Short Communication

Synthesis of Dimethyl and Diethyl 4-(Phenylethynyl)-2,6-pyridinedicarboxylate

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Takalo, H. and Kankare, J., 1987. Synthesis of Dimethyl and Diethyl 4-(Phenylethynyl)-2,6-pyridinedicarboxylate. – Acta Chem. Scand., Ser. B 41: 219–221.

Owing to our interest in the properties of metal complexes of 4-substituted 2,6-pyridinedicarboxylic acids, which we shall report on later, we investigated methods for the preparation of dialkyl 4-(phenylethynyl)-2,6-pyridinedicarboxylates.

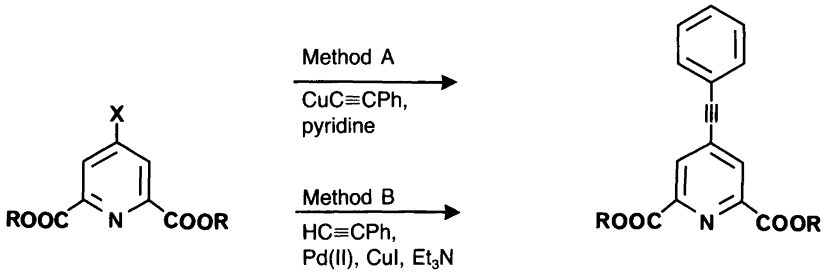
The widely-accepted procedure for the synthesis of unsymmetric diarylacetylenes is the Stephens-Castro coupling reaction between aryl iodide and copper(I) arylacetylide in pyridine under reflux (Scheme 1, method A).[1–5] The scope of this method is somewhat limited by the harsh reaction conditions and by difficulties in the preparation of cuprous acetylides.

It has been reported that aryl halides react with arylacetylenes in the presence of a small amount of a palladium catalyst and copper(I) iodide in a suitable solvent system to give diarylacetylenes (Scheme 1, method B).[6–9] The reaction proceeds under mild conditions in good yield. With this method there is no need for cuprous acetylide, and bromo- and even some chloroarenes can also be used. Recently, Rossi *et al.*[9] reported a one-pot synthesis of unsymmetrical diarylacetylenes using 2-methyl-3-butyn-2-ol as the protected acetylene starting material. Unfortunately, this method cannot be used with compounds which have base-sensitive groups.

We now report the synthesis of dimethyl (**4**) and diethyl (**5**) 4-(phenylethynyl)-2,6-pyridinedicarboxylate by method A and/or B (Scheme 1).

Results and discussion

The reaction conditions and results are summarized in Table 1. Dimethyl 4-iodo-2,6-pyridinedicarboxylate (**3**)[10] reacts with copper(I) phenyl-



1: X=Cl, R=Et
2: X=Br, R=Et
3: X=I, R=Me

4: R=Me
5: R=Et

Scheme 1.

Table 1. Preparation of dimethyl (**4**) and diethyl (**5**) 4-(phenylethynyl)-2,6-pyridinedicarboxylate.

Reactants	Reaction temp./°C	Reaction time/h	Yield/%
Method A			
1 + PhC≡CCu	110	20	[a]
3 + PhC≡CCu	110	9	54
Method B			
1 + PhC≡CH	80	24	poor
2 + PhC≡CH	40–50	2	75
3 + PhC≡CH	20–25	2	84

[a] *according to TLC.*

acetylide[11] in pyridine to form **4** in moderate yield, whereas diethyl 4-chloro-2,6-pyridinedicarboxylate (**1**)[12] failed to react, even though the chlorine is in a rather reactive position. However, **1–3** all react with phenylacetylene in the presence of bis-(triphenylphosphine)palladium(II) acetate and copper(I) iodide in triethylamine. The order of halogen reactivity is I > Br > Cl. Although **3** gives slightly better yields than **2**, its synthesis involves two more steps.

More vigorous reaction conditions are needed in method A than in method B. Moreover, the preparation of the easily autoxidized copper(I) acetylide adds one tedious step to the synthetic path. Finally, method B gives much better results than method A.

Experimental

^{1}H NMR spectra were recorded at 60 and 400 MHz. Mass spectra under electron impact conditions were recorded at 70 eV ionization energy.

Diethyl 4-bromo-2,6-pyridinedicarboxylate, **2**. To a vigorously stirred solution of bromine (47.6 g, 0.298 mol) in petroleum ether (100 ml, b.p. 40–60 °C) was added phosphorus tribromide (96.8 g, 0.358 mol). After stirring for a few minutes at room temperature, the resulting yellow phosphorus pentabromide was washed several times with petroleum ether by decantation and was dried *in vacuo*. Dry 4-hydroxy-2,6-pyridinedicarboxylic acid (20.0 g, 0.099 mol) was added to the same reaction vessel and after thorough mixing, the temperature of the bath was raised to 90 °C and maintained at that temperature for 3 h. The cooled mixture was stirred with chloroform (150 ml) and filtered. Absolute ethanol (400 ml) was added to the filtrate in small portions and the solution was concentrated *in vacuo*. The crude product crystallized on standing overnight in the cold and was recrystallized from hexane after decantation from insoluble material. The yield was 19.2–23.7 g (64–79 %); m.p. 95–96 °C. ^{1}H NMR ($CDCl_3$): δ 1.35 (6 H, t), 4.45 (4 H, q), 8.35 (2 H, s). IR (KBr): 1720, 1330, 1240 cm^{-1} (C=O and C–O). MS [*m/z* (rel. int.)]: 301 (0.06, M), 303 (0.06, M). Anal. $C_{11}H_{12}BrNO_4$: C, H, Br, N.

Method A. To a reaction vessel equipped with a nitrogen inlet stopcock, a magnetic stirring bar, a condenser fitted with a nitrogen outlet stopcock, an oil trap and a thermometer was added copper(I) phenylacetylide[11] (0.61 g, 3.7 mmol). The system was deaerated with nitrogen for 20 min, and then pyridine (20 ml) was added. The resulting mixture was stirred for 20 min under a nitrogen atmosphere and then **1**[12] or **3**[10] (3.3 mmol) was added. The reaction temperature was raised to 110 °C and maintained at that temperature for 9 h. Pyridine was removed by evaporation *in vacuo*. To the residue was added water (15 ml) and chloroform (15 ml). The mixture was shaken, filtered and the chloroform layer separated. The aqueous layer was extracted with chloroform (3 × 15 ml). The combined chloroform extract was shaken with cold concentrated aqueous ammonia (10 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (4 × 15 ml). The combined organic phase was washed with water (10 ml), dried with anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethanol or methanol.

Method B. A mixture of **1**, **2** or **3** (5 mmol), palladium(II) acetate (22 mg, 0.1 mmol), triphenylphosphine (53 mg, 0.2 mmol), copper(I) iodide (38 mg, 0.2 mmol) and phenylacetylene (0.51 g, 5 mmol) in dry triethylamine (10 ml) was deaerated with nitrogen and heated to the desired temperature (Table 1). After the reaction was complete, the mixture was evaporated *in vacuo*. The residue was dissolved in chloroform (40 ml), and the solution was washed with water (3 × 15 ml) and dried with anhydrous sodium sulfate. Removal of the solvent by evaporation yielded a

crude material which was recrystallized from ethanol or methanol:

Dimethyl 4-(phenylethynyl)-2,6-pyridinedicarboxylate, **4**. M.p. 153–154 °C. ^{1}H NMR ($CDCl_3$): δ 4.04 (2 Me, s), 7.20–7.70 (Ph, m), 8.35 (3- and 5-H, s). IR (KBr): 2220 cm^{-1} (C≡C), 1755, 1720, 1280, 1260, 1259 cm^{-1} (C=O and C–O). MS [*m/z* (rel. int.)]: 295 (14, M). Anal. $C_{17}H_{13}NO_4$: C, H, N.

Diethyl 4-(phenylethynyl)-2,6-pyridinedicarboxylate, **5**. M.p. 100 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (2 CH_3, t), 4.50 (2 CH_2, q), 7.38–7.60 (Ph, m), 8.33 (3- and 5-H, s). IR (KBr): 2220 cm^{-1} (C≡C), 1740, 1725, 1265, 1250, 1230 cm^{-1} (C=O and C–O). MS [*m/z* (rel. int.)]: 323 (4, M). Anal. $C_{19}H_{17}NO_4$: C, H, N.

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Received December 15, 1986.