89 %), respectively.

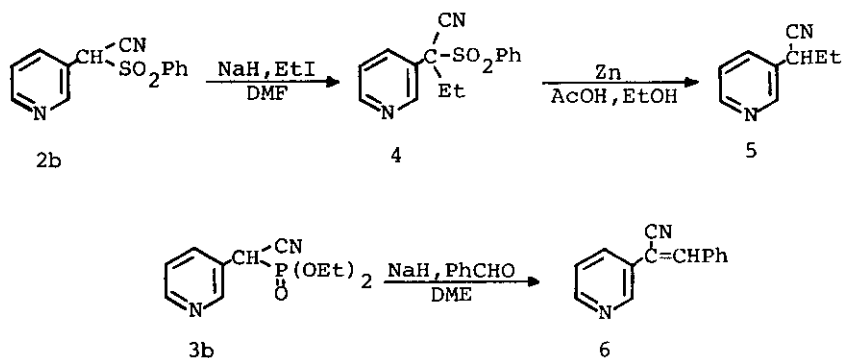
As well as phenylsulfonylacetonitrile, ethyl cyanomethylphosphonate reacted with

1a-c, and the corresponding diethyl  $\alpha$ -pyridylcyanomethylphosphonates (3a: mp 80-81°C, 72 %; 3b: viscous oil, 79 %; 3c: mp 194-195°C, 71 %) <sup>4</sup> were obtained as shown in Scheme 1. On the other hand, the reaction of 1a-c with other active methylene compounds such as diethyl malonate, acetylacetone, ethyl acetoacetate, and acetonitrile was not promoted with the palladium(0) catalyst. Based on these results including those described in the preceding paper, <sup>1</sup> it seems that acetonitriles containing electron-withdrawing groups are allowed to react with halopyridines in the presence of the palladium(0) catalyst, while the reaction proceeds at the 2-, 3-, and 4-positions in a similar level.



Scheme 1

In addition to the investigation on the condensation, the conversion of the side-chains introduced to another functional groups was examined. As shown in Scheme 2, the alkylation of 2b with ethyl iodide gave  $\alpha$ -ethyl- $\alpha$ -phenylsulfonylpyridine-3-acetonitrile (4) <sup>4</sup> (mp 85-86°C, 94 %), which was desulfurized with zinc dust at room temperature to provide  $\alpha$ -ethylpyridine-3-acetonitrile (5) <sup>4</sup> (bp 90°C/5 mmHg, 89 %) as expected. The reaction of 3b with benzaldehyde in the presence of sodium hydride gave  $\alpha$ -benzylidenepyridine-3-acetonitrile (6) <sup>4</sup> (mp 103-105°C, 74 %) as a sole product, while the E-Z configuration of 6 was not determined.



Scheme 2

The application of these reactions described above to other nitrogen-heteroaromatics will be reported elsewhere in the near future.

## REFERENCES AND NOTES

1. T. Sakamoto, E. Katoh, Y. Kondo, and H. Yamanaka, Chem. Pharm. Bull., in press.
2. As a substrate of this reaction, 4-bromopyridine is not so stable that 1c was used as a representative of 4-halopyridines.
3. Suzuki et al.<sup>5,6</sup> reported the copper(I) iodide-mediated reaction of aryl halides with phenylsulfonylacetonitrile and ethyl cyanomethylphosphonate, but the reaction with the palladium(0) catalyst proceeds under milder conditions than that with copper(I) iodide.
4. <sup>1</sup>H-NMR ( $\delta$  ppm) spectra of the products are as follows.
 

2a (CDCl<sub>3</sub>): 5.49 (0.41H, s), 6.5-6.8 (0.59H, m), 7.1-8.2 (8H, m), 8.52 (0.41H, dd,  $J=4$  and 7 Hz), 11.9-12.8 (0.59H, broad).

2b (CDCl<sub>3</sub>): 5.26 (1H, s), 7.2-7.5 (1H, m), 7.5-8.0 (6H, m), 8.49 (1H, d,  $J=2$  Hz), 8.71 (1H, dd,  $J=5$  and 2 Hz).

2c (DMSO-d<sub>6</sub>): 2.39 (6H, s), 6.8-7.3 (2H, m), 7.5-8.1 (5H, m).

3a (CDCl<sub>3</sub>): 1.38 (6H, t,  $J=7$  Hz), 3.9-4.4 (4H, m), 6.3-6.7 (1H, m), 7.1-7.7 (3H, m), 12.7-14.0 (1H, broad).

3b (CDCl<sub>3</sub>): 1.31 (6H, t,  $J=7$  Hz), 3.9-4.7 (5H, m), 7.2-7.6 (1H, m), 7.7-8.1 (1H, m), 8.6-8.9 (2H, m).

3c (DMSO-d<sub>6</sub>): 1.25 (6H, t,  $\underline{J}$ =7 Hz), 2.32 (6H, s), 3.7-4.3 (4H, m), 6.4-6.7 (1H, broad), 7.0-7.3 (1H, broad), 11.7-12.6 (1H, broad).

4 (CDCl<sub>3</sub>): 1.06 (3H, t,  $\underline{J}$ =7 Hz), 2.72 (2H, q,  $\underline{J}$ =7 Hz), 7.2-7.8 (7H, m), 8.5-8.8 (2H, m).

5 (CCl<sub>4</sub>): 1.09 (3H, t,  $\underline{J}$ =7 Hz), 1.93 (2H, dq,  $\underline{J}$ =7 Hz), 3.79 (1H, t,  $\underline{J}$ =7 Hz), 7.1-7.4 (1H, m), 7.4-7.8 (1H, m), 8.4-8.7 (2H, m).

6 (CDCl<sub>3</sub>): 7.2-7.7 (5H, m), 7.7-8.2 (3H, m), 8.63 (1H, dd,  $\underline{J}$ =5 and 2 Hz), 8.94 (1H, dd,  $\underline{J}$ =5 and 2 Hz).

5. H. Suzuki, K. Watanabe, and Q. Yi, Chem. Lett., 1779 (1985).

6. H. Suzuki, Q. Yi, J. Inoue, K. Kusume, and T. Ogawa, Chem. Lett., 887 (1987).

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