## A USEFUL PREPARATION OF SUBSTITUTED ALKOXYACETYLENES

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Abstract: R'Cu(CN)ZnX reagents have been found to react rapidly with iodo alkoxyacetylenes to provide coupled products in synthetically useful yields.

Recently we reported<sup>1</sup> a remarkably efficient preparation of a variety of alkoxyacetylenes (III, eq 1), well-studied compounds with numerous synthetic applications.<sup>2</sup> We discovered during a subsequent program however that certain R' groups (e.g., neopentyl) were, not unexpectedly, difficult to introduce using this approach (path a). In this communication we wish to report an alternative procedure based on Knochel-type coupling<sup>3</sup> of iodo alkoxyacetylenes (path b).

Although halo alkoxy- and aryloxyacetylenes have been reported to be unstable,<sup>2a,b,4</sup> it was found that the derivatives 1, 3, and 5 (Table) could readily be secured through the addition of molecular iodine to the appropriate lithium acetylide in THF at -90 °C (76, 93, and 86 % yields, respectively).<sup>3c</sup> These substrates reacted surprisingly fast<sup>3</sup> with copper reagents<sup>5</sup> generated from organozinc derivatives and CuCN-2LiCl to give the easily purified coupled products 2, 4, and 6 in moderate to good yields (Table). lodo alkoxyacetylenes were found to couple somewhat more effectively than bromo alkoxyacetylenes, but all reactions were rapid at -84 to -55 °C. Secondary organozinc reagents produced mainly III (H).

This preparation of substituted alkoxyacetylenes makes easily accessible a variety of new derivatives that would otherwise be difficult to obtain. Representative experimental procedures are provided below: lodo alkoxyacetylene 1. *n*-Butyllithlum (1.6 M in hexane, 6.3 mL, 10.1 mmol) was added dropwise to a stirred solution of 2.00 g (10.0 mmol) of (*trans*-2-phenylcyclohexyloxy)acetylene, prepared in the usual manner (88 % yield),<sup>1</sup> in 20 mL of THF at 0 °C under argon. After being stirred at 0 °C for 20 min, the reaction mixture was cooled to -90 °C and treated over 5 min with 2.54 g (10.0 mmol) of lodine dissolved in 20 mL of THF. The resulting mixture was then diluted with hexane and water. The organic phase was washed with aq sodium thiosulfate and brine, dried over magnesium sulfate, and concentrated. The crude product was subjected to column chromatography (silica gel pretreated with 2.5 % v/v of triethylamine) with 10 % dichloromethane in hexane and then recrystallized from dichloromethane-hexane to give 2.49 g (76 %) of 1: mp 75-80 °C (dec); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  7.37-7.18 (m, 5H), 4.15 (dt, J=10.7, 4.4 Hz, 1H), 2.72 (pseudo dt, J=11.2, 3.5 Hz, 1H), 2.43-2.36 (m, 1H), 1.98-1.85 (m, 2H), 1.80-1.28 (m, 5H); IR(Nujol) 3055, 3030, 2920, 2855, 2195, 1600, 1455, 1190, 1165, 985, 920, 890, 860 cm<sup>-1</sup>. Anal. Calc for C<sub>14</sub>H<sub>15</sub>IO: C, 51.55; H, 4.64. Found: C, 51.63; H, 4.77.

Alkoxyacetylene 2 (R'=(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>). A stirred mixture of 465 mg (7.11 mmol) of zinc powder and 20  $\mu$ L of 1,2-dibromoethane in 0.8 mL of THF was refluxed for 1 min and then treated at 25 °C with 20  $\mu$ L of chlorotrimethylsilane.<sup>3a</sup> After 20 min a solution of 1.21 g (5.00 mmol) of ethyl 4-iodobutyrate in 2 mL of THF was added and the resulting mixture was stirred at 37 °C for 24 h, whereupon It was allowed to cool to room temperature and was diluted with THF to give a volume of 5 mL. A 1-mL sample of the supernatant from this reaction was added at -10 °C to a solution of 89 mg (1.0 mmol) of cuprous cyanide and 85 mg (2.0 mmol) of lithium chloride in 1 mL of THF. After being stirred at 0 °C for 25 min, the solution was diluted with 3.0 mL of THF and cooled to -84 °C. A solution of 100 mg (0.31 mmol) of iodide 1 in 0.5 mL of THF was added, and the reaction mixture was allowed to warm to -55 °C over 40 min, whereupon it was poured into aq ammonium chloride-brine. The crude product was isolated with ether in the usual way and purified by column chromatography (silica gel pretreated with 2.5 % v/v of triethylamine) with 5 % ethyl acetate in hexane to give 54 mg (56 %) of 2 (R'=(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  7.35-7.16 (m, 5H), 4.11 (q, J=7.1 Hz, 2H), 4.00 (dt, J=10.7, 4.5 Hz, 1H), 2.71 (dt, J=11.2, 3.6 Hz, 1H), 2.41-2.31 (m, 3H), 2.12 (t, J=6.8 Hz, 2H), 1.95-1.90 (m, 2H), 1.78-1.31 (m, 7H), 1.24 (t, J=7.1 Hz, 3H); IR(film) 3055, 3030, 2940, 2855, 2250, 1740, 1600, 1450, 1240, 1210, 1150, 1000, 930, 860 cm<sup>-1</sup>; mass spectrum, m/e 314 (M<sup>+</sup>). Anal. Calc for C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>: C, 76.40; H, 8.34. Found: C, 76.55; H, 8.29.



<sup>a</sup>Halide used to generate organozinc (or Grignard) reagent. <sup>b</sup>Ylelds are for purified, homogeneous (TLC, NMR) material. <sup>c</sup>The organozinc reagent was obtained with zinc chloride from the Grignard reagent. <sup>d</sup>The bromo alkoxyacetylene gave a 40 % yield. <sup>e</sup>The Grignard reagent was used.

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## Notes and References

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5. Best results were obtained with 3 equiv of the copper reagents. (Received in France 9 October 1990)