

***N*-formylmorpholine as green solvent for esterification of α -hydroxy carbonyls**

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

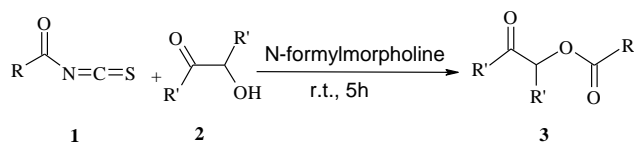
Keywords: Acid chlorides, Ammonium thiocyanate, *N*-formylmorpholine, 3-Hydroxy-2-butanone, Esterification.

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], methyltrialkoxo phosphonium tetrafluoroborate salts [13], *t*butyl 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/Ph₃P/diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and potassium carboxylate/Ph₃P/CCl₄ [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 Ph₃P=O and unreacted Ph₃P. 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*-formylmorpholine led to benzoate derivatives **4** in excellent yields (Scheme 1).

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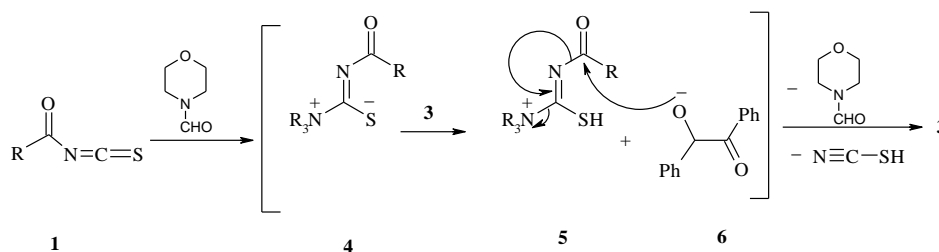
3	R	R'	Yield (%) of 3
a	Ph	Ph	95
b	4-Me-C ₆ H ₄	Ph	92
c	4-NO ₂ -C ₆ H ₄	Ph	94
d	4-Br-C ₆ H ₄	Ph	90
e	4-Cl-C ₆ H ₄	Ph	85
f	(CH ₃) ₃ C	Ph	87
g	4-Me-C ₆ H ₄	CH ₃	83
h	(CH ₃) ₃ C	CH ₃	75

Scheme 1: Synthesis of ester derivatives in NFM.

Result and Discussion

Structures of compounds **3a–3h** were assigned by IR, ¹H NMR, ¹³C NMR and mass spectral data. The ¹H- and ¹³C-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 these reactions, *N*-formylmorpholine is nucleophile and the reactions weren't carried out between only **1** and **2**. Also, these reactions weren't performed between **1** and **2** in the presence of *N*-formylmorpholine as a nucleophile.

Mechanistically, the reaction starts with formation of alkanoyl or aroyl isothiocyanate **4**, followed by addition of *N*-formylmorpholine to generate the intermediate **5**. Intermediate **5** would be attacked by negative charge in **6** and loss of *N*-formylmorpholine and NCSH to produce **3** (Scheme 2).



Scheme 2: Proposed mechanism for the synthesis of **3**

Conclusion

In summary, the results obtained in the one-pot reaction of acid chlorides, ammonium thiocyanate, α -hydroxy carbonyls and catalytic amount of *N*-formylmorpholine are depicted in Scheme 1. All these reactions yielded a mixture of only **3a–h** as major products, which could be easily purified by recrystallization 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. ¹H-, and ¹³C-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 Et₂O (2 mL) to afford the pure title compounds.

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

White powders; m.p. 170-171 °C; yield: 0.57 g (95%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1701, 1697, 1585, 1449, 1275, 1112. ¹H NMR (500.13 Hz, CDCl₃): 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, ³J = 7.4 Hz, 2 CH), 8.04 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.16 (2 H, d, ³J = 7.8 Hz, 2 CH) ppm. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 193.7 (CO) ppm. Anal. Calc. for C₂₁H₁₆O₃ (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: 175-177°C; yield: 0.61 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1690, 1683, 1595, 1276, 1245, 1176, 1101. ¹H NMR (500.13 Hz, CDCl₃): δ = 2.40 (3 H, s, Me), 7.15 (1 H, s, CH), 7.25 (2 H, d, ³J = 8.0 Hz, 2 CH), 7.35-7.43 (5 H, m, 5 CH), 7.51 (1 H, t, ³J = 7.3 Hz, CH), 7.62 (1 H, d, ³J = 7.1 Hz CH), 8.06 (4 H, t, ³J = 8.3 Hz, 4 CH) ppm. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 193.9 (CO) ppm. MS: *m/z* (%) = 330 (M⁺, 10), 211 (70), 119 (100), 105 (98), 77 (64). Anal. Calc. for C₂₂H₁₈O₃ (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 °C; yield: 0.68 g (94%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1711, 1685, 1515, 1341, 1275, 1244, 1091. ¹H NMR (500.13 Hz, CDCl₃): 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. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 192.8 (CO) ppm. Anal. Calc. for C₂₁H₁₅NO₅ (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 °C; yield: 0.71 g (90%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1708, 1683, 1580, 1398, 1347, 1247, 1099. ¹H NMR (500.13 Hz, CDCl₃): 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. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 193.4 (CO) ppm. Anal. Calc. for C₂₁H₁₅BrO₃ (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 °C; yield: 0.59 g (85%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1710, 1675, 1512, 1345, 1300, 1295, 1109. ¹H NMR (500.13 Hz, CDCl₃): 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. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 195.4 (CO) ppm. Anal. Calc. for C₂₁H₁₅ClO₃ (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 °C; yield: 0.52 g (87%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1725, 1645, 1557, 1445, 1227, 1112. ¹H NMR (500.13 Hz, CDCl₃): 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. ¹³C NMR (125.7 Hz, CDCl₃): 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 (CO₂), 197.5 (CO) ppm. Anal. Calc. for C₁₉H₂₀O₃ (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 °C; yield: 0.34 g (83%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1734, 1625, 1498, 1427,

1200, 1015. ^1H 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 $\text{C}_{12}\text{H}_{14}\text{O}_3$ (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) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1767, 1638, 1354, 1154, 1028. ^1H 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 $\text{C}_9\text{H}_{16}\text{O}_3$ (172.22): C, 62.77; H, 9.36 found: C, 62.68; H, 9.26%.

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