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Copper(II) tetrafluoroborate as a novel and highly efficient catalyst for acetal formation

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Dedicated to Professor Mark S. Cushman

Abstract—Commercially available copper(II) tetrafluoroborate hydrate has been found to be a highly efficient catalyst for dimethyl/diethyl acetal formation in high yields from aldehydes and ketones by reaction with trimethyl/triethyl orthoformate at room temperature and in short period. Acetalisation was carried out under solvent-free conditions with electrophilic aldehydes/ketones. For weakly electrophilic aldehydes/ketones (e.g., benzaldehyde, cinnamaldehyde and acetophenone) and for aldehydes having a substituent that can coordinate with the catalyst, the corresponding alcohol was used as solvent.

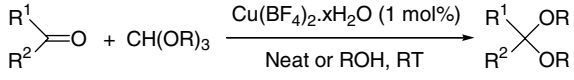
1. Introduction

Protection of aldehyde and ketone carbonyl groups is a frequently desired exercise in organic synthesis as it is often necessary to carry out a reaction on a multifunctional substrate without affecting an aldehyde/ketone group. One convenient method of protecting aldehydes and ketones is to convert them into the corresponding acetals.[1] Acetalisation can be achieved by treatment with alcohols in the presence of a protic[1,2] or Lewis[1,3] acid catalyst. A common regimen for acetal formation is protic[1,4] or Lewis[1,5] acid catalysed reaction of aldehydes and ketones with trialkyl orthoformates. Other methods use MeOH–$PhSO_2NHOH$–MeONa,[1b] alkoxysilanes in the presence of TMSOTf,[1b] $(EtO)_3CH$–DDQ–EtOH[6] and CAN–Na_2CO_3–ROH.[7] However, these methods have one or more drawbacks such as long reaction times, high temperatures, use of costly reagents/catalysts, use of additional reagents, requirement of special efforts for catalyst preparation, requirement of stoichiometric amount of the catalysts, the need to use special apparatus and moderate yields and side reactions. Thus, the development of an improved method is still desirable.

2. Results and discussions

When designing a new method, we realised that the use of trialkyl orthoformates as the acetalisation agent in the presence of a suitable transition metal catalyst should constitute a better procedure operable under mild conditions. The efficiency of the method would depend upon the coordination property of the metal catalyst to activate trialkyl orthoformate and/or the carbonyl substrate. Recently, we have reported that copper(II) tetrafluoroborate is an excellent catalyst for electrophilic activation during acylation,[8] diacetate formation[9] and thia-Michael addition[10] reactions. In this report, we disclose a highly efficient acetal formation reaction catalysed by copper(II) tetrafluoroborate (Scheme 1).

Various aldehydes and ketones were treated with trimethyl orthoformate in the presence of $Cu(BF_4)_2{\cdot}xH_2O$



Scheme 1. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed acetal formation.

Keywords: Dimethyl acetals; Diethyl acetals; Aldehydes; Ketones; Copper(II) tetrafluoroborate hydrate; Catalyst; Trimethyl orthoformate; Triethyl orthoformate.
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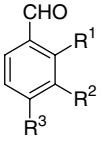
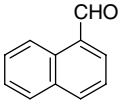
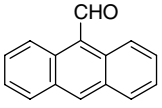
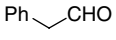
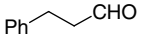
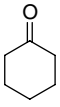
Table 1. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed dimethyl acetal formation from aldehydes/ketones under solvent-free conditions[a]

Entry	Aldehyde/ketone	Time (min)	Yield (%)[b,c]
			
1	$R^1 = R^2 = H$; $R^3 = Me$	5	92
2	$R^1 = R^2 = H$; $R^3 = Cl$	5	90
3	$R^1 = R^2 = H$; $R^3 = NO_2$	3	92
4	$R^1 = R^2 = H$; $R^3 = OCOPh$	5	91
5	$R^1 = Br$; $R^2 = R^3 = H$	5	88
6	$R^1 = Cl$; $R^2 = R^3 = H$	5	90
7	$R^1 = R^3 = H$; $R^2 = NO_2$	8	92
8		15	85
9		15	82[d]
10		2	85
11		3	86
12		5	78
13		2	95

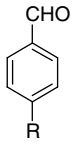
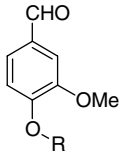
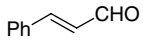
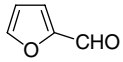
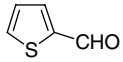
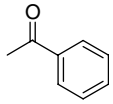
[a] The aldehyde/ketone (2.5 mmol) was treated with $CH(OMe)_3$ (2.0 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) at room temperature (~25–30 °C) under neat conditions.
[b] Isolated yield of the corresponding acetal.
[c] The products were characterised by IR, NMR.
[d] The reaction was carried out using 3 equiv of $CH(OMe)_3$.

(1 mol %) at ~25–30 °C under neat conditions. The reactions were monitored by IR and GCMS and the optimum results are provided in Table 1. Substituted benzaldehydes with Me, Cl, Br, NO_2 and OCOPh groups (entries 1–7), 1-naphthaldehyde (entry 8), 9-anthraldehyde (entry 9), aryl alkyl aldehydes (entries 10 and 11) and saturated cyclic ketones (entries 12 and 13) afforded excellent results after 2–15 min. The reactions could also be monitored visually: immediately after the addition of the catalyst to the mixture of aldehyde and trimethyl orthoformate an exothermic reaction takes place and the reaction mixture becomes homogeneous (for solid aldehydes) indicating completion of acetal formation. In the case of 9-anthraldehyde, as the product was solid, a small excess (3 equiv) of trimethyl orthoformate was required.

In the cases of benzaldehyde, cinnamaldehyde, acetophenone and aldehydes bearing substituents that are capable of coordinating with the metal ion, the acetal formation was slow under neat conditions. However, in these cases, the reactions proceeded well using MeOH as solvent affording excellent yields (Table 2).

The phenyl/styryl groups in benzaldehyde, cinnamaldehyde and acetophenone made aldehyde/ketone carbonyl less electrophilic due to resonance and inhibited the effective formation of coordinate bonds with the catalyst. For aldehydes bearing substituents that can coordinate with the metal cation (e.g., OR, F, CN, NMe_2, etc.) no effective activation of trimethyl orthoformate by the metal salt took place and acetal formation was retarded. The moderate yield obtained with 4-dimethylaminobenzaldehyde after 12 h (Table 2, entry 6) supported the role of a coordinating effect of the substituent in influencing acetal formation. Comparison of acetal formation from 4-methylbenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde (Table 1, entries 1–3) with those from 4-methoxybenzaldehyde, 4-fluorobenzaldehyde and 4-cyanobenzaldehyde (Table 2, entries 2–4), respectively, highlighted the coordinating effect of the substituents in the latter cases. The role of MeOH may be explained by the fact that initial reaction of

Table 2. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed dimethyl acetal formation from aldehydes/ketones in dry MeOH[a]

Entry	Aldehyde/ketone	Time (min)	Yield (%)[b,c]
			
1	R = H	5	93[d]
2	R = F	10	95
3	R = CN	10	92
4	R = OMe	20	91
5	$R = NMe_2$	12 h	58
			
6	R = Me	30	88
7	R = *c*-C_5H_9	10	92
8		20	91
9		30	85
10		20	82
11		1.5 h	96

[a] The aldehyde/ketone (2.5 mmol) in dry methanol (1 mL) was treated with $CH(OMe)_3$ (2.0 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) at room temperature (~25–30 °C).
[b] Isolated yield of the corresponding acetal.
[c] The products were characterised by IR and NMR.
[d] A 36% yield was obtained on carrying out the reaction under neat conditions.

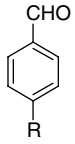
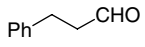
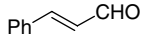
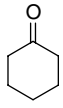
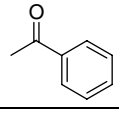
aldehyde with MeOH leads to the formation of a hemiacetal, which undergoes nucleophilic attack on trimethyl orthoformate complexed with $Cu(BF_4)_2{\cdot}xH_2O$ and results in acetal formation.[4]

Since there are limited reports for diethyl acetal formation,[3e,f,4,5c–e,g] we planned to evaluate the catalytic efficiency of $Cu(BF_4)_2{\cdot}xH_2O$ during the reaction of a few representative aldehydes and ketones with triethyl orthoformate (Table 3).

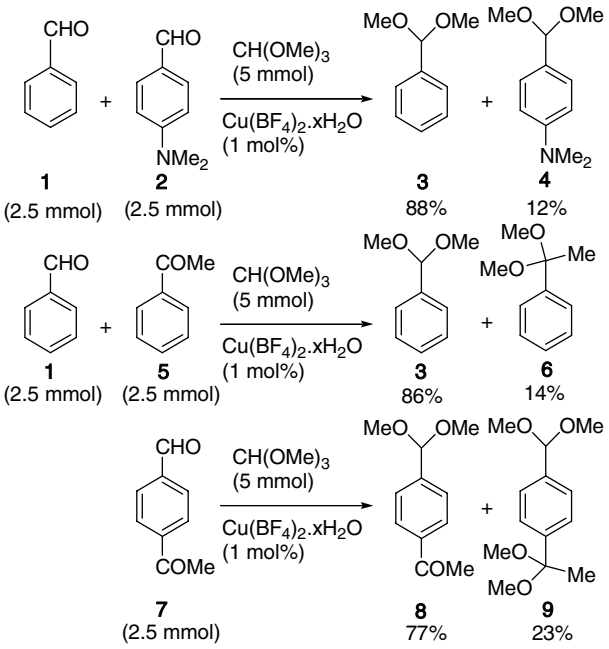
Excellent results were obtained in each case. As observed in the case of dimethyl acetal formation, the reactions of benzaldehyde, cinnamaldehyde and acetophenone required dry EtOH as solvent for diethyl acetal formation.

A comparison of the results of entries 1 and 6 (Table 2) prompted us to study selective acetal formation during intermolecular competition between benzaldehyde **1** and 4-dimethylaminobenzaldehyde **2**. Thus, a mixture of **1** (2.5 mmol) and **2** (2.5 mmol) in dry MeOH (1 mL) was treated with trimethyl orthoformate (5 mmol) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) for 5 min at room temperature (Scheme 2). Excellent selectivity was observed, (dimethoxymethyl)benzene **3** and 4-(dimethoxymethyl)-*N*,*N*-dimethylaniline **4** were formed in a ratio of 88:12 (NMR). Similarly, the difference in the rate of reaction of **1** and acetophenone **5** (Table 2, compare the results of entries 1 and 11) encouraged us to study the selectivity of acetal formation during inter- and intramolecular competition studies involving aldehyde and ketone carbonyl groups. The

Table 3. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed diethyl acetal formation from aldehydes and ketones[a]

Entry	Aldehyde/ketone	Time (min)	Yield (%)[b,c]
			
1	R = H	10	93[d]
2	R = Me	3	95
3	R = NO_2	5	95
4		10	92
5		30	80[d]
6		3	75
7		2 h	82[d]

[a] The aldehyde/ketone (1 equiv) was treated with $CH(OEt)_3$ (2.0 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) at rt (~25–30 °C) in the absence of solvent (except for entries 1, 5 and 7).
[b] Isolated yield of the corresponding acetal.
[c] The products were characterised by IR, NMR.
[d] The reaction was carried out in dry ethanol (1 mL).



Scheme 2. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed selective acetal formation during inter- and intramolecular competition studies.

reaction of **1** (2.5 mmol) and **5** (2.5 mmol) with trimethyl orthoformate (5 mmol) in dry MeOH (1 mL) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) at room temperature for 5 min (Scheme 2) resulted in the formation of **3** and 2,2-dimethoxy-1-phenylethane **6** in a ratio of 86:14 (NMR). The reaction of 4-acetylbenzaldehyde **7** (2.5 mmol) with trimethyl orthoformate (5 mmol) in MeOH (1 mL) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) for 5 min at room temperature resulted in the formation of 4-(dimethoxymethyl)acetophenone **8** and 2,2-dimethoxy-(4′-dimethoxymethyl)-1-phenylethane **9** in a ratio of 77:23 (GCMS).

3. Conclusions

We have described herein the use of $Cu(BF_4)_2{\cdot}xH_2O$ as a highly efficient and reusable catalyst for dimethyl and diethyl acetal formation at room temperature. The advantages include, (i) the use of a cheap, easy to handle and commercially available catalyst, (ii) room temperature reaction conditions, (iii) short reaction times, (iv) high yields and (v) excellent chemoselectivity.

4. Experimental

4.1. Typical procedure for acetal formation under neat conditions

To a magnetically stirred mixture of 4-methylbenzaldehyde (0.3 g, 2.5 mmol) and trimethyl orthoformate (0.53 g, 5 mmol), $Cu(BF_4)_2{\cdot}xH_2O$ (6.0 mg, 0.025 mmol, 1 mol %) was added and the mixture was stirred at 25–30 °C until completion of the reaction (5 min, TLC, IR). The mixture was diluted with saturated aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The

combined EtOAc extracts were washed with water (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 4-(dimethoxy)methylbenzene (colourless oil, 0.415 g, 92%, entry 1, Table 1), IR (neat): 2936, 2828, 1618, 1447, 1353, 1201, 1105, 1054, 912, 807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H), 3.30 (s, 6H), 5.35 (s, 1H), 7.15 (d, 2H, $J = 7.6$ Hz), 7.32 (d, 2H, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.2$, 52.53, 103.16, 126.56, 128.81, 135.13, 138.06, identical with an authentic sample.[5e]

5. Representative experimental procedure for acetal formation in the presence of solvent

To a magnetically stirred mixture of 4-cyanobenzaldehyde (0.327 g, 2.5 mmol) and trimethyl orthoformate (0.53 g, 5 mmol) in dry MeOH (1 mL), $Cu(BF_4)_2{\cdot}xH_2O$ (6.0 mg, 0.025 mmol, 1 mol %) was added and the mixture was stirred at 25–30 °C until completion of the reaction (10 min, TLC, IR). The reaction mixture was diluted with saturated aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with water (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford pure 4-(cyano)dimethoxymethylbenzene (colourless oil, 0.407 g, 92%, entry 3, Table 2), IR (neat): 2938, 2832, 2229, 1353, 1209, 1101, 1057, 988, 822, 556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.32$ (s, 6H), 5.43 (s, 1H), 7.50 (d, 2H, $J = 8.3$ Hz), 7.68 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.56$, 101.62, 112.14, 118.52, 127.45, 131.91, 143.10, identical with an authentic sample.[2c]

The remaining reactions were carried out following these general procedures. On each occasion, the spectral data (IR, ^1H NMR and ^{13}C NMR) of the prepared known compounds were found to be identical with those reported in the literature. The following compounds had not been reported.

2-(Bromo)dimethoxymethylbenzene (Table 1, entry 5): IR (neat): 2933, 2829, 1468, 1364, 1204, 1103, 1057, 980, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.35$ (s, 6H), 5.55 (s, 1H), 7.14 (t, 1H, $J = 7.5$ Hz), 7.28 (t, 1H, $J = 7.5$ Hz), 7.52 (d, 1H, $J = 7.6$ Hz), 7.59 (d, 1H, $J = 7.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 53.57$, 102.71, 122.75, 126.92, 128.18, 129.84, 132.66, 136.68. Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found. C, 46.80; H, 4.82. *2-(Chloro)dimethoxymethylbenzene* (Table 1, entry 6): IR (neat): 2934, 2830, 1366, 1201, 1107, 1058, 981, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.37$ (s, 6H), 5.62 (s, 1H), 7.22–7.29 (m, 2H), 7.33–7.36 (m, 1H), 7.60–7.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 53.68$, 100.86, 126.45, 128.02, 129.50, 129.65, 133.11, 135.28. Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found. C, 57.91; H, 5.97. *9-Dimethoxymethylanthracene* (Table 1, entry 9): Mp: 107–108 °C IR (KBr): 2932, 1448, 1186, 1105, 1066, 891, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.50$ (s, 6H), 6.53 (s, 1H), 7.38–7.61 (m, 4H), 7.93 (d, 2H, $J = 8.4$ Hz), 8.39 (s, 1H), 8.68 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 53.68$, 100.86, 126.45, 128.02, 129.50, 129.65, 133.11, 135.28. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found. C, 80.96; H, 6.41. *3,4-(Dimethoxy)dimethoxymethylbenzene* (Table 2, entry 6): IR (neat): 2937, 2832, 1607, 1594, 1414, 1259, 1194, 1136, 1102, 990, 863, 863, 795, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.32$ (s, 6H), 3.88 (s, 3H), 3.90 (s, 3H), 5.33 (s, 1H), 6.84–6.97 (m, 1H), 6.98–6.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.34$, 55.53, 102.86, 109.33, 110.40, 119.00, 126.48, 130.61, 148.64. Anal. Calcd for $C_{11}H_{16}O_4$ C, 62.25; H, 7.60. Found. C, 62.23; H, 7.63. *4-Cyclopentyloxy-3-methoxy dimethoxymethylbenzene* (Table 2, entry 7): IR (neat): 2954, 2829, 1607, 1510, 1351, 1264, 1160, 1102, 1053, 988, 862, 804 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$–1.61 (m, 2H), 1.79–1.97 (m, 6H), 3.32 (s, 6H), 3.85 (s, 3H), 4.73–4.79 (m, 1H), 5.31 (s, 1H), 6.84 (d, 1H, $J = 8.1$ Hz), 6.93–6.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.03$, 32.77, 52.75, 55.95, 80.32, 103.29, 110.10, 114.16, 119.07, 130.54, 147.73, 149.81. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found. C, 67.63; H, 8.35.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.168.

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