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A simple and one-pot synthesis of imine derivatives under solvent-free conditions

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Abstract: An efficient synthesis of imine derivatives is described *via* an one-pot reaction between acid chlorides, ammonium thiocyanate, 3-amino-2-butanone and catalytic amount of KF/CP under solvent-free conditions at room temperature in good yiels

Keywords: Acid chlorides, Ammonium thiocyanate, KF/CP, 3-amino-2-butanone, Solvent-free, One-pot reaction.

Introduction

There is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [1, 2]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [3–5]. In recent times, use of KF (potassium fluoride) supported on zeolites and clays due to new natural and cheep solid base system was attractive [6-14]. One of the natural zeolites is clinoptilolite much more important because of its high interchange power for cations especially for K+ and having high internal surface area. Consequently, free fluoride anions as an effectual base could be react with other compounds [15].

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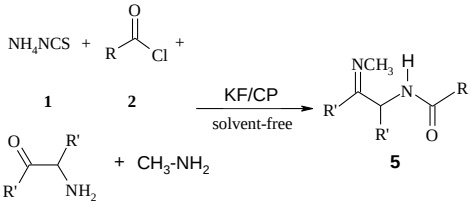
Also, the production of potassium fluoride combined with Clinoptilolite (KF/CP) is very simple and easy without any pre-activation of compounds [16, 17]. Thus, the reaction of ammonium thiocyanate **1**, acid chlorides **2**, 3-amino-2-butanone **3**, methyl amine **4** and catalytic amount of KF/CP led to imine derivatives **5** in excellent yields (Scheme **1**).



5	R	R'	Yield (%) of **5**
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. Synthesis of imin derivatives **5**

Result and discussion

Structures of compounds **5a**–**5h** 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 these reactions, KF/CP 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 KF/CP as a nucleophile. Mechanistically, the reaction starts with formation of alkanoyl or aroyl isothiocyanate **5**, followed by addition of KF/CP to generate the intermediate **6**. Intermediate **7** would be attacked by Negative charge in **9** and loss of NCSH to produce **5** (Scheme **2**).

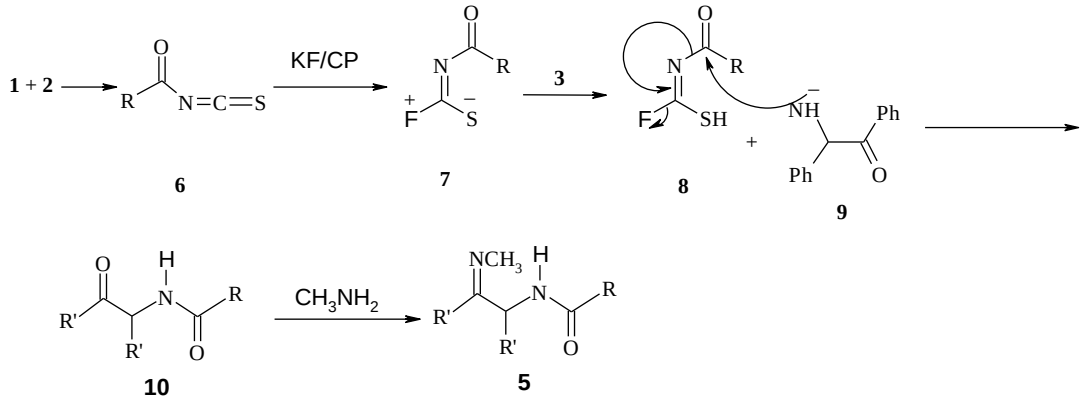
The results obtained in the one-pot reaction of acid chlorides, ammonium thiocyanate, α-amino carbonyls and catalytic amount of *N*-methyl imidazole are depicted in Scheme **1**. All these reactions yielded a mixture of only **5a-h** as major products, which could be easily purified by recrystalization 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 **5**

A stirred mixture of ammonium isothiocyanate **1** (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 3-amino-2-butanone **3** (2 mmol) and methyl amine **4** (2 mmol) was added slowly. The mixture was allowed to cool to r.t. and KF/CP (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.



Scheme 2. Proposed mechanism for the preparation of **5**

2-oxo-1, 2-diphenylethyl benzoate (5a):

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 (5b):

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, ^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. ^{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 (5c):

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 (5d):

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 (5e):

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 (5f):

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 (5g):

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 (5h):

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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