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A new and practical synthesis of vinyl dichlorides via a non-Wittig-type approach

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Abstract

A practical approach for the conversion of aldehydes to vinyl dichlorides has been developed. These are three-step, one-pot reactions involving the formation of trichlorocarbinol by treatment of aldehydes with trichloroacetic acid and sodium trichloroacetate followed by in situ protection and elimination reactions to form the desired vinyl dichlorides in 85 to 95% yields.

In connection with the project of development of efficient and economical synthesis of Efavirenz (Sustiva™, DMP 266), a marketed anti-HIV medicine developed by our company,[1] we have studied new methodologies for the synthesis of cyclopropylacetylene **1** (CPA). We anticipated that one carbon homologation from aldehyde for the synthesis of **1** is one of the most efficient approaches, for example, via vinyl halide,[2] 1,1-dihalo- or 1,1,1-trichlorocarbinol-derived intermediates.[3,4] We have also been interested in the synthesis of **1** starting from cyclopropylcarboxaldehyde via its corresponding one carbon extended vinyl dihalide intermediate, which can be prepared by Wittig-type (such as Corey–Fuchs) reactions.[5,6] However, the requirements of phosphorous reagents to promote Wittig-type reactions for the conversion of aldehydes to vinyl dihalides limit their industrial attractiveness and efficiency of their applications due to the problems of toxicity and volume of the waste streams generated. In this report, we wish to present an alternative approach for the conversion of aldehydes to vinyl dichlorides. This methodology involves a one-pot, three-step reaction sequence: (1) addition of trichloromethyl anion generated in situ from trichloroacetic acid to aldehydes **2** to form trichloroalcohols **3**; (2) transformation of **3** to trichloroacetate **4**; and (3) elimination of chloride and acetate in **4** by the treatment of **4** with acetic acid and zinc powder in the same pot to generate the desired vinyl dichloride **5**, as shown in Scheme 1.

Trichlorocarbinols in this sequence were prepared according to the procedure developed by the Corey group.[7] In the presence of aldehydes, trichloromethyl anion was generated by decarboxylation at room temperature when trichloroacetic acid was mixed with sodium trichloroacetate in DMF, which in turn added to aldehydes **2** to form the desired trichloromethyl carbinols **3**. The release of carbon dioxide of

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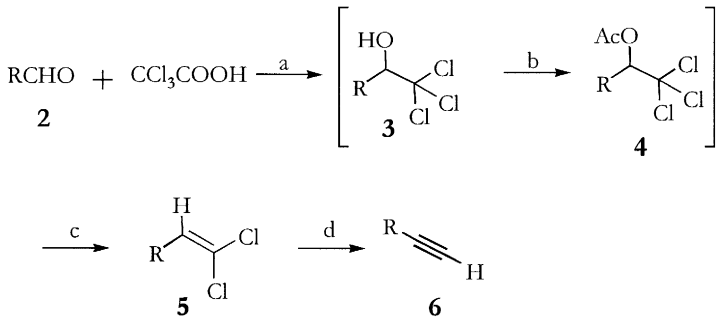

Scheme 1. General methods for vinyl dichloride and 1-alkyne preparation. Reagents: (a) CCl_3COONa, 1.5 equiv./DMF, 25–35°C; (b) Ac_2O, 0–25°C; (c) HOAc/Zn, 25–60°C; (d) 3.0 equiv. MeLi/THF, −10°C; then H_3O^+

this reaction was observed during the first 5 to 10 min after the addition of sodium trichloroacetate in one portion; however, it took 1.5 to 2.0 h for the completion of the decarboxylation. In a large-scale reaction, the release of carbon dioxide could be controlled by the portionwise addition of sodium trichloroacetate. After the addition was completed, the reaction mixture was stirred at room temperature for an additional 3–4 h. The trichlorocarbinols **3** could be efficiently transformed into their corresponding acetates **4** in situ by the addition of acetic anhydride after the reaction mixtures were cooled to 5°C; and then stirred at room temperature for 1 h. The acetates **4** were converted to their corresponding vinyl dichlorides **5** in the same reactor through the treatment of the reaction mixture with acetic acid and zinc powder at 25–60°C for 1 h followed by regular workup and distillation in 85 to 95% yields. Our results are summarized in Table 1. The trichlorocarbinols **3** could also be converted to their corresponding vinyl dichlorides **5** directly by the treatment of the acetic acid and zinc powder; however, in somewhat lower yields (<80%).

Table 1
Summary of the yields of vinyl dichlorides **5** and acetylenes **6**

Entry	R-CHO	**5a-i** % Yield[a]	**6a-i** % Yield[a]
a	cyclopropyl	92	89
b	cyclohexyl	88	91[c]
c	iso-butyl	93	90
d	*n*-octyl	95[b]	93[c]
e	*t*-butyl	92	90
f	isopropyl	89	82
g	phenyl	86	92
h	2-phenylethyl	85[b]	90[c]
i	styrene	85[b]	dec.

(a) Yield of pure compound after distillation unless otherwise stated.
(b) Yield of pure compound after flash column chromatography (SiO_2, Hex./EtOAc (9:1)).
(c) Crude yield.

To meet our project needs, as anticipated, the vinyl dichlorides were easily transformed into their corresponding terminal alkynes through elimination reactions with strong bases, such as methyllithium or sodamide/DMSO, as summarized in Table 1. We have applied this procedure to the synthesis of our target, cyclopropylacetylene (**1**, entry a in Table 1), on a 100 g scale in approximately 81% yield.

In summary, we have identified an efficient and economical conversion of aldehydes into vinyl dihalides. It is of great practical significance that this conversion does not involve phosphorous-containing reagents. Subsequent conversion of the vinyl dichlorides to terminal alkynes was further accomplished smoothly and in high yields.[8]

Acknowledgements

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8. Preparation of 1,1-dichloro-3-cyclopropylethene **4** is a typical example of this procedure. To a stirred solution of trichloroacetic acid (105 g, 0.642 mol) and cyclopropylcarboxaldehyde (30 g, 0.428 mol) in DMF (300 mL) at 25°C was added sodium trichloroacetate (119 g, 0.642 mol) in portions. The internal temperature was kept below 35°C by addition control. After addition was completed, the mixture was stirred at room temperature for 4 h with continuous evolution of CO_2. The solution was cooled to 5°C and acetic anhydride (80.77 mL, 0.856 mol) was carefully added. Strong CO_2 evolution was observed. The mixture was allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was diluted with acetic acid (400 mL) and cooled to 0°C. To the solution, the zinc powder (55.9 g, 0.856 mol) was added in one portion. The solution was stirred for 1 h at 60°C and then was cooled to room temperature. To the solution, water was added and then extracted with hexanes. The combined organic phases were washed with water and saturated aqueous solution of sodium chloride. The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude 1,1-dichloro-2-cyclopropylethylene was obtained in a relative good purity. Both flash chromatography (hexane:EtOAc, 9:1) and distillation (bp=47–5°C/2 torr) methods for the purification of this compound had been applied. Purification by distillation yielded 44.07 g (88%) of the desired compound, **4**. Preparation of cyclopropylacetylene **1** (CPA) is a typical example for this procedure: To a stirred solution of 1,1-dichloro-2-cyclopropylethylene (29.10 mmol) in dried THF (40 mL) at −30°C was added MeLi (1.4 M in ether, 32 mmol, 1.2 equiv.) dropwise via an additional funnel. After the addition was completed, the solution was allowed to slowly warm to 0°C over a 1 h period. The reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with heptane. The aqueous phase was extracted with heptane. The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After filtration a 95% solution yield of CPA in THF:heptane (1:6) was obtained. Fractional distillation at atmosphere pressure (b.p. 54–56°C) afforded neat CPA **1**, 1.71 g (89%).