A Simple, Efficient and General Procedure for Acetalization of Carbonyl Compounds and Deprotection of Acetals under the Catalysis of Indium(III) Chloride

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Abstract: Indium(III) chloride efficiently catalyzes the protection of a variety of aldehydes and ketones to their corresponding 1,3-dioxolanes and dialkyl acetals in refluxing cyclohexane. On the other hand, deprotection of acetals is also achieved in refluxing aqueous methanol under the catalysis of indium(III) chloride.

Keywords: acetals; aldehydes; deprotection; indium(III) chloride; ketones; protecting groups

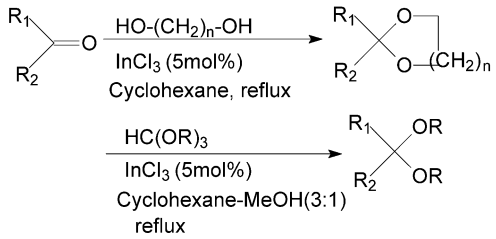
Introduction

The protection of a carbonyl group as an acetal and its deprotection in a later stage are two important reactions widely used in a multistep organic synthesis. Thus, it is of prime importance to select a procedure or reagent that is compatible with other sensitive functional groups present in the molecule. Although a plethora of procedures has been reported for the acetalization of carbonyl compounds and deacetalization of acetals,[1,2] procedures providing mild reaction conditions where other acid-sensitive protected hydroxy groups could survive are limited.[2l–p] Moreover, many of the reported procedures lack generality, being applicable only to aldehydes or suitable for the formation of dioxolanes only. Stoichiometric amounts of costly catalysts are also required in a number of processes. Thus, a simple, general, catalytic and efficient procedure avoiding damage to sensitive functional groups is still of high demand.

Results and Discussion

Indium halides have been the subject of current interest because of their potential as Lewis catalysts in various organic transformations.[3] As a part of our interest in this area[4] we have discovered that in the presence of a catalytic amount of indium(III) chloride carbonyl compounds are converted to their corresponding dioxolanes or *O,O*-acetals in refluxing cyclohexane (Scheme 1).

The experimental procedure is very simple. A mixture of the carbonyl compound and 1,2-ethanediol (or 1,3-propanediol) was refluxed in cyclohexane in the presence of a catalytic amount (5 mol %) of indium(III) chloride for a few hours (TLC). Extraction with ether and usual work-up followed by purification through column chromatography provided the corresponding dioxolanes. For the formation of dialkyl acetals trialkyl orthoformate and methanol were used in place of 1,2-ethanediol or 1,3-propanediol.



R_1= alkyl / aryl; R_2 = H/ alkyl / aryl; R= Me / Et; n= 1/2

Scheme 1.

This reaction proceeds efficiently in cyclohexane and benzene while some other solvents such as 1,2-dichloromethane, 1,2-dichloroethane, THF, acetonitrile are not very effective. Obviously, with benzene being carcinogenic cyclohexane is the obvious choice.

A wide range of aldehydes and ketones was converted to the corresponding 1,3-dioxolanes by treatment with 1,2-ethanediol and 1,3-propanediol using this procedure. The results are summarized in Table 1. A variety of substitutions such as Cl, NO_2, OMe, *O*-alkyl, and acid-sensitive groups like OTBDMS and CO_2Et survived under the reaction conditions. A variety of aldehydes and ketones was also protected as dialkyl acetals by this procedure using trialkyl orthoformate and the corresponding alkanol. The results are presented in Table 2.

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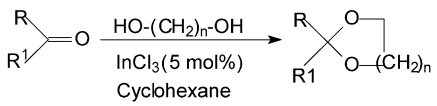
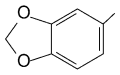
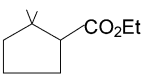
Several-acid sensitive heterocyclic aldehydes (entries 8 and 9) such as 2-furaldehyde and 2-thiophenealdehyde also form acetals in high yields. A hindered ketone, benzophenone (entry 17) which is very difficult to protect as its acetal is also converted to the corresponding dimethyl acetal. This shows the better efficiency of $InCl_3$ as catalyst compared to other related Lewis acids such as $FeCl_3$, $TiCl_4$, $AlCl_3$, and $ZnCl_2$ which are reported to be less efficient in the acetalization of sensitive molecules like furfural and aromatic ketones.[2b]

The deprotection of both 1,3-dioxolanes and dialkyl acetals was also efficiently achieved by the catalysis of indium(III) chloride in refluxing aqueous methanol. The results are presented in Tables 3 and 4. Most significantly, highly sensitive group like OTBDMS (entry 6) remained intact in this deprotection procedure.

In general, protection as well as deprotection processes are very clean and high yielding. The amount of indium(III) chloride has been optimized to 5 mol %

Table 1. Protection of carbonyl compuounds as 1,3-dioxolanes

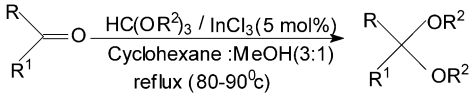


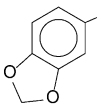
Entry	R	R^1	n	Time (h)	Yield(%)[a]	Ref.
1	Ph	H	2	8	93	[2f]
2	Ph	H	1	10	90	[2d]
3	*p*-Cl-C_6H_4	H	1	7	91	
4	*p*-NO_2-C_6H_4	H	1	5	95	[2i]
5	*m*-(OTBDMS)-C_6H_4	H	1	9	87	
6	*m*-(O-allyl)-C_6H_4	H	1	10	85	
7		H	1	16	90	[2i]
8	Ph-CH=CH(t)	H	1	14	92	[2d]
9	*p*-(MeO)-C_6H_4	H	1	15	85	[2i]
10	CH_3-$(CH_2)_8$-	H	1	10	98	
11	CH_3CH_2	Et	1	8	90	
12	$(CH_3)_2CHCH_2$	CH_3	1	5	95	[2b]
13	$(CH_3)_2C$=CH	CH_3	1	16	87	
14	Ph	CH_3	1	12	95[b]	[2d]
15			1	12	90	[2d]
16			1	13	91	
17			1	12	85	[2d]

[a] Yields refer to isolated pure product unless otherwise stated.

[b] The reaction was carried out in benzene.

Table 2. Protection of carbonyl compuounds as dialkyl acetals



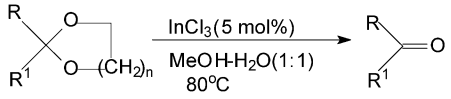
Entry	R	R^1	R^2	Time (h)	Yield(%)[a]	Ref
1	Ph	H	Me	10	92	[2a]
2	*p*-(MeO)-C_6H_4	H	Me	12	86	[2a]
3	*p*-Cl-C_6H_4	H	Me	8	96	[2a]
4	*p*-NO_2-C_6H_4	H	Me	6	92	[2a]
5		H	Me	14	86	[2i]
6	*p*-(OH)-C_6H_4	H	Me	12	86	[2i]
7	*o*-(OH)-C_6H_4	H	Me	12	84	[2i]
8		H	Me	11	82[b]	[2a]
9		H	Me	12	80[b]	[2a]
10	CH_3-$(CH_2)_8$-	H	Et	12	95	
11	PhCH=CH(t)	H	Me	12	90	[2i]
12			Me	10	90	[2a]
13			Et	12	88	[2b]
14			Et	10	94	
15	Ph	Me	Me	14	80	[2a]
16	Ph	Et	Me	12	87[c]	[2a]
17	Ph	Ph	Me	16	80[c]	[2a]

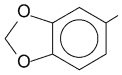
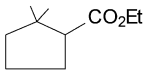
[a] Yields refer to isolated pure products unless otherwise stated.

[b] The reaction was carried out at 60°C.

[c] The reaction was carried out in benzene.

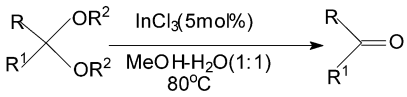
Table 3. Deprotection of 1,3-dioxolanes

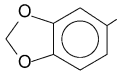


Entry	R	R^1	n	Time (min)	Yield(%)[a]
1	Ph	H	1	60	89
2	Ph	H	2	70	93
3	*p*-Cl-C_6H_4	H	1	50	93
4	*p*-(MeO)-C_6H_4	H	1	65	91
5	*m*-(O-allyl)-C_6H_4	H	1	60	88
6	*m*-(OTBDMS)-C_6H_4	H	1	65	92
7		H	1	50	89
8	Ph-CH=CH(t)	H	1	70	87
9	CH_3-$(CH_2)_8$-	H	1	85	86
10	CH_3-$(CH_2)_6$-	H	1	80	90
11	Ph	Me	1	70	94
12	*p*-Cl-C_6H_4	Me	1	70	91
13			1	90	89
14			1	90	85
15			1	85	84
16	$(CH3)_2CH$-CH_2	Me	1	80	86

[a] Yields refer to isolated pure products unless otherwise stated.

Table 4. Deprotection of dialkyl acetals



Entry	R	R^1	R^2	Time (min)	Yield(%)[a]
1	Ph	H	Me	60	92
2	*p*-Cl-C_6H_4	H	Me	65	96
3	*p*-NO_2-C_6H_4	H	Me	50	95
4	*p*-(MeO)-C_6H_4	H	Me	60	93
5		H	Me	75	94
6	PhCH=CH(t)	H	Me	70	86
7		H	Me	120	85
8		H	Me	110	84
9	*p*-(OH)-C_6H_4	H	Me	70	86
10	CH_3-$(CH_2)_8$-	H	Et	85	96
11	CH_3-$(CH_2)_6$-	H	Me	70	92
12	$(CH_3)_2CH$-CH_2	Me	Me	60	93
13	Ph	Me	Me	65	90
14	Ph	Ph	Me	60	95
15			Me	70	84
16			Et	80	90

[a] Yields refer to isolated pure product unless otherwise stated

with respect to carbonyl compound or acetal. Although the reaction proceeds with lower amounts of indium (III) chloride a longer time is required for completion. It has also been observed that the reaction does not go at all in the absence of $InCl_3$.

Conclusion

In conclusion, the present procedure using indium(III) chloride as a catalyst provides a very simple, efficient and general methodology for the protection of a variety of structurally diverse aldehydes and ketones to the corresponding 1,3-dioxolanes and dialkyl acetals. On the other hand the same catalyst has been used successfully for the deprotection of both dioxolanes and acetals in a different solvent system. The significant advantages offered by this method are: (a) general applicability to all types of carbonyl compounds providing dioxolanes as well as acetals, (b) high yields, (c) considerably lower catalyst loading, (d) reaction conditions mild enough to be compatible with acid-sensitive moieties, (e) no migration of double bonds during acetalization. Thus, we believe that this procedure will provide a practical and better alternative to the existing procedures for acetalization and deacetalization. Moreover, this demonstrates the potential of indium(III) chloride as a catalyst.

Experimental Section

NMR spectra were recorded on a Bruker DPX 300 instrument at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR in $CDCl_3$ solutions. IR spectra were measured on a FT-8300 Shimadzu spectrometer as neat samples. Cyclohexane was distilled over sodium metal. All reagents and carbonyl compounds were distilled before use. Indium(III) chloride (98%) was purchased from Aldrich and was used as such.

Conversion of 4-Chlorobenzaldehyde to the Corresponding 1,3-Dioxolane; Typical Procedure (entry 3, Table 1)

A stirred solution of 4-chlorobenzaldehyde (141 mg, 1 mmol) and 1,2-ethanediol (93 mg, 1.5 mmol) was heated at reflux (oil bath 90 °C) in cyclohexane (10 mL) in the presence of indium(III) chloride (11 mg, 0.05 mmol, 5 mol % with respect to aldehyde) using a Dean–Stark water separator. After the reaction was complete (7 h as indicated by TLC) the reaction mixture was extracted with ether (3 × 10 mL) and the ether extract was washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the crude product over silica gel (hexane-Et_2O, 90:10) furnished the pure 1,1-ethylenedioxy-1-(4-chlorophenyl)methane as a colorless liquid; yield: 168 mg (91%); R_f: 0.55; IR: $\nu = 1614, 1249$ cm^{-1}; ^{1}H NMR: $\delta = 7.42$ (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 5.76 (s, 1H), 3.98 – 4.10 (m, 4H); ^{13}C NMR: $\delta = 136.9, 135.3, 128.9$ (2C), 128.4 (2C), 103.4, 65.7 (2C); anal. calcd. for $C_9H_9O_2Cl$: C 58.55, H 4.91; found: C 58.52, H 4.88.

This procedure is followed for the conversion of all the carbonyl compounds to the corresponding 1,3-dioxolanes listed in Table 1.

Conversion of 4-Chlorobenzaldehyde to the Corresponding Dimethyl Acetal; Typical Procedure (entry 3, Table 2)

The procedure reported in the previous experiment for the formation of 1,3-dioxolanes was followed using trimethyl orthoformate (1 mmol) in place of 1,2-ethanediol and a mixture of cyclohexane and methanol (3:1, 10 mL) instead of pure cyclohexane. The corresponding dimethyl acetal was obtained as a colorless oil whose identity was established by comparison of its spectroscopic data (IR, ^{1}H NMR) with those reported;[2a] yield: 178 mg (96%).

This procedure is followed for the protection of all the carbonyl compounds as dialkyl acetals listed in Table 2. The known compounds are identified by comparison of their spectroscopic data (IR, ^{1}H, ^{13}C NMR) with those reported. The spectral (IR, ^{1}H and ^{13}C NMR) data and elemental analyses of the compounds which are not readily found are provided below.

1,1-Ethylenedioxy-1-(3-ter-butyldimethylsilyloxy)methane (entry 5, Table 1): Colorless liquid; R_f: 0.55; IR: $\nu = 1602, 1487$ cm^{-1}; ^{1}H NMR: $\delta = 7.17 – 7.27$ (m, 1H), 7.03 (t, $J = 8.5$ Hz, 1H), 6.86 – 6.93 (m, 1H), 6.61 – 6.65 (m, 1H), 5.57 (s, 1H), 3.82 – 3.92 (m, 4H), 0.73 (s, 9H), 0.03 (s, 6H); ^{13}C NMR: $\delta = 155.6, 140.4, 133.5, 128.9, 128.6, 128.2, 125.6, 64.8$ (2C), 64.1, 28.1 (3C), – 4.35 (2C); anal. calcd. for $C_{15}H_{24}O_3Si$: C 64.24, H 8.62; found: C 64.25, H 8.60.

1,1-Ethylenedioxy-1-(3-allyloxy)methane (entry 6, Table 1): Colorless liquid; R_f: 0.50; IR: $\nu = 1485, 1263$ cm^{-1}; ^{1}H NMR: $\delta = 7.25 – 7.36$ (m, 1H), 7.05 – 7.15 (m, 2H), 6.89 – 6.93 (m, 1H), 5.99 – 6.17 (m, 1H), 5.79 (s, 1H), 5.25 – 5.45 (m, 2H), 4.54 (d, $J = 5.1$ Hz, 2H), 3.99 – 4.13 (m, 4H); ^{13}C NMR: $\delta = 160.0, 139.8, 133.3, 129.5, 119.0, 117.7, 115.9, 112.5, 103.6, 69.4, 65.7$ (2C); anal. calcd. for $C_{12}H_{14}O_3$: C 69.88, H 6.84; found: C 69.85, H 6.80.

1,1-Ethylenedioxydecane (entry 10, Table 1): Colorless liquid; R_f: 0.85; IR: $\nu = 1465, 1407$ cm^{-1}; ^{1}H NMR: $\delta = 4.82$ (t, $J = 4.8$ Hz, 1H), 3.77 – 3.99 (m, 4H), 1.25 – 1.41 (m, 14H), 0.09 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 104.8, 64.9$ (2C), 34.0, 31.9, 29.7 (2C), 29.6, 29.4, 24.1, 22.7, 14.2; anal. calcd. for $C_{12}H_{24}O_2$: C 71.95, H 12.07; found: C 71.94, H 12.03.

3,3-Ethylenedioxypentane (entry 11, Table 1): Colorless liquid; R_f: 0.80; IR: $\nu = 1463$ cm^{-1}; ^{1}H NMR: $\delta = 3.89$ (s, 4H), 1.58 (q, $J = 7.5$ Hz, 4H), 0.85 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR: $\delta = 112.7, 65.4$ (2C), 29.7 (2C), 8.4 (2C); anal. calcd. for $C_7H_{14}O_2$: C 64.58, H 10.83; found: C 64.58, H 10.85.

2,2-Ethylenedioxy-4-methylpent-3-ene (entry 13, Table 1): Colorless liquid; R_f: 0.60; IR: $\nu = 1444$ cm^{-1}; ^{1}H NMR: $\delta = 5.16$ (s, 1H), 3.74 – 3.87 (m, 4H), 1.73 (s, 3H), 1.63 (s, 3H), 1.39 (s, 3H); ^{13}C NMR: $\delta = 136.4, 127.2, 108.2, 64.2$ (2C), 26.7, 25.5, 18.4; anal. calcd. for $C_8H_{14}O_2$: C 67.57, H 9.92; found: C 67.55, H 9.90.

1,1-Ethylenedioxycyclooctane (entry 16, Table 1): Colorless liquid; R_f: 0.85; IR: $\nu = 1471, 1112$ cm^{-1}; ^{1}H NMR: $\delta = 3.82 – 3.84$ (m, 4H), 1.71 – 1.73 (m, 4H), 1.50 – 1.54 (m, 10H); ^{13}C NMR: $\delta = 112.7, 64.5$ (2C), 34.4 (2C), 28.3 (2C), 25.0, 22.5 (2C); anal. calcd. for $C_{10}H_{18}O_2$: C 70.55, H 10.65; found: C 70.43, H 10.62.

1,1-Diethoxydecane (entry 10, Table 2): Colorless liquid; R_f: 0.75; IR: $\nu = 1467$ cm^{-1}; ^{1}H NMR: $\delta = 4.42$ (t, $J = 5.7$ Hz, 1H), 3.38 – 3.65 (m, 4H), 1.51 – 1.58 (m, 2H), 1.16 – 1.21 (m, 14H), 1.14 (t, $J = 7.0$ Hz, 6H), 0.82 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 103.3, 61.1$ (2C), 33.9, 32.2, 29.8, 29.7, 29.6, 25.1, 23.0, 15.6 (2C), 14.4 (2C); anal. calcd. for $C_{14}H_{30}O_2$: C 72.98, H 13.12; found: C 72.85, H 13.10.

1,1-Diethoxycycloheptane (entry 16, Table 2): Colorless liquid; R_f: 0.85. IR: $\nu = 1456, 1444$ cm^{-1}; ^{1}H NMR: $\delta = 3.38$ (q, $J = 7.1$ Hz, 4H), 1.73 – 1.76 (m, 4H), 1.46 – 1.50 (m, 8H), 1.11 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR: $\delta = 104.7, 55.5$ (2C), 37.4 (2C), 29.5 (2C), 22.1 (2C), 15.9 (2C); anal. calcd. for $C_{11}H_{22}O_2$: C 70.92, H 11.90; found: C, 70.84; H, 12.01.

Deprotection of 1,3-Dioxolanes and Dialkyl Acetals; Typical Procedure

A stirred solution of 1-(4-chlorophenyl)-1,1-dimethoxymethane (entry 2, Table 4) (186 mg, 1 mmol) in aqueous methanol (1:1, 3 mL) was heated at reflux (90 °C) in the presence of indium(III) chloride (11 mg, 0.05 mmol, 5 mol %) for 1 h (TLC). The reaction mixture was then extracted with ether and the ether extract was washed with brine, dried (Na_2SO_4) and evaporated to leave the crude product. This was purified by column chromatography over silica gel (hexane-Et_2O, 90:10) to provide pure 4-chlorobenzaldehyde which was identified by comparison with an authentic sample.

This procedure was followed for the deprotection of all 1,3-dioxolanes and dialkyl acetals listed in Tables 3 and 4. The

generated carbonyl compounds were identified by comparison with authentic samples.

Acknowledgements

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