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ORIGINAL PAPER

"On water" organic synthesis: three-component one-pot synthesis of novel bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates

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Abstract An efficient synthesis of novel bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates (**4a–k**), considering as organic building blocks for natural products and drugs, via the reaction of fumaric acid, various aldehydes and cyclohexyl isocyanide in water using one-pot three-component approach under mild condition and without catalyst is described. This rapid method produced the products in short reaction times (10–15 min) and excellent yields (85–95 %) at room temperature. The structures of the products were deduced from their elemental analyses and spectroscopic data.

Keywords On water · Green chemistry · MCRs · Bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate · Passerini reaction

Introduction

Acceleration of reactions is the most fundamental interest of chemists [1] and several approaches such as increasing reaction temperature, use of high pressure and catalysts are quite general. Another influence on reaction rate can be observed in aqueous solvents. The use of water as a solvent for organic transformations offers several "green chemistry" benefits [2]. Water is the lingua franca of life on our planet and is the solvent of choice for nature to carry out her syntheses [3]. Water possesses many unique physical and chemical properties and considerable rate of acceleration is often observed in reactions carried out under these conditions over those in organic solvents [4]. For example, a 300-fold rate acceleration in the reaction of cyclopentadiene with methyl vinyl ketone in water as compared to acetonitrile has been reported [5]. On the other hand, multicomponent reactions (MCRs) are convergent reactions in which three or more reagents are combined to react in a one-pot procedure [6] and are very efficient synthetic methods [7]. Isocyanide-based multicomponent reactions (IMCRs) have been of particular interest because of the large number of starting materials available as well as powerful tools in the modern drug discovery process and allow rapid, automated, and high-throughput generation of organic compounds [8, 9]. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity are often observed [10]. They serve as C-nucleophiles toward imines and aldehydes, resulting in nitrilium ion electrophiles, which enable the Ugi 4CR and Passerini 3CR, respectively [11]. This approach fills an important niche in library synthesis by providing direct access to library compounds and by serving as starting points for diversity-oriented synthesis (DOS) [12]. MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds [13]. Recent advances in the application of IMCRs

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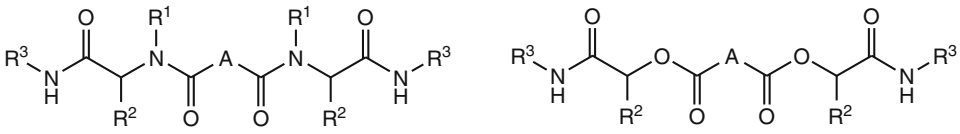
Fig. 1 Hormone mimics (erythropoietin)

Hormone Mimics (erythropoietin)
Synthesized by the ugi and Passerini reactions



Library 1
Ugi dicarboxylic acid

Library 2
Passerini dicarboxylic acid

in drug discovery summarize the various chemo types used to probe biological targets [14]. Dömling et al. [15] prepared two libraries of several compounds each utilizing the Ugi and Passerini reactions (Fig. 1) using rational design approaches to mimic the hormone erythropoietin (EPO). The compounds were screened as crude mixtures in a functional EPO assay in search of agonists of the hormone. Several promising compounds were identified and are now in the process of further evaluation.

The Passerini reaction is an interesting reaction because it is has 100 % atom-economy. This means that every atom in the starting material is incorporated in the product. Consequently, there is no intrinsic chemical waste associated with the reaction [16]. In this report, we attempt to use Passerini reaction for the synthesis of novel bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates, performed on water under the conditions defined by Sharpless and coworkers: when insoluble reactant(s) are stirred in aqueous emulsions or suspensions without the addition of any organic co-solvents [17].

Experimental

Chemicals and apparatus

Melting points were measured on an Electrothermal 9100 apparatus. FT-IR spectra were determined on a Shimadzu FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz Bruker DRX-500 in $CDCl_3$ as solvent and TMS as an internal standard. Elemental analyses were done on a Carlo-Erba EA1110 CNOS analyzer and agreed with the calculated values. Chemicals were purchased from Merck and Aldrich. All solvents used were dried and distilled according to the standard procedures.

General procedure for the synthesis of bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate derivatives

A mixture of fumaric acid (**1**) (1.0 mmol, 0.106 g), cyclohexyl isocyanide (**2**) (2.0 mmol, 0.218 g), aliphatic and aromatic aldehydes (**3**) (2.0 mmol) and H_2O (5 mL) in a round bottom flask was stirred for 10–15 min at room temperature. The solid product was isolated by filtration, washed with 3 × 1 mL of 10 % $NaHCO_3$ and 2 × 1 mL water and dried under high vacuum. The product was recrystallized from ethanol to produce bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate derivatives (**4a–k**) as pure crystalline products in 85–95 % yields (Table 1).

Table 1 Synthesis of bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate derivatives (**4a–k**)

Product 4	R	MP (°C)	Time (min)	Yield (%)[a,b]
a	3-$O_2NC_6H_4$	245–247	10	90
b	2-Thienyl	210–212	12	95
c	2-$O_2NC_6H_4$	214–216	10	90
d	4-$O_2NC_6H_4$	180–182	10	95
e	C_6H_5	220–222	12	85
f	4-ClC_6H_4	250–252	10	90
g	4-$MeOC_6H_4$	230–232	15	90
h	3,4-$(MeO)_2C_6H_3$	214–217	10	95
i	Pyridin-4-yl	180–182	14	85
j	Pyridin-3-yl	208–210	10	95
k	*n*-C_3H_7	200–202	14	90

[a] Isolated yields. [b] Identified by spectroscopic (FT-IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses

Selected spectral data of the products

But-2-enedioic acid bis-[cyclohexylcarbamoyl-(3-nitrophenyl)-methyl] ester (4a)

Light yellow powder; yield: 0.57 g (90 %); m.p.: 245–247 °C; FT-IR (KBr): ν_{max} = 3,270, 3,070, 2,930, 2,850, 1,720, 1,700, 1,655, 1,530, 1,350, 1,150 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (2H, m, CH), 1.10 (3H, m, CH), 1.42 (1H, m, CH), 1.53 (3H, m, CH), 1.72 (1H, m, CH), 3.51 (1H, m, CH), 6.03 (1H, s, NH), 6.94 (1H, s, CH), 7.39 (1H, t, J = 8 Hz, HAr), 7.44 (1H, d, J = 7.8 Hz, HAr), 7.73 (1H, d, J = 7.5 Hz, HAr), 8.02 (1H, d, J = 8.0 Hz, HAr), 8.25 (1H, s, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 24.9, 25.6, 32.4, 32.6, 48.3 (CHNH),

75.2 (CHO), 122.4, 124.0, 130.6, 133.9, 134.2, 138.0, 148.1, 163.7 (C=O, ester), 166.1 (C=O, amide) ppm. Anal. Calcd. for $C_{32}H_{36}N_4O_{10}$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.25; H, 5.74; N, 8.71.

But-2-enedioic acid bis-(cyclohexylcarbamoyl-thiophen-2-yl-methyl) ester (4b)

White powder; yield: 0.53 g (95 %); m.p.: 210–212 °C; FT-IR (KBr): ν_{max} = 3,280, 3,090, 2,940, 2,860, 1,730, 1,665, 1,560, 1,170, 970 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (3H, m, CH), 1.33 (2H, m, CH), 1.59 (1H, m, CH), 1.67 (2H, m, CH), 1.88 (2H, m, CH), 3.78 (1H, m, CH), 6.11(1H, s, NH), 6.36 (1H, s, CH), 6.97 (1H, t, J = 4.29 Hz, HAr), 6.99 (1H, s, CH), 7.17 (1H, d, J = 3.28 Hz, HAr), 7.33 (1H, d, J = 5.08 Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 24.8, 25.4, 26.4, 29.4, 29.7, 31.3, 32.0, 32.2, 32.8, 48.7 (CHNH), 71.8 (CHO), 125.0, 127.0, 127.6, 128.6, 133.9, 135.2, 136.6, 163.0 (C=O, ester), 165.6 (C=O, amide) ppm. Anal. Calcd. for $C_{28}H_{34}N_2O_6S_2$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.11; H, 6.19; N, 4.95.

But-2-enedioic acid bis-[cyclohexylcarbamoyl-(2-nitro-phenyl)-methyl] ester (4c)

Light yellow powder; yield: 0.57 g (90 %); m.p.: 214–216 °C; FT-IR (KBr): ν_{max} = 3,320, 3,050, 2,960, 2,860, 1,720, 1,670, 1,570, 1,530, 1,340, 1,150, 1,020 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (2H, m, CH), 1.24–1.37 (3H, m, CH), 1.57 (2H, m, CH), 1.69 (1H, m, CH), 1.78 (1H, m, CH), 1.95 (1H, m, CH), 3.75 (1H, m, CH), 6.28 (1H, d, J = 8.0 Hz, NH), 6.68 (1H, d, J = 3.0 Hz, CH), 7.03 (1H, s, CH), 7.55 (1H, t, J = 7.8 Hz, HAr), 7.69 (1H, t, J = 7.5 Hz, HAr), 7.82 (1H, dd, J = 7.0, 4.0 Hz, HAr), 8.02 (1H, d, J = 8.18 Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 25.4, 32.6, 32.7, 32.8, 48.7 (CHNH), 71.6 (CHO), 124.9, 129.8, 129.9, 130.2, 133.8, 134.0, 148.0, 163.2 (C=O, ester), 165.1 (C=O, amide) ppm. Anal. Calcd. for $C_{32}H_{36}N_4O_{10}$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.29; H, 5.55; N, 8.68.

But-2-enedioic acid bis-[(4-nitro-phenyl)-cyclohexylcarbamoyl-methyl] ester (4d)

Light yellow powder; yield: 0.61 g (95 %); m.p.: 180–182 °C; FT-IR (KBr): ν_{max} = 3,280, 3,050, 2,950, 2,840, 1,710, 1,655, 1,610, 1,540, 1,340, 1,260, 1,200, 1,160 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04–1.26 (5H, m, CH), 1.52 (1H, m, CH), 1.62 (2H, m, CH), 1.71 (1H, m, CH), 1.80 (1H, m, CH), 3.63 (1H, m, CH), 6.12 (1H, s, CH), 7.02 (1H, d, J = 1.9 Hz, CH), 7.04 (1H, t, J = 8.7 Hz, NH), 7.63 (2H, d, J = 8.7 Hz, HAr), 8.14 (2H, d, J = 8.7 Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 24.9, 25.5, 32.4, 32.6, 48.3 (CHNH), 75.4 (CHO), 124.1, 128.8, 133.9, 143.0, 148.0, 163.7 (C=O, ester), 165.9 (C=O, amide) ppm. Anal. Calcd. for $C_{32}H_{36}N_4O_{10}$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.25; H, 5.52; N, 8.85.

But-2-enedioic acid bis-(cyclohexylcarbamoyl-phenyl-methyl) ester (4e)

White powder; yield: 0.46 g (85 %); m.p.: 220–222 °C; FT-IR (KBr): ν_{max} = 3,295, 3,070, 2,950, 2,860, 1,730, 1,660, 1,540, 1,150, 970 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (3H, m, CH), 1.21 (2H, m, CH), 1.38 (1H, m, CH), 1.72 (2H, m, CH), 1.93 (2H, m, CH), 3.82 (1H, m, CH), 5.93 (1H, t, J = 7.0 Hz, NH), 6.15 (1H, s, CH), 7.06 (1H, d, J = 1.5 Hz, CH), 7.41 (3H, m, HAr),7.46 (2H, m, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.9, 25.0, 25.6, 32.5, 32.7, 48.2 (CHNH), 76.4 (CHO), 127.7, 127.8, 128.9, 129.1, 129.9, 133.9, 136.0, 163.9 (C=O, ester), 166.8 (C=O, amide) ppm. Anal. Calcd. for $C_{32}H_{38}N_2O_6$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.14; H, 7.13; N, 5.02.

But-2-enedioic acid bis-[(4-chloro-phenyl)-cyclohexylcarbamoyl-methyl] ester (4f)

White powder; yield: 0.55 g (90 %); m.p.: 250–252 °C; FT-IR (KBr): ν_{max} = 3,290, 3,060, 2,940, 2,860, 1,730, 1,660, 1,550, 1,250, 1,090, 1,020 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (3H, m, CH), 1.22 (2H, m, CH), 1.52 (1H, m, CH), 1.60 (2H, m, CH), 1.71 (1H, m, CH), 1.79 (1H, m, CH), 3.64 (1H, m, CH), 5.98 (1H, s, CH), 6.65 (1H, d, J = 7.9 Hz, NH), 6.94 (1H, d, J = 1.86 Hz, CH), 7.24 (2H, d, J = 8.5 Hz, HAr), 7.33 (2H, d, J = 8.5 Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 25.4, 32.8, 32.9, 48.5, 48.6 (CHNH), 73.4 (CHO), 75.7 (CHO), 128.2, 128.99, 129.0, 129.2, 133.5, 133.9, 135.4, 166.1 (C=O, ester), 170.6 (C=O, amide) ppm. Anal. Calcd. for $C_{32}H_{36}Cl_2N_2O_6$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.27; H, 5.78; N, 4.41.

But-2-enedioic acid bis-[cyclohexylcarbamoyl-(4-methoxy-phenyl)-methyl] ester (4g)

White powder; yield: 0.55 g (90 %); m.p.: 230–232 °C; FT-IR (KBr): ν_{max} = 3,300, 3,050, 2,910, 2,860, 1,730, 1,660, 1,545, 1,510, 1,250, 1,150, 1,030 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (3H, m, CH), 1.38 (2H, m, CH), 1.65 (1H, m, CH), 1.73 (2H, m, CH), 1.92 (2H, m, CH), 3.81 (1H, s, CH), 3.83 (3H, m, OCH_3), 5.84 (1H, t, J = 7.15 Hz, NH), 6.11 (1H, s, CH), 6.93 (2H, d,

$J = 8.7$ Hz, HAr), 7.02 (1H, d, $J = 1$ Hz, CH), 7.38 (2H, d, $J = 8.7$ Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 24.81, 25.4, 32.9, 33.0, 48.4 (CHNH), 55.4 (CH_3O), 76.1 (CHO), 114.3, 127.1, 129.3, 133.9, 160.3 (C=O, ester), 163.2, 166.8 (C=O, amide) ppm. Anal. Calcd. for $C_{34}H_{42}N_2O_8$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.19; H, 6.87; N, 4.51.

But-2-enedioic acid bis-[cyclohexylcarbamoyl-(3,4-dimethoxy-phenyl)-methyl] ester (4h)

White powder; yield: 0.63 g (95 %); m.p.: 214–217 °C; FT-IR (KBr): ν_{max} = 3,280, 3,050, 2,920, 2,860, 1,730, 1,660, 1,600, 1,560, 1,150 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (3H, m, CH), 1.36 (2H, m, CH), 1.60 (1H, m, CH), 1.68 (2H, m, CH), 1.88 (2H, m, CH), 3.79 (1H, m, CH), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.78 (1H, d, $J = 8.19$ Hz, NH), 6.06 (1H, s, CH), 6.85 (1H, d, $J = 8.21$ Hz, HAr), 6.95 (1H, d, $J = 1.91$ Hz, HAr), 6.98 (1H, dd, $J = 8.21$, 1.91 Hz, HAr), 7.02 (1H, d, $J = 1.18$ Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 25.4, 32.9, 33.0, 48.5 (CHNH), 55.96 (CH_3O), 55.99 (CH_3O), 76.3 (CHO), 110.7, 111.1, 120.6, 127.3, 133.9, 149.2, 149.9, 163.3 (C=O, ester), 166.7 (C=O, amide) ppm. Anal. Calcd. for $C_{36}H_{46}N_2O_{10}$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.73; H, 6.82; N, 4.10.

But-2-enedioic acid bis-(cyclohexylcarbamoyl-pyridin-4-yl-methyl) ester (4i)

Light brown powder; yield: 0.47 g (85 %); m.p.: 180–182 °C; FT-IR (KBr): ν_{max} = 3,366, 3,074, 2,932, 2,855, 1,710, 1,655, 1,520, 1,263, 1,022 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (2H, m, CH), 1.35 (2H, m, CH), 1.63 (2H, m, CH), 1.70 (2H, m, CH), 1.90 (2H, m, CH), 3.78 (1H, m, CH), 5.91 (1H, d, $J = 8.08$ Hz, NH), 6.09 (1H, s, CH), 7.11 (1H, s, CH), 7.38 (2H, d, $J = 5.92$ Hz, HAr), 8.65 (2H, d, $J = 5.92$ Hz, HAr) ppm. Anal. Calcd. for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.50; H, 6.68; N, 10.05.

But-2-enedioic acid bis-(cyclohexylcarbamoyl-pyridin-3-yl-methyl) ester (4j)

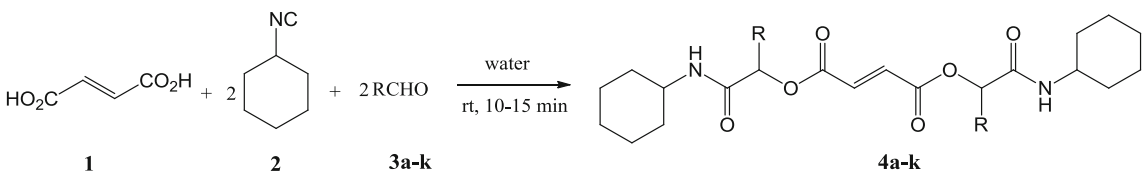
Light brown powder; yield: 0.52 g (95 %); m.p.: 208–210 °C; FT-IR (KBr): ν_{max} = 3,295, 3,070, 2,960, 1,730, 1,660, 1,540, 1,320, 1,270, 1,160 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (3H, m, CH), 1.26 (2H, m, CH), 1.52 (1H, m, CH), 1.63 (2H, m, CH), 1.75 (1H, m, CH), 1.82 (1H, m, CH), 3.67 (1H, m, CH), 6.07 (1H, d, $J = 1.77$ Hz, CH), 6.81 (1H, d, $J = 6.87$ Hz, NH), 6.98 (1H, s, CH), 7.24 (1H, m, HAr), 7.76 (1H, dt, $J = 8.0$, 1.82 Hz, HAr), 8.52 (1H, dd, $J = 4.8$, 1.46 Hz, HAr), 8.64 (1H, d, $J = 2.0$ Hz, HAr). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2, 25.3, 25.9, 32.0, 32.9, 48.7 (CHNH), 74.7 (CHO), 124.5, 132.3, 134.3, 135.7, 149.4, 150.7, 164.2 (C=O, ester), 166.7 (C=O, amide) ppm. Anal. Calcd. for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.52; H, 6.49; N, 10.14.

But-2-enedioic acid bis-(1-cyclohexylcarbamoyl-butyl) ester (4k)

White powder; yield: 0.43 g (90 %); m.p.: 200–202 °C; FT-IR (KBr): ν_{max} = 3,285, 3,080, 2,910, 2,860, 1,730, 1,655, 1,550, 1,380, 1,310, 1,240, 1,145, 970 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (3H, m, CH_3), 1.20 (3H, m, CH), 1.42 (4H, m, CH), 1.66 (1H, m, CH), 1.73 (2H, m, CH), 1.91 (4H, m, CH), 3.82 (1H, m, CH), 5.24 (1H, t, $J = 5.76$ Hz, CH), 5.80 (1H, d, $J = 7.68$ Hz, NH), 7.02 (1H, d, $J = 1.0$ Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 18.5, 25.2, 25.8, 33.4, 34.0, 34.3, 48.6 (CHNH), 75.5 (CHO), 134.3, 164.0 (C=O, ester), 168.4 (C=O, amide) ppm. Anal. Calcd. for $C_{26}H_{42}N_2O_6$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.11; H, 8.65; N, 5.60.

Results and discussion

Chemical transformations in aqueous solvents have attracted the attention of scientists for many years and have been regularly and comprehensively reviewed in the literature [4, 18–24].



1 **2** **3a-k** **4a-k**

R: n-C_3H_7, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, C_6H_5, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, pyridin-3-yl, 3,4-$(MeO)_2C_6H_3$, pyridin-4-yl, 2-thienyl

Scheme 1 Synthesis of bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates (**4a–k**)

Table 2 Effect of various solvents in the synthesis of **4a** under mild condition

Solvent	Time (min)	Yield (%)[a]
DMF	120	30
CH_3CN	100	35
CH_2Cl_2	140	30
1,4-Dioxane	120	30
H_2O	10	90

[a] Isolated yields

Following our preliminary experiments demonstrating that Passerini reaction is significantly accelerated on water, and in connection with our continued research on environmentally benign methodologies in organic synthesis [25–31], we became interested in developing versatile and efficient one-pot synthesis of bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates (**4a–k**) utilizing the reaction of fumaric acid (**1**) (1 mmol), cyclohexyl isocyanide (**2**) (2 mmol) and aldehydes (**3a–k**) (2 mmol) in water at room temperature (Scheme 1). This rapid method produced the products in short reaction times (10–15 min) and excellent yields (85–95 %) (Table 1). The structures of the products were deduced from their elemental analyses and spectroscopic data.

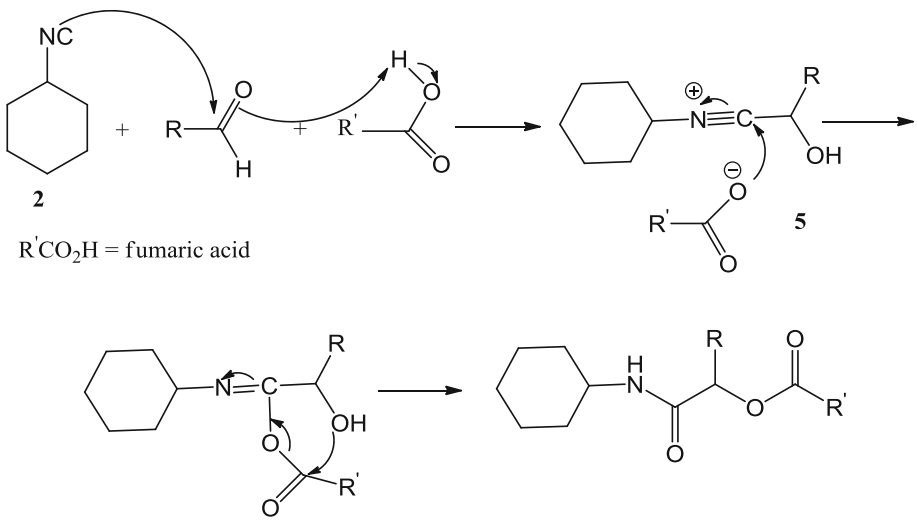
In this study, for cyclohexyl ring carbons in the ^{13}C NMR spectra due to symmetrical nature of the products, six distinct peaks were observed at region 24.6–48.7 ppm. However, in the case of **4b**, because of the symmetry distortion of the molecule, in the ^{13}C NMR spectrum two sets of peaks (one at 48.3 ppm for the ipso-carbon of cyclohexyl ring and 10 peaks for the remaining carbons of cyclohexyl rings) appeared at the expected region 23.5–32.8 ppm. It is worth mentioning that ^{1}H NMR and FT-IR spectra as well as elemental analysis all confirmed the structure of the bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarates (**4a–k**).

The effect of several solvents (1,4-dioxane, CH_3CN, DMF, CH_2Cl_2, H_2O) on the efficiency of the reaction was also examined by using synthesis of **4a** as model reaction. The results are presented in Table 2. This study revealed that H_2O is the solvent of choice.

Mechanistically the formation of the products (**4a–k**) can be visualized by initial nucleophilic attack of isocyanocyclohexane (**2**) on aldehyde to form intermediate **5**, followed by nucleophilic addition of the carboxylate ion to intermediate **5** and subsequent rearrangement to furnish the desired Passerini compounds (Scheme 2). In addition due to mild reaction conditions used in this protocol the trans-stereochemistry of the starting fumaric acid is retained in the final product.

Conclusions

In conclusion, we have developed an efficient synthesis of novel bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate derivatives (**4a–k)** via the reaction of fumaric acid, various aldehydes and cyclohexyl isocyanide in water without catalyst using one-pot three-component approach which could be used as organic building blocks for natural products and drugs. The reaction conditions are mild and the reaction gives excellent yields of the products. This method does not involve the use of toxic solvents, catalyst and tedious workup procedure and thus is an environmentally friendly process.



Scheme 2 Proposed mechanism for the formation of bis(1-(cyclohexylamino)-1-oxoalkyl or aryl) fumarate derivatives

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References

1. M.C. Pirrung, K.D. Sarma, Tetrahedron **61**, 11456 (2005)
2. M.C. Pirrung, K.D. Sarma, J. Am. Chem. Soc. **126**, 444 (2004)
3. P. Ball, *H2O: a Biography of Water* (Phoenix Press, London, 2000)
4. A. Chanda, V.V. Fokin, Chem. Rev. **109**, 725 (2009)
5. R. Breslow, Acc. Chem. Res. **24**, 159 (1991)
6. T. Bousquet, M. Jida, M. Soueidan, R. Deprez-Poulain, F. Agbossou-Niedercorn, L. Pelinski, Tetrahedron Lett. **53**, 306 (2012)
7. E. Soleimani, M. Zainali, S. Samadi, Tetrahedron Lett. **52**, 4186 (2011)
8. L. Weber, Curr. Med. Chem. **9**, 1241 (2002)
9. A. Dömling, I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
10. M.M. Heravi, S. Moghimi, J. Iran Chem. Soc. **8**, 306 (2011)
11. A. Dömling, Chem. Rev. **106**, 17 (2006)
12. J.E. Biggs-Houck, A. Younai, J.T. Shaw, Curr. Opin. Chem. Biol. **14**, 371 (2010)
13. A. Dömling, Curr. Opin. Chem. Biol. **6**, 306 (2002)
14. I. Akritopoulou-Zanze, Curr. Opin. Chem. Biol. **12**, 324 (2008)
15. A. Dömling, B. Beck, W. Baumbach, G. Larbig, Bioorg. Med. Chem. Lett. **17**, 379 (2007)
16. P.T. Anastas, J.C. Warner, *Green Chemistry: Theory and Practice* (Oxford Univ. Press, New York, 1998)
17. S. Narayan, J. Muldoon, M.G. Finn, V.V. Fokin, H.C. Kolb, K.B. Sharpless, Angew. Chem. Int. Ed. **44**, 3275 (2005)
18. C.J. Li, Chem. Rev. **93**, 2023 (1993)
19. U.M. Lindström, Chem. Rev. **102**, 2751 (2002)
20. S. Kobayashi, K. Manabe, Acc. Chem. Res. **35**, 209 (2002)
21. C.J. Li, Chem. Rev. **105**, 3095 (2005)
22. C.J. Li, L. Chen, Chem. Soc. Rev. **35**, 68 (2006)
23. U.M. Lindström, *Organic Reactions in Water: Principles Strategies and Applications* (Blackwell, Oxford, 2007)
24. E. Vessally, A. Ramazani, E. Yaaghubi, Monatsh. Chem. **142**, 1143 (2011)
25. R. Hosseinnia, M. Mamaghani, K. Tabatabaeian, F. Shirini, M. Rassa, Bioorg. Med. Chem. Lett. **22**, 5956 (2012)
26. A.A. Roshan, M. Mamaghani, N.O. Mahmoodi, F. Shirini, J. Chin. Chem. Lett. **23**, 395 (2012)
27. M. Mamaghani, A. Loghmanifar, M.R. Taati, Ultrason. Sonochem. **18**, 45 (2011)
28. M. Nikpassand, M. Mamaghani, F. Shirini, K. Tabatabeian, Ultrason. Sonochem. **17**, 301 (2010)
29. M. Mamaghani, S. Dastmard, Ultrason. Sonochem. **16**, 445 (2009)
30. M. Nikpassand, M. Mamaghani, K. Tabatabaeian, M. Kupaei Abiazi, Mol. Divers. **13**, 389 (2009)
31. H.A. Samimi, M. Mamaghani, K. Tabatabaeian, J. Heterocycl. Chem. **45**, 1765 (2008)