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Tetrahedron Letters 44 (2003) 1191–1193

TETRAHEDRON
LETTERS

A remarkable bismuth nitrate-catalyzed protection of carbonyl compounds

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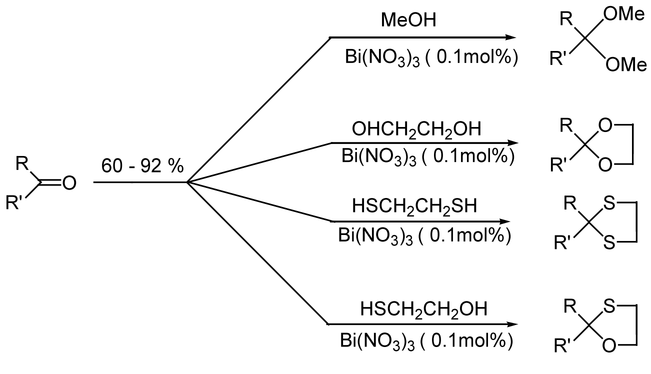
Received 20 November 2002; revised 11 December 2002; accepted 12 December 2002

Abstract—Bismuth nitrate has been found to be an outstanding catalyst for the protection of carbonyl compounds as acetal, ketal, mixed ketal and thioketal with an excellent yield. © 2003 Elsevier Science Ltd. All rights reserved.

The protection of carbonyl groups plays an important role in organic, medicinal, carbohydrate, and drug design chemistry. Tremendous effort has been made to search for a suitable protective group for carbonyl compounds.[1] In spite of these efforts, acetal, 1-3-dioxalane, mixed ketal, and thioketal protection remains the most practical choice.[2] In general, this method requires protic or Lewis acids as catalysts.[2] Lanthanides and other metal-catalysts are found to be excellent in the acetalization of carbonyl compounds.[3,4] The most important shortcomings of the acid-induced methods are the long reaction time, high temperature conditions (removing the water as an azeotrope with benzene), and stoichiometric amounts of reagents.[1,2] On the other hand, lanthanides and Lewis-catalysts are substrate selective, but a general method can not be achieved by using these catalysts.[3,4] Development of a catalytic version of these methods with low-toxic, readily available, economic reagents should greatly contribute to the realization of environmentally benign processes.

We have been engaged in bismuth-based organic transformations.[5] During this course of study, we have discovered that aromatic nitration,[5a,b] the oxidation of alcohols[5c] and the deprotection of oximes[5d] can all be mediated by commercially available bismuth nitrate. In principle, these reactions require the presence of acids. Moreover, this reagent has been used for the deprotection of acetal-types of groups.[6] As a result of these studies and recognizing that acetalization–deacetalization reactions are reversible reactions, we hypothesized that bismuth nitrate would be an efficient catalyst for protection of the carbonyl groups. In this paper, we describe our study of the protection of carbonyl compounds as acetals, dioxalones, mixed ketals and thioketals using a general bismuth nitrate method at room temperature. Using this method, a facile diastereoselective synthesis of dioxolanones and oxathiolanones has also been achieved. Notably, bismuth nitrate has been found to be highly effective in the protection of aldehydes and ketones, even with 0.1 mol% of the reagent (Scheme 1).

At the beginning of the study, several carbonyl compounds were protected as acetals using catalytic amounts of bismuth nitrate and methanol. A higher proportion of bismuth nitrate (5 mol%) can accelerate the reaction. However, this can cause serious setbacks as well. Proper maintenance of the reaction time and conditions is absolutely necessary for the success of the reaction. Otherwise, a considerable amount of product



Scheme 1.

Keywords: bismuth nitrate; catalyst; protection; diastereoselectivity.

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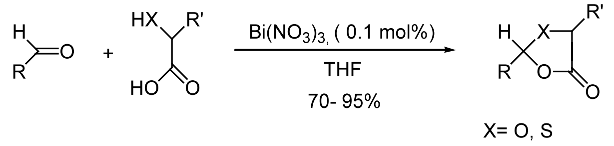
PII: S0040-4039(02)02821-6

can revert to the starting carbonyl compound. After a great deal of experimentation, we found that 0.1 mol% bismuth nitrate was sufficient to obtain the desired compounds in excellent yield and within a few hours (Scheme 1, Table 1, entries 1–21). Nearly all types of carbonyl compounds can be used with success. We prepared other ketals, the results of which are promising. For example, dioxalones, mixed ketals, and thioketals prepared under these conditions posed no problems. In general, these reactions required a relatively longer time to reach completion.

In light of Ram Mohan' s report,[6] our results deserve special comments. It was reported that bismuth triflate (0.1–1 mol%) catalyzes the protection of carbonyl compounds in the presence of methanol/ethanol and trialkylorthoformate. In this report, the actual protective group was delivered from the trialkylorthoformate: methanol or ethanol served as the catalyst. There is no doubt that this method is excellent when compared with the other methods in this field.[1–4] However, our bismuth nitrate-catalyzed method is more practical, and is more convenient than the bismuth triflate-catalyzed process. The first advantage of bismuth nitrate is its commercial availability. Bismuth triflate is not commercially available and must be prepared by one of the following ways: the reaction of triflic acid on bismuth tris-trifluoroacetate,[7] the addition of triflic anhydride on bismuth oxide,[8] the reaction of a mixture of triflic acid and its anhydride on bismuth oxide,[8] or reaction of triflic acid on triphenylbismuth.[9] Therefore, effectively in all cases an excess of expensive triflic reagent has to be used. In most of the cases, the bismuth triflate obtained from these procedures was obtained in its hydrated form. The second advantage of our method is that an alcohol is the actual reagent and, in contrast with the bismuth triflate-catalyzed process, trialkylorthoformate is not required. The third advantage is in reagent stability, bismuth nitrate is a solid and a much more stable reagent compared with bismuth triflate. However, the catalytic activity of the two reagents is almost identical. The fourth advantage is that the bismuth nitrate catalyzed reaction proceeds exceedingly well at room temperature.

Realizing the versatility of our bismuth nitrate-catalyzed protection of carbonyl compounds, we envision that this method can provide easy access to dioxolanones. Compounds of this type are frequently used as starting materials for the synthesis of many natural and non-natural compounds.[10] The reaction of racemic or optically active lactic acid, thiolactic acid and mandelic acid with aldehydes, in principle, can produce two isomeric compounds under these conditions. In conformity of hypothesis, our bismuth nitrate-catalyzed reaction produced a diastereoselective mixture of *cis* and *trans* (85:15) dioxolanones and oxathiolanones with an excellent yield (Scheme 2, Table 2). The isomeric ratios were calculated by comparison of the NMR spectra of authentic samples and those produced by our method.[10] Bronsted acid-catalyzed acetalization with azeotropic removal of water and Lewis acid-mediated reaction also produced a similar mixture of isomers.

For a successful bismuth nitrate-catalyzed reaction of this type, one would expect generation of nitric acid in the reaction medium. A reaction in the presence of a catalytic amount of nitric acid results in low yield of the



Scheme 2.

Table 1. Protection of carbonyl compounds by catalytic amounts (0.1 mol%) of bismuth nitrate

Entries	Carbonyl compounds	Alcohols/thiols	Time (h)	Yield (%)
1	Benzaldehyde	MeOH	6	75
2	2-Bromobenzaldehyde	MeOH	5	90
3	*trans*-Cinnamaldehyde	MeOH	5	70
4	*p*-Anisaldehyde	MeOH	5	60
5	Decyl aldehyde	MeOH	5	92
6	3-Bromobenzaldehyde	MeOH	5	76
7	Cyclohexanone	MeOH	4	72
8	4-Methylcyclohexanone	MeOH	4	76
9	4-*tert*-Butylcyclohexanone	MeOH	4	70
10	Benzaldehyde	Mercaptoethanol	5	75
11	2-Bromobenzaldehyde	Mercaptoethanol	5	70
12	*trans*-Cinnamaldehyde	Mercaptoethanol	5	75
13	*p*-Anisaldehyde	Mercaptoethanol	5	70
14	Cyclohexanone	Ethylene glycol	6	70
15	4-Methylcyclohexanone	Ethylene glycol	6	72
16	Benzaldehyde	Ethylene glycol	6	60
17	*trans*-Cinnamaldehyde	Ethylene glycol	5	65
18	*p*-Anisaldehyde	Ethylene glycol	5	75
19	Benzaldehyde	Ethanedithiol	5	78
20	*trans*-Cinnamaldehyde	Ethanedithiol	5	75
21	*p*-Anisaldehyde	Ethanrdithiol	5	75

Table 2. Protection of aldehydes with α-hydroxy acids and thiolactic acid using 0.1 mol% of bismuth nitrate

Carbonyl compounds	Acids	Time (h)	Yields (%)	*cis*/*trans*
Pivaldehyde	L(+)-Lactic acid	6	95	78/22
Pivaldehyde	Mandellic acid	8	90	85/15
Pivaldehyde	Thiolactic acid	6	90	76/24
Dihydrocinnamaldehyde	Thiolactic acid	10	70	65/35

products (Table 1, entries 1, 7, 14 and 21). Precise control of the acidity in a small-scale reaction with corrosive nitric acid or any other strong acid is extremely difficult. Considering the reversible nature of these processes, this low yield is expected.

In summary, the present bismuth nitrate-catalyzed method of protection of carbonyl compounds is very general, mild, cost-effective and convenient. We believe that none of the other methods previously described in the literature demonstrate this kind of simplicity and effectiveness.[11]

Acknowledgements

We gratefully acknowledge the funding support received for this research project from the University of Texas M. D. Anderson Cancer Center for the partial support of this research. We are thankful to NIH Cancer Center Support Grant 5-P30-CA16672-25, in particular, the shared resources of the Pharmacology and Analytical Center Facility.

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11. General acetalization procedure: The carbonyl compound (1 mmol) was dissolved in methanol (4 mL), and bismuth nitrate (0.1 mmol) was added while stirring. After the starting material was consumed as indicated by TLC, the methanol was evaporated. The crude product was extracted with dichloromethane, washed with saturated $NaHCO_3$, and dried over Na_2SO_4, and the solvent was evaporated. Finally the pure products were obtained by purification through basic alumina using ethyl acetate-hexane (10:90) as the solvent. A similar procedure was adopted with ethylene glycol, ethanedithiol, mercaptoethanol, α-hydroxy acids and thiolactic acid in THF. All the compounds were characterized by comparison with an authentic sample (^{1}H NMR).