Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2018, Vol. 34, No.(1):
Pg. 152-160

Eco-friendly Access to β-ketoamides: One-step Catalyst-and Solvent-free Amidation of β-ketoesters Under Microwave Irradiation

KHADIDJA DECHIRA[1,2], ASSYA TALEB[1], AOUICHA BENMAATI[1], SALIH HACINI[1] and HADJIRA HABIB ZAHMANI[1]*

[1]Laboratoire de Chimie Fine, Faculte des Sciences Exactes et Appliquées, Universite d'Oran1 Ahmed Benbella, B.P -1524 Menouar, 31000 Oran, Algerie.
[2]Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques (C.R.A.P.C.) B.P 384, Bou-Ismail RP 42004 Tipaza, Algerie.
*Corresponding author E-mail: habibzahmanihadjira@gmail.com

http://dx.doi.org/10.13005/ojc/340117

(Received: September 25, 2017; Accepted: December 20, 2017)

ABSTRACT

A highly efficient and facile catalyst- and solvent-free one step amidation of β-ketoesters, without using any additional reagents, is described. Therefore, β-ketoamides are obtained in good to excellent yields by condensation of β-ketoesters with various primary or secondary amines. This eco-friendly protocol has been developed under microwave irradiation.

Keywords: Amidation, β-ketoesters, β-ketoamides, Catalyst-free, Solvent-free, Microwave irradiation.

INTRODUCTION

Catalyst-free methodologies for synthesis of organic compounds are of great interest for the development of a sustainable chemistry. In addition to the simplicity of the procedure and the reduced cost, this also makes it possible to considerably reduce the chemical waste in our environment[1]. In this communication, we report a simple and rapid, catalyst-free one-step synthesis of various β-ketoamides. These products are very useful compounds to access to a wide variety of Chemical structures (heterocycles, natural products) and targets of pharmaceutical research[2]. Various synthetic methods have been reported in the literature to prepare amides, but the processes of access to β-ketoamides are rather limited. Among these, mention may be made of the nucleophilic amidation of electrophiles such as β-ketoacids[3], β-ketoesters [4], β-thioesters[5] and keten dimmers[6].

Other methods are based on Dieckmann cyclization of amidoesters[7], treatment of carboxamides with phosgene or phosphoryl chloride[8], diketenes[9], enzymatic hydrolysis of β-ketonitriles[10] and aminolysis of β-ketoesters[11], organocatalytic multicomponent of polyfunctional substrates[12]. β-Ketoamides can also be prepared via Wolf rearrangement of diazodiketones in the presence of amines[13].

Among these approaches, the amidation is the most frequently used reactions. In general this process involves specific reaction conditions as the use of a specific catalysts, vigorous reaction conditions and prolonged reaction times. These reactions often lead to unsatisfactory yields of 1,3-ketoamides due to the competitive enaminoester formation, or requires uncommercial starting materials. In our efforts to develop greener and simpler amidation method, we focused on the catalyst-free approach. Therefore, a facile one-pot process for the synthesis of N-mono-and di-substitued β-ketoamides has been elaborated from readily available cyclic β-ketoesters in the presence of amines. Amines, amongst the most important reagents in organic synthesis by their basic and nucleophilic characters, are used in our strategy as reagent and as catalyst. Realizing a combination process of temperature and pressure to activate this reaction was a key contribution.

EXPERIMENTAL

General procedure for the synthesis of β-Ketoamides:

To an open glass tube (G4), were added β-ketoesters (1.0 mmol) and primary or secondary amines (1.1 mmol) in solvent - free. The tube was positioned in the centre of the microwave cavity, and irradiated (850 W) until the temperature reached 180 °C for 15 to 60 minutes. Purificationof the resultant product by short column chromatography over silica gel (40–63 mesh) afforded the pure products.

2-(morpholine-4-carbonyl)cyclohexanone (1c). Brown solid; mp = 77.7 °C; *Rf* (EtO_2/PE: 4/6) = 0.25; IR: μ 2941, 2859, 1705, 1626, 1186, 1109 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (dt, J= 13.60, 4.34 Hz, 1H) , 3,71 (t, J= 4.81 Hz, 2H) , 3,67 (t, J= 4.81 Hz, 2H), 3.57–3.47 (m, 2H), 3.34 (dd, J= 6.04, 3.96 Hz, 1H), 2.54(dt, J= 6.04, 3.96, 1H), 2.41– 2.17 (m, 2H), 2.15–1.96 (m, 3H), 1.92–1.81 (m, 1H), 1.79–1.62 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.35(C), 168.06(C), 66.82(CH_2), 66.59(CH_2), 54.12(C), 46.26(CH_2), 42.29 (CH_2), 41.98 (CH_2), 30.17(CH_2), 27.09(CH_2), 23.64(CH_2) ppm.

N,N-diallyl-2-oxocyclohexanecarboxamide (2c). Brown oil; Rf (EtO_2/PE: 6/4) = 0.33; IR: ν3082, 2983, 1720, 1631, 1190, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80–5.69 (m, 2H), 5.25–5.08 (m, 4H), 4.28 (dd, J = 15.5, 4.3 Hz, 1H), 3.84–3.79 (m, 1H), 3.72 (dd, J = 5.0, 1.6 Hz, 1H), 3.68 (d, J = 5.5 Hz, 1H), 3.48 (dd, J = 10.0, 5.3 Hz, 1H), 2.53 (dt, J = 13.3, 4.5 Hz, 1H), 2.33 – 2.14 (m, 2H), 1.99 (dqd, J = 12.4, 5.2, 2.7 Hz, 3H), 1.85–1.73 (m, 1H), 1.68–1.57 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.60(C), 169.95(C), 133.71(CH), 133.08(CH), 117.07(CH_2), 116.67(CH_2), 54.65(CH), 49.50 (CH_2), 48.17(CH_2), 42.17(CH_2), 30.69(CH_2), 27.24 (CH_2), 23.85(CH_2) ppm.

2-(4-phenylpiperazine-1-carbonyl) cyclohexanone (3c). White solid; m.p. = 102.9 °C; *Rf* (EtO_2/PE: 6/4) = 0.28; IR: ν 2861, 1692, 1640, 1596, 1183, 729, 669 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.6 Hz, 2H), 7.25–6.93 (m, 3H), 4.17 –3.97 (m, 1H), 3.83–3.75 (m, 1H), 3.58 (ddd, J = 21.9, 10.9, 9.9 Hz, 2H), 3.26(s, 3H), 2.63–2.55 (m, 1H), 2.45–2.35 (m, 1H), 2.30–2.22 (m, 1H), 2.17–1.94 (m, 3H), 1.92–1.66 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.43(C), 167.97(C), 150.71(C), 129.25(CH), 120.69(CH), 116.75(CH), 54.26(CH_2), 49.67(CH_2), 45.67(CH_2), 41.98(CH_2), 41.79(CH_2), 30.94(CH_2), 30.29(CH_2), 27.13(CH_2), 23.60(CH_2) ppm.

2-(morpholine-4-carbonyl) cyclopentanone (4c). White oil; *Rf* (EtO_2/PE: 6/4) = 0.32; IR: ν 2967, 1735, 1623, 1109, 1067 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ =3.86 (dd, J = 13.4, 1.8 Hz, 1H), 3.78–3.67 (m, 3H), 3.54 (ddd, J = 11.3, 2.8, 1.4 Hz, 1H), 3.44–3.28 (m, 3H), 2.56–2.44 (m, 1H), 2.24 (dd, J = 8.4, 6.6 Hz, 2H), 2.18–2.07 (m, 2H), 1.90–1.76 (m, 1H),1.28–1.14(m 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.28(C), 166.79(C), 67.13(CH_2), 66.88(CH_2), 51.62(CH), 46.68(CH_2), 42.75(CH_2), 38.72(CH_2), 27.14(CH_2), 21.08(CH_2) ppm.

N,N-diallyl-2-oxocyclopentanecarboxamide (5c). Yellow oil; *Rf* (EtO_2/PE: 4/6) = 0.26; IR: ν 3461, 1738, 1632, 1413, 921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.86–5.64 (m, 2H), 5.14 (dd, J = 13.7, 3.2 Hz, 3H), 5.09 (d, J = 5.8 Hz, 1H), 4.30 (d, J = 3.2 Hz, 1H), 4.25 (d, J = 4.6 Hz, 1H), 3.80 (dd, J = 18.1, 4.5 Hz, 1H), 3.65 (dd, J = 15.5, 5.9 Hz, 1H), 3.35 (t, J = 8.6 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.26 (dd, J = 8.8, 6.3 Hz, 2H), 2.19– 2.07 (m, 2H), 1.88– 1.72 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.60 (C), 168.95(C), 133.23(CH), 132.68(CH), 116.85 (CH2), 116.37(CH_2), 51.97(CH), 49.22(CH_2), 48.18 (CH_2), 38.52(CH_2), 27.50(CH_2), 20.97(CH_2) ppm.

2-oxo-N,N-dipropylcyclopentanecarboxamide (6c). Brawn oil; *Rf* (EtO_2/PE: 6/4) = 0.29; IR: ν 2872, 1739, 1630, 1509, 1103, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ = δ: 3.55–3.41 (m, 2H), 3.34 (t, J = 8.5 Hz, 1H), 3.18–3.06 (m, 2H), 2.48–2.36 (m, 1H), 2.29–2.23 (m, 2H), 2.19–2.08 (m, 2H), 1.89–1.76 (m, 1H), 1.34–1.20 (m, 4H), 0.93 (dd, J = 15.7, 7.4 Hz, 6H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$) : δ = 214.72(C), 168.72(C), 51.59(CH), 47.86(CH_2), 46.04(CH_2), 38.48(CH_2), 31.36(CH_2), 29.76(CH_2), 27.68(CH_2), 21.01(CH_2), 20.03(CH_2), 20.00(CH_2), 13.76(CH_3), 13.72(CH_3) ppm.

2-(piperidine-1-carbonyl)cyclopentanone (7c). yellow oil; *Rf* (EtO_2/PE: 6/4) = 0.36; IR: ν 2851, 1739, 1626, 1433, 1217, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ = 3.58 (dddd, J = 16.7, 14.4, 10.8, 5.5 Hz, 4H), 2.86 (t, J = 7.2 Hz, 1H), 2.54–2.41 (m, 1H), 2.34–2.28 (m, 1H), 2.23–2.10 (m, 2H), 2.0–1.80 (m, 2H), 1.72–1.55(m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.07(C), 166.66(C), 66.86 (CH2), 66.60(CH_2), 51.37(CH), 46.42(CH_2), 42.46 (CH_2), 38.23 (CH_2), 26.91(CH_2), 20.82(CH_2) ppm.

2-(isoindoline-2-carbonyl)cyclopentanone (8c). white solid; m.p. = 91 °C; *Rf* (EtO_2/PE: 4/6) = 0.29; IR: ν 2892, 1731, 1648, 1594, 1196, 725, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.1 Hz, 1H), 7.18 (dd, J = 7.1, 5.9 Hz, 2H), 7.03 (t, J = 7.9 Hz, 1H), 4.54 (td, J =10.1, 6.1 Hz, 1H), 4.07 (td, J = 10.1, 7.3 Hz, 1H), 3.48 (t, J = 10.2, 6.6 Hz, 1H), 3.33–3.07 (m, 2H), 2.67–2.50 (m, 1H), 2.36 (dd, J = 8.2, 2.6 Hz, 1H), 2.33 (s, 1H), 2.31–2.18(m, 2H), 1.99–1.83(m, 1H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$): δ = 214.32(C), 166.81(C), 142.83(C), 131.66(C), 127.49(CH), 124.61(CH), 124.09(CH), 117.32(CH), 54.82(CH_2), 48.33(CH_2), 38.70(CH), 27.94(CH_2), 27.04(CH_2), 21.04(CH_2) ppm.

2-(morpholine-4-carbonyl)-3,4-dihydrona phthalen-1(2H)-one (9c). White solid; *Rf* (EtO_2/PE: 5/5) = 0.51; ^1H NMR (300 MHz, $CDCl_3$): δ= 8.02 (dd, J = 7.8, 1.1 Hz, 1H), 7.55 (td, J = 7.5, 1.4 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 3.95 (dt, J = 3.7, 3.7 Hz, 1H), 3.90–3.82 (m, 1H), 3.80 (d, J = 4.7 Hz, 1H), 3.77 (t, J = 4.2 Hz, 3H), 3.64–3.43 (m, 3H), 3.12 (dt, J = 16.8, 4.5 Hz, 1H), 3.05 (td, J = 11.4, 5.3, 4.5 Hz, 1H), 2.53 (dtd, J = 13.7, 11.5, 4.8 Hz, 1H), 2.31 (dq, J = 13.6, 4.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.16 (C), 168.39(C), 144.10(C), 133.90(C), 132.00(CH), 128.84(CH), 127.63(CH), 126.86(CH), 66.89(CH_2), 51.33(CH), 46.72(CH_2), 42.47(CH_2), 28.40(CH_2), 26.36(CH_2) ppm.

1-morpholinobutane-1,3-dione (10c). Yellow oil; *Rf* (EtO_2/PE: 5/5) = 0.33; IR: ν 2922, 1716, 1623, 1110, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.65 (dd, J = 8.3, 5.2 Hz, 6H), 3.55 (s, 2H), 3.41 (s, 2H), 2.26 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ 202.19(C), 165.08(C), 66.62 (CH2), 66.51(CH2), 49.66(CH2), 46.73(CH2), 42.09(CH2), 30.30(CH3).

N-tert-butyl-2-oxocyclohexanecarboxamide and N-tert-butyl-2-hydroxycyclohex-1-ene carboxamide (11c). White solid; mp = 98-100 °C; *Rf* (EtO_2/PE: 8/2) = 0.7; IR: ν 3336, 1702, 1630, 1424, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ =14.29 (s, 1H), 6.65 (s, 1H), 5.14 (s, 1H), 3.02 (ddd, J = 9.6, 5.6, 1.1 Hz, 1H), 2.41–2.34 (m, 1H), 2.16–2.10 (m, 1H), 2.00–1.98-1.93 (m, 1H), 1.92–1.83 (m, 3H), 1.61–1.57 (m, 2H), 1.32 (s, 9H), 1.27 (s, 9H) ppm; ^{13}CNMR (101 MHz, $CDCl_3$): δ= 210.66(C), 172.58 (C), 169.78(C), 167.87(C), 97.34(C), 56.56 (CH), 51.15(C), 51.01(C), 41.97(CH_2), 30.98(CH_2), 29.29(CH_3), 28.89(CH_3), 28.63(CH_2), 27.10(CH_2), 23.85(CH_2), 22.96(CH_2), 22.58(CH_2), 21.93(CH_2) ppm.

N-benzyl-2-hydroxycyclohex-1-enecarboxamide and N-benzyl-2-oxocyclohexanecarboxamde (12c). White oil; *Rf* (EtO_2/PE: 7/3) = 0.7; ^1H NMR (300 MHz, $CDCl_3$): δ =14.16 (s, 1H),7.28 (s, 1H), 7.27–7.20 (m, 5H), 6.15 (s, 1H), 4.43–4.35 (m, 2H), 3.18–3.12 (m, 1H), 2.36–2.25(m, 1H), 2.20–2.19(m, 2H), 2.09–2.07 (m, 1H), 1.92–1.88 (m, 2H), 1.65–1.60 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.63(C),

171.43(C), 169.14(C), 168.36(C), 137.47(C), 137.30(C), 127.57(CH), 127.49(CH), 126.50(CH), 126.42(CH), 126.29(CH), 126.16(CH), 96.05(C), 55.28(C), 42.17(CH_2), 41.88(CH_2), 40.97(CH_2), 30.11 (CH_2), 28.21(CH_2), 26.12 (CH_2), 22.99(CH_2), 21.50(CH_2), 21.46(CH_2), 20.83(CH_2) ppm.

2-oxo-N-phenylcyclopentanecarboxamide (13c). White solid; mp = 88-90 °C; *Rf* (EtO_2/PE: 5/5) = 0.4; IR: ν 3050, 1951, 1739, 1664, 1533, 1442, 1311, 1146 cm^{-1}; ^1H NMR (300 MHZ, $CDCl_3$): δ = 8.74 (s, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 3.15 (t, J = 9.4 Hz, 1H), 2.46–2.27 (m, 4H), 2.12–2.05 (m, 1H), 1.91–1.84 (m, 1H) ppm; RMN13C (300 MHZ, $CDCl_3$): δ = 217.06 (C) , 164.59 (C), 137.83 (C), 129.10 (CH), 124.43 (CH), 119.97 (CH), 54.81(CH), 39.22 (CH_2), 25.82 (CH_2), 20.35 (CH_2) ppm.

N-tert-butyl-2-oxocyclopentanecarboxamide (14c). White solid; m.p.= 96-98 °C; Rf (EtO2/ PE: 8/2) = 0.54; IR: μ 3312, 1741, 1663, 1548, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.57 (s, 1H), 2.91 (t, J = 9.1 Hz, 1H), 2.43–2.22 (m, 4H), 2.11–1.99 (m, 1H), 1.98–1.73 (m, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.05(C), 165.66(C), 54.82(CH), 51.24(C), 38.95(CH2), 28.73(CH_3), 25.75(CH_2), 20.28(CH_2) ppm.

N-(furan-2-ylmethyl)-2-oxocyclopentane-carboxamide(15c). Brown solid; *Rf* (AcOEt/PE: 1/1) = 0.38; IR: ν 3050, 1951, 1739, 1664, 1533, 1442, 1311, 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (t, J = 1.8 Hz, 1H), 6.34 (dd, J = 3.1, 1.9 Hz, 1H), 6.26 (dd, J = 3.2, 1.7 Hz, 1H), 4.54 (dd, J = 15.5, 5.8 Hz, 1H), 4.43 (dd, J = 15.5, 5.4 Hz, 1H), 3.05 (t, J = 9.4 Hz, 1H), 2.43–2.29 (m, 4H), 2.12–2.08 (m, 1H), 1.90–1.88 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.9 (C), 166.7 (C), 151.0 (C), 142.1 (CH), 110.1(CH), 106.9 (CH), 54.1 (CH_2), 38.6 (CH2), 36.4 (CH_2), 25.8 (CH_2), 20.3 (CH_2) ppm.

N-allyl-2-oxocyclopentanecarboxamide (16c). white solid; *Rf* (EtO_2/PE: 7/3) = 0.46; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.95 (s, (NH)1H), 5.74 (ddt, J = 17.1, 10.5, 5.4 Hz, 1H), 5.13 (ddd, J = 17.2, 3.1, 1.6 Hz, 1H), 5.04 (ddd, J = 10.3, 2.9, 1.4 Hz, 1H), 3.80 (tt, J = 5.6, 1.6 Hz, 2H), 2.95 (t, J = 9.3 Hz, 1H), 2.31–2.22 (m, 4H), 2.19–2.0 (m, 1H), 1.80–1.67 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.0 (C), 166.9 (C), 133.7 (CH), 115.7 (CH_2), 54.2 (CH), 41.4 (CH_2), 38.6 (CH_2), 25.9 (CH_2), 20.1 (CH_2) ppm.

N-allyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide (17c). White solid; *Rf* (PE/ ACEt2: 8/2) = 0.75; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dd, J = 7.8, 1.0 Hz, 1H), 7.43 (td, J = 7.5, 1.4 Hz, 1H), 7.25-7.22 (m, 1H), 7.18 (d, J = 7.6 Hz, 1H), 5.87 – 5.71 (m, 1H), 5.15 (ddd, J = 17.2, 3.1, 1.6 Hz, 1H), 5.05 (ddd, J = 10.3, 2.8, 1.4 Hz, 1H), 3.94 – 3.83 (m, 2H), 3.35 (t, J = 7.2 Hz, 1H), 3.05 (dt, J = 16.7, 5.3 Hz, 1H), 2.83 (ddd, J = 23.2, 14.7, 7.4 Hz, 1H), 2.38 (td, J = 7.4, 5.3 22Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.2 (C), 167.7 (C), 144.6 (C), 134.1 (CH), 133.9 (CH), 131, 7 (C), 128.7 (CH), 127.5 (CH), 126.6 (CH), 115.7 (CH_2), 52.8 (CH), 42.0 (CH_2), 27.8 (CH_2), 25.4 (CH_2) ppm.

N-tert-butyl-3-oxobutanamide (18c). White oil; *Rf* (EtO_2/PE: 7/3) = 0.75; IR: ν 3316, 1714, 1646, 1544, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.66 (s, 1H), 3.31 (s, 2H), 2.24 (s, 3H), 1.34 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.87(C), 164.49(C), 51.33(CH2), 50.92(C), 30.99(CH3), 28.35(CH3) ppm.

MATERIALS AND METHODS

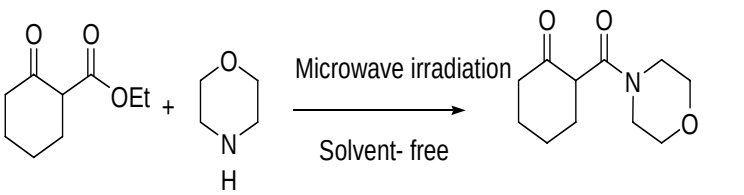
Solvents and reagents were purchased from Sigma-Aldrich and used as received. The reactions under microwave irradiation were performed in a microwave apparatus Anton Paar, Monowave 300 model power 850 W. The reactions were monitored by TLC visualized by UV (254 nm) and/or with p-anisaldehyde. The melting points were determined on an M-560 melting point apparatus and are uncorrected. Purification of reaction products was carried out by flash chromatography using silical-gel (40-63 mm) eluted with AcOEt/PE or EtO_2/PE. NMR data were recorded at 300 or 400 MHz (Bruker Avance spectrometers) in $CDCl_3$ using as internal standards the residual $CHCl_3$ signal for ^1H NMR (d = 7.26 ppm) and the deuterated solvent signal for ^{13}C NMR (d = 77.16ppm). IR spectra were obtained with a Alpha-p Brucker ATR diamond FT-IR spectrophotometer.

RESULTS AND DISCUSSION

The environment-friendly methods developed in our work have now evolved to microwave-accelerated solvent free aminolysis procedure. In this context, to appraise the combination of temperature and pressure effect we tested the feasibility of amidation at several temperatures. We initiated our studies of the amidation of cylohexanone-ester 1a with morpholine 1b. For the experimental procedure we simply mixed 1equiv. of ester 1a with 1,1 equiv of amine 1b and irradiated the reaction mixtures in a MW oven in the absence of solvent (Schema 1). As summarized in Table. 1, formation of β-ketoamide 1c generally required high temperatures; at 80 °C, 100 °C and 120 °C the isolated yields of amide just slightly increased. On the other hand, we observed that an increased temperature from 160 °C to 180 °C did increase the conversion from 94% to quantitative and speed up the time of reaction. We show here that the ester 1a and amine 1b can only react when they collide by heating the mixture, as particles move faster and collide more frequently.

In a second stage, the scope of the reaction was investigated with variety of secondary amines 1b-6b and cyclic β-ketoesters (five (C5) and six (C6) membered rings). The solvent-free methodology appeared to be applicable to prepare a wide range of N-disubstitued β-ketoamides compounds, as reported Table. 2.

A variety of secondary amines were efficiently converted to the corresponding products in moderate to excellent yields (52%-quantitative). The reaction of cyclopentanone-ester 2a with morpholine and dipropylamine (Table. 2, entries 4 and 6) provide excellent yields of 4c and 6c. Actually, in most of the cases, aminolysis occurred to be more efficient under solvent-free conditions (table 2, entries 1, 4, 6, 7 and 8). Furthermore we studied the reactivity of morpholine toward ethyl 1-oxo-1,2,3,4-tetrahydronaphtalene-2-carboxylate 3a and acyclic ketoester; ethyl acetoacetate 4a (Table 2, entries 9 and 10). Aminolysis of 3a gave the corresponding amide 9c with good yield (90%), however, only moderate catalytic activity was observed in the case of ethyl acetoacetate 4a which product yield 10c do not exceed 52%.



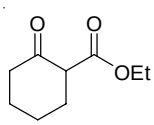
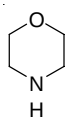
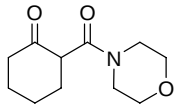
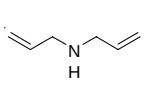
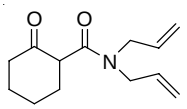
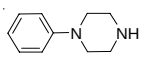
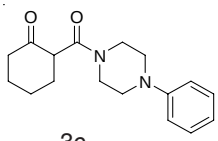
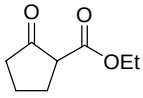
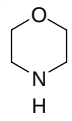
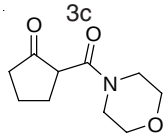
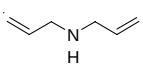
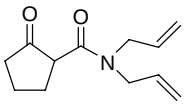
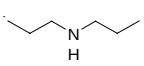
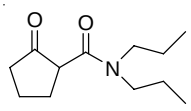
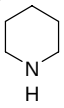
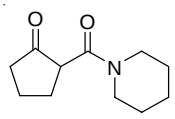
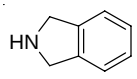
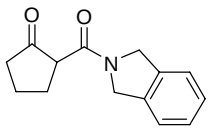
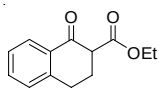
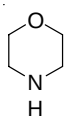
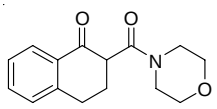
1a **1b** **1c**

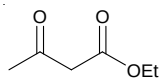
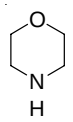
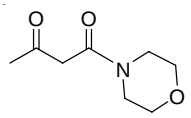
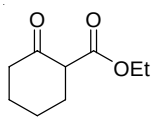
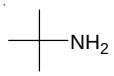
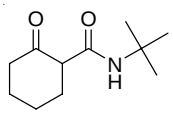
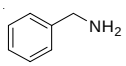
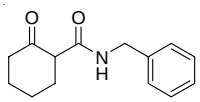
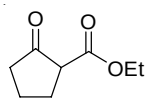
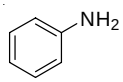
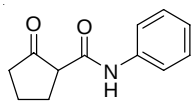
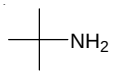
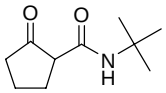
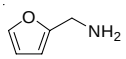
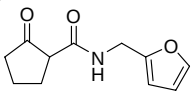
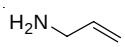
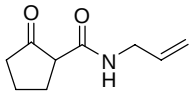
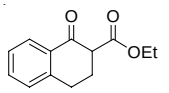
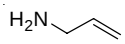
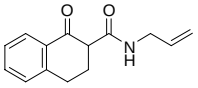
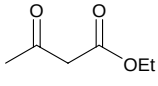
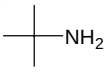
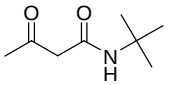
Scheme 1

Table. 1: Reaction temperatures tested for the amidation of 1a

Entry	Temp.(°C)	Time (min.)	yield % (1c)
1	80	120	Trace
2	100	120	20
3	120	120	37
4	160	60	95
5	180	30	Quantitative

Table. 2: Solvent-free and catalyst-free synthesis of various β-ketoamide under MW irradiation

Entry	β-Ketoester	Amine	β-Ketoamide	Reaction time (min.)	Yield [b] %
1	 1a	 1b	 1c	60	Quantitative
2		 2b	 2c	30	73
3		 3b	 3c	30	74
4	 2a	 1b	 4c	30	Quantitative
5		 2b	 5c	30	79
6		 4b	 6c	30	90
7		 5b	 7c	30	64
8		 6b	 8c	30	74
9	 3a	 1b	 9c	30	90

10	 4a	 1b	 10c	30	52
11	 1a	 7b	 11c	30	70
12		 8b	 12c	45	40
13	 2a	 9b	 13c	45	Quantitative
14		 7b	 14c	15	80
15		 10b	 15c	30	50
16		 11b	 16c	30	67
17	 3a	 11b	 17c	30	77
18	 4a	 7b	 18c	45	85

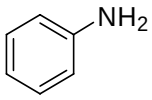
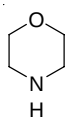
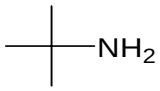
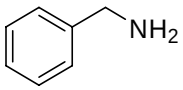
Following the same protocol, we directed our attention to the amidation of primary amine which are known by their low reactivity. All reactions were performed using 1.1 equiv of amine to form

N-disubstitued ketoamide from Ketoesters and were obtained with moderate to good yield (40% -quantitative). As is evident from Table. 2, aniline and tertbutylamine produced the best yields compared to other amines (Table 2, entries 13, 14 and 18). Benzylamine and furfurylamine, the less reactive amines, produce slightly low yields (40 and 50%), (Table. 2, entries 12 and 15).

In evaluating the amine catalysts effects we noticed that the aminolysis performance depends strongly on the amines basicity as shown in Table. 3. It is clear that the yield of the reaction decreased with increasing p*K*a.

Thus, this new approach allows us to understand the basic catalytic activity of amine in aminolysis process. In this method, reactions are faster, safer and with higher chemical yields, that is why this method becomes superior to the conventional method. Furthermore these results reveal that the present method is useful for aromatic as well as for aliphatic amines.

Table. 3: Influence of the pKa of the amine on the yield of the reaction.

Entry	Amine	pKa	Keto-ester	% yield
1		4.6	2a	Quantitative yield
2		8.3	1a	Quantitative yield
3		10.68	2a	80
4		11.6	1a	40

CONCLUSION

In conclusion, a highly efficient and facile one-step synthesis of N-mono-and di-substitued β-ketoamides has been described. This method involves the formation of new bond in solvent free aminolysis without the use of any additional reagents or catalyst and provided the product in good to excellent yield. The feasibility of activating reaction by the mean of temperature and pressure in microwave irradiation has been demonstrated. This eco-friendly procedure show notable advantages as: (a) operational simplicity; (b) fast reaction; (c) ecological advantages; (d) economic experience and (e) good yield.

REFERENCES

1. (a) Horváth, I. T.; Anastas, P.T. *Chem. Rev.* **2007**, *107*, 2169-2173; (b) Liu, S.; Xiao, J. *J. Mol. Catal. A: Chem.* **2007**, *270,* 1-43; (c) Anastas, P.T. ; Zimmerman, J. B. *Environ. Sci. Technol.* **2003**, *37*, 94A-101A.
2. (a) Bagley, M. C.; Chapaneri, K., Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389-1399, (b) Griffin, R. J.; Fontana, G.;

Golding, B. T.; Guiard, S.; Hardcastle, I. R.; Leahy, J. J.; Martin, N.; Richardson, C.; Rigoreau, L.; Stockley, M.; Smith, G. C. M. *J. Med. Chem*. **2005**, *48*, 569-585; (c) Takayama, K.; Iwata, M.; Hisamichi, H.; Okamoto, Y.; Aoki, M.; Niwa, A. *Chem. Pharm. Bull*. **2002**, *50*, 1050-1059; (d) Szczepankiewicz, B. G.; Heathcock, C. H. *J. Org. Chem*. **1994**, *59*, 3512-3513.

3. Meyer, C.; Piva, O.; Pete. J-P. *Tetrahedron* **2000**, *56*, 4479-4489.
4. (a) Cossy, J.; Thellend, A. *Synthesis* **1989**, *10*, 753-755; (b) Miriyala, B.; Williamson, J. S. *Tetrahedron Lett*. **2003**, *44*, 7957-7959; (c) Štefane, B.; Polanc, S. *Synlett.* **2004**, *4*, 698-702; (d) Štefane, B.; Polanc, S. *Tetrahedron* **2007,** *63*, 10902-10913. (e) Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem*. **1991**, *56*, 1713-1718.
5. Ley, S. V.; Woodward, P. R. *Tetrahedron Lett*. **1987**, *28*, 3019-3020.
6. Sung, K.; Wu, S. Y. *Synth. Commun*. **2001**, *31*, 3069-3074.
7. Johnson, D. H. *J. Chem. Soc*. **1958**, *0*, 1624-1628.
8. Bredereck, H.; Gompper, R.; Klemm, K. *Chem Ber*. **1959**, *92*, 1456-1460.
9. Clemens, R. *J. Chem. Rev*. **1986**, *86*, 241-318.
10. Gotor, V.; Liz, R.; Testera, A. M. *Tetrahedron* **2004**, *60*, 607-618.
11. (a) Garcia, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron Lett*. **1993**, *34*, 6141-6142; (b) Ponde, D. E.; Deshpande, V. H.; Bullrile, V. J.; Sudalai, A.; Gajare, A. S. D. *J. Org. Chem*. **1998**, *63*, 1058-1063.
12. Neo, A. G.; Delgado, J.; Polo, C.; S. Marcaccini.; Marcos, C. F. *Tetrahedron Lett*. **2005**, *46*, 23-26.
13. (a) Dudognon, Y.; Presset, M.; Rodriguez, J.; Bugaut, X.; Constantieux, T. *Chem. Commun*. **2016**, *52*, 3010-3013. (b) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415-418; (c) Leung-Toung, R.; Wentrup, C. *J. Org. Chem*, **1992**, *57*, 4850-485; (d) Cossy, J.; Leblanc, C. *Tetrahedron Lett*. **1991**, *32*, 3051-3052; (e) Wolff, L. *Justus Liebigs Ann. Chem*. **1912**, *394*, 86-108.