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Selective Monobromination of 1,3-Diones with *N*-Bromosaccharin/$Mg(ClO_4)_2$ System in Solution and under Solvent-Free Conditions

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N-Bromosaccharin/$Mg(ClO_4)_2$ is an effective and regioselective system for α-monobromination of 1,3-dicarbonyl compounds. A wide variety of β-keto esters and 1,3-diketones in reaction with this system afforded a regioselectively α-monobrominated products. The bromination reaction can be conducted at 0-5 °C either in solution or under solvent-free conditions.

Key Words : Bromination, 1,3-Diones, *N*-Bromosaccharin, Lewis acid, Solvent free conditions

Introduction

α-Bromination of carbonyl compounds is an important organic transformation as they are useful intermediates in organic synthesis.[1] α-Brominated carbonyls serve as valuable building blocks in the synthesis of both natural and non-natural products.[2] It has been reported that bromination at the reactive position in a 1,3-keto compound enhances bio-activity, particularly cytotoxicity against breast cancer 1A9 cells, with respect to the unsubstituted compound.[3]

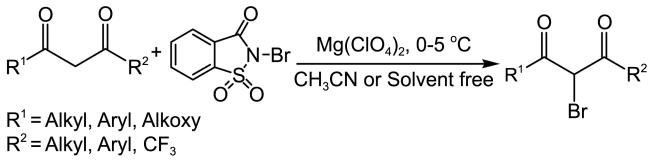
Some of reagents reported for this transformation include molecular bromine,[4] $CuBr_2$ with [hydroxy(tosyloxy)iodo] benzene,[2] NBS/Et_3N,[5,6] NBS/$Mg(ClO_4)_2$,[7] NBS/Amberlyst-15,[8] NBS/silica-supported $NaHSO_4$,[9] NBS/ionic liquids,[10] NBS/sulfonic acid functionalised silica,[11] NBS under solvent free conditions,[12] bromodimethylsulfoniumbromide,[13] ethylene bis(*N*-methylimidazolium) ditribromide,[14] H_2O_2-HBr,[15] V_2O_5-H_2O_2 catalysed oxidation of ammonium bromide,[16] trihaloisocyanuric acids,[17] and pyridinium bromochromate.[18] Although most of these methods provide good yields, many of them suffer from one or more disadvantages. Thus molecular bromine, the simplest brominating agent, suffers from several drawbacks: it is hazardous and difficult to handle and to maintain the stoichiometric ratio during the reaction. Other problems associated with these methods are tedious work-up procedures and long reaction times.

N-Bromosaccharin has been used as oxidants and brominating agent. It is a white powder and easy to handle.[19] *N*-Bromosaccharin has been asserted to be a useful reagent for various organic transformations, such as conversion of alcohols into the corresponding bromide,[20] oxidation of thiols to their corresponding disulfides,[21] halogenation of aromatic compounds and co-halogenation of alkenes,[22] oxidative cleavage of oximes to the corresponding aldehydes and ketones[23] and halogenation of benzylic and carbonylic positions.[24] On the other hand, the chelation of Lewis acids to the two carbonyl groups of dione compounds promotes the enol formation and thus changes the electronic property of the α-carbon,[25] and also cause to decrease of reaction time and increase regioselectivity.[7]

In this paper we report a facile method for the α-monobromination of 1,3-dicarbonyl compounds with NBSac in the presence of $Mg(ClO_4)_2$ as a catalyst in acetonitrile and solvent free conditions (Scheme 1).

Results and Discussion

Our first experiments were carried out on 1-phenylbutane-1,3-dione (1 mmol) with 1 mmol of NBSac in acetonitrile (5 mL) and solvent free condition at 0-5 °C in order to find the best reaction conditions. The reaction was examined in the



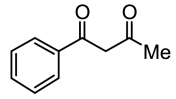
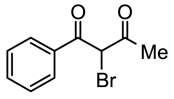
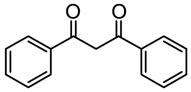
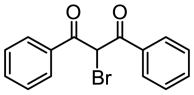
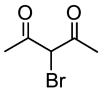
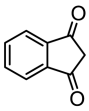
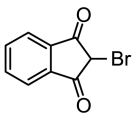
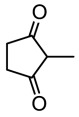
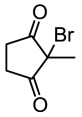
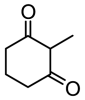
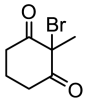
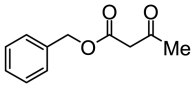
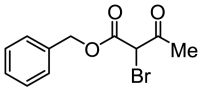
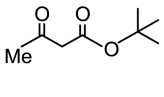
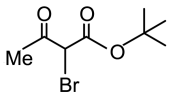
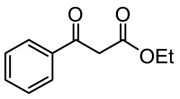
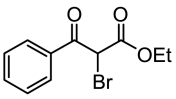
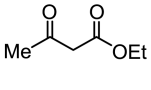
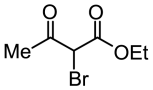
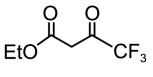
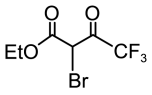
Scheme 1

Table 1. Investigation of Effect of Various Catalysts on the Mono α-Bromination of 1-Phenylbutane-1,3-dione[a]

Entry	Catalyst	Mol %	Time (min)[b]	Yield %[c]
1	-	-	25	70
			(10)	(77)
2	$Mg(ClO_4)_2$	1	12	75
			(2)	(80)
3	$Mg(ClO_4)_2$	2.5	8	81
			(1)	(85)
4	$Mg(ClO_4)_2$	5	5	92
			(Immediately)	(95)
5	$AlCl_3$	5	5	85
			(Immediately)	(89)
6	TiO_2	5	5	82
			(Immediately)	(87)
7	ZnO	5	5	79
			(Immediately)	(83)

[a]Reaction conditions: 1-phenylbutane-1,3-dione (1 mmol), NBSac (1 mmol), catalyst and 0-5 °C, in CH_3CN and solvent free conditions, catalyst. [b]The numbers in parentheses represent the results obtained in the solvent free conditions. [c]Yield refers to isolated products.

Table 2. Selective α-Monobromination of Active Methylene Compounds Using NBSac & $Mg(ClO_4)_2$ in Acetonitrile and Solvent Free Conditions[a]

Entry	Substrate	Product[b]	Time/min[c]	Yield/%[d]	mp/°C	Reference
1			5 (Immediately)	92 (95)	31-32	11
2			5 (Immediately)	95 (98)	92-93	15
3			15 (Immediately)	81 (84)	-	14
4			20 (1)	74 (80)	114-116	26
5			10 (Immediately)	91 (94)	-	14
6			10 (Immediately)	93 (98)	-	15
7			10 (Immediately)	71 (80)	-	13
8			10 (Immediately)	85 (90)	-	13
9			10 (Immediately)	80 (84)	-	15
10			10 (Immediately)	82 (85)	-	17
11			15 (Immediately)	79 (85)	-	27
12	$NCCH_2COOEt$	NCCHBrCOOEt	35 (2)	50 (50)	-	28

[a]Reaction conditions: Substrate (1 mmol), NBSac (1 mmol), $Mg(ClO_4)_2$ (0.05 mmol), 0-5 °C, in CH_3CN and solvent free conditions. [b]All of the products were identified by comparing melting point and ^1H NMR with those of authentic samples reported in literature. [c]The numbers in parentheses represent the results obtained in the solvent free conditions. [d]Yields refer to isolated products.

presence of different catalysts. It is clear from Table 1 that Lewis acid catalysts $Mg(ClO_4)_2$, $AlCl_3$, TiO_2 and ZnO are effective in bromination of activated methylens with *N*-bromo saccharin (Table 1, entry 2-7). However, we employed $Mg(ClO_4)_2$ as a catalyst because of slightly higher yield of bromination reaction (Table 1, entry 4). An optimum catalytic amount of 5 mol % of $Mg(ClO_4)_2$ is sufficient to afford the desired product in excellent yield. In the absence of catalyst, longer time required and lower yield of product was obtained (Table 1, entry 1).

Having these data in hand, these optimal conditions were exerted for transformation of wide range of active methylene compounds such as β-keto esters and 1,3-diketones into the corresponding α-monobrominated products.

As shown in Table 2, various unsubstituted 1,3-diones were α-monobrominated in good to excellent yields and trace to 5% dibrominated products were also obtained (Table 2, entries 1-4 and 7-11). Monoalkyl substituted 1,3-diketone was also brominated regioselectively at the α-position (Table 2, entries 5, 6). Under these reactions conditions, ethyl cyanoacetate was monobrominated at moderate yield (Table 2, entry 12).

Conclusion

In conclusion, we have developed a general method for the mild α-monobromination of 1,3-diones using NBSac and Mg(ClO$_4$)$_2$. NBSac is alternative and attractive reagent to perform bromination of 1,3-diones without the ring bromination. Furthermore, the reaction conditions are easy, fast, safe and this reagent is easily prepared by commercial sodium saccharin.

Experimental

Materials were purchased from Merck and Aldrich companies. NBSac was prepared according to the reported procedure.[29] The structure of all products was characterized by spectral data (^{1}H NMR, ^{13}C NMR and IR).

General Procedure for the Lewis Acid-Catalyzed α-Bromination of 1,3-Diones in Acetonitrile. To a stirred solution of dione (1 mmol) in acetonitrile (5 mL) was added Lewis acid Mg(ClO$_4$)$_2$ (0.05 mmol) at 0-5 °C. Then NBSac (1 mmol) was added to the mixture after 5 min. When the reaction was completed, the reaction mixture was then extracted with *n*-hexane. After evaporation of the solvent, the crude product was purified by filtration through a short silica gel column chromatography [eluent; *n*-hexane:ethyl acetate (19:1)]. The spectroscopic data for the known products compared well with the reported data.

General Procedure for the Lewis Acid-Catalyzed α-Bromination of 1,3-Diones under Solvent Free Conditions. Dione (1 mmol) and Lewis acid Mg(ClO$_4$)$_2$ (0.05 mmol) were triturated together in a porcelain mortar at 0-5 °C. Then NBSac (1 mmol) was added to the mixture after 5 min. After completion of the reaction, the reaction mixture was extracted with *n*-hexane (25 mL) and filtered.

After evaporation of the solvent, the crude product was purified through a short silica gel column chromatography [eluent; *n*-hexane:ethyl acetate (19:1)]. The spectroscopic data for the known products compared well with the reported data.

Spectroscopic Data of All Products:

1) 2-Bromo-1-phenyl botane-1,3-dione: mp 31-32 °C ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.48 (s, 3H), 5.65 (s, 1H), 7.61-7.68 (m, 2H), 8 (d, *J* = 7.6, 2H), 8.13 (m, 1H)

2) 2-Bromo-1,3-diphenyl propan-1,3-dione: mp 92-93 °C ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.61 (s, 1H), 7.48 (t, *J* = 7.6, 4H), 7.61 (t, *J* = 7.2, 2H), 8.02 (d, *J* = 7.2, 4H)

3) 3-Bromo-pentane-2,4-dione: ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.14 (s, 3H), 2.15 (s, 3H), 5.23 (m, 1H)

4) 2-Bromo-2-H-indene-1,3-dione: mp 114-116 °C ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.9 (s, 1H), 7.79- 7.90 (m, 4H)

5) 2-Bromo-2-methylcyclopentone-1,3-dione: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.50 (s, 3H), 2.56-2.57 (m, 2H), 2.66-2.77 (m, 2H)

6) 2-Bromo-2methyl-cyclohexane-1,3-dione: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.70-1.80 (m, 1H), 1.83 (s, 3H), 2.24-2.34 (m, 1H), 2.55 (t, *J* = 4.8, 1H), 2.59 (t, *J* = 4.8, 1H), 3.30-3.39 (m, 2H)

7) 2-Bromo-benzyl-3-oxo-butanoate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.42 (s, 3H), 2.22 (s, 2H), 5.34 (s, 1H), 7.28-7.41 (m, 5H)

8) 2-Boromo-trtiobutyl-3-oxo-butanoate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.50 (s, 9H), 2.55 (s, 3H), 4.69 (s, 1H)

9) 2-Bromo-ethyl-oxo-3-phenylpropanoate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.26 (t, *J* = 7.2, 3H), 4.29 (q, *J* = 7.2, 2H), 5.69 (s, 1H), 7.49-7.53 (m, 2H), 7.62-7.66 (m, 1H), 7.99-8.02 (m, 2H)

10) 2-Bromo-ethyl-3-oxo-butanoate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34 (t, *J* = 6.8, 3H), 2.46 (s, 3H), 4.31 (t, *J* = 6.8, 2H), 4.48 (s, 1H)

11) 2-Bromo-ethyl-4,4,4-trifluo-3-oxo-butanoate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.37 (t, *J* = 7.2, 3H), 4.60 (t, *J* = 7.2, 2H), 5.19 (s, 1H)

12) 2-Bromo-ethyl-2-cyanoacetoacetate: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.36 (t, *J* = 7.2, 3H), 4.47 (t, *J* = 7.2, 2H), 5.32 (s, 1H)

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