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A new synthesis of 2-substituted-1,3-dithianes from trichloromethyl compounds

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Abstract—Trichloromethyl compounds are efficiently converted into 1,3-dithianes upon reaction with a disodium 1,3-propanedithiolate-1,3-propanedithiol mixture in DMF solution at 0 °C. This synthesis is limited to those substrates where the substituent attached to the trichloromethyl group is an electron-withdrawing group.

The generation of 1,3-dithianes is an important process in modern synthetic organic chemistry.[1] Among the most important characteristics of these compounds, is their stability under both acidic and basic conditions[2] and their potential utility in organic synthesis as acyl carbanion equivalents in carbon–carbon bond forming reactions.[3,4] In general, 1,3-dithianes are prepared by Brönsted or Lewis acid catalyzed condensation of aliphatic or aromatic aldehydes with 1,3-propanedithiol using for example, PTSA,[5a] BF_3–OEt_2,[5b] $ZnCl_2$,[5c] $ZrCl_4$–SiO_2,[5d] $LiBF_4$,[5e] $InCl_3$,[5f] NBS,[5g] I_2,[5h] $Y(OTf)_3$[5i] or $RuCl_3$.[5j] Recently, Ricci[6] reported a facile synthesis of chiral oxazolidine-1,3-dithianes and their use as ligands for asymmetric catalysis. Although some of these syntheses are carried out under mild conditions, all of them necessarily require the use of aldehydes. Interestingly, although a great variety of methods are known for the preparation of 2-acyl-1,3-dithianes, the most important, is the direct acylation of 2-lithio-1,3-dithiane derivatives with nitriles or alkyl chloroformates.[7a–c] Additionally, Rozen reported that 2-ethoxycarbonyl-1,3-dithianes reacted with BrF_3 to form the corresponding α,α-difluoro derivatives,[7d] and Takeda developed the preparation of alkylcyclopropanes by the reaction of terminal olefins with the alkylcarbene complexes generated by the desulfurization of 2-alkynyl-1,3-ditianes.[7e] In the context of developing a synthetic utility of trichloromethyl compounds, we have reported that a variety of this substrates bearing electron-withdrawing groups react with sodium thiophenolate[8a] or sodium thiolacetate[8b] in the presence of the thiol to give the corresponding phenylthiomethyl or thiolacetylmethyl derivatives. Given that in at least one instance,[8c] a bisphenylthiomethyl species was an intermediate in the formation of the phenylthiomethyl compound, it was reasonable to expect that 1,3-dithianes should be obtainable from trichloromethyl compounds and 1,3-propanedithiol under appropriate conditions.

The initial experiments were carried out using the trichloroacetylpyrrole[9] **1a** (Scheme 1). As expected, the reaction of **1a** with 6 equiv of 1,3-propanedithiol and 4 equiv of sodium hydride in anhydrous THF at room temperature did indeed give the 1,3-dithiane **2a**, but only in a 24% yield. The major product isolated (64%) was the 3-mercaptopropylthiomethyl compound **3a**. Additionally, disulfide **5** was also obtained.

It was thought that the reductive cleavage of **2a** (Scheme 2) might be a function of temperature and therefore low temperature conditions were studied.

The reaction of **1a** with 5 equiv of 1,3-propanedithiol and 3 equiv of sodium hydride in anhydrous THF at

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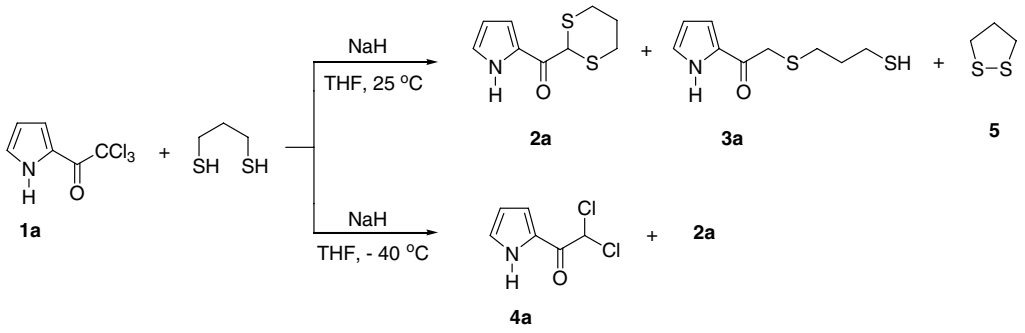
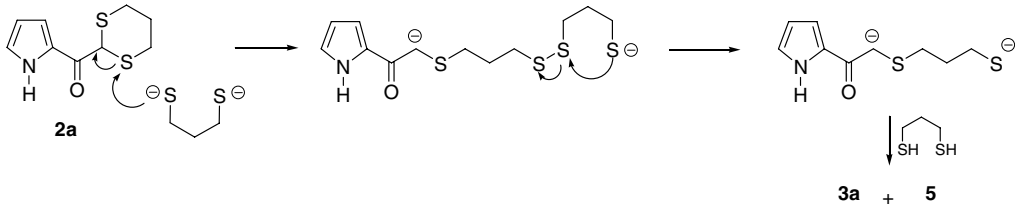


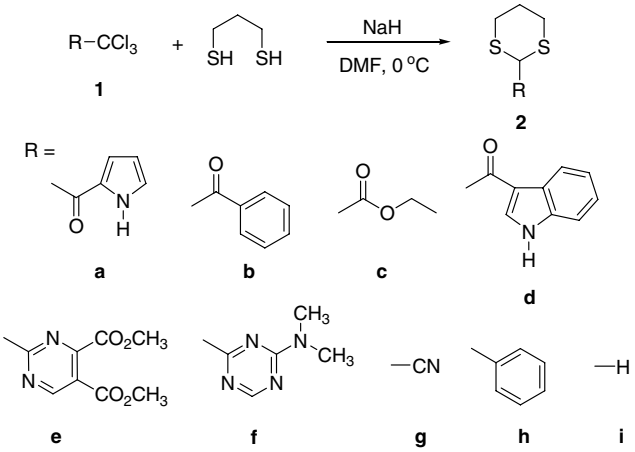
Scheme 1. Reductive reaction of **1a**.



Scheme 2. Reductive cleavage of **2a**.

−40 °C rapidly produced (20 min) dichloromethylpyrrole **4a** as the major product (71%) and only traces of 1,3-dithiane **2a**. After considerable experimentation it was found that reaction of **1a** with 5 equiv of 1,3-propanodithiol and 8 equiv of sodium hydride in DMF solution at −5 °C reproducibly gave **2a** as the major product[10] (Table 1, entry 1). Under these optimized conditions trichloromethyl compounds **1b–f** were also rapidly and efficiently converted into the corresponding 1,3-dithianes **2b–f** (Table 1). Several aspects of the data given in Table 1 deserve comment. Firstly, this method is operationally simple. Secondly, although the reaction is very useful for the preparation of the 1,3-dithianes from trichloromethyl compounds, it is limited to those

Table 1. Formation of 1,3-dithianes **2** from trichloromethyl compounds **1**



Entry	Substrate	Time (min)	Product	Yield[a] (%)	Mp (°C)
1	**1a**	20	**2a**	92	132–133
2	**1b**	30	**2b**	82	87–88
3	**1c**	15	**2c**	85	Oil
4	**1d**	15	**2d**	92	150–152
5	**1e**	25	**2e**	88	Oil
6	**1f**	15	**2f**	90	113–114
7	**1g**	5	**2g**	[b]	Oil
8	**1h**		No reaction		
9	**1i**		No reaction		

[a] Yields refer to pure isolated products, properly characterized by spectral data.
[b] Difficulties were encountered to obtain the product in a pure form.

cases where the substituent attached to the trichloromethyl group is a carbonyl moiety (entries **a**–**d**) or an electron-withdrawing heterocyclic system (e.g., entries **e** and **f**). However, with trichloroacetonitrile (entry **g**), the reaction was very fast even at low temperatures and difficulties were encountered to obtain the product in a pure form. The reaction fails to occur with compounds such as trichlorotoluene (entry **h**) and chloroform (entry **i**), where such activation is absent. Lastly, this method may offer a strategically similar but tactically complementary alternative for the preparation of 1,3-dithianes bearing an electron-withdrawing group at C-2 without the use of aldehydes.

In summary, we have demonstrated that trichloromethyl compounds, bearing a highly carbanion stabilizing substituent, are efficiently converted into the corresponding 1,3-dithiane derivatives using a disodium 1,3-propanedithiolate-1,3-propanedithiol mixture in DMF solution at 0 °C. This process is expected to be particularly useful in those instances where the heteroaryl or the α-carbonyl aldehydes, the usual precursors of these 1,3-dithiane derivatives, are not readily available.

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9. 2-Trichloroacetylpyrole **1a**, ethyl trichloroacetate **1c**, trichloroacetonitrile **1g**, trichlorotoluene **1h**, 1,3-propanedithiol and sodium hydride were purchased from Aldrich and used as received. Compounds **1b**, **1d**–**f** were synthesized by literature methods.[8]
10. *Typical procedure*: To a stirred suspension of sodium hydride (50% suspension in mineral oil) (384 mg, 8 mmol) in anhydrous DMF (25 mL) under argon, was added 1,3-propanedithiol (541 mg, 0.5 mL, 5 mmol) in DMF (5 mL) at room temperature. After 10 min, the reaction mixture was cooled to 0 °C and 2-trichloroacetylpyrrole **1a** (212 mg, 1 mmol) in DMF (5 mL) was added dropwise. The reaction was stirred under argon for 20 min at 0 °C and monitored by TLC (hexane:AcOEt, 80:20). The reaction was quenched with satd aq ammonium chloride solution, the product was extracted with AcOEt (3×50 mL), the organic layer was dried over Na_2SO_4. Following solvent removal in vacuo, the product was purified by silica gel column chromatography (hexane–AcOEt, 85:15) to afford pure 2-(2′-pyrroloyl)-1,3-dithiane **2a** 187 mg (88%) as a solid, mp 132–133 °C (hexanes–dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05–2.19 (m, 2H), 2.71 (dt, 2H), 3.46 (dt, 2H), 4.86 (s, 1H), 6.30 (m, 1H), 6.92 (m, 1H), 7.08 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ: 184.11, 128.69, 125.91, 116.96, 111.10, 42.75, 29.70, 27.05, 25.25. EIMS *m*/*z* 213 (M^+, 45), 119 (100). Compound **2b** was purified by silica gel chromatography using hexane–AcOEt 97:3, it was obtained as a solid, mp 87–88 °C (hexanes–dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.96–2.20 (m, 2H), 2.62–2.83 (m, 2H), 3.37 (td, 2H), 5.16 (s, 1H), 7.42–7.61 (m, 3H), 7.92–7.97 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ: 192.6, 134.5, 133.3, 128.6, 42.4, 26.3, 25.0. EIMS *m*/*z* 224 (M^+, 20), 119 (100). Compound **2c** was purified by silica gel chromatography using hexane–AcOEt 95:5, it was obtained as an oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H), 1.96–2.20 (m, 2H), 2.60 (m, 2H), 3.41 (m, 2H), 4.17 (s, 1H), 4.24 (c, 2H). ^{13}C (75 MHz, $CDCl_3$) δ: 169.8 (C), 61.6, 40.0, 25.9, 25.0, 14.0. EIMS *m*/*z* 192 (M^+, 65), 119 (100). Compound **2d** was purified by silica gel chromatography using hexane–AcOEt 70:30, it was obtained as a solid, mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.11 (m, 2H), 2.73 (m, 2H), 3.38 (m, 2H), 5.01 (s, 1H), 7.28–7.32 (m, 2H), 7.40–7.43 (m, 1H), 7.99 (d, 1H), 8.36–8.39 (m, 1H), 8.73 (br, 1H). ^{13}C (75 MHz, $CDCl_3$) δ: 191.2, 136.2, 131.7, 126.0, 123.9, 122.9, 122.5, 114.7, 111.4. 46.66, 29.39, 27.82, 25.48. EIMS *m*/*z* 263 (M^+, 12), 144 (100). Compound **2e** was

purified by silica gel chromatography using hexane–AcOEt 85:15, it was obtained as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.12–2.20 (q, $J = 5.58$ Hz, 2H), 2.73–2.84 (m, 2H), 3.58–3.66 (m, 2H), 3.95 (s, 3H), 4.01 (s, 1H), 5.30 (s,1H), 9.18 (s, 1H). ^{13}C (75 MHz, $CDCl_3$) δ: 171.6, 171.5, 165.3, 163.5, 159.5, 118, 53.3, 52.98, 43.23, 28.9, 28.1, 26.2. EIMS m/z 314 (M^+, 5), 210 (100). Compound **2f** was purified by silica gel chromatography using hexane–AcOEt 95:5; it was obtained as a solid, mp 113–114 °C (hexanes–dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 211–217 (m, 2H), 2.81–2.90 (m, 2H), 3.20 (s, 3H), 3.23 (s, 3H), 3.28–3.33 (m, 2H), 4.89 (s, 1H), 8.52 (s, 1H), ^{13}C (75 MHz, $CDCl_3$) δ: 175.1 (C), 165.87 (CH), 164.2 (C), 49.3 (CH), 36.4 (CH_2), 36.3 (CH_2), 28.7 (CH_3), 25.4 (CH_2). EIMS m/z 242 (M^+, 12), 209 (100).