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Facile and Efficient Method for α-Monobromination of Dicarbonyl Compounds with N-Bromosuccinimide

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The α-monobrominated products were prepared fast in presence of *p*-TsOH as catalyst in very high yields using various 1,3-diketones and β-keto-esters with N-bromosuccinimide in CH_2Cl_2.

Key Words: N-bromosuccinimide, Bromination, Dicarbonyl compounds, β-Keto esters.

INTRODUCTION

α-Bromination of 1,3-dicarbonyl compounds is a very useful reaction in organic synthesis[1]. But monobromination of α-unsubstituted dicarbonyl compounds is difficult because the dibrominated products usually are formed in the same time[2]. Although many synthetic reactions have been developed recently, simple and high efficient methods are still rare. According to the literatures, N-bromosuccinimide (NBS) was proved to be superior to other brominating reagents[3] for its availability and easy handling. These α-bromination reactions of 1,3-dicarbonyl compounds with N-bromosuccinimide were proceeded smoothly in presence of NaH[4], Et_3N[5], NH_4OAc[6], $MgClO_4$[7], amberlyst[8], pyridinium bromochromate[9], sulfonic acid functionalized silica[10] under solvent-free conditions[11]. However, in our preparation work[12] of α-monobrominated compounds reactions using N-bromosuccinimide, most of the above methods did not give satisfactory results because the longer reaction times or the lower yields than those had been reported. Here we report that N-bromosuccinimide combined with *p*-TsOH in CH_2Cl_2 can afford a facile α-monobromination method of 1,3-dicarbonyl compounds. In term of its short reaction time, easy post-treatment and high yield, this method is very convenient and efficient.

EXPERIMENTAL

Typical procedure for bromination: To a solution of the dicarbonyl compound (1 mmol) in CH_2Cl_2 (10 mL), N-bromosuccinimide (1.1-1.3 mmol), *p*-TsOH·H_2O (0.2 mmol) was added and the mixture was stirred at room temperature for the specified period of time (Table-1). After the reaction was completed (monitored by TLC), the reaction mixture was filtered, washed with water (2 × 10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (petroleum ether-EtOAc, 15:1) to afford the corresponding pure product. All of the products were characterized by comparison of their spectral and physical data with those of authentic samples. The spectral data of some representative compounds were given below:

Ethyl-2-bromo-3-oxobutanoate (Table-1, entry 2): ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.69 (1H, s), 4.24 (2H, q, *J* = 7.0 Hz), 2.41 (3H, s), 1.29 (3H, t, *J* = 7.0 Hz); EI-MS: m/z (%) 210 (55), 208 (65).

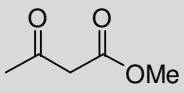
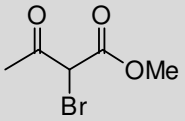
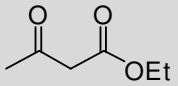
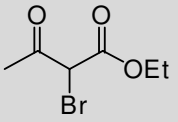
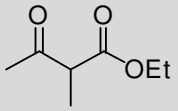
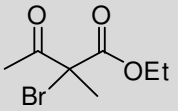
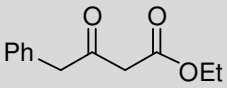
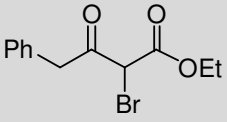
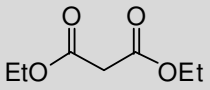
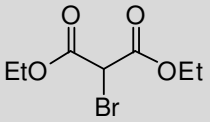
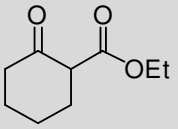
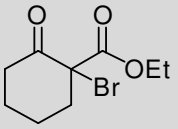
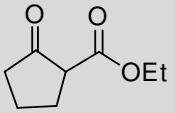
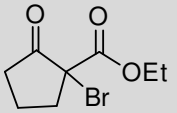
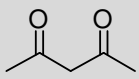
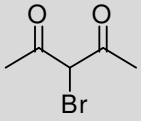
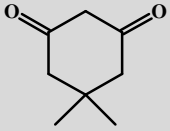
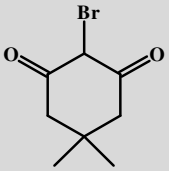
Ethyl 1-bromo-2-oxocyclohexanecarboxylate (Table-1, entry 6): ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.16 (q, 2H, *J* = 7.1 Hz), 2.76-2.72 (m, 2H), 2.34 (m, 1H), 2.09 (m, 1H), 1.81-1.63 (m, 4H), 1.17 (t, 3H, *J* = 7.1Hz); FAB$^+$-MS m/z (%): 249 (100), 251 (100).

2-Bromocyclohexane-1,3-dione (Table-1, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 1.10 (s, 6H), 2.47 (s, 4H), 6.63 (s, 1H). EI-MS m/z (%): 220 (75), 218 (65).

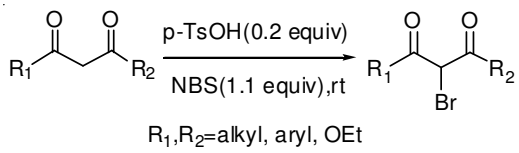
RESULTS AND DISCUSSION

All α-monobromination reactions of β-keto esters and 1,3-diketones were conducted in presence of *p*-TsOH at room temperature and in CH_2Cl_2 solvent (**Scheme-I**). As shown in Table-1, various α-substituted and unsubstituted 1,3-dicarbonyl compounds were converted to their brominated products in good yields (Table-1, entries 1-9).

TABLE-1
α-MONOBROMINATION OF DICARBONYL COMPOUNDS BY N-BROMOSUCCINIMIDE IN PRESENCE OF *p*-TsOH*

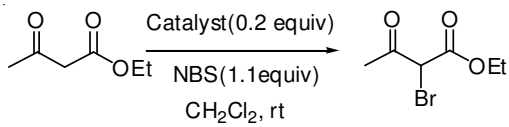
Entry	Substrate	Product**	Time (min)	Yield***
1			25	94
2			35	94
3			20	97
4			25	92
5			15	92
6			20	98
7			20	97
8			10	94
9			10	95

*All reactions were carried out with 1 mmol of substrate and 1.0-1.3 mmol N-bromosuccinimide in 10 mL of CH_2Cl_2 solvent in the presence of *p*-TsOH·H_2O (0.2 equiv). ** Experimental procedure and spectral data see references and notes. ***Isolated yields.



Scheme-I: α-Monobromination of β-keto-esters and 1,3-diketones using N-bromosuccinimide and *p*-TsOH

Both acyclic and cyclic 1,3-dicarbonyl compounds also reacted smoothly and gave the corresponding products in excellent yield (Table-1, entries 1-7 and 9). There were no dibrominated products observed in present experiments when using 1.05-1.2 equiv. of N-bromosuccinimide with the α-unsubstituted β-ketoesters (Table-1, entry 1, 2, 4 and 5), but the dibrominated products would generate if the N-bromosuccinimide exceeds too much (more than 1.5 equiv). In order to achieve the convincing results, we also preformed the bromination reactions with the same substrate in the presence or absence of some basic and acid catalysts (**Scheme-II**). It was observed that *p*-TsOH turned out to be the best catalyst among Et_3N, NH_4OAc, $Mg(ClO_4)_2$ and *p*-TsOH (Table-2). It was worth while pointing out that the α-monobromination method of 1,3-dicarbonyl compounds catalyzed by *p*-TsOH was established by chance in present experiments and the detailed mechanism of this method will be investigated in future.



Scheme-II: α-Bromination of ethyl acetoacetate using N-bromosuccinimide and different kinds of catalysts (All reactions were performed as done as **Scheme-I** with 1 mmol of ethyl acetoacetate and 1.2 mmol N-bromosuccinimide in 10 mL of CH_2Cl_2)

TABLE-2
α-MONOBROMINATION OF ETHYL ACETOACETATE BY N-BROMOSUCCINIMIDE IN PRESENCE OF VARIOUS CATALYSTS[d]

Entry	Catalyst	Reaction time (min)	Isolated yield (%)
1	*p*-TsOH	35	94
2	$MgClO_4$	55	83
3	NH_4OAc	70	67
4	Et_3N	80	55
5	No	90	33

Conclusion

A method for α-monobromination of dicarbonyl compounds with N-bromosuccinimide and *p*-TsOH in CH_2Cl_2 has been developed. In various basic and Lewis acid catalysts, *p*-TsOH was shown to be the better one than others.

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