ORGANIC LETTERS

2003
Vol. 5, No. 2
213−216

Synthesis and Derivatization of Ethynyl α,α-Dibromomethyl Ketones: Formation of Highly Functionalized Vinyl Triflates

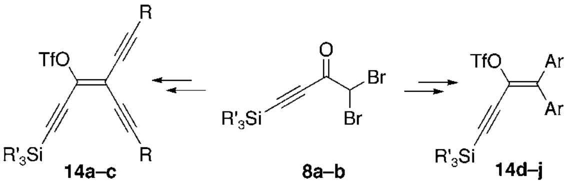
Trent Rankin and Rik R. Tykwinski*

Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

rik.tykwinski@ualberta.ca

Received November 11, 2002

ABSTRACT



We describe the synthesis of α,α-dibromomethyl ynones (8) and their subsequent derivatization to vinyl acetates (10). These vinyl acetates feature a 1,1-dibromo-olefin moiety, which is readily exploited in palladium-catalyzed Sonogashira, Stille, and Suzuki cross-coupling reactions with alkynes, stannanes, and boronic acids, respectively. A novel one-pot process then directly converts the resulting vinyl acetates 11–13 to the vinyl triflate derivatives 14a–j.

Vinyl triflates are versatile building blocks for the synthesis of a diverse range of organic compounds.[1,2] This is particularly true as a result of the vast array of palladium-catalyzed cross-coupling reactions developed for use with vinyl triflates, including the Heck,[3] Stille,[4] Suzuki,[5] and related cross-coupling reactions.[6]

We have been interested in the use of suitably substituted vinyl triflates as precursors for the iterative assembly of extended, cross-conjugated oligomers and macrocycles.[7] The first generation of these highly unsaturated compounds was derived from simple alkyl- or phenyl-substituted vinyl triflates and afforded novel systems such as the *iso*-PDAs (**1**) and expanded radialenes (**2**), as shown schematically in Figure 1. For the synthesis of these oligomers, the requisite vinyl triflates are accessible by using reported methods that involve a sequence of Friedel−Crafts acylation of an acid chloride (**3**) with bis(trimethylsilyl) acetylene to give ketone **4**,[8] followed by triflation with base and triflic anhydride to give **5**.[9]

In our quest for more highly functionalized derivatives of **1** and **2**, however, synthetic routes appropriate to the necessary vinyl triflates were unavailable. For example, per(ethynylated) derivatives of the triflate **5** ($R = C{\equiv}CR'$) would be remarkably versatile modules for the construction of conjugated oligomers, but the necessary precursors, α,α-diethynyl carboxylic acids or acid chlorides **3**, are to the best of our knowledge an unknown class of molecules. Conversely, alkoxyl-substituted diaryl acetic acid chlorides (**3**, $R = MeOC_6H_4$) are available via reported methods.[10]

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[1] Mitchell, T. N. *Synthesis* **1992**, 803−815.

[2] Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85−126.

[3] Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.

[4] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

[5] Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208

[6] (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1997. (b) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 127−160. (c) Ritter, K. *Synthesis* **1993**, 735−762. (d) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47−54.

[7] (a) Tykwinski, R. R.; Zhao, Y. *Synlett* **2002**, 1939−1953. (b) Slepkov, A. D.; Hegmann, F. A.; Zhao, Y.; Tykwinski, R. R.; Kamada, K. *J. Chem. Phys.* **2002**, *116*, 3834−3840. (c) Campbell, K.; McDonald, R.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 1133−1140. (d) Zhao, Y.; Campbell, K.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 336−344. (e) Zhao, Y.; Campbell, K.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 2805−2812. (f) Zhao, Y.; Tykwinski, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 458−459. (g) Eisler, S.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1940−1943.

[8] Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45−56.

[9] Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438−440.

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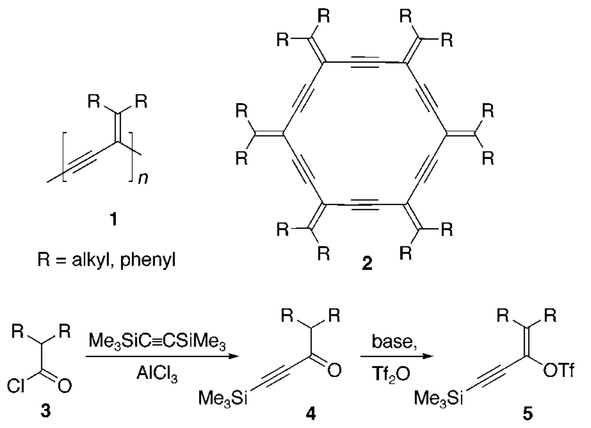
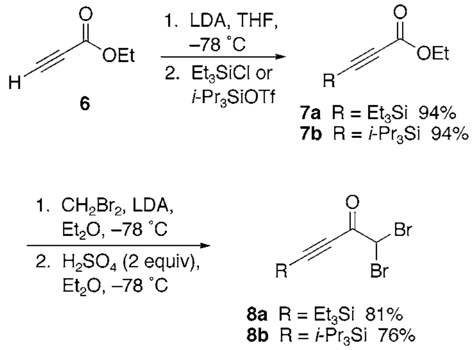


Figure 1. Friedel−Crafts acylation based synthesis of ethynyl vinyl triflates **5**, the precursors to *iso*-PDAs (**1**) and expanded radialenes (**2**).

Unfortunately, we have been unable to successfully convert such acid chlorides to ethynyl ketones using either Friedel−Crafts acylation or palladium-catalyzed coupling procedures.[11,12] As a result, we have developed, and report herein, a general and versatile method for the formation of highly functionalized vinyl triflate building blocks via the divergent derivatization of ethynyl α,α-dibromomethyl ketones.

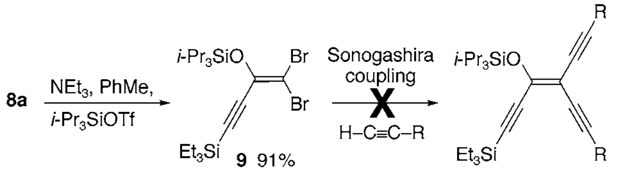
Trialkylsilyl protected propynone derivatives, the α,α-dibromomethyl ynones **8a**,**b**, were targeted as progenitors to functionalized vinyl triflates (Scheme 1). To the best of our knowledge, 1,1-dibromo-4-phenyl-2-butynone is the only analogue of **8** that has been reported in the literature,[13] and it was synthesized from the 3-phenyl ethyl propynoate. With the intent of emulating this reported procedure, the terminal alkyne of ethyl propynoate (**6**) was silylated via deprotonation with LDA at −78 °C, followed by reaction with either Et$_3$SiCl or *i*-Pr$_3$SiOTf to give **7a** and **7b** in excellent yields. Employing the Barluenga protocol,[13] reaction of esters **7a**,**b** with dibromomethyllithium (2 equiv), generated in situ from LDA and CH$_2$Br$_2$, provided disappointingly low yields of the dibromoketones **8a**,**b**. Changing the reaction solvent to Et$_2$O and carefully quenching the reaction at low temperature, however, substantially improved the outcome.[14] Thus, ketones **8a**,**b** can be isolated in high yields, via rapidly passing the impure reaction residue through a plug of silica. It is worth noting that the reaction to **8a**,**b** can be readily scaled up (e.g., producing up to 6 g of **8a**) and the products **8a**,**b** can be stored indefinitely under refrigeration (4 °C) without observable decomposition.

Scheme 1



Our initial efforts to derivatize the dibromo ketones **8a**,**b** targeted the synthesis of the silyl enol ether derivative **9**. It was envisioned that the dibromo olefin moiety of **9** would be a suitable partner for subsequent palladium-catalyzed cross-coupling reactions. Thus, dibromo ketone **8a** was readily converted to **9** in 91% yield via reaction with NEt$_3$ and *i*-Pr$_3$SiOTf in toluene (Scheme 2). All attempts at alkynylation of **9** via Sonogashira cross-coupling[15] have to date been unsuccessful.[16] It is quite likely that these reactions fail due to the electron-rich nature of enol ether **9**, which would be expected to substantially retard this cross-coupling reaction by slowing the oxidative addition of palladium into the vinyl bromide bond.[17]

Scheme 2



In an attempt to provide a substrate that would facilitate palladium-catalyzed cross-coupling reactions, an electron-

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(10) Baarschers, W. H.; Vukmanich, J. P. *Can. J. Chem.* **1986**, *64*, 932−935.

(11) Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289−294.

(12) Chernick, E. T.; Tykwinski, R. R. Unpublished results.

(13) Barluenga, J.; Llavona, L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 297−301.

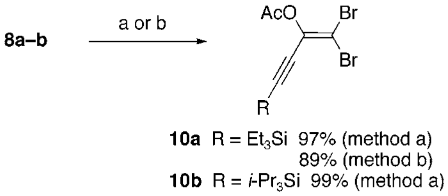
(14) General procedures. **8a**: To a stirred solution of dibromomethane (0.331 mL, 4.72 mmol) and **7a** (500 mg, 2.32 mmol) in Et$_2$O (10 mL) at −78 °C was added LDA (4.72 mmol) in Et$_2$O (10 mL) over a period of 10 min. The mixture was stirred for 20 min at −78 °C, and H$_2$SO$_4$ (0.25 mL) in Et$_2$O (2 mL) was then added; this mixture was stirred for 30 min at −78 °C. The now heterogeneous mixture was filtered through Celite, the organic solvents evaporated, and the residue passed through a plug of silica gel (hexane/EtOAc 30:1) to yield **8a** (638 mg, 81%) as a light yellow oil. **10a**: Compound **8a** (457 mg, 1.34 mmol) in THF (10 mL) was cooled to −78 °C, LiHMDS (1.61 mmol) in THF (5 mL) was added, and the mixture was stirred for 30 min at −78 °C. Ac$_2$O (0.190 mL, 206 mg, 2.02 mmol) was added, and the mixture was allowed to warm to room temperature over a period of 4 h. The reaction was quenched with saturated NH$_4$Cl (10 mL) and extracted with Et$_2$O (2 × 20 mL), and the organic layer was washed with brine (20 mL), dried (Na$_2$SO$_4$), filtered, and evaporated. The residue was purified by filtration through a plug of silica gel (hexane/Et$_2$O 20:1) to yield **10a** (499 mg, 1.31 mmol, 97%) as an amber oil.

(15) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(16) Unsuccessful conditions include Pd(PPh$_3$)$_4$ or PdCl$_2$(PPh$_3$)$_2$, Et$_3$N or *i*-Pr$_2$NH (with or without THF cosolvent), CuI, at reflux. More active catalysts such as that reported by Fu and Buchwald, however, have not yet been attempted, see: Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731.

(17) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453−4457.

Scheme 3 [a]



[a] Reagents and conditions: (a) LiHMDS, Ac_2O, THF, −78 °C; (b) NEt_3, Ac_2O, DMAP, THF, rt.

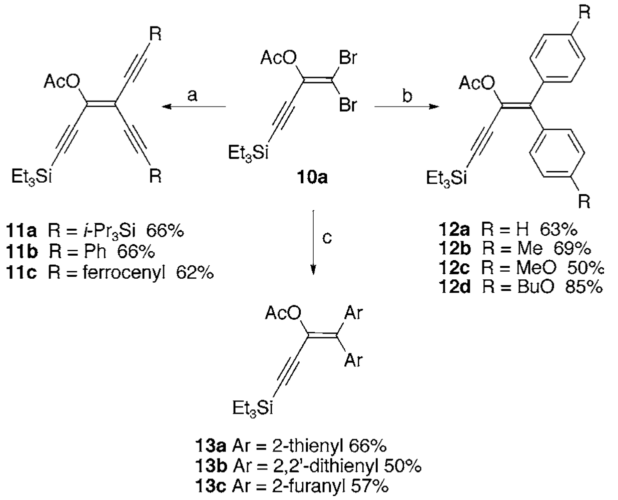
withdrawing enol protecting group was targeted. Thus, ketones **8a**,**b** were converted in excellent yields to vinyl acetates **10a**,**b** via deprotonation with LiHMDS at −78 °C, followed by reaction with acetic anhydride (method a, Scheme 3). Alternatively, for large-scale production of **10a** it was determined that a comparable yield could be obtained with NEt_3 and acetic anhydride (method b).[18] The acetates **10a**,**b** were easily purified via passing the reaction mixture, following work up, through a short plug of silica gel, and both **10a** and **10b** are stable indefinitely under refrigeration.

Palladium-catalyzed cross-coupling reactions with vinyl acetates **10a** and **10b** were considerably more successful than those attempted for enol ether **9**.[19] Sonogashira cross-coupling of **10a** with terminal alkynes at room temperature required reaction times of ca. 24 h with a slight excess of the alkyne and $PdCl_2(PPh_3)_2$ as the catalyst (Scheme 4). Under these conditions, the triyne products **11a**−**c**, incorporating triisopropylsilyl, phenyl, and ferrocenyl actylenes, respectively, were generated and isolated in good yields by column chromatography on silica; all are stable.

Equally successful was the use of acetate **10a** in palladium-catalyzed Suzuki cross-coupling with boronic acids.[20] With use of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as the base, the diarylated vinyl acetates **12a**−**d** were produced in yields of 50−85% (Scheme 4). These reactions were complete in less than 24 h at 110 °C. It is noteworthy that both the vinyl acetate and triethylsilyl moieties tolerate these reaction conditions, as long as the reaction is kept strictly anhydrous. As for **11a**−**c**, the products **12a**−**d** were easily isolated by column chromatography.

Elaboration of acetate **10a** to heteroaryl-substituted vinyl acetates was possible through the use of Stille cross-coupling methods. The use of aryl trialkylstannane precursors can be advantageous due to their more facile synthesis in comparison to many boronic acids, which can be difficult to purify. Vinyl acetates **13a**−**c** were prepared with $Pd(PPh_3)_4$ as catalyst in DMF at 120 °C with reaction times of 2−4 h (Scheme 4). All products were isolated by column chromatography on silica gel as stable oils.

Scheme 4 [a]



[a] Reagents and conditions: (a) H−C≡C−R, $PdCl_2(PPh_3)_2$, CuI, NEt_3, rt; (b) $(HO)_2B$−Ar, $Pd(PPh_3)_4$, K_2CO_3, 110 °C; (c) DMF, $ArSnBu_3$, $Pd(PPh_3)_4$, 120 °C.

Direct conversion of triyne vinyl acetates **11a**−**c** to the corresponding ketones was attempted by employing a number of methods known to effect acetate removal, including reaction with KCN, MeLi, and $Mg(OMe)_2$.[21] Spectral evidence (^{1}H NMR and IR spectroscopies) suggested that the generation of the desired α,α-diethynylated ketones had been successful. All attempts toward isolation of pure material were unproductive, however, due to an inherent instability of the products, presumably the result of facile isomerization to the α-allenyl ketones.[22]

As a result, a direct conversion sequence from acetate to the desired triflates **14a**−**c** was explored (Scheme 5). It was anticipated that the enolate resulting from removal of the acetate moiety could be trapped in situ,[23] via reaction with an appropriate triflating reagent.[24] Several combinations of deprotection reagents (*t*-BuOK, MeLi) and triflate sources ($PhNTf_2$, Tf_2O) were employed, with varying levels of success. Ultimately, optimized conditions for this process were developed based on acetate removal with MeLi in THF at low temperature, followed by reaction with triflic anhydride, also at low temperature. Overall isolated yields over these two steps for **14a**−**c** were quite good, ranging from 60 to 81%. Contrasting the instability encountered with the corresponding ketones, vinyl triflates **14a**−**c** are stable and easily handled.

The ketones derived from **12a**−**d** and **13a**−**c** would be expected to be stable, potentially allowing for a stepwise

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(18) Cousineau, T. J.; Cook, S. L.; Secrist, J. A., III *Synth. Commun.* **1979**, *9*, 157−163.

(19) Palladium-catalyzed couplings were optimized with vinyl acetate **10a** because of the more facile removal of the triethylsilyl in comparison to the triisopropylsilyl moiety. Transformations conducted with derivative **10b** under analogous conditions have been equally successful.

(20) Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379−381.

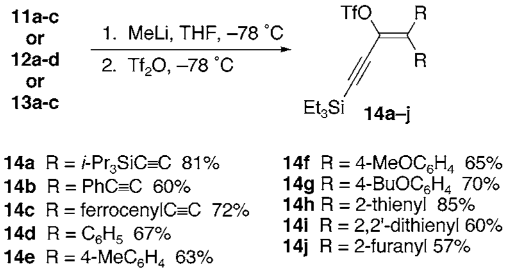
(21) (a) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790−791. (b) Xu, Y.-C.; Bizuneh, A.; Walker, C. *Tetrahedron Lett.* **1996**, *37*, 455−458.

(22) α-Ethynylated ketones are known to be stable, see: Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2002**, *4*, 2209−2211 and references therein.

(23) Duhamel, P.; Cahard, D.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2509−2511.

(24) (a) McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982. (b) Dunn, P. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1585−1592.

Scheme 5



sequence of acetate removal and subsequent triflate formation, as in Figure 1 (**4** → **5**). From a practical standpoint, however, a stepwise route was problematic, due to difficulties anticipated in the conversion of the ketone to the desired vinyl triflate. For example, standard protocol for the formation of **14d** ($R = C_6H_5$) directly from the ynone precursor requires reaction times on the order of 1 week and affords yields of ca. 50%.[9]

Thus, the facile, one-pot reaction sequence successful in the formation of **14a**−**c** was applied to diaryl precursors **12a**−**d** and heteroaryl compounds **13a**−**c**. Subjecting **12a**−**d** or **13a**−**c** to 2 equiv of MeLi at −78 °C effected enolate formation, and the subsequent addition of triflic anhydride provided vinyl triflates **14d**−**j**. Reaction times for these transformations are on the order of 30 min, and the products are readily isolated in good to excellent yields by column chromatography.

In conclusion, we have outlined general conditions for the synthesis of highly unsaturated, functionalized vinyl triflate building blocks. The compatibility of the dibromovinyl acetate **10a** with the Sonogashira, Stille, and Suzuki cross-coupling conditions allows for the rapid, divergent elaboration to a range of 2,2-diethynyl and -diaryl derivatives. These vinyl acetates, **11**−**13**, can then be directly converted to vinyl triflates **14**, in a one-pot sequence of acetate removal and triflation. The propensity of several of these novel vinyl triflate products to be elaborated into extended oligomeric systems such as **1** and **2** is being investigated and will be reported in due course.

Acknowledgment. Financial support for this work from The University of Alberta and the National Science and Research Council of Canada is gratefully acknowledged.

Supporting Information Available: Synthetic and characterization details; ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027267I