Tetrahedron Letters 54 (2013) 5137–5139

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An unexpected one step domino conversion of TMS-alkynes to protected ketones in 4-chromenone system

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ARTICLE INFO

Article history:
Received 24 May 2013
Revised 11 July 2013
Accepted 12 July 2013
Available online 20 July 2013

Keywords:
Chromenone
Deprotection
Domino reaction
Ketal
Alkyne

ABSTRACT

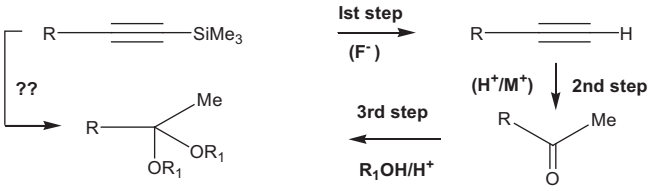
An unexpected metal-free high yielding one step domino procedure for TMS-deprotection and simultaneous conversion of resulting alkynes to protected carbonyls (ketals) in 4-chromenone systems is reported. A mechanistic rationale involving an allene intermediate is also proposed based on dynamic NMR and mass spectra.

Silyl-deprotection of TMS-acetylenes, subsequent hydration of resulting terminal alkynes and ketalization of the carbonyl are three simple but important transformations in synthetic organic chemistry. Although fluorides[1] are the usual reagents for silyl deprotection, the process may also be carried out under basic,[2] acidic conditions[3] or Ag(I) catalysis.[4] The hydration of alkynes[5] requires the use of toxic mercury(II) salts or expensive transition metal catalysts (Ru, Rh, Pt, Au etc.).[5] Other alternatives require the presence of acids[7] (H_2SO_4, HCOOH, TfOH or *p*-TsOH),[5] which may not be compatible in terms of selectivity in the case of functionalized substrates. Ketalization is done with alcohols under anhydrous acidic conditions (Scheme 1).

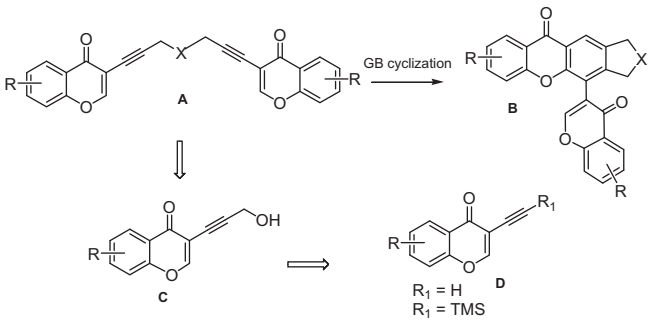
It will be of great importance if all the three steps can be combined to convert a TMS-acetylene to a ketal in a single step (domino reaction). In this Letter we report a single step conversion of 3-trimethylsilyl alkynyl 4-chromenones to fully protected 3-keto methyl 4-chromones in high yields. A mechanistic rationale is also proposed.

Our initial intention was to synthesize chromenonyl xanthones via GB cyclization[6] of bis chromonyl propargyl sulfones (Scheme 2). For that we required 3-ethynyl 4-chromenone[7] which are accessible from the corresponding trimethylsilyl ethynyl derivative. With this intention, the latter was prepared via Sonogashira[8] coupling of 3-iodo 4-chromenone derivative[9] with TMS-acetylene.

Attempted desilylation of **1a** with potassium fluoride (KF) in methanol, however, did not afford the expected alkyne as revealed by the absence of ethynyl hydrogen in the ^{1}H NMR spectrum (Fig. 1) of the crude reaction mixture. It also indicated the formation of predominantly one major (singlets at δ 8.3, 3.2 and 1.8)



Scheme 1. 3-Step protocol for the conversion of TMS-acetylene to ketals.



Scheme 2. Proposed synthesis of xanthones based on GB cyclization.

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http://dx.doi.org/10.1016/j.tetlet.2013.07.082

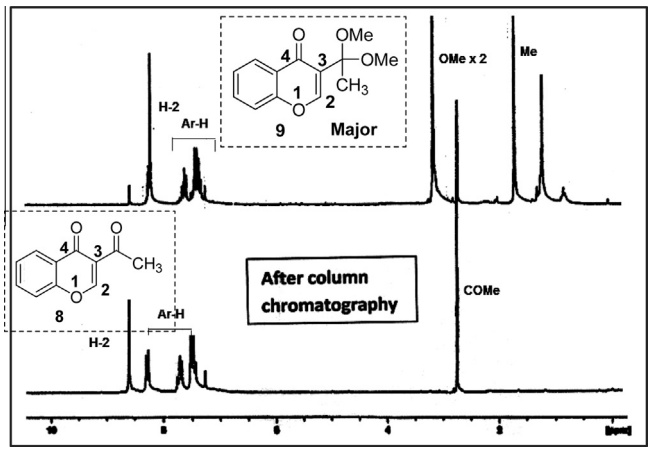
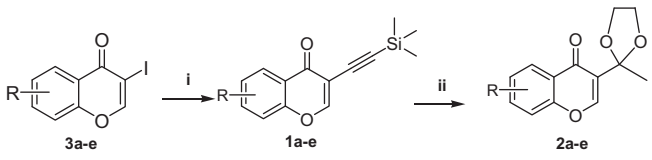


Figure 1. ^{1}H NMR of crude reaction and chromatographically isolated product.

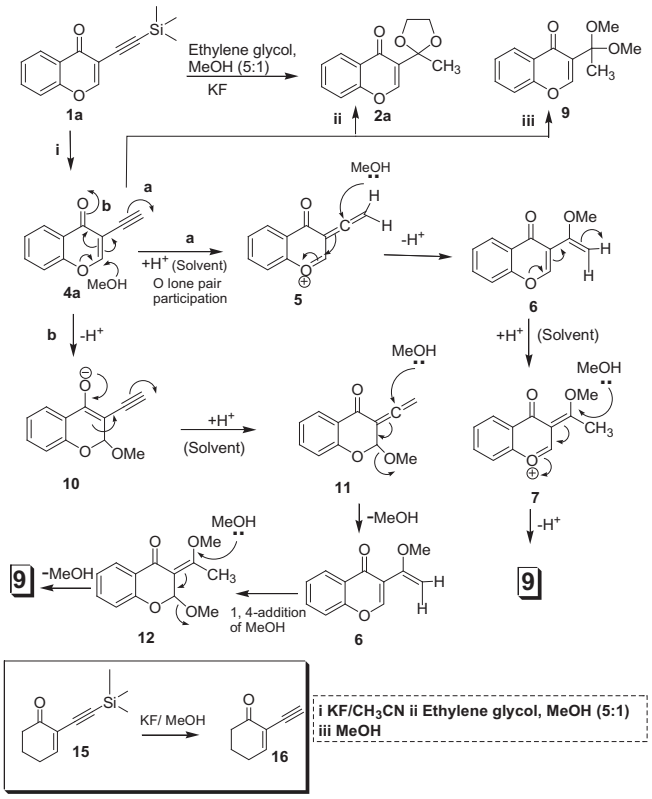
Table 1
Results of one step conversion of TMS-acetylene to cyclic ketals



i = $Pd(PPh_3)_2Cl_2$, CuI, TMS-acetylene; ii = KF, ethylene glycol-MeOH (5:1 mL), 45 °C, 16-18 h

Substrate	Product	Time (h)	Yield (%)
1a	2a	18	82
1b	2b	16	83
1c	2c	16	85
1d	2d	16	84
1e	2e	17	85

and a minor product (singlets at δ 8.6 and 2.7). Interestingly, upon chromatographic purification, the ^{1}H NMR resembled only that of the minor product, indicating complete conversion of the major product to the minor one during chromatography. The product isolated after chromatography was characterized as the methyl



Scheme 3. Proposed mechanism.

ketone **8**. The same product was obtained after chromatography when the reaction was done in ethanol or by replacing KF with CsF or TBAF. The reaction was then repeated with super dry methanol in the presence of dry CsF/KF. The chromatographic purification was done quickly and the NMR was taken in acid-free $CDCl_3$ which was now same as the crude and the product was characterized as dimethyl ketal **9**. Realizing the origin of the methyl ketone via hydrolysis of the unstable dimethyl ketal, we thought of preparing a more stable cyclic ketal. Thus, the reaction was carried out in a mixture of ethylene glycol and methanol[10] (5:1) in the presence of KF or CsF. The reaction now furnished a stable cyclic ketal **2a** in excellent yields.

The reaction was repeated with various substituted chromones and in all cases, excellent yields of ketals **2a–e** were obtained in a single step. The results are shown in Table 1. Interestingly, our original target acetylene could be obtained in high yields using KF in a non-protic solvent like CH_3CN (Scheme 3).

Two possible mechanisms (pathways **a** and **b**) have been proposed as shown in Scheme 3, both of which involved intermediacy of the free alkyne **4a**. This was supported by the conversion of free alkyne to the ketal when a solution of the alkyne in ethylene glycol-methanol (5:1) was stirred at rt for 14 h. To gain further insight, the ^{1}H NMR (Fig. 2) of a d_4-MeOH solution of alkyne **4a** was recorded at different time intervals which indicated initial formation of the enol ether (appearance of signals in the region of δ 7.1 for aryl-hydrogens and a singlet at δ 6.2 for the vinylic-H) for the proposed intermediate **6** or **11**. These signals slowly disappeared and the formation of a new product was indicated by a new set of signals in the aromatic region. ESI mass analysis indicated the presence of two compounds: a major nona-deuteriated ketal **13** and a minor trideuteriated methyl ketone **14** (Fig. 3). The latter was presumably formed by hydrolysis of the ketal. It also indicated the exchange of alkyne hydrogen with deuterium during the reaction.

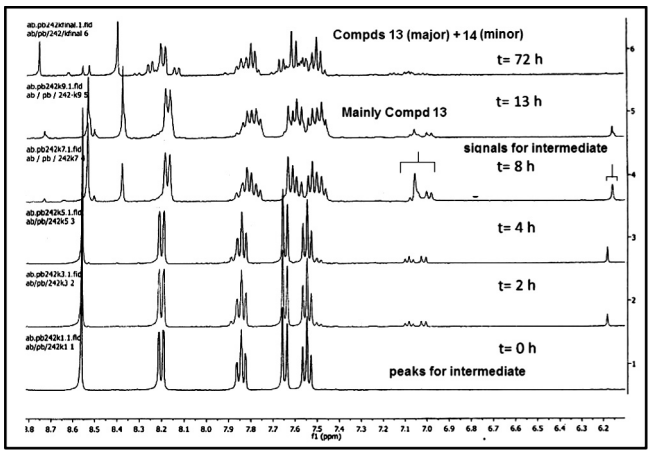


Figure 2. ^{1}H NMR of a d_4-MeOH solution of the alkyne taken at different time points.

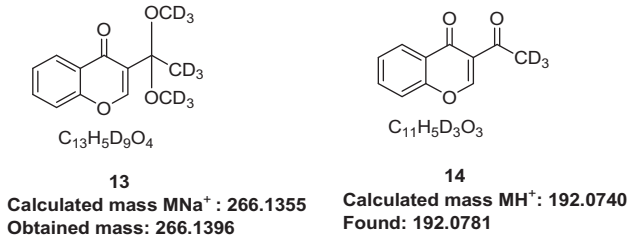


Figure 3. Structures of deuteriated products formed in d_4-MeOH.

Although it is difficult to distinguish between the two mechanisms, path **b** may appear to be more favoured in view of the reported facile 1, 4-addition in 4-chromenone systems.[11] The nucleophile in this case is probably the alcohol which is activated via the strong H-bond by the fluoride anion, a well known activator of the Michael reaction.[12] On the other hand, in a further experiment, it has been shown that the fluoride-mediated deprotection of 2-trimethylsilylethynyl 2-cyclehexenone **15** followed the expected route producing the corresponding 2-ethynylcyclohexenone **16** (Scheme 3). Thus, the participation of ring oxygen lone pair is necessary for this unexpected conversion. This result seems to favour the mechanism as depicted in path **a**.

In conclusion, we have developed an unexpected one-pot domino conversion of TMS-acetylene to ketal[13] in excellent yields in 4-chromenone systems. Currently we are exploring other heterocyclic systems for carrying out similar conversion to explore the generality of such conversions.

Acknowledgements

P.B. is grateful to CSIR, Government of India for a research fellowship (to PB). DST is thanked for providing funds for the project and for the JC Bose Fellowship awarded to AB.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.082.

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10. Controlled amount of methanol was added for solubility reasons.
11. Hydroxyl amine addition to 3-alkynyl 4-chromones leading to isoxazole derivatives via a similar allenic intermediate has been reported: Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **1876**, *2010*, 12.
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13. ***General procedure for one-step conversion of TMS-acetylene to ketal.***
To the solution of the TMS-acetylenes (0.12 mmol) in MeOH (3 mL) and ethylene glycol (15 mL), KF (11 mg) was added and stirred at 45 °C for 16–18 h. The progress of the reaction was monitored by TLC. The reaction was finally quenched with water. The organic layer was extracted with DCM (20 mL) and washed with brine. The mixture was concentrated in vacuo and the pure cyclic ketal was isolated by flash column chromatography of the crude residue over Si gel, using petroleum ether–ethyl acetate (ratio ranging from 7:1 to 3:1) as eluent.
All compounds were characterized by NMR (400 MHz for ^{1}H and 100 MHz for ^{13}C) and mass spectral analysis. Spectral data of some selected compounds are mentioned:
Compound ***2a***: State: solid; mp 85 °C; yield: 82%; δ_H 8.25 (1H, d, J = 8.0 Hz), 8.12 (1H, s), 7.67–7.63 (1H, m), 7.44–7.37 (2H, m), 4.10–4.06 (2H, m), 3.93–3.89 (2H, m), 1.84 (3H, s); δ_C 176.4, 156.4, 153.6, 133.7, 126.3, 125.3, 125.0, 124.4, 118.1, 106.9, 64.9, 25.1; Calculated for $C_{13}H_{12}O_4$+H$^+$ 233.0814 found 233.0851.
Compound ***2b***: State: solid; mp 87 °C; yield: 83%; δ_H 8.09 (1H, s), 8.02 (1H, br s), 7.46 (1H, dd, J = 8.5, 1.8 Hz), 7.33 (1H, d, J = 8.5 Hz), 4.09–4.06 (2H, m), 3.92–3.89 (2H, m), 2.44 (3H, s), 1.84 (3H, s); δ_C 176.4, 154.7, 153.5, 135.3, 135.0, 125.6, 124.7, 124.1, 117.9, 107.0, 64.9, 25.1, 21.1; Calculated for $C_{14}H_{14}O_4$+H$^+$ 247.0970 found 247.0960.
Compound ***2c***: State: solid; mp 86 °C; yield: 85%; δ_H 8.14 (1H, d, J = 8.9 Hz), 8.03 (1H, s), 6.95 (1H, dd, J = 8.9, 2.1 Hz), 6.80 (1H, d, J = 2.1 Hz), 4.08–4.05 (2H, m), 3.91–3.89 (5H, m), 1.82 (3H, s); δ_C 175.7, 164.2, 158.2, 153.1, 127.7, 124.2, 118.9, 114.6, 107.0, 100.2, 64.9, 56.0, 25.2; Calculated for $C_{14}H_{14}O_5$+H$^+$ 263.0919 found 263.0958.
Compound ***2d***: State: solid; mp 146 °C; yield: 84%; δ_H 8.16 (1H, d, J = 9.0 Hz), 8.03 (1H, s), 7.45–7.35 (5H, m), 7.04 (1H, dd, J = 9.0 Hz, 2.3 Hz), 6.88 (1H, d, J = 2.3 Hz), 4.08–4.05 (2H, m), 3.91–3.88 (2H, m), 1.83 (3H, s); δ_C 175.7, 163.2, 158.1, 153.2, 135.8, 128.9, 128.6, 127.8, 127.7, 124.2, 119.1, 115.1, 107.0, 101.4, 70.7, 64.9, 25.2; Calculated for $C_{20}H_{18}O_5$+H$^+$ 339.1232 found 339.1270.
Compound ***2e***: State: solid; mp 89 °C; yield: 85%; δ_H 8.48 (1H, dd, J = 8.0 Hz, 0.4 Hz), 8.32 (1H, s), 8.19 (1H, d, J = 8.6 Hz), 7.93 (1H, dd, J = 8.2 Hz, 1.0 Hz), 7.76 (1H, d, J = 8.6 Hz), 7.30–7.65 (2H, m), 4.13–4.09 (2H, m), 3.97–3.93 (2H, m), 1.89 (3H, s); δ_C 176.2, 153.9, 152.8, 136.0, 129.5, 128.3, 127.3, 125.7, 125.5, 124.1, 122.4, 121.4, 121.2, 107.0, 65.0, 25.1; Calculated for $C_{17}H_{14}O_4$+H$^+$ 283.0970 found 283.1009.