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Addition of Amines to the Triple Bond in α,α,α-Trichloromethylpropargyl Mesylate: Synthesis of α,α-Dichloromethylenaminones and Preparation of 2-Phenyl-4-dichloromethylquinolines

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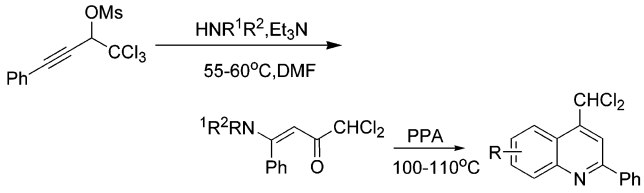

Addition of amines to the triple bond in α,α,α-trichloromethylpropargyl mesylate to give α,α-dichloromethylenaminones and its use in the preparation of 2-phenyl-4-dichloromethylquinolines in good yields are reported.

Enaminones are important synthetic intermediates, particularly in heterocyclic chemistry.[1] Heterocycles prepared from enaminones include carbazolequinone alkaloids,[2] prrroles,[3] pyrimidinones,[4] pyrazoles,[5] and quinolines.[6] The preparation of enaminones has been documented.[1] A common method for the synthesis of enaminones involves reaction between ammonia or a primary or secondary amine and a 1,3-diketone or 3-keto ester. Alternatively imine anion can be acylated at the β-carbon to give enaminones.[7] In an ongoing project in our laboratory on the alkynylation of C=O and C=N bonds,[8] an unexpected addition of amines to the triple bond in α,α,α-trichloromethylpropargyl mesylate to produce α,α-dichloromethylenaminones was discovered. We herein report the details about this reaction and its use in the preparation of 2-phenyl-4-dichloromethylquinolines. In addition, the efficient transformation of the trichloromethyl- or tribromomethylpropargylic alcohol into versatile building blocks of vinyl triflates was also described. The vinyl triflates are important in a vast array of palladium-catalyzed cross-coupling reactions for the development of functional molecular architecture.[9]

Alkynylation of chloral and bromal with phenylacetylene gave propargyl alcohol **1a** and **1b** in 95% and 83% yield, respectively, in the presence of $ZnCl_2$ and Et_3N according to our previously reported procedure.[10] Initially we envisioned that treatment of the trichloromethylpropargyl mesylate **2a** with benzylamine might lead to the transformation of the trichloromethylpropargyl mesylate into the corresponding propargylamine via the nucleophilic substitute of mesyl with an amine. However, when trichloromethylpropargyl mesylate **2a** was treated with benzylamine (1.1 equiv) in DMF in the presence of Et_3N (1.5 equiv) at 35 °C for 4 h, an unexpected addition product enaminone **3a** was isolated in 71% yield after workup (Scheme 1). Further experimental optimization showed that the yield of enaminone **3a** could be increased to 90% by treatment of trichloromethylpropargyl mesylate with benzylamine (1.5 equiv) in DMF in the presence of Et_3N (2.5 equiv) at 55−60 °C for 8 h.

Under the above normal conditions, a variety of primary, secondary, and aromatic amines added to the trichloromethylpropargyl mesylate **2a** giving the corresponding enaminones **3** in good to excellent yields (Scheme 2). The results revealed the electron-rich aromatic amines gave higher yields than the electron-deficient aromatic amines in the enaminone formation reaction. The structures of these compounds were supported by NMR spectroscopy, elemental analysis, and/or high-resolution mass spectrometry. A single-crystal X-ray analysis of enaminone **3d** showed that these compounds exist in the (*E*)-configuration (see the Supporting Information). To demonstrate the utility of these kinds of enaminones, treatment of the enaminones which derived from some aromatic amine and trichloromethylpropargyl mesylate with PPA at 100−110 °C gave the desired cyclization compounds 2-phenyl-4-dichloromethylquinolines **4** in excellent yields (Scheme 3).[11]

To understand the mechanism of the reaction, we conducted the reaction without the addition of the nucleophilic amine. Treatment of the trichloromethylpropargyl mesylate **2a** with 1.1 equiv of Et_3N in DMF at 30 °C for 2 h gave the hydrogen chloride elimination product **5a** isolated in quantitative yield (Scheme 4). Under other basic conditions, K_2CO_3/DMF, Py/CH_2Cl_2, the reaction gave a similar result. Treating the elimination product **5a** with benzylamine in DMF also gave the **3a** enaminone. Properglic alcohol **1** underwent mesylation and elimination to give the vinyl mesylate compound **5a** and **5b** in high yield in the presence of 1.2 equiv of MsCl and 2.5 equiv of Et_3N. Properglic alcohol **1b**

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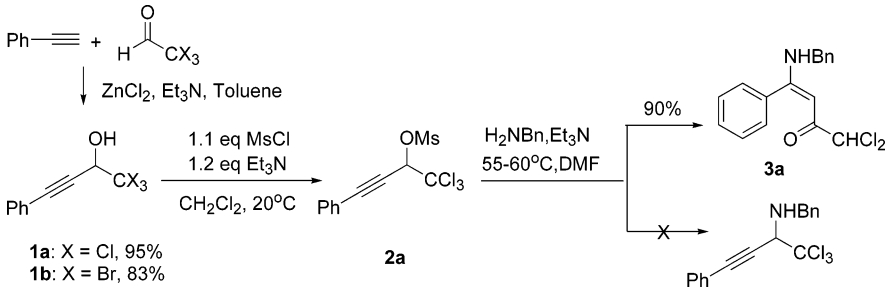
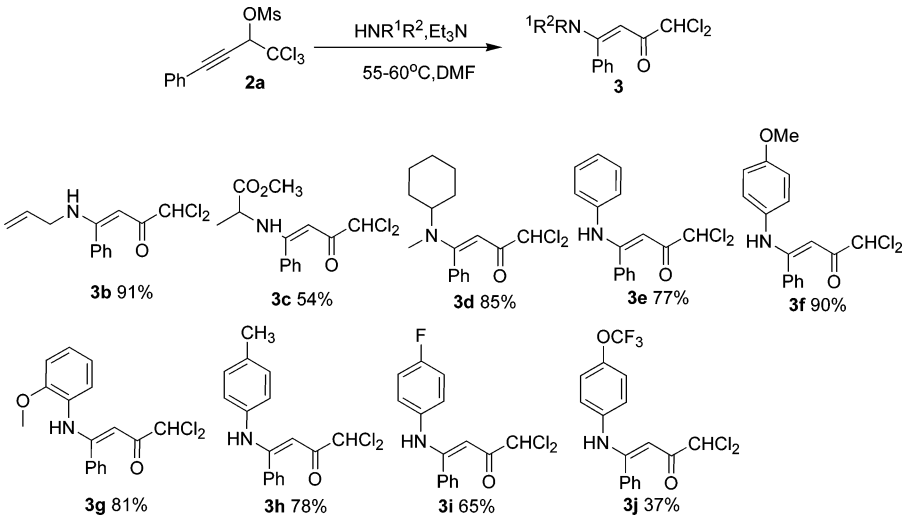
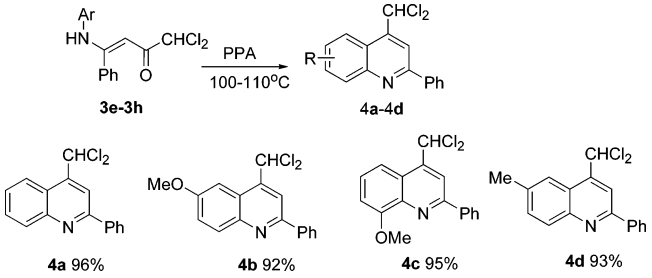
SCHEME 1. Formation of Enaminone 3a



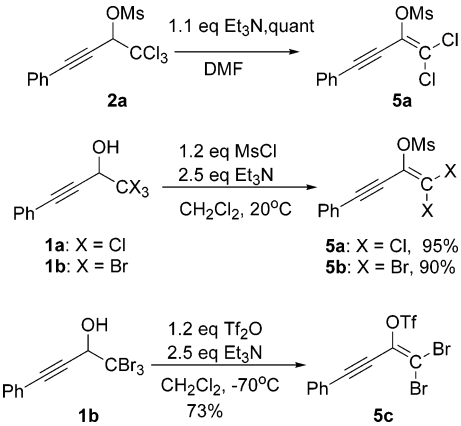
SCHEME 2. Synthesis of Enaminones 3



SCHEME 3. Synthesis of 2-Phenyl-4-dichloromethyl Quinolines 4



SCHEME 4. Formation of the Vinyl Mesylate and Triflate 5



underwent trifluoromesylation and elimination to give the vinyl triflate compound **5c** in high yield in the presence of 1.2 equiv of trifluoromethanesulfonic anhydride and 2.5 equiv of Et_3N at −70 °C. On the basis of these results, the reaction can be understood by the following postulated mechanism as shown in Scheme 5. At first, hydrogen chloride was eliminated from the trichloromethylpropargyl mesylate **2** to give the phenylethynylvinyl mesylate **5**. The amine then attacked the triple bond in **5** through 1,4-addition to form the allene. The mesyl group left from the allene to give the allenol anion. The allenol anion was protonated and followed by isomerization to give the enaminone **3**.

In summary, an unexpected addition reaction of amines to the triple bond in trichloromethylpropargyl mesylate to give α,α-dichloromethylenaminones and its use in the preparation of 2-phenyl-4-dichloromethylquinolines were reported. The intermediate phenylethynyldichlorovinyl mesylate or triflate **5** produced in the reaction also can serve as an important, highly unsaturated synthetic building block. Synthesis of such mesylates or triflates cannot be easily accomplished with previously described methodology.[12]

Experimental Section

General Procedure for the Preparation of Enaminones 3. To a solution of 1-trichloromethyl-3-phenyl-2-propyn-1-ol mesylate (1.63 g, 5 mmol) in DMF (10 mL) was added Et_3N (1.8 mL, 12.5 mmol). The amine (5.5 mmol) was added after the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was stirred at 55−60 °C for 10 h. After cooling

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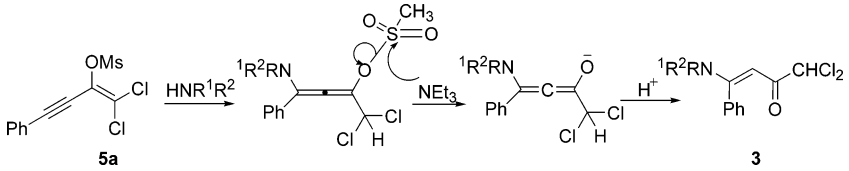
SCHEME 5. Proposed Mechanism for the Formation of Enaminone 3



to room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous. The mixture was extracted with EtOAc (2 × 40 mL). After removal of solvent, the crude product was purified by flash chromatography on silica gel (hexane: EtOAc = 15:1) to afford the enaminones **3**.

1,1-Dichloro-4-benzylamino-4-phenylbut-3-en-2-one (3a). FTIR (neat) 3197, 1604, 1586, 1570, 1487, 1339 cm^{-1}; ^1H NMR δ 11.12 (br s, 1H), 7.50−7.18 (m, 10H), 5.90 (s, 1H), 5.49 (s, 1H), 4.43 (d, J = 6.3 Hz, 2H); ^{13}C NMR δ 185.0, 169.7, 137.5, 134.4, 130.5, 129.1, 129.0, 128.0, 127.8, 127.2, 91.2, 70.8, 49.1; MS (EI) *m/e* 319 (M^+, 7.6), 284 (8.6), 248 (10.7), 236 (100), 91 (93.3). Anal. Calcd for $C_{17}H_{15}NCl_2O$: C, 63.95; H, 4.70; N, 4.38. Found: C, 64.12; H, 4.82; N, 4.28.

General Procedure for the Preparation of Quinolines 4. Enaminone (1 mmol) and 3 g of PPA were warmed to 110 °C for 4−8 h and then cooled to room temperature. The resulted mixture was poured into 10 mL of ice water and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. After removal of solvent, the crude product was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1) to afforded the quinolines **4**.

4-Dicholromethyl-2-phenylquinoline (4a). FTIR (KBr) 2970, 1599, 1350, 765 cm^{-1}; ^1H NMR δ 8.29−8.20 (m, 5H), 7.83 (m, 1H), 7.66 (m, 1H), 7.54 (m, 3H), 7.40 (s, 1H); ^{13}C NMR δ 156.1, 147.8, 142.7, 137.8, 129.7, 128.9, 128.7, 127.9, 126.4, 126.0, 121.6, 121.2, 115.4, 67.3; MS (EI) *m/e* 287 (M^+, 100), 252 (84.6), 217 (64.8), 189 (14.4), 108 (26.3). Anal. Calcd for $C_{16}H_{11}NCl_2$: C, 66.90; H, 3.83; N, 4.88. Found: C, 66.58; H, 3.86; N, 4.60.

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Supporting Information Available: Detailed experimental procedures, spectral characterization data for compounds **3**, **4**, and **5**, and X-ray analysis of compound **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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