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ORIGINAL PAPER

One-pot, three-component reaction of isocyanides, dialkyl acetylenedicarboxylates, and non-cyclic anhydrides: synthesis of 2,5-diaminofuran derivatives and dialkyl (*E*)-2-[(*N*-acyl-*N*-alkylamino)carbonyl]-2-butenedioates

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Abstract Isocyanides, dialkyl acetylenedicarboxylates, and non-cyclic anhydrides, for example acetic anhydride or benzoic anhydride, react in one-pot to afford 2,5-diaminofuran derivatives and dialkyl (*E*)-2-[(*N*-acyl-*N*-alkylamino) carbonyl]-2-butenedioates in fairly good yields at room temperature.

Keywords Isocyanides · Acetylenic ester · Acetic anhydride · Multicomponent reaction

Introduction

Multicomponent reactions are well established as a powerful tool for rapid construction of complex and structurally diverse compounds from relatively simple building blocks [1–3]. Simple procedures, high atom-economy, chemical efficiency, and convergence are typical features of such one-pot condensations of at least three different starting materials. Because of the remarkably high purity of libraries, multicomponent reactions are well-suited for both combinatorial chemistry and high-speed parallel synthesis, and therefore have high exploratory power [4, 5]. Isocyanide-based [6–10] multicomponent reactions, especially, have been emerging fields of interest in the last decade, but the construction of heterocycles via multicomponent reactions has also attracted interest recently [11–14].

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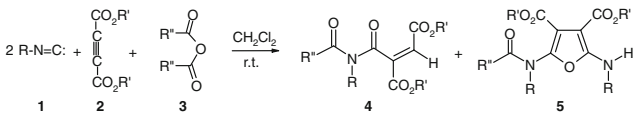
Polysubstituted furans play an important role in organic chemistry, not only because of their presence as key structural units in many natural products [15] and in important pharmaceuticals [16] but also because of their use in synthetic chemistry as building blocks. For this reason the synthesis of polysubstituted furans continues to attract the interest of many synthetic chemists.

Although the trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with aldehydes [17], aromatic anhydrides [18, 19], 1,3-diones [20], benzoyl chlorides [21], benzoyl cyanides [22], quinones [23], malimide, and succinimides [24] has been studied in detail by a number of research groups [6–10], trapping of the initial 1:1 intermediate formed with acetic or benzoic anhydride has not been reported.

Dimethyl acetylenedicarboxylate (DMAD) and isocyanides undergo a variety of cycloadditions with a third component containing a carbonyl group to form diverse heterocyclic scaffolds. For example the reaction of DMAD, an isocyanide, and phthalic anhydride derivatives produces benzofused spirolactones [18, 19]. We planned to test a similar reaction between DMAD, isocyanide, and acetic anhydride or benzoic anhydride for construction of iminolactone derivatives, which was also based on the work of Esmaili and Bodaghi [18] and Shaabani et al. [19]. In these experiments we found that the reaction was different. We now report a simple one-pot synthesis of 2,5-diaminofuran derivatives and highly functionalized enone compounds using alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of acetic anhydride (**3a**) or benzoic anhydride (**3b**) as trapping agents for the reactive zwitterionic intermediate. This three-component condensation reaction produces highly functionalized compounds **4** and **5** in fairly good yields (Scheme 1).



4, 5	R	R'	R"	Ratio 4:5
a	Cyclohexyl	Me	Me	7.8:1
b	*t*-Bu	Me	Me	1:8
c	*t*-Bu	*t*-Bu	Me	1:2
d	*t*-Bu	Et	Ph	1:0
e	*t*-Bu	Me	Ph	8.5:1.2
f	*t*-Bu	Et	Me	0:1
g	Cyclohexyl	Et	Ph	1:0
h	Cyclohexyl	Me	Ph	8:1
i	Cyclohexyl	Me	*i*-Pr	7.8:1
j	Cyclohexyl	*t*-Bu	Me	1:0
k	Cyclohexyl	Et	Me	2:1

Scheme 1

Results and discussion

The one-pot, three-component condensation reactions of alkyl isocyanides **1** with electron-deficient acetylenic esters **2** in the presence of acetic anhydride (**3a**) or benzoic anhydride (**3b**) proceeded spontaneously at room temperature in dichloromethane and was complete after 1 day, affording the corresponding dialkyl (*E*)-2-[(*N*-acyl-*N*-alkylamino)carbonyl]-2-butenedioates **4** and dialkyl 2-(*N*-acyl-*N*-alkylamino)-5-(alkylamino)-3,4-furandicarboxylates **5** in moderate to good yields. ^{1}H NMR spectra of the crude reaction mixture clearly indicated the formation of compounds **4** and **5** even in 1:1:1 (isocyanide: DMAD: Ac_2O) experiments. The structures of compounds **4a**–**4k** and **5a**–**5k** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. For example, the ^{1}H NMR spectrum of **4a** exhibits a multiplet for the cyclohexyl ring (δ = 1.24–2.20 ppm) and four sharp singlets for the acetoxy group (δ = 2.39 ppm), two methoxy groups (δ = 3.67 and 3.84 ppm), and the vinylic proton (δ = 6.61 ppm). The *E* configuration of the carbon–carbon double bond in **4** is based on the chemical shift of the olefinic proton. The ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the proposed structure. Two signals (δ = 122.68 and 143.98) ppm are readily assigned to the olefinic carbon atoms.

The ^{1}H NMR spectrum of **5b** exhibits five sharp singlets for two *tert*-butyl groups (δ = 1.36 and 1.42 ppm), the acetoxy group (δ = 1.96 ppm), and two methoxy groups (δ = 3.77 and 3.84 ppm), and a broad signal (δ = 6.90 ppm) for the NH group. The ^{13}C NMR spectrum of **5b** showed 14 distinct resonances in agreement with the proposed structure. Four signals (δ = 85.91, 113.63, 139.66, and 159.61 ppm) are readily assigned to the furan carbon atoms. The mass spectra of compounds **4** and **5** displayed molecular ion peaks at appropriate *m*/*z* values.

A plausible mechanism for the formation of **4** is shown in Scheme 2. On the basis of the well-established chemistry of isocyanides [25–28] it is reasonable to assume that compound **4** results from initial addition of alkyl isocyanide **1** to the acetylenic ester and subsequent protonation of the 1:1 adduct **6** by acid from hydrolysis of the anhydride, followed by attack of the carboxylate anion of the positively charged ion **7** to form an imidoyl carboxylate **8**, which undergoes rearrangement [29, 30] to produce the enone **4**. Compound **4** is trapped by isocyanide to give the 2,5-diaminofuran derivative **5**.

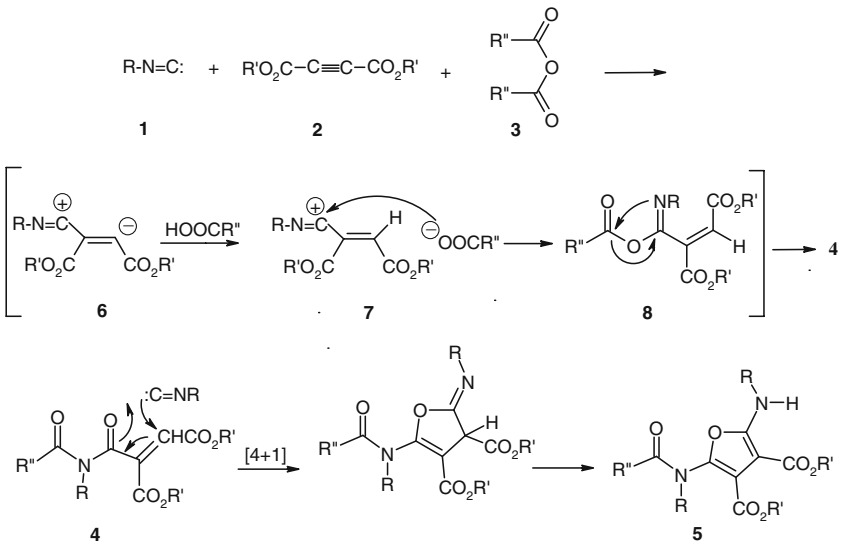
We extended our studies to various reaction conditions. The reaction in the presence of a 1:1 mixture of anhydride and the corresponding carboxylic acid or replacing the anhydride by carboxylic acid resulted in better yields of the products. When the solvent was carefully dried and the reaction was carried out under nitrogen atmosphere, the corresponding 2,5-dihydro-5-imino-2-alkylfuran-3,4-dicarboxylate **9** was obtained in 30–40% yields (Scheme 3). It is conceivable that the intermediate **6** adds to a carbonyl group of the anhydride which undergoes cyclization to **9**. Furthermore, when few drops of water were added to the reaction mixture, the reaction proceeded smoothly to afford the desired products in good yields and reduced formation of **9**.

In conclusion, the three-component reaction of alkyl isocyanides with electron-deficient acetylenic esters in the presence of acetic anhydride or benzoic anhydride provides a simple entry to the synthesis of 2,5-diaminofuran derivatives and polyfunctionalized enones of potential synthetic interest. This procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

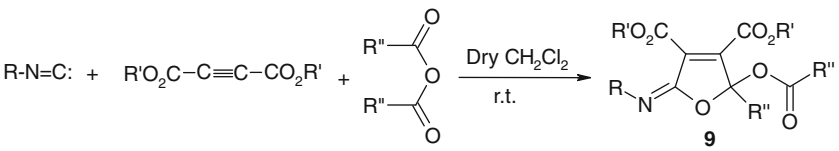
Experimental

Dialkyl acetylenedicarboxylates, alkyl isocyanides, and other reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification. NMR spectra were recorded with a Bruker DRX-300 Avance instrument (299.9 MHz for ^{1}H and

Scheme 2



Scheme 3



75.4 MHz for ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constants (J) are reported in Hertz (Hz). Melting points were measured with an Electrotherma1 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded with a Shimadzu QP-GC Mass 1100-EX spectrometer operating at an ionization potential of 70 eV. IR spectra were measured with Bruker Tensor 27 spectrometer.

General procedure

To a stirred solution of the anhydride (1 mmol) and dialkyl acetylenedicarboxylate (1 mmol) in 10 cm^3 dichloromethane was added the isocyanide (2 mmol) in 2 cm^3 dichloromethane at room temperature over 10 min via a syringe. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (Merck silica gel 60, 70–230 mesh) using hexane–ethyl acetate (8:2) as eluent.

Dimethyl (E)-2-[(N-acetyl-N-cyclohexylamino)-carbonyl]-2-butenedioate (**4a**, $C_{15}H_{21}NO_6$)
Pale yellow oil; 0.244 g (78%); IR (KBr): $\bar{\nu}$ = 1,710, 1,685 (C=O), 1,645 (C=C), 1,300, 1,250 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24–2.20 (10H, m, 5 CH_2), 2.39 (3H, s, CH_3CO), 3.74 (1H, m, NCH), 3.67, 3.84 (6H, 2s, 2 OCH_3), 6.61 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.2, 25.4, 26.7, 29.2, 29.8 (5 CH_2), 25.4 (CH_3CO), 52.3 and 53.0 (2 OCH_3), 60.1 (NCH), 122.7 (C=*C*H), 143.9 (*C*=CH), 163.2 (NCO), 165.0, 166.7 (2 *C*O_2CH_3), 174.2 (CH_3*C*ON) ppm; MS: *m*/*z* (%) = 311 (M^+, 0.4), 170 (3), 155 (3), 86 (17), 84 (40), 60 (35), 43 (100).

Dimethyl 2-(N-acetyl-N-cyclohexylamino)-5-(cyclohexyl-amino)-3,4-furandicarboxylate (**5a**, $C_{22}H_{32}N_2O_6$)
Yellow oil; 0.04 g (10%); IR (KBr): $\bar{\nu}$ = 3,288 (NH), 1,750, 1,712 (C=O), 1,294, 1,170 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12–2.30 (20H, m, 10 CH_2), 3.10 (3H, s, CH_3CO), 3.20–3.45 (2H, m, 2 NCH), 3.87, 3.89 (6H, 2s, 2 OCH_3), 6.91 (1H, br s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.2, 24.4, 25.1, 25.2, 25.5, 25.5, 26.2, 28.2, 29.8, 30.1, 31.1 (10 CH_2, *C*H_3CO), 52.7, 52.9 (2 OCH_3), 53.5, 60.9 (2 NCH), 89.2 (furan-C_4), 118.2 (furan-C_3), 135.7 (furan-C_5), 161.7 (furan-C_2), 161.7, 162.4 (2 *C*O_2CH_3), 173.2 (C=O) ppm; MS (M^+ = 420).

Dimethyl (E)-2-[(N-acetyl-N-tert-butylamino)carbonyl]-2-butenedioate (**4b**, $C_{13}H_{19}NO_6$)
Yellow oil; 0.028 g (10%); IR (KBr): $\bar{\nu}$ = 1,710 and 1,685 (C=O), 1,645 (C=C), 1,300 and 1,250 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (9H, s, $NCMe_3$), 2.12 (3H, s, CH_3CO), 3.98, 3.99 (6H, 2s, 2 OCH_3), 6.34 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.4

(CH_3CO), 28.7 (NC*Me*$_3$), 52.9, 53.1 (2 OCH_3), 123.0 (C=*C*H), 144.1 (*C*=CH), 163.3 (NCO), 165.2, 166.7 (2 *C*O_2CH_3), 173.8 (CH_3*C*ON) ppm; MS ($M^+ = 285$).

Dimethyl 2-(N-acetyl-N-tert-butylamino)-5-(tert-butylamino)-3,4-furandicarboxylate (**5b**, $C_{18}H_{28}N_2O_6$)
Yellow powder; 0.296 g (80%); IR (KBr): $\bar{\nu} = 3{,}285$ (NH), 1,737, 1,710, 1,651 (C=O), 1,367, 1,296 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (9H, s, C*Me*$_3$), 1.42 (9H, s, C*Me*$_3$), 1.96 (3H, s, CH_3CO), 3.77, 3.84 (6H, 2s, 2 OCH_3), 6.90 (1H, br s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.5$ (*C*H_3CO), 28.1, 29.7 (2 C*Me*$_3$), 51.2, 52.3 (2 OCH_3), 52.7, 60.2 (2 *C*Me$_3$), 85.9 (furan-C_4), 113.6 (furan-C_3), 139.7 (furan-C_5), 159.6 (furan-C_2), 163.3, 165.1 (2 *C*O_2CH_3), 172.5 (C=O) ppm; MS ($M^+ = 368$).

Di-tert-butyl (E)-2-[(N-acetyl-N-tert-butylamino)-carbonyl]-2-butenedioate (**4c**, $C_{19}H_{31}NO_6$)
Pale yellow oil, 0.114 g (30%); IR (KBr): $\bar{\nu} = 1{,}720$, 1,691 (C=O), 1,658 (C=C), 1,251, 1,245, 1,180 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$, 1.49, 1.50 (27H, 3s, 3 CMe_3), 2.49 (3H, s, CH_3CO), 6.58 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 25.5$ (CH_3CO), 27.7, 28.3 (2 C*Me*$_3$), 28.8 (NC*Me*$_3$), 60.6 (N*C*Me$_3$), 82.3, 83.2 (2 *C*Me$_3$), 122.5 (C=*C*H), 144.2 (*C*=CH), 163.2 (NCO), 165.2, 166.7 (2 *C*O_2CMe$_3$), 174.2 (CH_3*C*ON) ppm.

Di-tert-butyl 2-(N-acetyl-N-tert-butylamino)-5-(tert-butylamino)-3,4-furandicarboxylate (**5c**, $C_{24}H_{40}N_2O_6$)
Orange powder, 0.272 g (60%); IR (KBr): $\bar{\nu} = 3{,}350$ (NH), 1,732, 1,710, 1,690 (C=O), 1,603 (C=C), 1,367, 1,260 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$, 1.40, 1.52, 1.53 (36H, 4s, 4 C*Me*$_3$), 1.99 (3H, s, CH_3CO), 6.45 (1H, s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.4$ (*C*H_3CO), 28.2, 28.3, 28.6, 29.8 (4 C*Me*$_3$), 52.4, 60.0 (2 N*C*Me$_3$), 80.4, 82.1 (2 O*C*Me$_3$), 87.6 (furan-C_4), 115.5 (furan-C_3), 138.3 (furan-C_5), 159.2 (furan-C_2), 161.8, 164.48 (2 *C*O_2CMe$_3$), 172.9 (C=O) ppm; MS: *m*/*z* (%) = 452 (0.2), 143 (5), 98 (5), 77 (7), 71 (16), 58 (68), 43 (100).

Diethyl (E)-2-[(N-benzoyl-N-tert-butylamino)carbonyl]-2-butenedioate (**4d**, $C_{20}H_{25}NO_6$)
Pale yellow powder; m.p.: 115–117 °C; 0.348 g (93%); IR (KBr): $\bar{\nu} = 1{,}739$, 1,722 (C=O), 1,668 (C=C), 1,598, 1,451 (Ph), 1,259, 1,174 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.28 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.60 (3H, s, CMe_3), 4.10 (2H, q, $^3J_{HH} = 7.0$ Hz, O*C*H_2CH$_3$), 4.20 (2H, q, $^3J_{HH} = 7.0$ Hz, O*C*H_2CH$_3$), 6.40 (1H, s, C=CH), 7.41 (2H, dd, $^3J_{HH} = 7.4$ Hz, $^3J_{HH} = 7.5$ Hz, 2 CH_{meta}), 7.56 (1H, t, $^3J_{HH} = 7.4$ Hz, CH_{para}), 7.81 (2H, d, $^3J_{HH} = 7.6$ Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 13.8$, 14.1 (2 CH_2*C*H_3), 28.5 (C*Me*$_3$), 59.8 (*C*Me$_3$), 61.5, 62.2 (OCH_2), 128.5 (C=*C*H), 128.6 (2 CH_{meta}), 130.6 (2 CH_{ortho}), 134.1 (CH_{para}), 135.9 (C_{ipso}), 141.7 (*C*=CH), 162.6 (NCO), 162.6, 163.5 (2 *C*O_2Et), 175.2 (Ph*C*ON) ppm; MS: *m*/*z* (%) = 375 (M^+, 0.2), 122 (21), 105 (44), 77 (100), 52 (86), 39 (28).

Dimethyl (E)-2-[(N-benzoyl-N-tert-butylamino)carbonyl]-2-butenedioate (**4e**, $C_{18}H_{21}NO_6$)
Pale yellow crystals; m.p.: 130–132 °C; 0.295 g (85%); IR (KBr): $\bar{\nu} = 1{,}726$, 1,689 (C=O), 1,650 (C=C), 1,603, 1,585, 1,435 (Ph), 1,210, 1,179 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.63$ (9H, s, CMe_3), 3.66, 3.77 (6H, 2s, 2 OCH_3), 6.46 (1H, s, C=CH), 7.42 (2H, dd, $^3J_{HH} = 7.5$ Hz, $^3J_{HH} = 7.5$ Hz, 2 CH_{meta}), 7.51 (1H, t, $^3J_{HH} = 7.4$ Hz, CH_{para}), 7.80 (2H, d, $^3J_{HH} = 7.4$ Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.4$ (C*Me*$_3$), 52.5, 52.8 (2 OCH_3), 59.9 (*C*Me$_3$), 128.5 (C=*C*H), 128.6 (2 CH_{meta}), 130.6 (2 CH_{ortho}), 134.2 (CH_{para}), 135.8 (C_{ipso}), 141.1 (*C*=CH), 162.3 (NCO), 163.0, 163.8 (2 *C*O_2Me), 175.2 (Ph*C*ON) ppm; MS: *m*/*z* (%) = 347 (M^+, 0.1), 171 (18), 105 (100), 77 (56), 57 (10), 41 (9).

Dimethyl 2-(N-benzoyl-N-tert-butylamino)-5-(tert-butylamino)-3,4-furandicarboxylate (**5e**, $C_{23}H_{30}N_2O_6$)
Yellow paste; 0.052 g (12%); IR (KBr): $\bar{\nu} = 3{,}328$ (NH), 1,730, 1,705, 1,682 (C=O), 1,608 (C=C), 1,251, 1,210 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$, 1.42 (9H, 2s, 2 C*Me*$_3$), 3.74, 3.79 (6H, 2s, 2 OCH_3), 6.90 (1H, s, NH), 7.42 (2H, dd, $^3J_{HH} = 7.3$ Hz, $^3J_{HH} = 7.4$ Hz, 2 CH_{meta}), 7.60 (1H, t, $^3J_{HH} = 7.3$ Hz, CH_{para}), 7.80 (2H, d, $^3J_{HH} = 7.3$ Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.1$, 29.7 (2 C*Me*$_3$), 51.2, 52.3 (2 OCH_3), 52.4, 60.3 (2 N*C*Me$_3$), 85.2 (furan-C_4), 114.1 (furan-C_3), 128.5 (CH_{para}), 130.2 (2 CH_{ortho}), 133.8 (2 CH_{meta}), 136.9 (C_{ipso}), 138.1 (furan-C_5), 159.0 (furan-C_2), 163.3, 164.4 (2 *C*O_2Me), 175.2 (C=O) ppm; MS ($M^+ = 430$).

Diethyl 2-(N-acetyl-N-tert-butylamino)-5-(tert-butylamino)-3,4-furandicarboxylate (**5f**, $C_{20}H_{32}N_2O_6$)
Colorless crystals; m.p.: 108–110 °C; 0.336 g (85%); IR (KBr): $\bar{\nu} = 3{,}352$ (NH), 1,732, 1,670 (C=O), 1,463 (C=C), 1,216 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 1.29 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.36 (9H, s, C*Me*$_3$), 1.40 (9H, s, C*Me*$_3$), 1.96 (3H, s, CH_3CO), 4.27 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 4.41 (2H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 6.90 (1H, s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 14.1$, 14.3 (2 *C*H_3CH$_2$), 24.5 (*C*H_3CO), 28.1, 29.7 (2 C*Me*$_3$), 52.6, 60.2 (2 *C*Me$_3$), 59.8, 61.4 (2 O*C*H_2CH$_3$), 86.1 (furan-C_4), 114.0 (furan-C_3), 139.0 (furan-C_5), 159.5 (furan-C_2), 163.1, 164.7 (2 *C*O_2Et), 172.6 (C=O) ppm; MS: *m*/*z* (%) = 143 (35), 125 (8), 98 (15), 81 (16), 56 (39), 53 (57), 43 (100).

Diethyl (E)-2-[(N-benzoyl-N-cyclohexylamino)carbonyl]-2-butenedioate (**4g**, $C_{22}H_{27}NO_6$)
Colorless crystals; m.p.: 114–116 °C; 0.362 g (90%); IR (KBr): $\bar{\nu}$ = 1,735, 1,690 (C=O), 1,660 (C=C), 1,601, 1,579 (Ph), 1,185, 1,120 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.34 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.83–2.40 (10H, m, 5 CH_2), 3.50 (1H, m, NCH), 4.22 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.28 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 6.43 (1H, s, C=CH), 7.42 (2H, dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 7.5 Hz, 2 CH_{meta}), 7.50 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para}), 7.80 (2H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9, 14.0 (2 CH_3), 25.2, 26.4, 26.4, 26.4, 29.3 (5 CH_2), 60.4, 61.5 (2 OCH_2), 62.2 (NCH), 128.5 (2 CH_{meta}), 128.6 (2 CH_{ortho}), 130.6 (C=*C*H), 134.6 (CH_{para}), 135.5 (C_{ipso}), 142.7 (*C*=CH), 162.7 (NCO), 164.3, 165.9 (2 *C*O_2Et), 175.1 (Ph*C*ON) ppm; MS: *m/z* (%) = 401 (M^+, 0.1), 123 (4), 122 (19), 105 (71), 77 (82), 52 (100).

Dimethyl (E)-2-[(N-benzoyl-N-cyclohexylamino)carbonyl]-2-butenedioate (**4h**, $C_{20}H_{23}NO_6$)
Pale yellow paste; 0.299 g (80%); IR (KBr): $\bar{\nu}$ = 1,741, 1,695 (C=O), 1,658 (C=C), 1,594, 1,460 (Ph), 1,279, 1,150 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51–2.40 (10H, m, 5 CH_2), 3.45 (1H, m, NCH), 3.76, 3.82 (6H, 2s, 2 OCH_3), 6.55 (1H, s, C=CH), 7.45 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH_{meta}), 7.60 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para}), 8.15 (2H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.4, 26.3, 26.5, 29.3 (5 CH_2), 52.4, 53.0 (2 OCH_3), 60.4 (NCH), 128.5 (C=*C*H), 128.6 (2 CH_{meta}), 130.6 (2 CH_{ortho}), 135.3 (CH_{para}), 135.5 (C_{ipso}), 142.5 (*C*=CH), 163.2 (NCO), 164.6, 165.8 (2 *C*O_2Me), 175.2 (Ph*C*ON) ppm; MS: *m/z* (%) = 373 (M^+, 0.2), 122 (21), 105 (100), 77 (78), 52 (96).

Dimethyl 2-(N-benzoyl-N-cyclohexylamino)-5-(cyclohexylamino)-3,4-furandicarboxylate (**5h**, $C_{27}H_{34}N_2O_6$)
Yellow paste; 0.048 g (10%); IR (KBr): $\bar{\nu}$ = 3,340 (NH), 1,730, 1,685 (C=O), 1,600 (C=C), 1,215 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10–2.25 (20H, m, 10 CH_2), 3.15–3.45 (2H, m, 2 NCH), 3.72, 3.81 (6H, 2s, 2 OCH_3), 6.80 (1H, br s, NH) 7.44 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH_{meta}), 7.64 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para}), 8.10 (2H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH_{ortho}) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.2, 24.4, 25.1, 25.2, 25.5, 25.5, 26.2, 29.8, 30.1, 31.1 (10 CH_2), 52.7, 53.1 (2 OCH_3), 53.6, 60.9 (2 NCH), 88.7 (furan-C_4), 114.7 (furan-C_3), 130.1 (CH_{para}), 130.2 (2 CH_{ortho}), 133.8 (2 CH_{meta}), 135.7 (furan-C_5), 136.9 (C_{ipso}), 159.9 (furan-C_2), 161.8, 162.6 (2 *C*O_2CH_3), 173.2 (C=O) ppm; MS: *m/z* (%) = 143 (4), 122 (22), 105 (54), 77 (100), 76 (22), 53 (18), 52 (96).

Dimethyl (E)-2-[(N-cyclohexyl-N-isobutyrylamino)-carbonyl]-2-butenedioate (**4i**, $C_{17}H_{25}NO_6$)
Pale yellow paste; 0.264 g (78%); IR (KBr): $\bar{\nu}$ = 1,725, 1,700 (C=O), 1,678 (C=C), 1,254, 1,055 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.90 (10H, m, 5 CH_2), 1.16 (6H, d, $^3J_{HH}$ = 6.8 Hz, *Me*$_2$CH), 2.55 (1H, hept, $^3J_{HH}$ = 6.8 Hz, Me_2CH), 3.65 (1H, m, NCH), 3.80, 3.92 (6H, 2s, 2 OCH_3), 6.55 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.2 (*Me*$_2$CH), 23.4, 23.9, 25.4, 26.3, 26.5, 29.3 (5 CH_2 and Me_2CH), 51.0 (NCH), 51.7, 52.2 (2 OCH_3), 122.2 (C=*C*H), 142.6 (*C*=CH), 159.7 (NCO), 160.5, 162.1 (2 *C*O_2Me), 171.0 (Me_2CHCON) ppm; MS (M^+ = 339).

Dimethyl 5-(cyclohexylamino)-2-(N-cyclohexyl-N-isobutyrylamino)-3,4-furandicarboxylate (**5i**, $C_{24}H_{36}N_2O_6$)
Yellow oil; 0.045 g (10%); IR (KBr): $\bar{\nu}$ = 3,295 (NH), 1,745, 1,720 (C=O), 1,250, 1,170 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10–2.30 (26H, m, 10 CH_2 and *Me*$_2$CH), 2.60 (1H, hept, Me_2CH), 3.20–3.45 (2H, m, 2 NCH), 3.81, 3.88 (6H, 2s, 2 OCH_3), 6.89 (1H, br s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.8, 23.2, 24.4, 25.1, 25.2, 25.5, 25.5, 26.2, 29.8, 30.1, 31.1 (10 CH_2 and *Me*$_2$CH), 42.2 (Me$_2$*C*H), 52.9, 53.3 (2 OCH_3), 53.3, 60.4 (2 NCH), 89.5 (furan-C_4), 118.4 (furan-C_3), 135.6 (furan-C_5), 161.7 (furan-C_2), 161.7, 162.3 (2 *C*O_2CH_3), 173.9 (C=O) ppm; MS (M^+ = 448).

Di-tert-butyl (E)-2-[(N-acetyl-N-cyclohexylamino)-carbonyl]-2-butenedioate (**4j**, $C_{21}H_{33}NO_6$)
Liquid oil; 0.316 g (80%), IR (KBr): $\bar{\nu}$ = 1,717, 1,695 (C=O), 1,650 (C=C), 1,282, 1,210 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12–1.90 (10H, m, 5 CH_2), 1.45, 1.50 (18H, 2s, 2 CMe_3), 2.41 (3H, s, CH_3CO), 3.56 (1H, m, NCH), 6.54 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.4 (CH_3CO), 24.1, 25.2, 26.4, 26.7, 29.2, 29.3 (5 CH_2), 27.8, 27.9 (2 C*Me*$_3$), 60.4 (NCH), 82.2, 83.2 (2 *C*Me$_3$), 126.8 (C=*C*H), 143.7 (*C*=CH), 161.7 (NCO), 163.6, 167.7 (2 *C*O_2CMe$_3$), 173.9 (CH_3CON) ppm; MS: *m/z* (%) = 156 (2), 142 (3), 95 (2), 60 (18), 59 (24), 58 (100), 56 (20), 44 (16), 43 (62), 41 (66).

Diethyl (E)-2-[(N-acetyl-N-cyclohexylamino)carbonyl]-2-butenedioate (**4k**, $C_{17}H_{25}NO_6$)
Yellow oil; 0.169 g (50%); IR (KBr): $\bar{\nu}$ = 1,726, 1,684 (C=O), 1,643 (C=C), 1,305, 1,250 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.95 (10H, m, 5 CH_2), 1.23, 1.26 (6H, 2t, 2 CH_3) 2.34 (3H, s, CH_3CO), 3.65 (1H, m, NCH), 4.17, 4.22 (4H, 2q, $^3J_{HH}$ = 7.2 Hz, 2 OCH_2), 6.56 (1H, s, C=CH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9, 14.1 (2 CH_3), 25.2, 25.4, 25.4, 26.4, 29.3,

29.85 (5 CH_2 and CH_3CO), 60.4 (NCH), 61.4, 62.2 (2 OCH_2), 123.6 (C=*C*H), 142.7 (*C*=CH), 162.7 (NCO), 164.3, 165.9 (2 *C*O_2Et), 175.1 (CH_3*C*ON) ppm; MS: *m*/*z* (%) = 339 (M^+, 0.2), 170 (8), 143 (16), 98 (14), 69 (13), 67 (16), 60 (28), 56 (48), 53 (100).

Diethyl 2-(N-acetyl-N-cyclohexylamino)-5-(cyclohexylamino)-3,4-furandicarboxylate (**5k**, $C_{24}H_{36}N_2O_6$)
Yellow paste; 0.112 g (25%); IR (KBr): $\bar{\nu}$ = 3,235 (NH), 1,742, 1,723 (C=O), 1,244, 1,167 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12–2.30 (26H, m, 10 CH_2 and 2 CH_3), 3.14 (3H, s, CH_3CO), 3.15–3.40 (2H, m, 2 NCH), 4.23 (2H, q, $^3J_{HH}$ = 7.4 Hz, OCH_2), 4.45 (2H, q, $^3J_{HH}$ = 7.4 Hz, OCH_2), 6.92 (1H, br s, NH) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2, 14.3 (2 CH_3), 23.2, 24.4, 25.1, 25.2, 25.5, 25.5, 26.2, 28.1, 29.8, 30.1, 31.1 (10 CH_2 and *C*H_3CO), 53.5, 60.9 (2 NCH), 59.7, 61.2 (2 OCH_2), 86.2 (furan-C_4), 114.1 (furan-C_3), 139.2 (furan-C_5), 159.5 (furan-C_2), 162.9, 163.8 (2 *C*O_2CH_3), 172.6 (C=O) ppm; MS (M^+ = 448).

References

1. Dondoni A, Massi A (2006) Acc Chem Res 39:451
2. Hulme C, Gore V (2003) Curr Med Chem 10:51
3. Bienayme H, Zhu J (2005) Applications of multicomponent reactions in drug discovery—lead generation to process developments. Wiley-VCH, Weinheim
4. Hulme C, Nixey T (2003) Curr Opin Drug Discovery Dev 6:92
5. Dömling A (2000) In: Fenniri H (ed) Combinatorial chemistry: a practical approach. Oxford University Press, Oxford, pp 287–302
6. Dömling A (2006) Chem Rev 106:17
7. Banfi L, Riva R (2005) Org React 65:1
8. Dömling A, Ugi I (2000) Angew Chem Int Ed 39:3168
9. Dömling A (2000) Curr Opin Chem Biol 4:318
10. Tietze LF, Modi A (2000) Med Res Rev 20:304
11. Orru RVA, de Greef M (2003) Synthesis 1471
12. Zhu J (2003) Eur J Org Chem 1133
13. Ugi I, Dömling A, Werner B (2000) J Heterocycl Chem 37:647
14. Ugi I, Werner B, Dömling A (2000) Targets Heterocycl Syst 4:1
15. Lipshutz BH (1986) Chem Rev 86:795
16. Nakanishi K (1974) Natural products chemistry. Kodansha, Tokyo
17. Yadav JS, Subba Reddy BV, Shubashree S, Sadashiv K, Krishna Rao D (2007) J Mol Catal A: Chemical 272:128
18. Esmaili AA, Bodaghi A (2003) Tetrahedron 59:1169
19. Shaabani A, Teimouri MB, Bijanzadeh HR (2002) J Chem Res (S) 381
20. Nair V, Rajeev SM, Ani D, Rema D, Biju AT (2005) Tetrahedron Lett 46:1337
21. Yavari I, Mokhtarporyani-Sanandaj A, Moradi L, Mirzaei A (2008) Tetrahedron 64:5221
22. Teimouri MB, Shaabani A, Bazhrang R (2004) Tetrahedron 62:1845
23. Nair V, Vinod AU, Nair JS, Sreekanth AR, Rath NP (2000) Tetrahedron Lett 41:6675
24. Shaabani A, Teimouri MB, Arab-Ameri S (2004) Tetrahedron Lett 45:8409
25. Ugi I (1971) Isonitrile chemistry. Academic Press, London
26. Marcaccini S, Torroba T (1993) Org Prep Proced Int 25:141
27. Walborsky HM, Presiasamy MP (1983) In: Patai S, Rappaport Z (eds) The chemistry of functional groups, suppl C. Wiley, New York
28. Ugi I (1982) Angew Chem Int Ed 21:810
29. Baker RH, Stanonis D (1951) J Am Chem Soc 73:699
30. Bock H, Ugi I (1997) J Prakt Chem 339:385