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Esterification of α-hydroxy carbonyls under Solvent-free conditions

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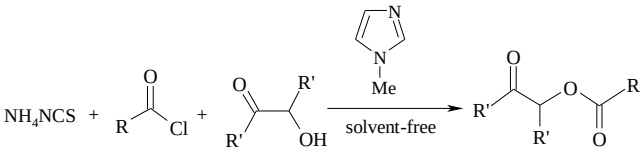
Abstract: An efficient synthesis of benzoate derivatives is described *via* an one-pot reaction between acid chlorides, ammonium thiocyanate, benzoin or 3-hydroxy-2-butanone and catalytic amount of *N*-methyl imidazol.

Keywords: Acid chlorides, Ammonium thiocyanate, *N*-methyl imidazole, 3-Hydroxy-2-butanone, Esterification, Solvent-free, One-pot reaction.

Introduction

Esterification is an important reaction due to the wide utility of esters in organic and bioorganic synthesis [1]. Esterification is extensively employed for the protection and further manipulation of the carboxylic acid functional group as well as the synthesis of natural products. There are numerous general methods for accessing carboxylic esters [1,2]. Among these, the direct esterification reaction of carboxylic acids with alcohols in the presence of a large number of different reagents and various conditions were established [1,2]. Moreover, the esterification of carboxylic acids or their salts with carbon electrophiles such as alkyl halides [3], sulfonates [3b,4], epoxides [5], aziridines [6], diazo compounds [7], quaternary ammonium salts [8], oxonium ions [9], acetals [10], trialkyl phosphates [11], trialkyl phosphites [12], methyltrialkoxy phosphonium tetrafluoborate salts [13], tbutyl ethers [14], ditosylamines [15], strained cycloalkanes [16] and multiple bonds [17] are well-known procedures. The reaction of carboxylic salts with carbon electrophiles is usually preferred because of easier handling, higher nucleophilicity, and simpler work-up and cleaner reaction in comparison with carboxylic acids. In view of the wide diversity of alcohols with respect to alkyl halides, the reaction of carboxylic salts with alcohols would seem to be a suitable and attractive strategy, and indeed there are a few reports that have exemplified the esterification of alcohols via carboxylic salts including: Mitsunobu conditions [18] using sodium [19] or zinc [20] carboxylate/Ph_3P/diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and potassium carboxylate/Ph_3P/CCl_4 [21]. The aforementioned methods have several drawbacks such as non-generality for various types of alcohols and carboxylic acids, the use of expensive DEAD or DIAD, low yields, long reaction times, tedious work-up as well as cumbersome separation from the generated Ph_3P=O and unreacted Ph_3P. Hence, there is still a need to develop practical and convenient methods for the esterification of alcohols with carboxylate salts. Therefore, we report an efficient synthetic route to ester derivatives. Thus, the reaction of ammonium thiocyanate **1**, acid chlorides **2**, benzoin or 3-hydroxy-2-butanone **3** and catalytic amount of *N*-methyl imidazol led to benzoate derivatives **4** in excellent yields (Scheme 1).



4	R	R'	Yield (%) of **4**
a	Ph	Ph	95
b	4-Me-C_6H_4	Ph	92
c	4-NO_2-C_6H_4	Ph	94
d	4-Br-C_6H_4	Ph	90
e	4-Cl-C_6H_4	Ph	85
f	$(CH_3)_3C$	Ph	87
g	4-Me-C_6H_4	CH_3	83
h	$(CH_3)_3C$	CH_3	75

Scheme 1

Result and discussion

Structures of compounds **4a–4h** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H- and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Spectral data for these compounds are given in the experimental section. The reactions between acid chlorides and alcohol in the presence of alkali were reported in the literature, but large alcohol such as benzoin wasn't performed these reactions under similar conditions. In

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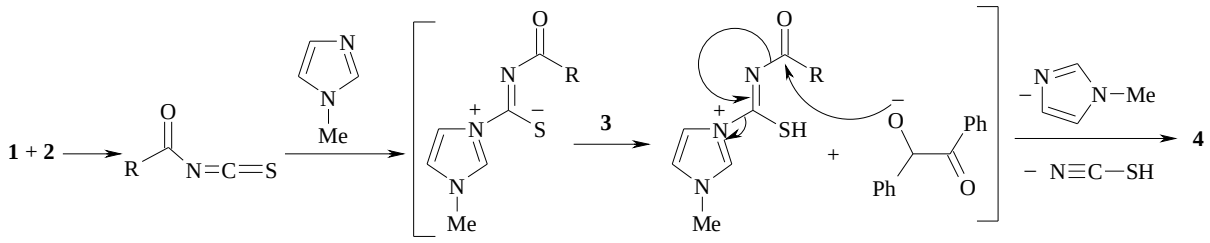
these reactions, *N*-methylimidazole is nucleophile and the reactions weren't carried out between only **2** and **3**. Also, these reactions weren't performed between **2** and **3** in the presence of *N*-methylimidazole as a nucleophile. Mechanistically, the reaction starts with formation of alkanoyl or aroyl isothiocyanate **5**, followed by addition of *N*-methyl imidazole to generate the intermediate **6**. Intermediate **7** would be attacked by Negative charge in **8** and loss of *N*-methyl imidazole and NCSH to produce **4** (Scheme 2).



5 **6** **7** **8**

Scheme 2

The results obtained in the one-pot reaction of acid chlorides, ammonium thiocyanate, α-hydroxy carbonyls and catalytic amount of *N*-methyl imidazole are depicted in Scheme 1. All these reactions yielded a mixture of only **4a-h** as major products, which could be easily purified by recrystalization with diethyl ether. The ester derivatives were isolated in high yield and to the best of our knowledge this strategy has not yet applied to the synthesis of such compounds. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials without solvent. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Experimental

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for the C and H were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz.

General Procedure for the Preparation of **4**

A stirred mixture of ammonium isothiocyanate (0.15 g, 2 mmol) and acid chloride 2 (2 mmol) was warmed at about 90°C in a water bath for 5 min and benzoin (0.42 g, 2 mmol) or 3-hydroxy-2-butanone (0.18 g, 2 mmol) was added slowly. The mixture was allowed to cool to r.t. and *N*-methylimidazole (0.032 g, 10 mol %) was added. The reaction mixture was stirred for 3 h at room temperature, and then poured into 15 mL of water. The resulting precipitate was separated by filtration and recrystallized by Et_2O (2 mL) to afford the pure title compounds.

2-oxo-1, 2-diphenylethyl benzoate (4a)

White powders; m.p. 170-171 ºC; yield: 0.57 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1701, 1697, 1585, 1449, 1275, 1112. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.15 (1 H, s, CH), 7.36-7.46 (8 H, m, 8 CH), 7.57 (1 H, m, CH), 7.61 (2 H, d, ^{3}J = 7.4 Hz, 2 CH), 8.04 (2 H, d, ^{3}J = 7.8 Hz, 2 CH), 8.16 (2 H, d, ^{3}J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.0 (CH), 128.4 (2 CH), 128.7 (CH), 128.8 (2 CH), 129.1 (2 CH), 129.3 (2 CH), 130.0 (2 CH), 130.8 (2 CH), 131.5 (CH), 132.0 (C), 132.7 (CH), 133.9 (C), 134.8 (C), 166.0 (CO_2), 193.7 (CO) ppm. Anal. Calc. for $C_{21}H_{16}O_3$ (316.35): C, 79.73; H, 5.10 found: C, 79.68; H, 4.98%.

2-oxo-1, 2-diphenylethyl 4-methylbenzoate (4b)

Pale yellow powders; mp: 175-177ºC; yield: 0.61 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1690, 1683, 1595, 1276, 1245, 1176, 1101. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 2.40 (3 H, s, Me), 7.15 (1 H, s, CH), 7.25 (2 H, d, ^{3}J = 8.0 Hz, 2 CH), 7.35-7.43 (5 H, m, 5 CH), 7.51 (1 H, t, ^{3}J = 7.3 Hz, CH), 7.62 (1 H, d, ^{3}J = 7.1 Hz CH), 8.06 (4 H, t, ^{3}J = 8.3 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 21.7 (Me), 77.8 (CH), 126.8 (C), 128.6 (2 CH), 128.7 (2 CH), 128.8 (CH), 129.1 (2 CH), 129.2 (2 CH), 129.3 (2 CH), 130.0 (2 CH), 133.4 (CH), 134.0 (C), 134.9 (C), 144.1 (C), 166.1 (CO_2), 193.9 (CO)

ppm. MS: *m/z* (%) = 330 (M^+, 10), 211 (70), 119 (100), 105 (98), 77 (64). Anal. Calc. for $C_{22}H_{18}O_3$ (330.38): C, 79.98; H, 5.49 found: C, 79.85; H, 4.35%.

2-oxo-1, 2-diphenylethyl 4-nitrobenzoate (4c)
Yellow crystal; m.p. 190-192 ºC; yield: 0.68 g (94%). IR (KBr) (ν_{max}/cm^{-1}): 1711, 1685, 1515, 1341, 1275, 1244, 1091. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.15 (1 H, s, CH), 7.38-7.45 (5 H, m, 5 CH), 7.54 (1 H, d, ^3J = 7.5 Hz, CH), 7.58 (2 H, m, 2 CH), 7.99 (2 H, d, ^3J = 7.3 Hz, 2 CH), 8.29 (4 H, t, ^3J = 8.0 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.8 (CH), 123.5 (2 CH), 128.7 (2 CH), 128.8 (CH), 129.3 (2 CH), 129.6 (2 CH), 131.0 (2 CH), 133.1 (C), 133.7 (2 CH), 133.4 (CH), 134.4 (C), 134.8 (C), 150.7 (C), 164.1 (CO_2), 192.8 (CO) ppm. Anal. Calc. for $C_{21}H_{15}NO_5$ (361.35): C, 69.80; H, 4.18; N, 3.88 found: C, 69.75; H, 4.15; N, 3.84%.

2-oxo-1, 2-diphenylethyl 4-bromobenzoate (4d)
Pale yellow powders; m.p. 185-187 ºC; yield: 0.71 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1708, 1683, 1580, 1398, 1347, 1247, 1099. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.11 (1 H, s, CH), 7.36-7.43 (5 H, m, 5 CH), 7.53 (1 H, t, ^3J = 7.4 Hz, CH), 7.58 (4 H, m, 4 CH), 8.00 (4 H, t, ^3J = 8.0 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.2 (CH), 128.4 (2 CH), 128.5 (C), 128.7 (CH), 128.8 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 129.4 (2 CH), 131.5 (C), 131.8 (2 CH), 133.5 (CH), 133.6 (C), 134.7 (C), 165.3 (CO_2), 193.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}BrO_3$ (395.25): C, 63.82; H, 3.83 found: C, 63.78; H, 3.80%.

2-oxo-1, 2-diphenylethyl 4-chlorobenzoate (4e)
White powders; m.p. 174-176 ºC; yield: 0.59 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1710, 1675, 1512, 1345, 1300, 1295, 1109. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.22 (1 H, s, CH), 7.42-7.48 (5 H, m, 5 CH), 7.62 (1 H, t, ^3J = 7.4 Hz, CH), 7.68 (4 H, m, 4 CH), 8.10 (4 H, t, ^3J = 8.0 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.5 (CH), 127.9 (2 CH), 128.4 (C), 128.8 (CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.0 (2 CH), 131.2 (C), 132.0 (2 CH), 133.8 (CH), 134.2 (C), 134.9 (C), 166.2 (CO_2), 195.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}ClO_3$ (350.80): C, 71.90; H, 4.31 found: C, 71.86; H, 4.25%.

2-oxo-1, 2-diphenylethyl pivalate (4f)
White powders; m.p. 145-147 ºC; yield: 0.52 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1725, 1645, 1557, 1445, 1227, 1112. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.23 (9 H, s, 3 Me), 7.27 (1 H, s, CH), 7.43 (3 H, m, 2 CH), 7.50 (1 H, m, CH), 7.58 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.95 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.14 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 27.5 (3 Me), 37.5 (C), 78.2 (CH), 123.4 (C), 124.7 (2CH), 127.6 (CH), 128.4 (2 CH), 128.6 (2 CH), 129.1 (2 CH), 131.7 (CH), 134.7 (C), 168.2 (CO_2), 197.5 (CO) ppm. Anal. Calc. for $C_{19}H_{20}O_3$ (296.36): C, 77.00; H, 6.80 found: C, 76.95; H, 6.78%.

1-methyl-2-oxopropyl 4-methylbenzoate (4g)
Yellow powders; m.p. 168-170 ºC; yield: 0.34 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1734, 1625, 1498, 1427, 1200, 1015. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.28 (6 H, d, ^3J = 7.5 Hz, 2 Me), 2.15 (Me), 2.36 (Me), 5.42 (1 H, q, ^3J = 7.5 Hz, CH), 7.58 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.75 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 16.5 (Me), 21.7 (Me), 24.3 (Me), 75.7 (CH), 127.6 (C), 127.8 (2CH), 128.4 (2 CH), 138.7 (C), 168.8 (CO_2), 200.6 (CO) ppm. Anal. Calc. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84 found: C, 69.85; H, 6.79%.

1-methyl-2-oxopropyl pivalate (4h)
Yellow oil; yield: 0.26 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1767, 1638, 1354, 1154, 1028. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.14 (9 H, s, 3 Me), 1.25 (3 H, d, ^3J = 7.3 Hz, Me), 2.24 (Me), 5.32 (1 H, q, ^3J = 7.3 Hz, CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 17.2 (Me), 24.8 (Me), 27.6 (3 Me), 41.5 (C), 76.8 (CH), 178.8 (CO_2), 204.2 (CO) ppm. Anal. Calc. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36 found: C, 62.68; H, 9.26%.

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