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Efficient and Chemoselective Conversion of Carbonyl Compounds to 1,3-Dioxanes Catalyzed with *N*-Bromosuccinimide under Almost Neutral Reaction Conditions

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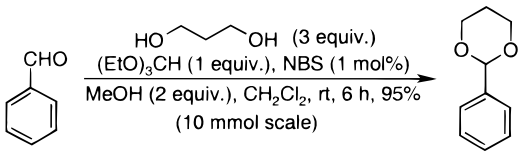
ABSTRACT



Various types of carbonyl compounds were converted to the corresponding 1,3-dioxanes in the presence of ethyl orthoformate, 1,3-propanediol, and a catalytic amount of NBS via an in situ acetal exchange process. In contrast to conventional acid-catalyzed acetalization reactions, acid-sensitive substrates such as THP ethers and TBDMS ethers remain intact under described reaction conditions.

Acetals are among the most popular protecting groups for carbonyl compounds.[1] In addition, chiral acetals are particularly important for the preparation of enantiomerically pure compounds.[2] Although the formation of acetals is generally achieved with protic acid catalysts, it has been shown that the use of Lewis acids in these transformations may be advantageous in some cases.[3] Very recently, we have shown that WCl_6 and $ZrCl_4$ are highly efficient catalysts for chemoselective acetalization of various types of carbonyl compounds.[4] However, these two catalysts were not suitable for the acetalization of carbonyl compounds containing other acid-sensitive functionalities, such THP ethers. We thus researched a milder catalytic system that would allow survival of other acid-sensitive groups.

NBS has already been known as a mild oxidizing reagent for chemoselective oxidative deprotection of *S,S*-acetals. A brief survey of the literature shows that free hydroxyl groups, disubstituted alkenes, and acid-sensitive functional groups such as MEM ethers, TBDPS ethers, 1,3-dioxanes, and phenolic benzyl ethers survive intact in the presence of NBS.[5] In our development of new methods for functional group

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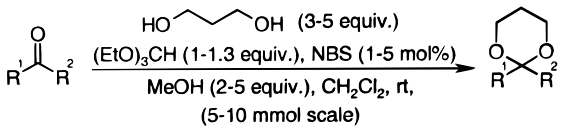
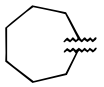
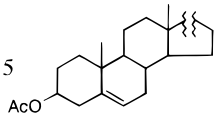
Scheme 1



transformations, we are especially interested in exploring the potential use of various types of neutral catalyst.[6] Along this line, we have found that various aldehydes are converted to the corresponding 1,3-dioxanes in excellent yields upon treatment with $(EtO)_3CH$ (1 equiv), dry MeOH (2 equiv), 1,3-propanediol (3 equiv), and a catalytic amount of NBS (0.01−0.02 equiv) (Scheme 1, Table 1, entries 1−6)[7]

Table 1. Acetalization of Carbonyl Compounds in the Presence of NBS

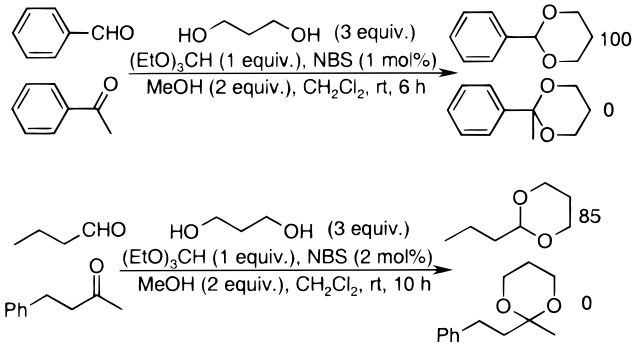
entry	R^1	R^2	subst./diol/ MeOH/$(EtO)_3CH$/ NBS	time (h)	yield[a] (%)
1	Ph	H	1:3:2:1:0.01	6	95
2	4-(Cl)C_6H_4	H	1:3:2:1:0.01	2.5	97
3	4-(NO_2)C_6H_4	H	1:3:2:1:0.02	6	92
4	4-(CH_3)C_6H_4	H	1:3:2:1:0.02	6	78
5	PhCH=CH	H	1:3:2:1:0.02	5	92
6	n-propyl	H	1:3:2:1:0.02	7.5	79
7	$PhCH_2CH_2$	CH_3	1:3:3:1.2:0.03	72	89
8	Ph	CH_3	1:3:3:1.2:0.03	72	81
9	4-(Cl)C_6H_4	CH_3	1:3:3:1.2:0.03	60	85
10	4-(NO_2)C_6H_4	CH_3	1:3:3:1.2:0.03	72	70
11			1:3:3:1.2:0.04	72	86
12	Ph	H	1:4:2:1:0.02	24	80[b]
13	Ph	CH_3	1:4:3:1.2:0.03	72	78[b]
14	Ph	Ph	1:5:5:1.3:0.05	168	22[c]
15			1:5:5:1.3:0.05	168	30[c]
16	(-)-camphor		1:5:5:1.3:0.05	168	25[c]
17	4-(OH)C_6H_4	H	1:3:3:1.2:0.03	168	-[d]

[a] Yields refer to isolated pure product unless otherwise stated. [b] (+)-Dimethyl tartrate was used instead of 1,3-propanediol. [c] Yields are based on NMR of the crude products. [d] No reaction.

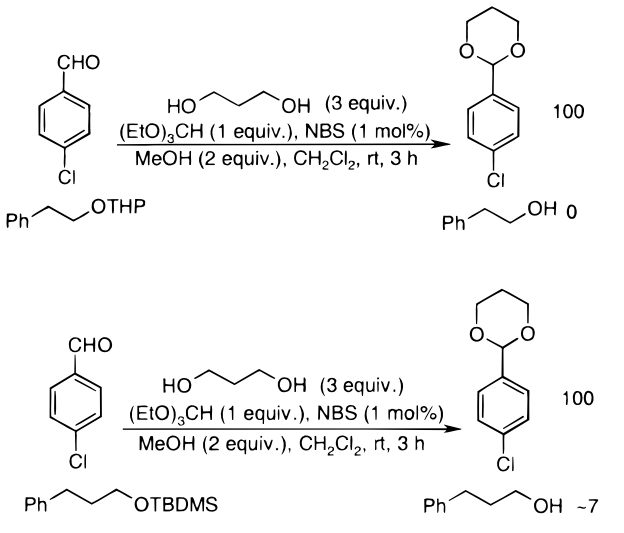
Aliphatic and aromatic ketones also formed the respective acetals under these conditions, although long reaction times were required to obtain satisfactory yields (Table 1, entries 7−11). The reaction of benzaldehyde and acetophenone with (+)-dimethyl tartrate in the presence of 2 and 3 mol % of NBS also furnished the corresponding optically active acetals in high yields (Table 1, entries 12 and 13). Moreover, acetalization of relatively hindered ketones such as (−)-camphor, benzophenone, and 3-β-acetoxyandrost-5-en-17-one was also achieved in low yields in the presence of 5 mol % of NBS after prolonged reaction times (Table 1, entries 14−16). On the other hand, 4-hydroxybenzaldehyde was recovered intact even after 7 days under similar reaction conditions.

Because ketones undergo acetalization considerably slower than aldehydes, it seemed plausible that our system could promote chemoselective protection of aldehydes in the presence of ketones. Indeed, benzaldehyde and butanal were converted to the acetals in the presence of acetophenone and benzylacetone with complete selectivity (Scheme 2).[8] This result suggests that our method may be generally useful for the conduction of similar chemoselective acetalization reactions. It is also worthy of note that acid-sensitive substrates such as THP ethers and TBDMS ethers remain intact under these conditions (Scheme 3).[9]

Scheme 2



Scheme 3



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The precise role of NBS is not clear in this method. One explanation for this process is that NBS probably generates small quantities of HBr, which may be the actual catalyst for the acetalization reactions. However, when we conduct similar acetalization reactions with benzaldehyde in the presence of a catalytic amount of a saturated HBr solution in benzene instead of NBS, a drastic rate enhancement was observed and the reaction was completed within minutes (15 min). This observation may be due to the fact that HBr is produced in smaller amounts in the NBS protocol than from the saturated solution of HBr. Another explanation is that NBS could act as a precursor for the formation of Br^+, which in turn could behave as a Lewis acid in the reaction medium. Nevertheless, at this time we have obtained no experimental evidence for these two features of NBS, and the actual role of this reagent should be further studied in detail.

In summary, we have demonstrated that NBS is a new, efficient, and practically neutral catalyst for 1,3-dioxanation of aldehydes and ketones. Work on other reactions promoted by NBS and related compounds is currently underway in our laboratory.

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(7) **General procedure for acetalization of carbonyl compounds catalyzed with NBS:** To a solution of carbonyl compound (10 mmol), $(EtO)_3CH$ (10−13 mmol), anhydrous methanol (20−50 mmol), and dry 1,3-propanediol (30−50 mmol) in CH_2Cl_2 (50 mL) was added NBS (0.1−0.5 mmol), and the resulting solution was stirred at room temperature. After completion of the reaction (TLC or GC), a cold aqueous solution of $NaHCO_3$ (10%, 25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with water (2 × 15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was proceeded by vacuum distillation or recrystalization to afford pure acetals (Table 1).

(8) The product ratios were determined by NMR spectroscopy.

(9) The product ratios were determined by GC and NMR.