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Copper(II) tetrafluoroborate as an extremely efficient catalyst for 1,3-dithiolane/dithiane formation from carbonyl compounds under solvent-free conditions at room temperature

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Dedicated to the memory of Professor Usha Ranjan Ghatak

Abstract—Copper(II) tetrafluoroborate hydrate is a new and extremely efficient catalyst for 1,3-dithiolane/dithiane formation from aromatic, heteroaromatic and aliphatic aldehydes and cyclic saturated ketones in 1–5 min under solvent-free conditions at room temperature. The reaction is compatible with other functionalities such as ether, ester, hydroxyl, halide, nitro and cyano groups and exhibits excellent chemoselectivity. α,β-Unsaturated aldehydes/ketones lead to selective formation of 1,3-dithiolanes instead of Michael addition products. For substrates bearing an aldehyde and a ketone carbonyl group, chemoselective dithiolane formation takes place with the aldehyde.

The formation of 1,3-dithiolanes is a versatile organic transformation as it (i) provides a means to protect carbonyl groups,[1] (ii) serves to generate umpoled carbonyls,[2] (iii) constitutes a key step for deoxygenation of carbonyl groups leading to the corresponding methylene derivatives,[3] and (iv) gives entry to titanium-alkylidene chemistry for carbonyl olefination.[4] 1,3-Dithiolane formation also gains importance due to the versatile biological activity of compounds containing this moiety. For example, 1,3-dithiolane-containing compounds have been reported to have in vitro and in vivo leishmanicidal activity at different concentrations against promastigotes and amastogotes of *L. donovani*.[5] Nucleosides bearing the 1,3-dithiolane moiety possess anti-HIV activity[6] and dithiolane analogs of lignans inhibit interferon-gamma and lipopolysaccharide-induced nitric oxide production in macrophages.[7] Other significant biological activities of 1,3-dithiolane-containing compounds include anticonvulsant,[8] radioprotective,[8,9] anti-tumor,[10] radical scavenging and hepatoprotective[11] activities. 1,3-Dithiolane derivatives are used for the synthesis of new antibacterial penem compounds.[12] Dithiolanes also find application as process stabilisers for polyolefins.[13] These factors have generated significant interest amongst organic and medicinal chemists for the synthesis of 1,3-dithiolanes.

Dithiolane formation is generally carried out by the condensation of a carbonyl compound with 1,2-ethanedithiol in the presence of various Lewis acid catalysts.[1] Recent endeavors towards the development of newer methods for conversion of carbonyl compounds to 1,3-dithiolanes have witnessed the use of halides, perchlorate, nitrates, acetylacetonate, tetrafluoroborate and triflates derived from alkali, transition and lanthanide metals,[1,14] clays[1] and supported reagents.[1,15] However, many of these methods have drawbacks such as moderate yields, long reaction times, harsh reaction conditions, tedious work-up, use of expensive reagents, use of solvents and toxic agents, special efforts required to prepare the catalyst, the requirement for special apparatus, etc. Thus, the development of more efficient methods is still in demand.

Recently, we reported that $Cu(BF_4)_2{\cdot}xH_2O$ induces 'electrophilic activation' for heteroatom acylation,[16]

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1,1-diacetate formation,[17] and thia Michael addition reactions.[18] We disclose herein our finding on the catalytic effect of $Cu(BF_4)_2{\cdot}xH_2O$ for 1,3-dithiolane formation from carbonyl compounds. To determine the optimum reaction conditions, benzaldehyde (2.5 mmol) was taken as the model substrate and was treated with 1,2-ethanedithiol in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ at rt varying the amount of the catalyst and thiol used and the reaction time. On each occasion, the progress of the reaction was monitored by TLC and GC–MS. The reaction was best carried out when a mixture of benzaldehyde, 1,2-ethanedithiol (1.2 equiv) and $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) was stirred magnetically at 25 °C for 1 min. 2-Phenyl-1,3-dithiolane was exothermically produced and isolated in 99% yield.

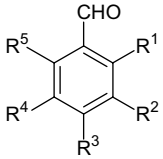
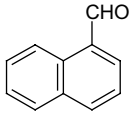
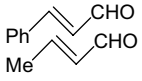
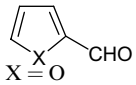
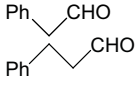
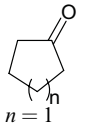
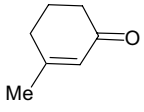
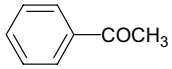
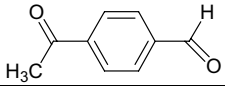
The generality of the $Cu(BF_4)_2{\cdot}xH_2O$ catalysed 1,3-dithiolane formation was established by subjecting various carbonyl compounds to reaction with 1,3-propanedithiol under similar conditions (Table 1). Aliphatic, aromatic and heteroaromatic aldehydes were efficiently and rapidly converted to the corresponding 1,3-dithiolanes in excellent yields in short times. Dithiolane formation was not affected by the presence of other functionalities such as, ether, ester, hydroxyl, halide, nitro and cyano groups (entries 3–15) that could be expected to compete with the carbonyl group for complex formation with the catalyst. The acid sensitive substrate furfural[19] (entry 19) provided the corresponding 1,3-dithiolane in excellent yield. Cyclic saturated and unsaturated ketones afforded the desired products in good to excellent yields (entries 24–27). Chemoselective dithiolane formation took place with α,β-unsaturated aldehydes (entries 17 and 18) and no competitive Michael addition was observed (GC–MS).[18] Surprisingly, the conversion of crotonaldehyde (entry 18) to the desired dithiolane could not be increased beyond 65% even after repeated attempts and the unreacted starting material remained unchanged (GC–MS) on each occasion. The desired dithiolane was obtained in 60% yield after subjecting the crude reaction mixture to chromatographic purification.

The GC–MS of the product isolated from the reaction of 3-methyl-2-cyclohexenone revealed the formation of the corresponding dithiolane in 80% yield along with a 12% yield of the dithiolane of the Michael adduct. The desired dithiolane was obtained in 66% yield after purification by column chromatography (entry 27). Sterically hindered 2,4,6-trimethoxy benzaldehyde (entry 8) provided an excellent yield of the dithiolane. The rate of the reaction was found to be very fast and in most cases, dithiolane formation was complete after 1–5 min (TLC, GC–MS) with excellent yields. An exothermic reaction (except for entry 12) took place after addition of $Cu(BF_4)_2{\cdot}xH_2O$ to the mixture of the substrate and 1,2-ethanedithiol, which indicated completion of the reaction. The rate of dithiolane formation was influenced by the electronic and steric factors of the carbonyl substrates. Substrates with electron withdrawing groups such as F, OCOPh, CF_3 and CN (entries 11, 12, 14 and 15; Table 1) required longer times. The longer time (30 min) needed for the reaction of 1-naphthaldehyde compared to that of benzaldehyde (1 min) was due to the steric hindrance offered by the *peri* hydrogen in 1-naphthaldehyde towards nucleophilic attack by the thiol on the aldehyde carbonyl group. The difference in the rate of dithiolane formation from benzaldehyde (Table 1, entry 1) and acetophenone (Table 1, entry 28) encouraged us to test the efficiency of the catalyst for chemoselective dithiolane formation during a competition reaction between an aldehyde and a ketone. Thus, 4-acetylbenzaldehyde (entry 29) was subjected to 1,3-dithiolane formation. Excellent chemoselective dithiolane formation with the aldehyde carbonyl group was observed.

To establish the generality with other dithiols, we carried out the reaction of 4-methoxybenzaldehyde, 4-nitrobenzaldehyde and cyclohexanone as representative electron rich and electron deficient aldehyde and cyclic ketone, respectively, with 1,3-propanedithiol in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) under solvent free conditions. The corresponding dithanes were obtained in 98%, 89% and 96% yields, respectively, in 1 min.

The present method is superior to the reported procedures with respect to the reaction time, yields, amount of the catalyst used, necessity to use solvent, etc. This claim is justified through the following examples in which the efficiency of $Cu(BF_4)_2{\cdot}xH_2O$ has been compared with that of other recently reported catalysts for the reaction of a representative unactivated (entry 1), an electron rich (entry 5), and an electron deficient (entry 13) aldehyde and a saturated ketone (entry 24). The $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) catalysed reaction of benzaldehyde with 1,2-ethanedithiol afforded 99% yield after 1 min in the absence of solvent. The corresponding reaction gave 97%, 89%, 95% and 78% yields in DCM, MeCN, MeCN and THF after 30, 30, 90 and 300 min in the presence of PPA–SiO_2 (150 mg/mmol),[15] $Pr(OTf)_3$ (5 mol %),[14g] $MoO_2(acac)_2$ (10 mol %)[14f] and $Bi(NO_3)_3$ (0.1 mol %),[14e] respectively. A 78% yield was obtained from the reaction of 4-hydroxybenzaldehyde with 1,2-ethanedithiol in MeCN in the presence of $Pr(OTf)_3$ (5 mol %) in 5 h[14g] whereas the $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) catalysed reaction afforded a 95% yield in 1 min under solvent-free conditions. The $Pr(OTf)_3$ (5 mol %) catalysed reaction of 4-nitrobenzaldehyde with 1,2-ethanedithiol led to an 80% yield in MeCN in 4 h[14g] compared to an 84% yield obtained in 1 min using $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) in the absence of solvent. We chose cyclopentanone as a representative saturated ketone as ketal/thioketal formation of a five-membered cyclic ketone is retarded due to the eclipsing effect involving the newly generated C–X bond and the adjacent hydrogen atoms of the cyclopentane ring.[20] The superiority of $Cu(BF_4)_2{\cdot}xH_2O$ over the recently reported PPA–SiO_2 and $MoO_2(acac)_2$ was reflected during the reaction of cyclopentanone with 1,2-ethanedithiol. Thus, compared to the 85% yield obtained after 1 min in the $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) catalysed reaction under solvent-free conditions, the corresponding dithiolane was obtained in 72% and 88% yields on carrying out the reaction in the presence of PPA–SiO_2

Table 1. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed 1,3-dithiolane formation from different carbonyl compounds with 1,2-ethanedithiol[a]

Entry	Substrate	Time (min)	Yield (%)[b,c]
			
1	$R^1 = R^2 = R^3 = R^4 = R^5 = H$	1	99
2	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$	1	94
3	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OMe$	1	96
4	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCH_2Ph$	1	96
5	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OH$	1	95
6	$R^1 = R^5 = H$; $R^2 = R^4 = OMe$; $R^3 = OH$	1	97[d]
7	$R^1 = R^2 = OMe$; $R^3 = R^4 = R^5 = H$	1	93[d]
8	$R^1 = R^3 = R^5 = OMe$; $R^2 = R^4 = H$	1	98
9	$R^1 = H$; $R^2 = OEt$; $R^3 = OH$; $R^4 = R^5 = H$	1	85[d]
10	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Cl$	1	83[e]
11	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = F$	5	96[d]
12	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCOPh$	5	89[f]
13	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NO_2$	1	84
14	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CF_3$	5	100[d]
15	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CN$	5	84
16		30	86
17		1	86
18		1	60
19	X = O	1	93
20	X = S	1	92
21		5	80
22		1	80
23		1	99
24	$n = 1$	1	85
25	$n = 2$	1	87
26	$n = 3$	5	92[d]
27		1	66[g]
28		60	90[h,i]
29		1	95[j]

[a] The substrate was treated with 1,2-ethanedithiol (1.2 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) under neat conditions (except for entry 12) at room temperature.

[b] Yield of the corresponding 1,3-dithiolane after purification.

[c] All compounds were characterised by IR, NMR (^1H and ^{13}C) and MS.

[d] Unknown compounds gave satisfactory spectral and elemental analyses.

[e] A 26% yield was obtained on carrying out the reaction under the catalytic influence of $LiBF_4$(10 mol %) in MeCN for 5 min.

[f] The reaction was carried out in MeCN.

[g] GC–MS revealed 80% conversion to the desired dithiolane along with 12% of the dithiolane of the Michael adduct.

[h] The reaction was carried out at 80 °C.

[i] The dithiolane was formed in 36% and 39% yields on carrying out the reaction at room temperature for 1 h under neat conditions and for 2 h in MeCN, respectively.

[j] The dithiolane formation took place exclusively with the aldehyde carbonyl.

(500 mg/mmol) in DCM after 30 min[15] and $MoO_2(acac)_2$ (10 mol %) in MeCN after 3 h,[14f] respectively.

After completion of this work, $LiBF_4$ was reported for 1,3-dithiane formation under solvent-free conditions.[21] Although this method avoided the handling of solvent during the workup, the necessity of distillation for product isolation limited its applicability for non-volatile products. However, the efficiency of the $Cu(BF_4)_2{\cdot}xH_2O$ was proved to be better than that of $LiBF_4$ as only a 26% yield was obtained in carrying out the reaction of 4-chlorobenzaldehyde with 1,2-ethanedithiol in the presence of $LiBF_4$ (10 mol %) for 5 min whereas the $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) catalysed reaction afforded an 83% yield in 1 min (entry 10). The superiority of $Cu(BF_4)_2{\cdot}xH_2O$ over the newly reported $LiBF_4$ reaction[21] was further demonstrated on comparing the results of dithiolane/dithiane formation with furfural (entry 19) and cyclopentanone (entry 24). Thus, compared to the 93% yield of 1,3-dithiolane obtained after 1 min at rt using $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %), the corresponding 1,3-dithiane was obtained in 100% yield under the catalytic influence of $LiBF_4$ (10 mol %) after 5 h at 0 °C[21] during the reaction of furfural with 1,2-ethanedithiol. The $LiBF_4$ (10 mol %) catalysed 1,3-dithiane formation from cyclopentanone with 1,2-ethanedithiol required 21 h[21] to afford a comparable yield of the corresponding 1,3-dithiolane after 1 min in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %).

The superiority of $Cu(BF_4)_2{\cdot}xH_2O$ for dithiane formation over the recently reported catalysts, for example, $LiBF_4$[21] and $Pr(OTf)_3$[14g] was evidenced by the reaction of 4-methoxybenzaldehyde, 4-nitrobenzaldehyde and cyclohexanone with 1,3-propanedithiol. The use of $Pr(OTf)_3$ (5 mol %) in MeCN afforded dithianes from 4-methoxybenzaldehyde and 4-nitrobenzaldehyde in 91% and 84% yields after 0.5 and 3 h, respectively.[14g] Compared to these observations, the corresponding dithianes were formed in 98% and 89% yields, respectively, after 1 min under solvent-free conditions in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %). The $LiBF_4$ (10 mol %) catalysed reaction afforded an 86% yield of the dithiane from cyclohexanone after 5 h compared to 96% yield obtained in 1 min from the $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) catalysed reaction.

In conclusion, $Cu(BF_4)_2{\cdot}xH_2O$ is a novel and highly efficient catalyst for 1,3-dithiolane/dithiane formation from carbonyl compounds. The advantages are chemoselectivity, high yields, extremely fast reaction times, low cost of the catalyst and operation at room temperature. With increasingly tight legislation on the release of waste and use of toxic substances, as a measure to control environmental pollution,[22] the solvent-free conditions employed in the present method make it 'environmentally friendly' and a practical approach for the synthesis of 1,3-dithiolanes/dithianes.

Typical experimental procedure: 2-phenyl-1,3-dithiolane: To a magnetically stirred mixture of benzaldehyde (0.26 g, 2.5 mmol) and 1,2-ethanedithiol (0.28 g, 3 mmol) was added $Cu(BF_4)_2{\cdot}xH_2O$ (6 mg, 0.025 mmol, 1 mol %) and the mixture was stirred at room temperature under a nitrogen atmosphere for 1 min (TLC). The reaction mixture was dissolved in EtOAc and filtered through a bed of anhydrous Na_2SO_4. The residue was washed with EtOAc and the combined filtrates were concentrated under vacuum to afford the product (450 mg, 99%) as colourless liquid. IR (Neat): 3063, 3022, 2924, 1685, 1598, 1491, 1445, 1429, 1276, 1240, 1158, 1071, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.22$–3.30 (m, 2H), 3.38–3.44 (m, 2H), 5.60 (s, 1H), 7.18–7.29 (m, 3H), 7.48 (d, $J = 7.5$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.0$, 56.0, 127.7, 127.7, 128.2, 140.1. MS (ESI): $m/z = 182$ (M^+), identical with the literature.[23] The spectral data (IR, ^1H and ^{13}C NMR, MS) of known compounds were identical with those of authentic samples. The following compounds were not reported previously.

2-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dithiolane: Mp 68–70 °C; IR (KBr): 3428, 2928, 1621, 1517, 1459, 1428, 1375, 1328, 1296, 1252, 1224, 1195, 1112, 721, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.30$–3.39 (m, 2H), 3.45–3.53 (m, 2H), 3.89 (s, 6H), 5.62 (s, 1H), 6.79 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.1$, 56.3, 57.1, 104.7, 130.4, 134.59, 146.8. MS (ESI): $m/z = 258$ (M^+). Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14; H, 5.46%. Found: C, 51.10; H, 5.48%. 2-(2,3-Dimethoxyphenyl)-1,3-dithiolane: Yellow oil; IR (neat): 2997, 2930, 2833, 1585, 1471, 1428, 1307, 1277, 1235, 1215, 1168, 1085, 1068, 1005, 813, 797, 751, 727, 607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.29$–3.38 (m, 2H), 3.41–3.49 (m, 2H), 3.84 (s, 3H), 3.89 (s, 3H), 6.08 (s, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 7.03 (t, $J = 8.0$ Hz, 1H), 7.32 (d, $J = 7.9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 39.8$, 48.8, 55.7, 61.1, 111.7, 120.2, 123.9, 134.4, 146.6, 152.3. MS (ESI): $m/z = 242$ (M^+). Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.51; H, 5.82%. Found: C, 54.54; H, 5.81%. 2-(3-Ethoxy-4-hydroxyphenyl)-1,3-dithiolane: White gum (low melting solid); IR (neat): 3436, 2979, 2926, 1602, 1511, 1476, 1437, 1395, 1269, 1221, 1121, 1041, 977, 952, 864, 826, 808, 752, 610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (t, $J = 6.9$ Hz, 3H), 3.27–3.36 (m, 2H), 3.42–3.50 (m, 2H), 4.10 (q, $J = 6.9$ Hz, 2H), 5.60 (s, 1H), 5.79 (br s, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 7.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.7$, 40.0, 56.6, 64.4, 111.1, 113.8, 120.8, 131.0, 145.5, 145.7. MS (ESI): $m/z = 242$ (M^+). Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.51; H, 5.82%. Found: C, 54.53; H, 5.83%. 2-(4-Fluorophenyl)-1,3-dithiolane: colourless oil; IR (neat): 1592, 1510, 1418, 1228, 1157, 850, 762, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.40$–3.49 (m, 2H), 3.40–3.49 (m, 2H), 5.60 (s, 1H), 6.94–7.00 (m, 2H), 7.45–7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.1$, 55.4, 115.0, 115.3, 129.4, 129.5, 135.8, 160.5, 163.8. MS (ESI): $m/z = 200$ (M^+). Anal. Calcd for $C_9H_9FS_2$: C, 53.97; H, 4.53%. Found: C, 53.94; H, 4.54%. 2-(4-Trifluoromethylphenyl)-1,3-dithiolane: Mp 50–54 °C; IR (KBr): 3428, 2925, 1650, 1428, 1323, 1163, 1121, 1066, 1011, 838, 759, 699, 602, 503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.33$–3.41 (m, 2H), 3.45–3.53 (m, 2H), 5.60 (s, 1H), 7.55 (d, $J = 7.9$ Hz, 2H), 7.62 (d, $J = 7.9$ Hz, 2H). ^{13}C NMR

(75 MHz, $CDCl_3$): $\delta = 40.3$, 55.3, 125.4, 128.3, 144.9. MS (ESI): $m/z = 250$ (M^+). Anal. Calcd for $C_{10}H_9F_3S_2$: C, 47.98; H, 3.62%. Found: C, 47.94; H, 3.61%. 1,4-Dithia-spiro[4.6]undecane: Mp 47–49 °C; IR (KBr): 2917, 2845, 1433, 1276, 963, 841, 684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.59$ (s, 8H), 2.19 (d, $J = 8.1$ Hz, 4H), 3.28 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.6$, 28.5, 38.8, 46.0, 71.8. MS (ESI): $m/z = 187$ $(M-1)^+$. Anal. Calcd for $C_9H_{16}S_2$: C, 57.39; H, 8.56%. Found: C, 57.42; H, 8.58%.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.059.

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