Efficient Syntheses of Cyclopropylacetylene, a Crucial Synthetic Intermediate for Efavirenz (DMP-266)

Shaun E. Schmidt,[a] Ralph N. Salvatore,[a] Kyung Woon Jung,[a]* Taesoo Kwon[b]*

[a] Department of Chemistry (CHE 305), University of South Florida and Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, 4202 E. Fowler Avenue, Tampa, Florida 33620-5250, USA

[b] SK Energy and Chemical, Inc., 22-10 Route 208 South Fair Lawn, New Jersey 07410, USA

Fax +1 (813) 974-1733; E-mail: kjung@chuma.cas.usf.edu

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Abstract: Efficient syntheses of cyclopropylacetylene were achieved from cyclopropyl methyl ketone. Different reaction pathways were investigated to avoid the concomitant formation of any side products.

Key words: cyclopropylacetylene, chlorination, dehydrochlorination

Recently, cyclopropylacetylene **1** has become an attractive synthetic target due to increasing demand as a building block for Efavirenz (DM*P*-266), which is a potent inhibitor of the human immunodeficieny virus type-1 (HIV-1) nonnucleoside reverse transcriptase (Figure 1).[1] Although a variety of syntheses have been reported in the literature for the target compound, these methods have remained cumbersome to reproduce, thus lacking in practicality for large scale manufacturing.[2] An efficient synthetic route to produce **1** in a pure form has been sought in our laboratories. Cost, practicality, and waste disposal have all been factors considered in the choice of reagents and solvents.

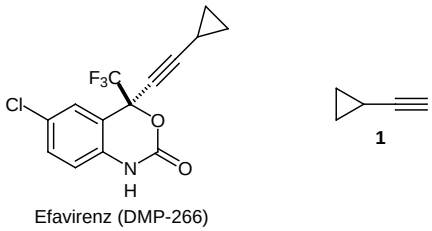
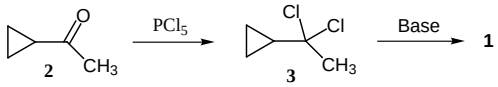


Figure 1



Scheme 1

As summarized in Scheme 1, a previously reported synthesis of cyclopropylacetylene employed chlorination of ketone **2** by phosphorus pentachloride to afford dichloride **3**, which, in turn, was converted to acetylene **1** through double dehydrochlorination.[2] Shortcomings to this protocol were low yield (22%),[2a] difficulty in isolation, and purification. Presumably, these problems were associated mainly with the concomitant formation of various side products including **4**, **5**, **6**, and **7** (Figure 2). Discussed herein are our efforts to eliminate such side products by deducing the mechanism for their formation, thus allowing for the development of a more efficient and convenient synthesis.

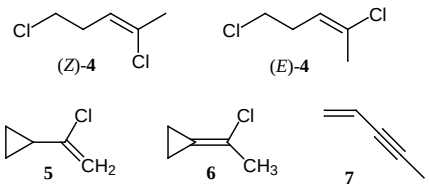
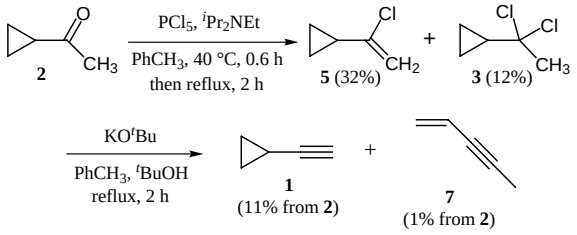


Figure 2

During chlorination under various conditions, we found that any *in situ* generated acidic species such as $POCl_3$ or HCl triggered ring opening of dichloride **3**, giving rise to the formation of a mixture of chloroolefins *(Z)*-**4** and *(E)*-**4** (20% - 70%). In the presence of any residual acid, the resultant product was completely decomposed within a few hours at ambient temperatures, and mostly destroyed overnight even at -15 °C. The formation of **4** was suppressed dramatically (less than 5% yield) by careful and complete elimination of all acid residues during an alkaline aqueous work-up at 0 °C.

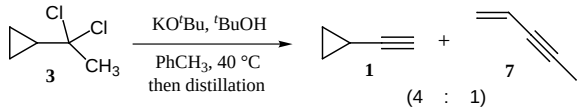
Since base was essential for both removal of residual acids and subsequent elimination, we attempted the intended chlorination and dehydrochlorination simultaneously in the presence of an appropriate base. Various bases such as $NaHCO_3$, potassium *tert*-butoxide, triethylamine, DBU, and Hünig's base were utilized. Hünig's base, $^{i}Pr_2NEt$, was found to excel in the complete conversion of ketone **2** as well as the exclusive formation of terminal chloroolefin **5** over the internal analog **6** as described in Scheme 2.

Although the intended one-pot direct conversion to **1** from **2** was not feasible, partial elimination occurred selectively to afford a mixture of olefin **5** and dichloride **3** in the absence of any other reported side products.[3] The isolation of the desired products using rigorous aqueous work-up procedures yielded trace ring opening products. In an ef-



Scheme 2

fort to avert these problems, it was found that steam distillation directly from the reaction mixture offered a quick and facile purification, delivering a toluene solution containing **5** and **3** in a 44% combined yield. Subsequently, the distilled mixture was subjected to elimination, leading to the production of acetylene **1** along with enyne **7**. Because of the failure to separate the two products, alternative conditions were sought to effect dehydrochlorination selectively without concomitant formation of enyne **7**.



Scheme 3

To investigate the source of enyne **7**, we then focused on the dehydrochlorination reaction of dichloride **3** (Scheme 3), which was obtained cleanly from the chlorination in absence of base.[4] It was found that double elimination of dichloride **3** resulted in a mixture of **1** and **7**, implying that **7** was generated from **3** but not **5** through a different mechanistic pathway. More importantly, at higher reaction temperatures, more enyne **7** was observed, suggesting an enhancement of a side reaction via a higher energy species such as the internal olefin **6** (Figure 3). Therefore, it was hypothesized that the formation of terminal olefin **5**, and subsequently **1**, was kinetically favored. This prompted us to employ use of a hindered base in a nonpolar media at a low temperature for optimum results. This approach was implemented successfully to prevent the production of enyne **7**, as delineated in the Scheme 4.

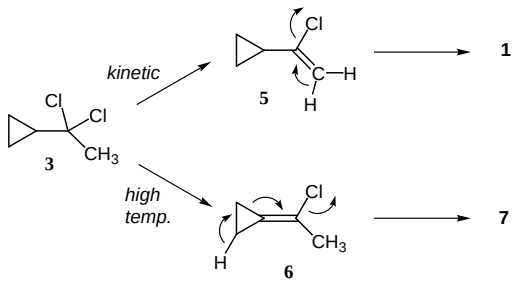
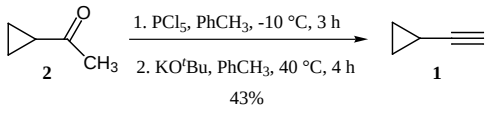


Figure 3

Keeping convenience and practicality in mind, a two step process was carried out without purification of intermediates under the preferred conditions which were explored in our laboratories (Scheme 4).[4] Presumably because a nonpolar solvent can help to suppress ring opening and enyne synthesis (*vide supra*), toluene was more efficient when compared with other polar solvents including dichloromethane, etheral solvents, etc. Due to its relatively high boiling point, the distillation directly from the reaction was anticipated to be facile, delivering the desired acetylene **1** in the distillate.



Scheme 4

At a low temperature, ketone **2** was smoothly converted to dichloride **3**, and the crude reaction mixture was treated with excess base to minimize the formation of ring opening product **4**. The toluene solution of the crude dichloride was subjected to elimination without further purification at low temperature. Although efficient stirring was inhibited by the formation of a brown gel, the reaction went to completion upon standing over 4 hours. Cyclopropylacetylene **1** was produced from cyclopropyl methyl ketone **2** in 43% yield after distillation and washing the distillate with water.[4]

Although the isolation yield of the target molecule is moderate, this methodology is an improvement over the known methods in terms of yield and reproducibility. Furthermore, these conditions were pragmatic and convenient, producing the desired acetylene **1** free from known side products. Moreover, this two step sequence simplifies the purification process, which was one of the most difficult shortcomings to overcome. As a consequence, this synthetic protocol is believed to be cost effective and facile on an industrial scale, offering an alternative route for the synthesis of cyclopropylacetylene.

References and Notes

(1) Efavirenz (DMP-266) was recently developed at Merck Research Laboratories. (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028. (b) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carrol, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I-W; Schleif, W. A.; Sardana, V. V.; Long, W. J., Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602. (c) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937.

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(3) The reaction progress and the product distribution were monitored by ^{1}H NMR analyses of small aliquots taken from the crude reaction mixture.

(4) The experimental procedures for the two step synthesis are described below. Lack of reasonable mass balance is believed to stem partially from the loss of **1** during the reaction, work-up, and distillation due to its high volatility. Its characteristic odor was detected during the entire process.

1,1-Dichloro-1-cyclopropylethane (3). Phosphorous pentachloride (230 g, 1.1 mol) was added to 300 mL of toluene at -10 °C. Cyclopropyl methyl ketone **2** (100 mL, 1.0 mol) was added dropwise over 25 minutes to the yellow slurry. Under a nitrogen atmosphere, the reaction was stirred for three hours at -10 °C. The resulting white suspension was poured into a mixture of 2 L of crushed ice and 1 L of 6 M NaOH solution. The heterogeneous solution was stirred for ten minutes, long enough to destroy any residual acidic species (pH of aqueous phase>10). The organic layer was washed with 300 mL of brine, dried over anhydrous sodium sulfate, and carried over to the next reaction without further purification. A 92% yield of **3** based on the ^{1}H NMR analysis was observed.

Cyclopropylacetylene (1). Powdered potassium *t*-butoxide (300g, 2.7 mol) was suspended in 100 mL of toluene. Crude dichloride **3** in a toluene solution, obtained from the previous reaction, was added slowly. The reaction suspension was warmed to 40 °C and kept for 4 hours. As the reaction proceeded, an orange gel formed which slowly turned to black, consequently preventing magnetic stirring. After crushed ice (200 mL) was added slowly, the resulting solution was washed three times with 200 mL of ice water, and followed by washing with 200 mL of brine and drying over 10-15 g of anhydrous Na_2SO_4. The filtered solution was distilled carefully to provide **1** at *ca.* 55 °C. Cyclopropylacetylene was obtained as the predominant product along with toluene and *t*-butanol (43% from cyclopropyl methyl ketone **2** in two steps based on ^{1}H NMR). *t*-Butanol was easily removed by washing the corresponding distillate with water.

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