A Convenient Synthesis of Propargylic Dithioacetals

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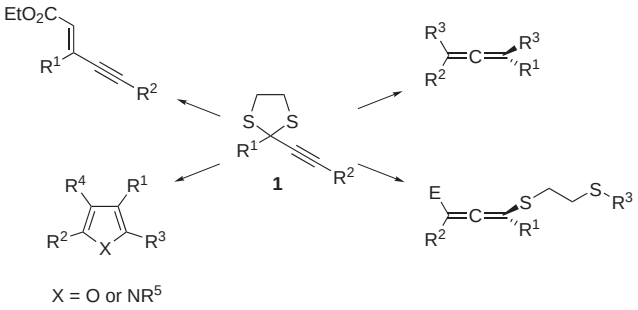
Dedicated to Professor Richard F. Heck in recognition of his outstanding contributions to modern organic synthesis

Abstract: Treatment of trimethylsilyl-substituted alkynyl ketones with 1,2-ethanedithiol in the presence of BF_3·OEt_2 in methanol afforded the corresponding dithioacetal. Removal of the silyl group under basic conditions followed by palladium-catalyzed coupling reactions with aryl iodides yielded the corresponding propargylic dithioacetals in excellent yield.

Key words: propargylic dithioacetals, alkynyl Grignard, cross-coupling reactions, desilylation

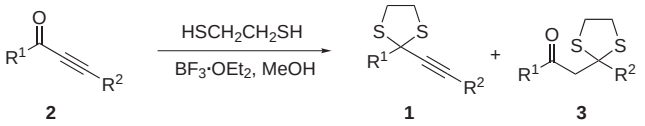
There has been an ever burgeoning interest in the use of propargylic systems in organic synthesis.[1,2] Depending on the nature of the substrates and reactions, a range of products with fascinating structures can be conveniently obtained. We recently reported that propargylic dithioacetals **1** are useful starting materials for the synthesis[2] of substituted allenes,[3] enynes,[4] pyrroles and tri- or tetrasubstituted furans[5,6] (Scheme 1). The reaction is particularly attractive for the regioregular synthesis of furan- or pyrrole-containing oligoaryls.[5] At the beginning of this research, the starting material **1** was prepared by the BF_3-catalyzed reaction of propargylic ketone **2** with 1,2-ethanedithiol in methanol.[7] However, a significant amount of the bis-Michael adduct **3** was also obtained as a side product in 12–48% yield (Equation 1). Tedious chromatographic separation is required to afford pure **1**.



Scheme 1 Synthetic applications of propargylic dithioacetals **1**

It is interesting to note that, when R^2 was a trimethylsilyl group, the reaction became regioselective, giving **1** (R^1 = Ph, R^2 = Me_3Si) exclusively in 95% isolated yield. Since the silyl moiety in alkynylsilanes can be easily removed to generate the corresponding terminal alkynes,[8] further coupling reactions[9] may provide a general procedure for the synthesis of **1** bearing different kinds of substituents R^2.

Palladium catalysts have been shown to be particularly useful for the alkynylation of various electrophiles.[10–12] We recently reported that palladium-catalyzed Kumada–Corriu cross-couplings of alkynyl Grignard reagents with alkyl iodides or bromides in the presence of triphenylphosphine.[12] It is envisaged that this protocol might be applicable to the synthesis of a variety of substituted propargylic dithioacetals **6** (Equation 2).



Equation 1 Dithioacetalization of propargyl ketone **2**

Treatment of **4** with 1,2-ethanedithiol in the presence of BF_3·OEt_2 in methanol followed by addition of aqueous NaOH and K_2CO_3 afforded **5** in good to excellent yields (Table 1). Alkyne **5** was allowed to react with MeMgI (2 M solution, Et_2O) at ambient temperature for 30 minutes to give the corresponding alkynyl Grignard reagent, which was then added dropwise to a THF solution of aryl iodide and a catalytic amount of $Pd_2(dba)_3$ (2.5 mol%) and Ph_3P (10 mol%). The mixture was refluxed for 10–12 hours followed by usual workup to yield **6** (Table 1).[13,14] Aryl iodides bearing different functional groups, such as methyl, methoxy, bromo, and methoxycarbonyl, afforded the corresponding dithioacetals **6** in excellent yield. Aryl bromides were, however, not suitable for these coupling reactions. It is interesting to note that the coupling reaction could also proceed at ambient temperature with similar results but a longer reaction time was necessary. As can be seen from Table 1, the substituent at C-2 of dithiolane can be aryl or alkyl groups. Sterically bulky substituents such as *tert*-butyl or adamantyl groups did not affect the yield of the coupling reactions.

A Sonogashira reaction can also be employed for the synthesis of **6** from **5**. Thus, treatment of **5** (R^1 = Ph) with PhI in the presence of 5 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% each of CuI and Ph_3P in DMF at 90 °C for 12 hours afforded **6** (R^1 = Ph) in 73% yield.

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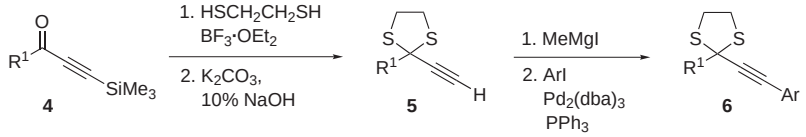


Equation 2 Two-step synthesis of substituted propargylic dithioacetal **6**

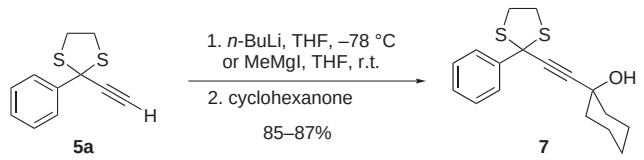
Table 1 Synthesis of Propargylic Dithioacetals from **4**

R^1	Yield of **5**	Ar	Yield of **6**[a]
Ph	**5a**, 97%	Ph	**6a**, 94% (90%)
		4-MeC_6H_4	**6b**, 91% (85%)
		4-$MeO_2CC_6H_4$	**6c**, 94% (88%)
		4-BrC_6H_4	**6d**, 91% (90%)
		4-$MeOC_6H_4$	**6e**, 92%
n-Pr	**5b**, 92%	Ph	**6f**, 96%
		4-$MeO_2CC_6H_4$	**6g**, 95%
		4-BrC_6H_4	**6h**, 89%
		4-$MeOC_6H_4$	**6i**, 95%
t-Bu	**5c**, 94%	4-$MeO_2CC_6H_4$	**6j**, 87%
		4-BrC_6H_4	**6k**, 90%
1-Ad	**5d**, 64%	4-$MeO_2CC_6H_4$	**6l**, 85%
		4-BrC_6H_4	**6m**, 83%
c-Hex	**5e**, 98	4-$MeO_2CC_6H_4$	**6n**, 93%

[a] The yields in parentheses are for reactions carried out at r.t. for 15 h.

Attempts to couple alkyl iodides with the Grignard reagent prepared from **5** under various conditions were unsuccessful. Under mild conditions (e.g. refluxing THF), starting **5** was recovered. On the other hand, when more drastic conditions were employed (e.g in refluxing toluene or dioxane), decomposition of **5** occurred. Presumably, the alkyl iodide was too unreactive under mild conditions, whereas the propargylic dithioacetal moiety was too labile under more vigorous conditions.

Organolithium or Grignard reagents obtained from **5** can react with carbonyl compounds to give the corresponding propargylic alcohols in good yield (Equation 3).



Equation 3 Reaction of **5a** with a carbonyl compound

In summary, we have demonstrated a convenient synthesis of propargylic dithioacetals by coupling reactions. Although the procedure requires extra steps, tedious chromatographic separation from by product(s) can be avoided. This protocol provides a large-scale synthesis of a range of useful starting propargylic dithioacetals for synthetic applications.[2–6]

Acknowledgment

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(13) **Synthesis of 5; General Procedure:** To a solution of **4** (50 mmol) in MeOH (100 mL) cooled to – 78 °C were added $BF_3{\cdot}OEt_2$ (60 mmol) and 1,2-ethanedithiol (51 mmol). The mixture was gradually warmed to r.t. and stirred for 12 h. After quenching with a 10% aq solution of NaOH, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with a 10% aq solution of NaOH, brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude propargylic dithioacetal which was dissolved in MeOH (100 mL). To this methanolic solution was added K_2CO_3 (200 mmol) and a 10% aq solution of NaOH (25 mL).[14] The mixture was stirred at r.t. overnight and then quenched with dilute HCl. CH_2Cl_2 was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane–EtOAc, 20:1) to give **5**.

Synthesis of 6; General Procedure A solution of $Pd_2(dba)_3$ (2.5–5.0 mol%) in THF (15 mL), PPh_3 (10–20 mol%), and aryl iodide (1.0 mmol) were heated at 65–70 °C under an Ar atmosphere; a solution of the Grignard reagent (1.0 mmol) in THF (15 mL) was added dropwise [prepared from the corresponding **5** (1 equiv) and MeMgI (2.0 M, Et_2O; 1.1 equiv)]. The mixture was refluxed for 10–12 h. After cooling to r.t., the mixture was quenched with a sat. solution of NH_4Cl. Et_2O was added and the organic layer was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated in vacuo, and the residue was chromatographed on silica gel (hexane–EtOAc, 20–30:1) to give **6**.

6b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.36 (s, 3 H), 3.65–3.90 (m, 4 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.30–7.45 (m, 5 H), 8.02 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 41.3, 62.4, 87.1, 90.3, 119.6, 127.7, 128.2, 128.3, 129.0, 131.5, 138.5, 138.8. **6c**: Mp 107–109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65–3.90 (m, 4 H), 3.93 (s, 3 H), 7.30–7.42 (m, 3 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.95–8.10 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 41.4, 52.2, 62.0, 86.0, 94.1, 127.4, 128.3, 128.5, 129.4, 129.6, 131.5, 138.3, 166.5. **6d**: Mp 56–58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.65–3.90 (m, 4 H), 7.30–7.55 (m, 7 H), 7.90–8.10 (m, 2 H). ^{13}C ($CDCl_3$, 100 MHz): δ = 41.4, 62.1, 85.7, 92.3, 121.7, 122.7, 127.6, 128.3, 128.4, 131.5, 133.1, 138.5. **6e**: Mp 66–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65–3.80 (m, 4 H), 3.82 (s, 3 H), 6.86 (d, *J* = 7.3 Hz, 2 H), 7.28–7.50 (m, 5 H), 8.02 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 41.3, 55.3, 62.4, 86.8, 89.6, 113.8, 114.8, 127.6, 128.2, 128.3, 133.1, 139.0, 159.7. **6f**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (t, *J* = 7.3 Hz, 3 H), 1.70–1.90 (m, 2 H), 2.15–2.35 (m, 2 H), 3.38–3.70 (m, 4 H), 7.28–7.55 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.0, 39.7, 46.0, 60.0, 84.1, 91.8, 122.8, 128.1, 131.5. **6g**: Mp 68–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03 (t, *J* = 7.3 Hz, 3 H), 1.70–1.86 (m, 2 H), 2.15–2.30 (m, 2 H), 3.44–3.70 (m, 4 H), 3.91 (s, 3 H), 7.47 (d, *J* = 6.7 Hz, 2 H), 7.96 (d, *J* = 6.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.0, 39.8, 45.8, 52.2, 59.8, 83.3, 95.0, 127.6, 129.3, 129.4, 131.5, 166.5. **6h**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (t, *J* = 7.3 Hz, 3 H), 1.60–1.82 (m, 2 H), 2.10–2.26 (m, 2 H), 3.35–3.66 (m, 4 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.43 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.0, 39.8, 46.0, 59.9, 83.0, 93.1, 121.8, 122.4, 131.4, 133.1. **6i**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (t, *J* = 7.3 Hz, 3 H), 1.68–1.85 (m, 2 H), 2.15–2.25 (m, 2 H), 3.48–3.65 (m, 4 H), 3.80 (s, 3 H), 6.81 (d, *J* = 7.3 Hz, 2 H), 7.34 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.0, 39.7, 46.3, 55.2, 60.3, 84.0, 90.4, 113.7, 114.9, 133.0, 159.5. **6j**: Mp 93–94 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.33 (s, 9 H), 3.45–3.65 (m, 4 H), 3.91 (s, 3 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.6, 40.2, 40.4, 52.2, 71.6, 83.9, 95.8, 128.0, 129.2, 129.3, 131.4, 166.6. **6k**: Mp 52–54 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.31 (s, 9 H), 3.35–3.48 (m, 2 H), 3.50–3.62 (m, 2 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.6, 40.3, 40.4, 71.6, 83.5, 93.9, 122.1, 122.2, 131.4, 132.9. **6l**: Mp 160–161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.60–1.80 (m, 6 H), 1.99 (br s, 6 H), 2.08 (br s, 3 H), 3.26–3.40 (m, 2 H), 3.45–3.60 (m, 2 H), 3.91 (s, 3 H), 7.48 (d, *J* = 8.3 Hz, 2 H), 7.96 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.7, 36.6, 39.1, 39.8, 41.1, 52.2, 72.1, 84.5, 95.2, 128.1, 129.2, 129.3, 131.5, 166.6. **6m**: Mp 66–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.60–1.80 (m, 6 H), 1.90–2.04 (m, 6 H), 2.06 (br s, 3 H), 3.30–3.42 (m, 2 H), 3.45–3.60 (m, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 37.4, 39.8, 40.5, 41.9, 72.7, 73.9, 84.5, 93.6, 122.2, 122.4, 131.4, 133.0. **6n**: Mp 97–98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40–1.58 (m, 5 H), 1.65–2.20 (m, 6 H), 3.40–3.64 (m, 4 H), 3.91 (s, 3 H), 7.47 (d, *J* = 7.1 Hz, 2 H), 7.96 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.8, 26.2, 31.7, 39.3, 50.0, 52.2, 66.1, 84.3, 94.3, 127.8, 129.3, 131.5, 166.5.

Sonogashira Reaction of 5a A solution of **5a** (206 mg, 1 mmol) in DMF (20 mL), iodobenzene (0.11 mL, 1 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%), Ph_3P (26 mg, 10 mol%), CuI (19 mg, 10 mol%), and Et_3N (0.42 mL, 3 mmol) was stirred under an Ar atmosphere at 90 °C for 12 h. After cooling to r.t., the mixture was filtered (silica gel–celite,1:1) and the solvent was removed in vacuo to give the residue which was chromatographed on silica gel (hexane–EtOAc, 3:1) to give **6a** as a white solid (205 mg, 73%).

1-[(2-Phenyl-1,3-dithiolan-2-yl)ethynyl]cyclohexanol (7) *n*-BuLi (2.5 M, hexane; 0.84 mL, 2.2 mmol) was added dropwise to a solution of **5a** (412 mg, 2 mmol) in THF (30 mL) at –78 °C, and the resulting mixture was stirred for 30 min. Cyclohexanone (0.20 mL, 2 mmol) was then added, the dry-ice bath was removed, and the mixture was stirred at r.t. for 2 h. The reaction was quenched with a sat. solution of NH_4Cl, Et_2O was added, and the organic layer was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane–EtOAc, 3:1) to give **7** as a white powder (527 mg, 87%); mp 72–74 °C. IR (KBr): 3403 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15–1.34 (m, 2 H), 1.48–1.65 (m, 4 H), 1.68–1.80 (m, 4 H), 1.97 (br s, 1 H), 3.62–3.80 (m, 4 H), 7.28–7.40 (m, 3 H), 7.94 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9, 25.6, 40.4, 41.6, 62.1, 69.3, 86.8, 90.9, 127.7, 128.4, 128.5, 138..8

(14) The reaction can also be carried out without NaOH, however, a higher reaction temperature (40–45 °C) was required.