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Short Communication

A Simple and Efficient Method for the Synthesis of α -Bromo Alicyclic Esters / Acids

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ABSTRACT

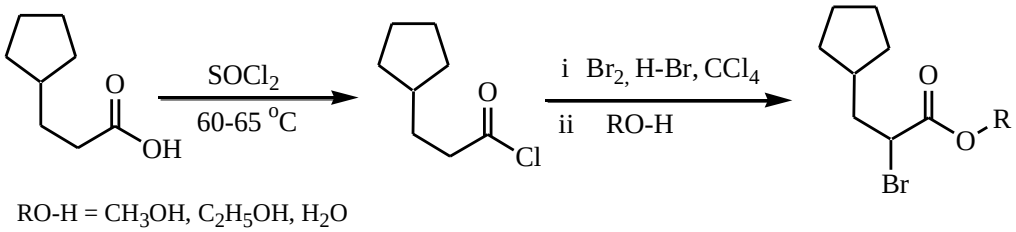
A simple, efficient and novel method for the synthesis of α-bromo alicyclic esters / acids is described. The process is applicable to different alicyclic acids tested and affords good to excellent yields of the desired α-bromo products under optimized reaction conditions.

Keywords: α-Bromination, alicyclic acid, esters, bromine.

INTRODUCTION

Synthesis of α-halo carbonyl compounds is one of the most important processes in organic chemistry as they contribute to be the key intermediate in synthesis of various pharmaceutical compounds [1-3]. Among halogenations, α-bromination of carbonyl compounds is most explored organic transformation[4-9]. α-Brominated carbonyls serve as valuable building blocks in the synthesis of both natural and non natural products [10,11]. There are only few reports on α-bromination of acids to get respective α-bromo acids [12-16]. Inspite of these developments, α-bromination of alicyclic acids are not explored.

Therefore, there is need to develop a method for the α-bromination of alicyclic acids, which can operate under milder reaction conditions. Hence, in the present paper, we report a novel and efficient method for the α-bromination of alicyclic acids. Excellent yields of desired α-bromo esters / acids were obtained under optimized reaction conditions (Scheme 1).



RO-H = CH_3OH, C_2H_5OH, H_2O

Scheme 1: α-Bromination of alicyclic acids.

MATERIALS AND METHODS

General: All chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals Ltd. with their highest purity available. The chemicals were used without any further purification. The selected products are well characterized by using analytical techniques like ^{1}H NMR (Varian 400 MHz), and MS-MS (Varian Inc, 410 Prostar 500 MS). TLC was carried out using Merck Kieselgel 60 PF254 plates. Column chromatography was performed using silica gel, 60–120 mesh.

General Procedure for synthesis of α-bromo alicyclic esters / acids: To a 50-mL RBF was added the alicyclic acid (2.0 mmol), and thionyl chloride (6.0 mmol). The mixture was heated at 60-65 °C and the progress of reaction was monitored by TLC, reaction is found to complete in 1h. The reaction mixture was cooled to RT and then to 0-5°C. Then at 0-5°C, charged bromine (2.0 mmol), HBr (4-5 drops) and CCl_4 (20.0 mL). The reaction mixture was refluxed and reaction was monitored using TLC. The reaction is found to complete in 2.0 to 2.5h. After completion of reaction, mixture was again cooled to 0-5°C and 30.0 mL of suitable solvent (alcohol or water) was added to it. The mixture was stirred for 30 min at 0-5 °C to obtain desired product. Finally, solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 60–120 mesh; petroleum ether/ethyl acetate, 60:80) to afford the desired α-bromo ester / acids.

2-bromo, 3-cyclopentyl propionic acid methy ester (Table 1, entry 1): Liquid. Yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.22-4.26 (t, *J* = 7.6 Hz, 1 H), 3.78 (s, 3 H), 2.01-2.11 (m, 2 H), 1.04-1.94 (m, 9 H) ppm.MS-MS (ESI^-): m/z calcd for (M+1): 235.10; found (M+1): 236.30.

2-bromo, 3-cyclopentyl propionic acid (Table 1, entry 3): Liquid. Yield: 82% .^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.30 (s, 1H), 4.23-4.39 (t, *J* = 7.4 Hz, 1 H), 2.02-2.11 (m, 2 H), 1.02-1.92 (m, 9 H) ppm.MS-MS (ESI^-): m/z calcd for (M+1): 221.12; found (M+1): 222.20.

RESULTS AND DISCUSSION

Initially, reaction of cyclopentyl propionic acid (CPPA) was chosen as model reaction. The product was achieved in two steps without isolation of intermediate. Initially, CPPA is converted into its acid chloride derivative using thionyl chloride as a chlorinating agent. The acid chloride so obtained was then subjected to bromination at α-position and finally converted into methyl ester by treating with methanol. The influence of various parameters such as temperature, solvent, acid reagent were examined on the model reaction (Table 1). The influence of solvents on α-bromination of CPPA was investigated (Table 1, entries 1–4). Solvents like CCl_4 (97 %), CH_2Cl_2 (69 %), $CHCl_3$ (38 %), and toluene (26 %) were screened. It was observed that the reaction gave better results with CCl_4 as a solvent. Next, we investigated effect of acid on rate of reaction. Among the various tested acids like HBr, HCl, H_2SO_4, $ZnCl_2$ (Table 1, entries 1 and 5–7); HBr found to give the desired product with excellent yield (97%).

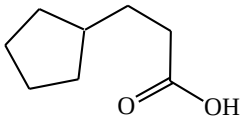
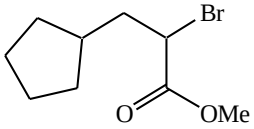
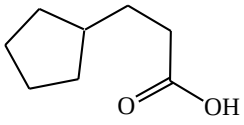
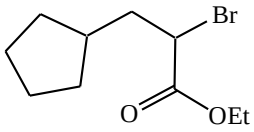
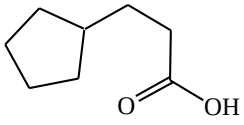
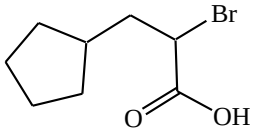
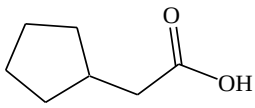
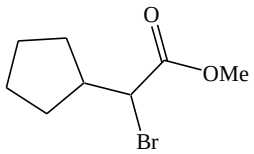
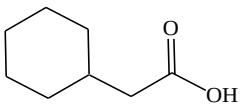
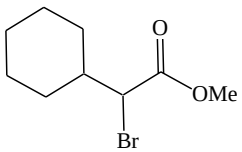
In order to examine the effect of temperature, reactions were carried out at different temperatures ranging from 50 to 85 °C (Table 1, entries 1 and 8-9). It was observed that reaction works well at reflux conditions (85 °C). With decrease in temperature the yield of product was found to decrease gradually.
The optimized reaction conditions were CPPA (2 mmol), thionyl chloride (6 mmol), bromine (2.0 mmol), HBr (4-5 drops), CCl_4 (20 mL) at 85 °C for 2.5 h. These conditions were applied for the synthesis of different α-bromo alicyclic esters / acids as a product (Table 2).
CPPA reacts efficiently under optimized reaction conditions, providing 97 % yield of the desired methyl ester product (Table 2, entry 1) when reaction was terminated with methanol. When reaction of CPPA was quenched with ethanol and water, α-bromo ethyl ester (89 %) and α-bromo acid (82 %) were obtained respectively (Table 2, entries 2-3).

Table 1. Effect of reaction parameters on α-bromination of CPPA. [a]

Entry	Solvent	Temperature (° C)	Acid	Yield (%)[b]
Effect of solvent				
1	CCl_4	85	HBr	97
2	CH_2Cl_2	42	HBr	69
3	$CHCl_3$	65	HBr	38
4	Toluene	115	HBr	26
Effect of acid				
5	CCl_4	85	HCl	56
6	CCl_4	85	H_2SO_4	62
7	CCl_4	85	$ZnCl_2$	36
Effect of temperature				
8	CCl_4	60	HBr	82
9	CCl_4	50	HBr	54

[a] Reaction conditions: CPPA (2 mmol), thionyl chloride (6 mmol), bromine (2.0 mmol), acid (4-5 drops), solvent (20 mL), 2.5 h, methanol (30 mL) [b] isolated yield.

Table 2. Synthesis of various α-bromo alicyclic esters / acids.[a]

Sr. No.	Substrate	Product	Yield (%)
1			97
2			89
3			82
4			88
5			76

[a] Reaction conditions: Alicyclic acid (2 mmol), thionyl chloride (6 mmol), bromine (2.0 mmol), HBr (4-5 drops), CCl_4 (20 mL), Time: 2.0-2.5 h, Temperature: 85 ° C, alcohol/water (30 mL). [b] isolated yield.

Under optimized reaction conditions cyclopentyl acetic acid furnishes methyl ester product with excellent yield (88 %) (Table 2, entry 4). We next examined reaction of cyclohexyl acetic acid under optimized reaction conditions, which delivered desired product in moderate amount (76 %) (Table 2, entry 5).

APPLICATIONS

This synthesis useful for preparation of different alicyclic α-bromo esters/acids.

CONCLUSIONS

We have developed a simple and efficient methodology for the synthesis of alicyclic α-bromo esters/acids. The reaction was optimized with respect to various parameters and could be used for the synthesis of different alicyclic α-bromo esters/acids, affording moderate to excellent yields of the desired products.

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