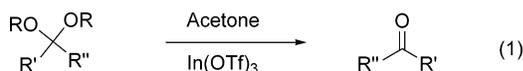# Indium(III) Trifluoromethanesulfonate as an Efficient Catalyst for the Deprotection of Acetals and Ketals

Brian T. Gregg,* Kathryn C. Golden, and John F. Quinn

Department of Medicinal Chemistry, AMRI, Albany, New York 12203

brian.gregg@amriglobal.com

$$ (1) $$

Acetals and ketals are readily deprotected under neutral conditions in the presence of acetone and catalytic amounts of indium(III) trifluoromethanesulfonate (<0.8 mol %) at room temperature or mild microwave heating conditions to give the corresponding aldehydes and ketones in good to excellent yields.

The use of acetals and ketals for the protection of aldehydes and ketones has been well established in the literature as an important part of many multistep synthetic protocols. The subsequent deprotection of these moieties is paramount to their successful use in these syntheses.[1] While a variety of methods are available for the deprotection of acetals and ketals to give the corresponding carbonyl compounds,[2–5] many of these procedures involve acidic conditions which have the potential to cause unwanted side reactions such as aldol condensation or result in the degradation of other protecting groups such as the *N-tert*-butyl carbamate moiety. Venanzi and co-workers have reported the ruthenium transitions metal complex [Ru(CH₃CN)₃(triphos)]-(OTf)₂ to be an effective catalyst for the nonacidic deprotection of acetals and ketals with good yields for a limited number of substrates.[6] The use of Bi(OTf)₃·xH₂O in water/THF[7a] has been shown to facilitate the deprotection of a wide variety of acetals and ketals; however, this system has been reported to be quite acidic (pH 2) and may not be amenable to acid-sensitive protecting groups.[7b] Additionally BiCl₃ in methanol has been reported to be an efficient Lewis acid for acetal and ketal deprotection.[8]

Procopio and co-workers have also reported the use of Ce(OTf)₃[9] in polar solvents such as CH₃NO₂ or CH₃CN saturated with water as a viable deprotection procedure. Most relevant is the work of Lipshutz[10] where the use of PdCl₂(CH₃CN)₂ and acetone was found to be a mild catalytic system for the deprotection of cyclic ketals and acetals. While this methodology has a wide range of application, it suffers from the competitive deprotection of TBS and THP functional groups under the ketal deprotection conditions. In our laboratories the use of pyridinium *p*-toluenesulfonate and *p*-toluenesulfonic acid in the presence of acetone[11] has been shown to facilitate the transacetalization deprotection of acetals and ketals with limited application and versatility. While many of these cited reagents do afford the desired carbonyl compounds in reasonable yields, they tend to have limitations such as (1) not being readily obtainable from commercial sources, (2) resulting in unwanted side reactions, or (3) not being easily applied to parallel or larger scale syntheses. It was our intention to find a catalytic system that facilitated the deprotection of a wide variety of acetals and ketals under mild, neutral conditions with reagents that are commercially available, easy to handle, cost-effective, and amenable to parallel synthetic applications. We herein describe the deprotection of acetals and ketals via transacetalization with acetone and indium(III) trifluoromethanesulfonate as the Lewis acid catalyst.

Our standard deprotection protocol involved preparing a solution of acetal or ketal (2 mmol) in acetone (25 mL) to which was added indium(III) trifluoromethanesulfonate (0.8 mol %). For these reactions there was no deleterious effect on the reactions due to moisture or air sensitivity of the catalyst and, as a result, all reagents were standard laboratory grade and used "as is" from commercial sources. Depending on the nature of the substrate, the reactions were conducted either at room temperature or with brief microwave heating. The selection of acetals and ketals that were deprotected by using our standard conditions are shown in Table 1. Commercially available reagents **1a**, **1b**, **3**, **5**, **7**, **9**, **11**, **17**, **19**, **21**, **23**, **25**, **29**, **31**, **33**, **35**, and **37** were used "as is" from the vendor. Additional reagents **13**, **15**, **27**, **39**, and **41** were prepared in-house and were fully characterized by ¹H, ¹³C, and HRES-MS.[12] The identity of commercially available reaction products **2**, **4**, **6**, **8**, **10**, **18**, **20**, **22**, **24**, **26**, **30**, **32**, **34**, **36**, **38**, and **40** was verified by comparison with published spectral data as well as comparing to authentic material. Additional reaction products **14**, **16**, **28**, and **42** were prepared in-house and were fully characterized by ¹H, ¹³C, and HRES-MS.[12]

In general, all deprotections involving aromatic or aliphatic acyclic acetals (entries 1, 2, 3, 7, and 8, Table 1) and ketals (entries 4 and 5, Table 1) were readily deprotected within 20 to

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*; 1st ed.; Georg Thieme Verlag: Stuttgart, Germany, 1994.

(2) Kaur, G.; Trehan, A.; Trehan, S. *J. Org. Chem.* **1998**, *63*, 2365.

(3) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932.

(4) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684.

(5) Marcantoni, E.; Nobili, F. *J. Org. Chem.* **1997**, *62*, 4183.

(6) Ma, S.; Venanzi, L. M. *Tetrahedron Lett.* **1993**, *34*, 8071.

(7) (a) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027. (b) Procopio and co-workers have reported that a suspension of Bi(OTf)₃·xH₂O in water/THF is acidic and that the aqueous layer from the workup was found to have a pH of 2.[9]

(8) Sabitha, G.; Babu, R. S.; Reddy, V.; Yadav, J. S. *Chem. Lett.* **2000**, 1074.

(9) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093.

(10) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(11) Unpublished results; reaction times typically require from 10 to 20 h; conversion to the corresponding carbonyl compounds is sometimes incomplete with additional byproducts being detected. Most common protecting groups (TBS, TBDMS, TBDPS) undergo complete or partial deprotection under the reaction conditions.

(12) In addition to many commercially available substrates several were prepared in-house (**13**, **14**, **15**, **16**, **27**, **28**, **39**, **41**, and **42**) with each starting material and product being fully characterized by ¹H, ¹³C NMR, and mass spectroscopy—see the Supporting Information for details.

TABLE 1. In(OTf)$_3$-Catalyzed Transacetalization Deprotection of Acetals and Ketals

entry	substrate	time	conditions[a]	product[b]	yield (%)[c]
1a	1a: R = Et; 1b: R = Me (**1**)	30 m	rt	**2**	93
1b		15 m	rt[d]		91
2	**3**	30 m	rt	**4**	94
3	**5**	30 m	rt	**6**	94
4	**7**	30 m	rt	**8**	92
5	**9**	300 s	100 °C[e]	**10**	91
6	**11**	900 s	100 °C[e]	**12**	32[i]
7a	**13**	2 h	rt[f]	**14**	91
7b		30 m	rt		92
8	**15**	30 m	rt	**16**	91
9	**17**	8 h	rt	**18**	89
10	**19**	300 s	100 °C[e]	**20**	89
11	**21**	4 h	rt	**22**	92
12	**23**	2.5 h	rt	**24**	93
13	**25**	500 s[g]	100 °C[e]	**26**	(43)[h] / 84
14	**27**	4.5 h	rt	**28**	82
15	**29**	400 s	100 °C[e]	**30**	90
16a	**31**	3.5 h	rt	**32**	51
16b		300s	100 °C[e]		94
17	**33**	300 s	100 °C[e]	**34**	89
18	**35**	300 s	100 °C[e]	**36**	91
19	**37**	300 s	100 °C[e]	**38**	89
20	**39**	4.5 h	rt	**40**	88
21	**41**	3.5 h	rt	**42**	92

[a] Typical reaction conditions: substrate (2 mmol), acetone (20 mL), and In(OTf)$_3$ (0.8 mol %) unless otherwise noted. [b] All products were characterized by mass and ^{1}H NMR spectroscopy. [c] Isolated yields. [d] Reaction conditions: substrate (150 mmol), acetone (800 mL), and In(OTf)$_3$ (0.07 mol %). [e] Reactions conducted under microwave irradiation. [f] Reaction conditions: substrate (5 mmol), acetone (100 mL), and In(OTf)$_3$ (0.1 mol %). [g] Reaction conditions: after 300 s at 100 °C, solvent removed under vacuum and fresh acetone added with no additional catalyst. Further heating for 200 s at 100 °C gave compete reaction. [h] Intermediate ^{1}H NMR yield after 300 s at 100 °C. [i] Yield is based on ^{1}H NMR yield of crude reaction mixture, isolation of final, purified product was unsuccessful.

30 min to give isolated yields in excess of 90% for the corresponding carbonyl compounds. A moderate increase in reactivity was observed for the deprotection of dimethylacetals as compared to the diethylacetals (entries 1a and 1b, Table 1); however, this difference was not considered significant. The versatility of this deprotection protocol is demonstrated in that electron-rich, electron-poor, and sterically hindered substrates undergo rapid deprotection with good conversion to the corresponding carbonyl compounds. An example of a heterocyclic acetal is 3-(dimethoxymethyl)-1*H*-pyrazole (entry 9, Table 1), which was deprotected at room temperature albeit requiring 8 h of reaction time, to give 1*H*-pyrazole-3-carboxaldehyde with an isolated yield of 89%.

As expected, cyclic acetals and ketals derived from aromatic carbonyl compounds (entries 10, 11 12, and 15−19, Table 1) were somewhat more resistant to deprotection and required longer reaction times (4 h) or mild microwave heating yet still proceeded in high yield. In particular, 2-(4-nitrophenyl)-1,3-dioxolane and 2-(3-cyanophenyl)-1,3-dioxolane (entries 15 and 16, Table 1) were particularly sluggish showing approximately 50% conversion after 3.5 h and approximately 85% conversion after 24 h. To help expedite these reactions we employed microwave irradiation. Relatively little has been reported in the literature concerning the microwave-assisted deprotection of acetals and ketals. Yadav and co-workers have reported the clay-supported ammonuim nitrate, "*Clayan*" methodology, in the solid state under microwave irradiation to deprotect acetals and

TABLE 2. Deprotection of 2-(4-Nitrophenyl)-1,3-dioxolane (29): Optimization of Microwave Heating Conditions to Generate 4-Nitrobenzaldehyde (30)

entry	time (s)	temp (°C)	% conversion[a]
1	60	60	25
2	60	100	55
3	120	100	75
4	400	100	90
5	900	100	67

[a] Percent conversion determined based on peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 210 and 254 nm.

ketals with good results.[13] Additionally, Hajipour and co-workers have reported the use of benzyltriphenylphosphonium peroxymonosulfate (PhCH$_2$PPh$_3$HSO$_5$) in 40 mol % in conjunction with a catalytic amount of BiCl$_3$ and an additional protocol using 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate as useful reagents under microwave irradiation conditions to facilitate the deprotection of acetals.[14,15] Using 2-(4-nitrophenyl)-1,3-dioxolane (Table 1, Entry 15) as a substrate we set out to optimize the microwave heating conditions anticipating the potential for unwanted byproducts or other thermal degradation reactions as reported for similar substrates (Table 2).

In general, most microwave-assisted reactions proceed with good conversion within 300−400 s at 100 °C. Shorter reaction times or lower temperatures gave incomplete conversion to the desired product as determined by ^{1}H NMR analysis of the reaction mixtures which showed the presence of starting material and the corresponding carbonyl compound. Excessive irradiation (900 s, 100 °C, entry 5, Table 2) showed significantly diminished product yield with multiple uncharacterized byproducts being formed. For reactions which fail to go to completion as a result of insufficient heating, the application of additional microwave irradiation has been successfully employed to drive these reactions to completion.[16] We note that 2-benzyl-1,3-dioxolane (**25**, entry 13, Table 1), was the only exception to this result. Careful ^{1}H NMR monitoring of this reaction in acetone-d_6 indicated a maximum of 43% conversion to **26** after microwave heating at 100 °C for 400 s. Neither additional catalyst nor further microwave heating led to increased **26** being generated. In developing a modified procedure for this substrate we have found that after an initial heating for 300 s at 100 °C, concentration of the reaction to remove the volatile organics, followed by the addition of fresh acetone and microwave heating for 200 s at 100 °C (no additional In(OTf)$_3$ added) was sufficient to fully deprotect **25** to give **26** in 84% yield. Microwave heating was successfully employed for a number of examples in Table 1, which under room temperature conditions would have either proceeded very sluggishly or gave incomplete reactions. We also note the conversion of 2,2-diethoxyacetophenone to the corresponding phenylglyoxal (entry 6, Table 1). This reaction was much more resistant to deprotection than all other substrates, requiring microwave heating for 900 s at 100 °C to give only

a modest yield of 32% (^{1}H NMR of reaction mixture) with no starting material remaining in the crude reaction mixture.

Of significant importance is the mild, neutral, deprotection conditions found when using indium(III) trifluoromethanesulfonate. The *N*-Boc protected substrates (entries 8 and 20, Table 1) are cleanly deprotected at room temperature with no observed products resulting from *N*-Boc deprotection. It is particularly noteworthy that the *N*-Boc protected dioxolane (entry 20, Table 1), even after 4.5 h at room temperature, showed no significant amount of *N*-Boc deprotection. To avoid thermal degradation of the *N*-Boc protecting group we chose not to subject this reaction to microwave heating. This is a significant advantage to the commonly used technique for acetal/ketal deprotection involving HCl or TFA[1] in an organic solvent or other methods previously mentioned that would facilitate the removal of both protecting groups. Additionally, our deprotection conditions are compatible with both TBS and THP protecting groups, allowing the selective unmasking of ketals in the presence of a protected alcohol (entries 14 and 21, Table 1). Substrates similar to these have been previously reported to suffer from competitive removal of both protecting groups under PdCl$_2$(CH$_3$CN)$_2$ and acetone conditions.[10] Upon treatment with indium triflate in acetone at room temperature these substrates smoothly undergo selective deprotection of the cyclic ketal. Prolonged reaction times (>24 h) or heating results typically showed removal of both the carbonyl and hydroxyl protecting groups to varying degrees.

This method is also amenable to larger scale reactions with the potential to utilize significantly lower catalyst loading as well. To demonstrate applicability of this methodology to scale-up, two large-scale test reactions were conducted. In the first example (entry 7a, Table 1), *N*-(3,3-diethylpropyl)-4-methylbenzamide (5 mmol) was cleanly converted to the corresponding aldehyde in 2 h in 91% isolated yield with indium triflate (0.1 mol %). Additionally, in our largest scale deprotection, benzaldehyde dimethylacetal (22.8 g, 150 mmol, entry 1b, Table 1) was cleanly converted to benzaldehyde in 15 min with acetone (800 mL) and an indium triflate loading of <0.01 mol %. Upon concentrating this reaction mixture to dryness, the crude material was in excess of 94% pure, and after purification the product was isolated analytically pure in 91% yield.

In conclusion, the use of indium(III) trifluoromethanesulfonate as a catalyst for the transacetalization deprotection of acetals and ketals in acetone is an effective and efficient method that can readily be scaled to multigram reactions. Most examples involving simple acetals and ketals are deprotected at room temperature and more stable substrates can be cleanly deprotected with the application of mild microwave heating for a short duration of time. Reactions possessing both the acid labile *N*-Boc protecting group and either an acetal or ketal chemoselectively generate the corresponding carbonyl compounds while keeping the *N*-Boc group intact. In our hands, many of these deprotection reactions only need be concentrated to dryness and can be used directly in the next step of a synthetic protocol due to the low concentration of catalyst used and the lack of undesired reaction products. Indium(III) trifluoromethanesulfonate is favored for this deprotection protocol due to the commercial availability, low cost, high turn-over rate, and ease of handling of this reagent.

(13) Meshram, H. M.; Sumithra, G.; Reddy, G. S.; Ganesh, Y. S. S.; Yadav, J. S. *Synth. Commun.* **1999**, *29*, 2807.

(14) Hajipour, A. R.; Mallakpour, S. E.; Baltork, I. M.; Adibi, H. *Synth. Commun.* **2001**, *31*, 1625.

(15) Hajipour, A. R.; Mallakpour, S. E.; Mohammadpoor-Baltork, I.; Khoee, S. *Synth. Commun.* **2002**, *32*, 611.

(16) To avoid the formation of byproducts due to prolonged microwave heating beyond reaction completion and given the speed with which microwave heated reactions are conducted, we advise the use of multiple, short-duration heating events.

Experimental Section

Deprotection of *N*-(3,3-Diethylpropyl)-4-methylbenzamide (13) (entry 7a, Table 1). To a 250 mL round-bottomed flask was charged *N*-(3,3-diethylpropyl)-4-methylbenzamide (**13**, 5.0 mmol) and acetone (100 mL) to which was added indium(III) trifluoromethanesulfonate (0.1 mol %). The reaction mixture was allowed to stir at room temperature for 2 h after which time ^{1}H NMR, HPLC, and TLC analyses indicated that the reaction was complete. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (100 g) with hexanes/ethyl acetate (10:1 to 4:1 gradient) as the eluent, giving 870 mg of 4-methyl-*N*-(3-oxopropyl)benzamide **14** (91% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 9.83 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.82 (br s, 1H), 3.71 (q, *J* = 5.9 Hz, 2H), 2.826 (t, *J* = 5.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm 201.7, 167.5, 141.9, 131.4, 129.2, 126.9, 43.8, 33.4, 21.4; HREI-MS *m/z* found 191.0937 (C$_{11}$H$_{13}$NO$_2$ requires 191.0946)

Deprotection of Benzaldehyde Dimethylacetal (1b). To a 3-L round-bottomed flask was added benzaldehyde dimethylacetal (22.8 g, 150 mmol) to which was added acetone (800 mL) followed by indium(III) trifluoromethanesulfonate (40 mg, 0.07 mmol). After 15 min the reaction was complete as indicated by TLC and ^{1}H NMR analyses. The volatile organics were removed under vacuum and the resulting residue was chromatographed with silica gel (600 mL) eluting with hexanes/ethyl acetate (20:1 to 4:1 gradient) to give 16.3 g of benzaldehyde (91% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 10.03 (s, 1H), 7.88 (d, *J* = 6.8 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm 192.3, 136.4, 134.4, 129.8, 129.0, 128.5.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **13**, **14**, **15**, **16**, **27**, **28**, **39**, **41**, and **42**, as well as ^{1}H NMR spectra of purified products **2**, **4**, **6**, **8**, **10**, **18**, **20**, **22**, **24**, **26**, **30**, **32**, **34**, **36**, **38**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0707075