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An efficient catalytic deprotection of thioacetals employing bismuth triflate: synthesis of pyrrolo[2,1-*c*] [1,4] benzodiazepines

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Abstract—A simple and efficient deprotection of thioacetals has been achieved by employing bismuth triflate. This method has been effectively employed in the preparation of DNA-binding pyrrolo[2,1-*c*] [1,4]benzodiazepine and its dimers.

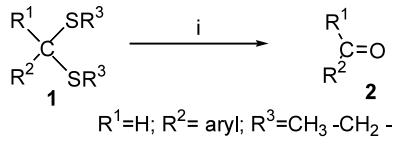
Thioacetals are frequently used to protect carbonyl compounds in the course of total synthesis of organic compounds and hence several reagents have been developed for their deprotection.[1,2] Despite the availability of many reagents and procedures for deprotection into their parent carbonyl compounds most are usually not straightforward. Therefore, considerable efforts have been directed towards developing mild and selective methods for thioacetal deprotection. Typically most of these methods require the use of protic or Lewis acids and a large number of these methods require drastic conditions or toxic reagents such as mercuric,[3] and Fe(III) reagents or heavy metal salts.[4] Thioacetals have also been deprotected by the combined use of molecular oxygen and catalytic amounts of $Bi(NO_3)_3{\cdot}5H_2O$.[5] Recently, some non-metallic reagents such as trimethyloxonium tetrafluoroborate,[6] methylfluorosulphonate[7] and oxides of nitrogen[8] have also been used for deprotection. Usually these methods are expensive and require multistep operations. More recently, we have reported a facile method for dethioacetalization employing $FeCl_3{\cdot}6H_2O$.[9] Herein we wish to report an extremely mild method for the deprotection of thioacetals **1** to the corresponding carbonyl compounds **2** with a catalytic amount of bismuth triflate in a biphasic system (Scheme 1).

Unlike the mercuric reagents that are usually employed in the laboratory, bismuth(III) salts have very low toxicity, are relatively stable to air and small amounts of moisture, and have advantages as reagents in organic synthesis.[10,11] Over the last few years, bismuth derivatives have attracted much attention, e.g. bismuth triflate, which has been employed as an efficient catalyst in organic synthesis that exhibits stronger activity than other known metal triflates. Bismuth triflate is not commercially available, but it can be easily synthesized in large quantities at a relatively low cost.[12] In the present procedure bismuth triflate was freshly prepared and employed for the dethioacetalization process.

The experimental procedure is simple and involves stirring the substrate in a solution of CH_2Cl_2/H_2O (8:2 v/v) in the presence of bismuth triflate as catalyst (0.1 mol%).

Representative thioderivatives of aldehydes were readily deprotected to give the parent carbonyl compounds in good yields and the results are described in Table 1. In addition to these results, it was observed that longer reaction times were required for the deprotection of thioacetals derived from propane and ethane dithiols.

We have an interest in the development of new synthetic strategies for the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system, that is known to interact with DNA in a sequence selective manner and as such has potential for the development of antitu-



Scheme 1. *Reagents and conditions*: (i) $Bi(OTf)_3{\times}H_2O$, rt 10–15 min.

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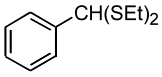
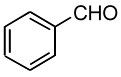
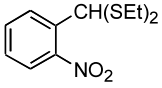
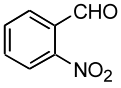
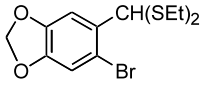
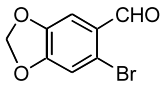
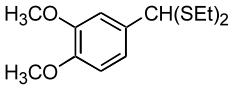
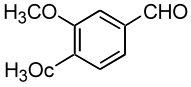
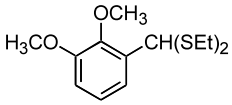
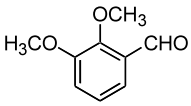
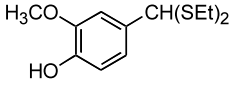
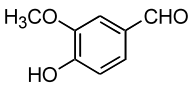
Table 1. Deprotection of thioacetals by $Bi(OTf)_3 \times H_2O$

Entry	Substrate(**1**)	Product[a] (**2**)	Time(min)	Yield(%)[b]
a.			15	95
b.			10	90
c.			15	85
d.			10	90
e.			10	90
f.			15	80

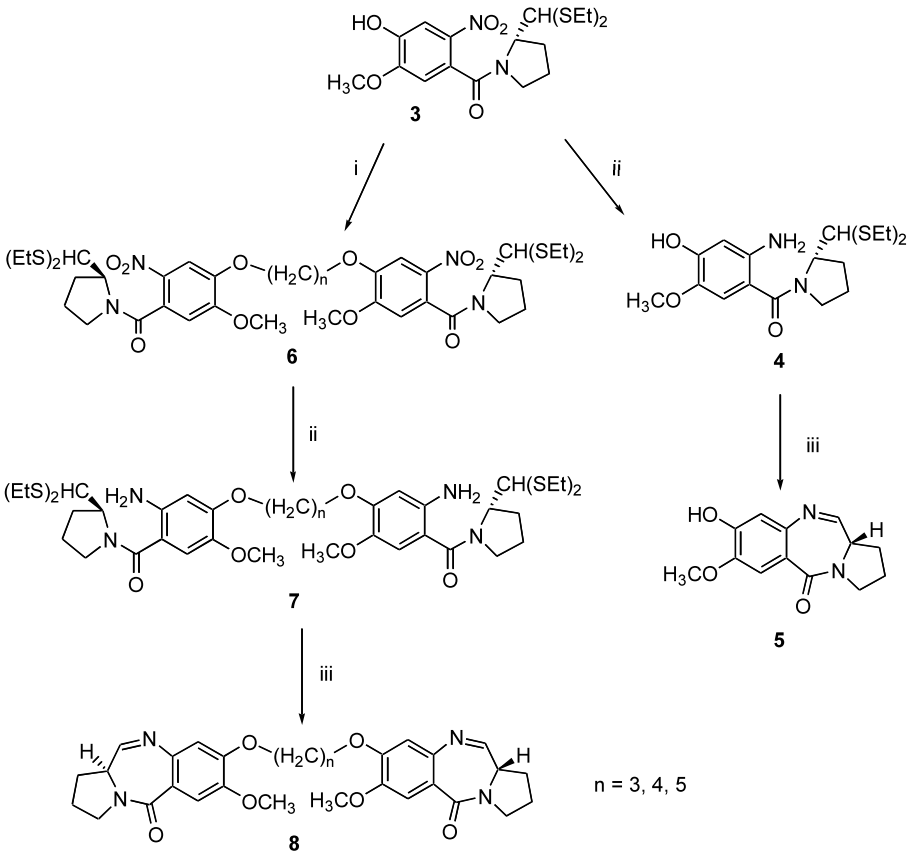
[a] Products were characterized by comparing IR, NMR, and mass spectra with those of authentic samples.[b]Isolated yields.

mour agents and gene targeting drugs.[13,14] A number of methods are known for the synthesis of this ring system via a dithioacetal deprotection that have met with varying degrees of success but which have different limitations.[15] The results obtained with bismuth triflate outlined above prompted us to extend such an environmentally friendly methodology to the benzodiazepines. This process would avoid the use of mercuric reagents for the well-known ethanethiol deprotective cyclization, thus enabling the introduction of a mild cyclization process where the product would be free from toxic mercuric salts.

The precursor, (2*S*)-*N*-(4-hydroxy-5-methoxy-2-aminobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetal **4** was prepared as described in the literature.[16] This upon deprotective cyclization with bismuth triflate afforded the desired PBD imine **5**. Unlike the general procedure for deprotection of thioacetals this deprotective cyclization required 2 mol% of bismuth triflate. This approach was also applied to the synthesis of PBD dimers. The precursor (2*S*)-*N*-(4-hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetal **3** was alkylated using a series of dibromoalkanes to obtain the 4,4′-(alkane-α,ω-diyldioxy)bis[(2*S*)-*N*-(5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetals **6**.[17] These upon reduction with $SnCl_2{\cdot}2H_2O$ gave the corresponding aminodiethylthioacetals **7**, which on deprotective cyclization with bismuth triflate afforded the PBD dimeric imines **8** in good yields 65–80% in the final step (Scheme 2).

Typical procedure: To a stirred solution of (2*S*)-*N*-(4-hydroxy-5-methoxy-2-aminobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetal **4** (185 mg, 0.5 mmol) in CH_2Cl_2/H_2O (8:2) was added $Bi(OTf)_3{\times}H_2O$ (6.5 mg, 2 mol%) at room temperature. After completion of the reaction (40 min) as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ (10 ml) and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate: hexane (9:1) to afford the pure PBD imine **5** in 80% yield.[18]

In summary, this work demonstrates a new method for the deprotection of thioacetals to their carbonyl compounds using bismuth triflate. We have further demonstrated its application towards the synthesis of the PBD ring system and its dimers resulting in significant improvements in yields and, most importantly, the products were devoid of contamination from mercuric salts. Therefore, this work will find use in organic synthesis involving thioacetal deprotection and also in the preparation of biologically significant PBD based DNA-interactive compounds.



Scheme 2. *Reagents and conditions*: (i) dibromoalkanes, K_2CO_3, acetone, reflux, 36–48 h, 93–95%; (ii) $SnCl_2 \cdot H_2O$, CH_3OH, reflux, 2 h, 80–85%; (iii) $Bi(OTf)_3 \times H_2O$, CH_2Cl_2:H_2O, rt, 40 min, 65–80%.

Acknowledgements

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17. Preparation of compound **6**: To a stirred solution of 1,3-dibromopropane (101 mg, 1.0 mmol) in dry acetone (30 ml) was added anhydrous potassium carbonate (410 mg, 3 equiv.) and the monomer **3** (400 mg, 1 mmol). The reaction mixture was refluxed for 36–48 h. After completion of the reaction as indicated by TLC, potassium carbonate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane (7:3) as eluent to afford pure PBD dimer ($n=3$) in 93% yield.
18. Selected spectroscopic data for compound **5**: ^{1}H NMR ($CDCl_3$): δ 2.01–2.09 (m, 2H), 2.29–2.35 (m, 2H), 3.54–3.61 (m, 1H), 3.70–3.74 (m, 1H), 3.79–3.85 (m, 1H), 3.96 (s, 3H) 6.40 (br s, 1H), 6.86 (s, 1H), 7.5 (s, 1H), 7.67 (d, 1H $J=4.2$ Hz); EI MS: m/z 246 (M^+); **8** ($n=3$). ^{1}H NMR ($CDCl_3$): δ 2.01–2.17 (m, 2H), 2.27–2.44 (m, 8H), 3.50–3.86 (m, 6H), 3.92 (s, 6H), 4.24–4.34 (m, 4H), 6.86 (s, 2H), 7.51 (s, 2H), 7.65 (d, 2H, $J=4.4$ Hz); FAB MS: m/z 533 (M+H).