Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1627

www.rsc.org/obc

PAPER

A novel α-isocyanoacetamide-based three-component reaction for the synthesis of dialkyl 2-acyl-5-aminofuran-3,4-dicarboxylates†

Riccardo Mossetti, Diego Caprioglio, Giampiero Colombano, Gian Cesare Tron and Tracey Pirali*

Received 3rd November 2010, Accepted 14th December 2010
DOI: 10.1039/c0ob00979b

α-Isocyanoacetamides, acyl chlorides and dialkylacetylenedicarboxylates undergo a smooth multicomponent reaction to produce dialkyl 2-acyl-5-aminofuran-3,4-dicarboxylates in good yield. The scope and mechanism of this new multicomponent transformation are discussed.

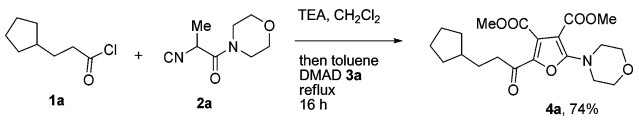
Introduction

Substituted furan rings can be broadly found in many natural products, as well as in pharmaceutically-relevant substances.[1] Besides the biological relevance of these compounds, furans have been extensively used as versatile building blocks in synthetic chemistry, thanks to their proclivity to undergo Diels–Alder cycloadditions, oxidations/reductions and hydrolysis transformations.[2] For these reasons, the search for novel and pragmatic methodologies for the synthesis of furans is actively pursued.

In recent years, there has been considerable interest in the development of efficient synthetic routes that allow the facile assembly of substituted furans under mild reaction conditions from simple and readily available starting materials, making their use feasible for a combinatorial approach.[3] In this context, isocyanide-based multicomponent reactions play a preeminent role over classical linear syntheses.[4] Three main approaches can be identified in the isocyanide-based multicomponent synthesis of tetrasubstituted furans developed so far. The first is based on a cycloaddition between a zwitterionic species, generated by reacting an isocyanide with an activated alkyne, and an electrophilic species.[5] The second involves the formation of a carbonylic α,β-unsaturated compound followed by a [4+1] cycloaddition with an isocyanide,[6] while the third concerns a 1,3-dipolar cycloaddition between oxazoles, generated by reacting isocyanoacetamides with electrophilic reagents, and activated acetylenes.[7]

Results and discussion

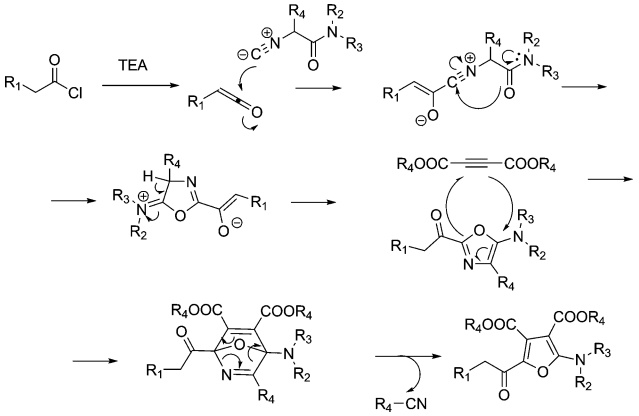
In connection with our ongoing study on the reactivity of α-isocyanoacetamides with acyl chlorides,[8] we report herein a novel three-component synthesis of scarcely represented[9] 2-acyl-5-aminofurans by reacting acyl chlorides, α-isocyanoacetamides and dialkyl acetylenedicarboxylates. Using 3-cyclopentylpropanoyl chloride (**1a**), 2-isocyano-1-morpholinopropan-1-one (**2a**) and dimethyl acetylenedicarboxylate (DMAD; **3a**) as test substrates, furan **4a** was isolated in 74% yield without the need for column chromatography (Scheme 1).



Scheme 1 Synthesis of furan **4a**.

The following optimized experimental procedure was used: to a solution of α-isocyanoacetamide (1.0 equiv.) in dry dichloromethane is added triethylamine (1.0 equiv.). A solution of acyl chloride (1.0 equiv.) in dry dichloromethane is then added dropwise over a period of 10 min, and the reaction is stirred at room temperature for 1 h in an atmosphere of nitrogen. Dry toluene and dialkylacetylene dicarboxylate (1.0 equiv.) are then added, and the reaction stirred under reflux overnight. The volatiles are evaporated under reduced pressure, and the solid washed with diethyl ether and filtered to give the desired furan.

A plausible reaction scenario is depicted in Scheme 2. The acyl chloride reacts with triethylamine, forming the corresponding ketene, which is then trapped by the isocyanide to produce the

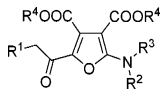


Scheme 2 Proposed reaction mechanism.

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100, Novara, Italy. E-mail: tracey.pirali@pharm.unipmn.it; Fax: +39 0321375853; Tel: +39 0321375821

† Electronic supplementary information (ESI) available: See DOI: 10.1039/c0ob00979b

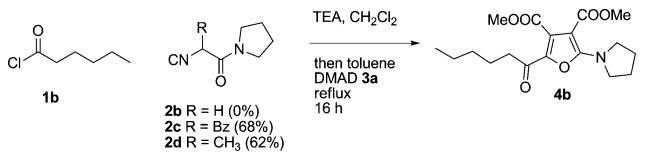
Table 1 Furans from α-isocyanoacetamides, acyl chlorides and dialkylacetylenedicarboxylates



R^1	R^2	R^3	R^4	Product	Yield (%)
CH_2Cyclopentyl	$-(CH_2)_2-O-(CH_2)_2-$		CH_3	**4a**	74
C_4H_9	$-(CH_2)_4-$		CH_3	**4b**	62
CH_3	$-(CH_2)_5-$		CH_3	**4c**	79
CH_3	$-(CH_2)_2-O-(CH_2)_2-$		CH_3	**4d**	65
CH_2Ph	$-(CH_2)_2-O-(CH_2)_2-$		CH_3	**4e**	59
CH_2Cyclopentyl	$-CH_3$	CH_2Ph	CH_3	**4f**	67
CH_2Ph	$-(CH_2)_5-$		CH_3	**4g**	68
CH_2Cyclopentyl	$-(CH_2)_4-$		CH_3	**4h**	57
CH_2Ph	$-CH_3$	CH_2Ph	CH_3	**4i**	69
CH_2Cyclopentyl	$-(CH_2)_5-$		CH_3	**4j**	74
C_4H_9	$-(CH_2)_5-$		C_2H_5	**4k**	73
C_4H_9	$-(CH_2)_2-O-(CH_2)_2-$		C_2H_5	**4l**	75
CH_3	$-(CH_2)_2-O-(CH_2)_2-$		C_2H_5	**4m**	60
CH_2Ph	$-CH_3$	CH_2Ph	C_2H_5	**4n**	72
CH_2Ph	$-(CH_2)_5-$		C_2H_5	**4o**	61
C_4H_9	$-(CH_2)_4-$		*t*Bu	**4p**	55

nitrilium ion. Subsequent cyclization and proton transfer lead to the 2-acyl-5-aminooxazole, prone to react with an activated alkyne to form a 2-acyl-5-aminofuran by a [4+2] cycloaddition and a [4+2] cycloreversion,[9] with the loss of a molecule of acetonitrile.[10]

The role of the leaving group in the cycloreversion step was explored. The best results in terms of reaction time, yield, atom economy and purification were achieved when acetonitrile was the leaving group (Scheme 3). Interestingly, when unsubstituted isocyanoacetamide **2b** was used, it failed to give the desired furan scaffold, although it can react with acyl chlorides to afford 2-acyl-5-aminooxazoles.[8] For this reason, α-methyl-substituted α-isocyanoacetamides were preferentially used. They were synthesized by the solventless aminolysis of methyl 2-isocyanopropanoate with secondary amines.[11]



Scheme 3 A comparison between variously substituted α-isocyanoacetamides.

The generality of this novel transformation was next examined. Four acyl chlorides, three dialkyl acetylenedicarboxylates and four isocyanoacetamides were used, affording sixteen dialkyl 2-alkanoyl-5-(alkylamino)furan-3,4-dicarboxylates (**4a–p**) in 55–79% yield (Table 1).

It has to be stressed that no chromatographic procedure was necessary for the purification of the furan products, but they were easily isolated in high purity by ether washing and filtration.

Conclusions

In conclusion, we have documented a straightforward synthesis of dialkyl 2-acyl-5-aminofuran-3,4-dicarboxylates, displaying four points of diversity and an unprecedented substitution pattern. The overall sequence includes six chemical reactions that follow one other in a single one-pot process, with the loss of only a molecule of acetonitrile and a molecule of hydrochloric acid. The ease of isolation of the products makes this procedure amenable to combinatorial exploitation, as well as the presence of a carbonyl group and two carboxyl moieties giving the possibility for further modifications.

Experimental section

Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). Toluene was dried by distillation from sodium and stored over activated molecular sieves (4 Å). When needed, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen.

Melting points were determined in open glass capillaries with a Stuart scientific SMP3 apparatus and are uncorrected. All the compounds were checked by IR (FT-IR THERMO-NICOLET AVATAR), ^{1}H and ^{13}C APT (JEOL ECP 300 MHz) and mass spectrometry (Thermo Finningan LCQ-deca XP-plus) equipped with an ESI source and an ion trap detector. Chemical shifts are reported in part per million (ppm). Column chromatography was performed on silica gel (Merck Kieselgel 70–230 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary, they were developed with $KMnO_4$. Elemental analysis (C, H, N) of all the new compounds were within ± 0.4% of the calculated values.

α-Isocyanoacetamides 2a–f

*2-Isocyano-1-(pyrrolidin-1-yl)ethanone (**2b**).* Methyl isocyanoacetate (1 equiv.) is reacted with pyrrolidine (1 equiv.) to give the α-isocyanoacetamide **2b** according to the previous literature.[11]

75%, δ_H(300 MHz, $CDCl_3$) 4.15 (2 H, s), 3.31 (2 H, m), 3.22 (2 H, m), 1.84 (2 H, m), 1.73 (2 H, m); δ_C(75 MHz, $CDCl_3$) δ 161.6, 160.4, 47.3, 46.8, 45.8, 26.8, 24.8; *m/z* 139 $(M + H)^+$

*2-Isocyano-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**2c**).* The subsequent alkylation, in the presence of caesium hydroxide, gives the α-substituted α-isocyanoacetamide **2c** according to the previous literature.[12] The volatiles are evaporated under reduced pressure and the crude material is purified by column chromatography on silica by using PE/EtOAc 7 : 3 as the eluent to give the desired α-isocyanoacetamide **2c**.

70%, δ_H(300 MHz, $CDCl_3$) 7.28 (5 H, m), 4.40 (1 H, t, *J* 7.4), 3.45 (3 H, m), 3.20 (2 H, m), 3.00 (1 H, m), 1.80 (4 H, m); δ_C(75 MHz, $CDCl_3$) δ 163.8, 160.0, 136.0, 130.1, 129.5, 128.3, 57.9, 47.4, 47.3, 39.8, 26.8, 24.7; *m/z* 251 $(M + Na)^+$

General procedure for the preparation of isocyanoacetamides 2a, 2d, 2e and 2f. Methyl-2-isocyanopropanoate (1 equiv.) is reacted with the amine (1 equiv.) to give the α-isocyanoacetamide. The reaction is stirred at room temperature overnight. The volatiles are evaporated under reduced pressure and the crude material is purified by column chromatography on silica by using petroleum ether/EtOAc as the eluent to give the α-isocyanoacetamide.

*2-Isocyano-1-morpholinopropan-1-one (**2a**).* Eluent: PE/EtOAc 4 : 6, 64%, light yellow oil, δ_H(300 MHz, $CDCl_3$) 4.46 (1 H, q, *J* 6.6), 3.71–3.25 (8 H, m), 1.42 (3 H, br d); δ_C(75 MHz, $CDCl_3$) δ 165.4, 159.7, 67.6, 67.2, 50.5, 47.2, 43.9, 19.8; *m/z* 169 $(M + H)^+$.

*2-Isocyano-1-(pyrrolidin-1-yl)propan-1-one (**2d**).* Eluent: PE/EtOAc 4 : 6, 65%, white solid, mp = 85–86 °C, δ_H(300 MHz, $CDCl_3$) 4.35 (1 H, q, *J* 6.6), 3.57 (1 H, m), 3.42 (3 H, m), 2.08–1.80 (4 H, m), 1.53 (3 H, d, *J* 6.6); δ_C(75 MHz, $CDCl_3$) δ 164.8, 159.2, 52.1, 47.8, 47.7, 27.2, 25.0, 19.5; *m/z* 153 $(M + H)^+$.

*2-Isocyano-1-(piperidin-1-yl)propan-1-one (**2e**).* Eluent: PE/EtOAc 5 : 5, 65%, light yellow solid, mp = 91–92 °C, δ_H(300 MHz, $CDCl_3$) 4.47 (1 H, q, *J* 6.9), 3.57–3.22 (4 H, m), 1.63–1.40 (9 H); δ_C(75 MHz, $CDCl_3$) δ 164.8, 159.2, 50.7, 47.9, 44.8, 27.0, 26.4, 25.2, 22.0; *m/z* 167 $(M + H)^+$.

N-*Benzyl-2-isocyano*-N-*methylpropanamide (**2f**).* Eluent: PE/EtOAc 7 : 3, 58%, light yellow oil, δ_H(300 MHz, $CDCl_3$) 7.40–7.11 (5 H, m), 4.63–4.47 (3 H, m), 2.98 (3 H, s), 1.60 (3 H, d, *J* 6.63); δ_C(75 MHz, $CDCl_3$) 165.1, 158.1, 135.6, 134.8, 127.6, 125.7, 51.2, 49.2, 34.3, 18.1; *m/z* 203 $(M + H)^+$.

General procedure for the preparation of 2-acyl-5-aminofuranes 4a–p

To a solution of α-isocyanoacetamide (1 equiv.) in dry dichloromethane, triethylamine (1 equiv.) is added. A solution of acyl chloride (1 equiv.) in dry dichloromethane is added drop wise in a period of ten minutes and the reaction is stirred at room temperature for 1 h in an atmosphere of nitrogen. Dry toluene and dialkylacetylene dicarboxylate (1 equiv.) are added and the reaction is stirred under reflux overnight. The volatile is evaporated under reduced pressure and the solid is washed with diethyl ether and filtered. Alternatively, the crude material is purified by column chromatography on silica by using petroleum ether/EtOAc as eluent to give furan **4**.

*Dimethyl 2-(3-cyclopentylpropanoyl)-5-morpholin-4-ylfuran-3,4-dicarboxylate (**4a**).* The crude material is purified by diethyl ether washing and filtration to give furan **4a** (74%) as a light yellow solid; mp = 93–95 °C; (found: C, 61.16; H, 6.99; N 3.56; $C_{20}H_{27}NO_7$ requires C, 61.06; H, 6.92; N 3.56%); ν_{max}(neat)/cm^{-1} 2950, 1744, 1708, 1668, 1565, 1450, 1232, 749; δ_H(300 MHz, $CDCl_3$) 3.91 (3 H, s), 3.80 (4 H, m), 3.71 (3 H, s), 3.67 (4 H, m), 2.62 (2 H, t, *J* 7.4), 1.76–1.43 (9 H, m), 1.06 (2 H, m); δ_C(75 MHz, $CDCl_3$) 188.6, 165.6, 163.2, 161.5, 140.2, 128.6, 95.2, 67.6, 54.0, 52.9, 49.5, 40.9, 38.7, 33.7, 31.1, 26.3; *m/z* 394 $(M + H)^+$.

*Dimethyl 2-cyclopentyl-5-hexanoylfuran-3,4-dicarboxylate (**4b**).* The crude material is purified by diethyl ether washing and filtration to give furan **4b** (62%) as a yellow amorphous solid (found: C, 61.68; H, 7.28; N 4.00; $C_{18}H_{25}NO_6$ requires C, 61.52; H, 7.17; N 3.99%); ν_{max}(neat)/cm^{-1} 1741, 1705, 1570, 1232, 732; δ_H(300 MHz, $CDCl_3$) 3.87 (3 H, s), 3.65 (7 H, m), 2.55 (2 H, t, *J* 3.4), 1.92 (4 H, quint, *J* 3.3), 1.59 (2 H, quint, *J* 7.1), 1.25 (4 H, m), 0.81 (3 H, t, *J* 7.1); δ_C(75 MHz, $CDCl_3$) δ 188.3, 165.9, 163.3, 160.0, 139.5, 129.2, 92.5, 53.9, 52.4, 51.0, 39.1, 32.5, 26.5, 24.6, 23.5, 15.0; *m/z* 352 $(M + H)^+$.

*Dimethyl 2-piperidin-1-yl-5-propionylfuran-3,4-dicarboxylate (**4c**).* The crude material is purified by diethyl ether washing and filtration to give furan **4c** (79%) as a yellow solid; mp = 83–85 °C (found: C, 59.30; H, 6.59; N 3.98; $C_{16}H_{21}NO_6$ requires C, 59.43; H, 6.55; N 4.33%); ν_{max}(neat)/cm^{-1} 1741, 1706, 1568, 1198, 734; δ_H(300 MHz, $CDCl_3$) 3.79 (3 H, s), 3.59 (3 H, s), 3.47 (4 H, m), 2.55 (2 H, q, *J* 7.1), 1.56 (4 H, m), 1.00 (5 H, m); δ_C(75 MHz, $CDCl_3$) 189.1, 166.0, 163.4, 161.9, 139.5, 128.9, 94.2, 54.1, 52.9, 50.6, 32.6, 26.9, 25.2, 8.70; *m/z* 346 $(M + Na)^+$.

*Dimethyl 2-morpholin-4-yl-5-propionylfuran-3,4-dicarboxylate (**4d**).* The crude material is purified by diethyl ether washing and filtration to give furan **4d** (65%) as a brown solid; mp = 159–161 °C (found: C, 55.46; H, 5.95; N 4.20; $C_{15}H_{19}NO_7$ requires C, 55.38; H, 5.89; N 4.31%); ν_{max}(neat)/cm^{-1} 1750, 1731, 1567, 1448, 1226; δ_H(300 MHz, $CDCl_3$) 3.93 (3 H, s), 3.81 (4 H, m), 3.72 (3 H, s), 3.67 (4 H, m), 2.68 (2 H, q, *J* 7.4), 1.39 (3 H, t, *J* 7.4); δ_C(75 MHz, $CDCl_3$) 189.3, 165.8, 163.3, 161.5, 140.1, 128.4, 95.3, 67.6, 54.3, 53.1, 49.5, 32.7, 9.94; *m/z* 348 $(M + Na)^+$.

*Dimethyl 2-(3-phenylpropanoyl)-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4e**).* The crude material is purified by diethyl ether washing and filtration to give furan **4e** (59%) as a light brown solid; mp = 118–120 °C (found: C, 62.85; H, 5.84; N 3.55; $C_{21}H_{23}NO_7$ requires C, 62.83; H, 5.78; N 3.49%); ν_{max}(neat)/cm^{-1} 1750, 1707, 1569, 1275, 1259, 764, 749; δ_H(300 MHz, $CDCl_3$) 7.30–7.08 (5 H, m), 3.92 (3 H, s), 3.78 (4 H, m), 3.72 (3 H, s), 3.64 (4 H, m), 2.96 (4 H, m); δ_C(75 MHz, $CDCl_3$) 188.1, 165.8, 163.4, 161.7, 142.4, 140.0, 130.0, 129.8, 129.0, 127.6, 95.6, 67.8, 54.5, 53.3, 49.6, 41.5, 31.0; *m/z* 424 $(M + Na)^+$.

*Dimethyl 2-[benzyl(methyl)amino]-5-(3-cyclopentylpropanoyl)furan-3,4-dicarboxylate (**4f**).* The crude material is purified by diethyl ether washing and filtration to give furan **4f** (67%) as a light yellow solid; mp = 125–127 °C (found: C, 67.30; H, 6.85; N 3.21; $C_{24}H_{29}NO_6$ requires C, 67.43; H, 6.84; N 3.28%); ν_{max}(neat)/cm^{-1} 1747, 1706, 1569, 668; δ_H(300 MHz, $CDCl_3$) 7.26 (5 H, m), 4.79 (2 H, m), 3.93 (3 H, s), 3.70 (3 H, s), 3.12 (3 H, s), 2.61 (2 H, t, *J* 7.4), 1.75–1.38 (9 H, m), 1.04 (2 H, m); δ_C(75 MHz, $CDCl_3$) 188.9, 166.0, 162.0 (2C), 137.3, 130.3, 129.3 (2C), 129.0 (2C), 94.8, 57.7, 54.4, 53.1, 41.1, 39.6, 39.0, 33.9, 31.5, 26.6; *m/z* 450 $(M + Na)^+$.

*Dimethyl 2-(3-phenylpropanoyl)-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4g**).* The crude material is purified by diethyl ether washing and filtration to give furan **4g** (68%) as a light

yellow solid; mp = 87–88 °C (found: C, 66.01; H, 6.28; N 3.42; $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.31; N 3.51%); ν_{max}(neat)/cm^{-1} 1746, 1704, 1569, 1449, 1259, 1227, 733; δ_H(300 MHz, $CDCl_3$) 7.19 (5 H, m), 3.90 (3 H, s), 3.70 (3 H, s), 3.56 (4 H, m), 2.94 (4 H, m), 1.64 (6 H, m); δ_C(75 MHz, $CDCl_3$) 187.0, 165.5, 163.0, 161.5, 141.9 (2C), 139.0, 129.4, 129.2, 127.0, 94.0, 53.8, 52.5, 50.2, 40.8, 30.5, 26.4, 24.8; *m/z* 422 (M + Na)$^+$.

*Dimethyl 2-(3-cyclopentylpropanoyl)-5-pyrrolidin-1-ylfuran-3,4-dicarboxylate (**4h**).* The crude material is purified by diethyl ether washing and filtration to give furan **4h** (57%) as a white amorphous solid (found: C, 63.71; H, 7.33; N 3.90; $C_{20}H_{27}NO_6$ requires C, 63.64; H, 7.21; N 3.71%); ν_{max}(neat)/cm^{-1} 1750, 1707, 1569, 1219, 749; δ_H(300 MHz, $CDCl_3$) 3.89 (3 H, s), 3.68 (7 H, m), 2.60 (2 H, t, *J* 7.4), 1.94 (4 H, quint, *J* 3.03), 1.79–1.42 (11 H, m); δ_C(75 MHz, $CDCl_3$) 188.4, 165.9, 163.3, 160.0, 139.5, 129.2, 92.5, 53.9, 52.4, 51.0, 40.8, 40.7, 33.4, 31.2, 26.5, 26.1; *m/z* 440 (M + Na)$^+$.

*Dimethyl 2-[benzyl(methyl)amino]-5-(3-phenylpropanoyl)-furan-3,4-dicarboxylate (**4i**).* The crude material is purified by column chromatography on silica by using petroleum ether/EtOAc 7 : 3 as the eluent to give furan **4i** (69%) as a yellow oil (found: C, 69.01; H, 5.70; N 3.33; $C_{25}H_{25}NO_6$ requires C, 68.95; H, 5.79; N 3.22%); ν_{max}(neat)/cm^{-1} 1742, 1706, 1569, 1453, 1218, 750; δ_H(300 MHz, $CDCl_3$) 7.25 (10 H, m), 4.78 (2 H, s), 3.94 (3 H, s), 3.71 (3 H, s), 3.09 (3 H, s), 2.94 (m, 4 H); δ_C(75 MHz, $CDCl_3$) 186.4, 164.8, 162.4, 161.8, 141.2, 138.5 (2C), 136.2, 129.3, 128.7, 128.5, 128.2, 127.9, 126.4, 93.5, 56.6, 53.2, 52.0, 40.3, 38.3, 29.9; *m/z* 458 (M + Na)$^+$.

*Dimethyl 2-(3-cyclopentylpropanoyl)-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4j**).* The crude material is purified by diethyl ether washing and filtration to give furan **4j** (74%) as a white solid; mp = 81–83 °C (found: C, 64.30; H, 7.41; N 3.50; $C_{21}H_{29}NO_6$ requires C, 64.43; H, 7.47; N 3.58%); ν_{max}(neat)/cm^{-1} 1750, 1731, 1718, 1275, 764, 749; δ_H(300 MHz, $CDCl_3$) 3.92 (3 H, s), 3.72 (3 H, s), 3.60 (4 H, m), 2.63 (2 H, t, *J* 7.4),1.81–1.48 (15 H, m), 1.09 (2 H, m); δ_C(75 MHz, $CDCl_3$) 189.0, 166.2, 163.6, 162.1, 139.9, 129.2, 94.7, 54.3, 53.0, 50.9, 41.1, 38.9, 33.9, 31.4, 27.0, 26.6, 25.4; *m/z* 414 (M + Na)$^+$.

*Diethyl 2-hexanoyl-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4k**).* The crude material is purified by diethyl ether washing and filtration to give furan **4k** (73%) as an orange solid; mp = 56–58 °C (found: C, 64.25; H, 7.99; N 3.68; $C_{21}H_{31}NO_6$ requires C, 64.10; H, 7.94; N 3.56%); ν_{max}(neat)/cm^{-1} 1714, 1701, 1560, 1222, 1193, 1084, 668; δ_H(300 MHz, $CDCl_3$) 4.35 (2 H, q, *J* 7.3), 4.15 (2 H, q, *J* 7.1), 3.57 (4 H, m), 2.59 (2 H, t, *J* 7.4), 1.61 (8 H, m), 1.34 (3 H, t, *J* 7.3), 1.27 (4 H, m), 1.23 (3 H, t, *J* 7.1), 0.84 (3 H, t, *J* 6.8); δ_C(75 MHz, $CDCl_3$) 186.7, 162.8, 160.6, 159.1, 137.8, 126.2, 92.7, 65.2, 60.9, 59.5, 47.0, 30.3, 12.9, 12.8, 6.3; *m/z* 394 (M + H)$^+$.

*Diethyl 2-hexanoyl-5-morpholin-4-ylfuran-3,4-dicarboxylate (**4l**).* The crude material is purified by diethyl ether washing and filtration to give furan **4l** (75%) as a light yellow solid; mp = 125–127 °C (found: C, 67.68; H, 7.30; N 3.51; $C_{20}H_{29}NO_7$ requires C, 60.74; H, 7.39; N 3.54%); ν_{max}(neat)/cm^{-1} 1706, 1569, 668; δ_H(300 MHz, $CDCl_3$) 4.38 (2 H, q, *J* 7.1), 4.18 (2 H, q, *J* 7.1), 3.81 (4 H, m), 3.68 (4 H, m), 2.6 (2 H, t, *J* 7.1), 1.64 (2 H, quint, *J* 7.1), 1.38 (3 H, t, *J* 7.1), 1.30 (4 H, m), 1.27 (3 H, t, *J* 7.1), 0.87 (3 H, t, *J* 6.8); δ_C(75 MHz, $CDCl_3$) 189.0, 165.9, 163.4, 161.8, 138.3, 129.2, 96.2, 68.2, 63.9, 62.4, 50.0, 40.0, 33.2, 25.2, 24.2, 15.9, 15.8, 15.7; *m/z* 418 (M + Na)$^+$.

*Diethyl 2-morpholin-4-yl-5-propionylfuran-3,4-dicarboxylate (**4m**).* The crude material is purified by diethyl ether washing and filtration to give furan **4m** (60%) as a white solid; mp = 142–143 °C (found: C, 58.50; H, 7.29; N 3.69; $C_{18}H_{27}NO_7$ requires C, 58.52; H, 7.37; N 3.79%); ν_{max}(neat)/cm^{-1} 1738, 1691, 1569, 1441, 1209, 1064, 668; δ_H(300 MHz, $CDCl_3$) 4.38 (2 H, q, *J* 7.1), 4.18 (2 H, q, *J* 7.1), 3.80 (4 H, m), 3.67 (4 H, m), 2.67 (2 H, q, *J* 7.4), 1.38 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.13 (3 H, t, *J* 7.4); δ_C(75 MHz, $CDCl_3$) 186.7, 162.8, 160.6, 159.1, 137.8, 126.2, 92.7, 65.2, 60.9, 59.5, 47.0, 30.3, 12.9, 12.8, 6.3; *m/z* 376 (M + Na)$^+$.

*Dimethyl 2-(3-phenylpropanoyl)-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4n**).* The crude material is purified by column chromatography on silica by using petroleum ether/EtOAc 7 : 3 as the eluent give furan **4n** (72%) as a yellow oil (found: C, 66.99; H, 6.35; N 3.11; $C_{27}H_{29}NO_6$ requires C, 69.96; H, 6.31; N 3.02%); ν_{max}(neat)/cm^{-1} 1739, 1701, 1568, 1212, 1075, 698; δ_H(300 MHz, $CDCl_3$) 7.40–7.18 (10 H, m), 4.78 (2 H, s), 4.41 (2 H, q, *J* 7.1), 4.16 (2 H, q, *J* 7.1), 3.08 (3 H, s), 2.90 (4 H, m), 1.38 (3 H, t, *J* 7.1), 1.22 (3 H, t, *J* 7.1); δ_C(75 MHz, $CDCl_3$) 186.2, 164.3, 162.0, 161.0, 141.2, 138.5 (2C), 136.2, 129.0, 128.7, 128.6, 128.1, 127.9, 126.3, 94.2, 62.2, 60.8, 56.5, 40.2, 38.3, 29.9, 14.2 (2C); *m/z* 486 (M + Na)$^+$.

*Diethyl 2-(3-phenylpropanoyl)-5-piperidin-1-ylfuran-3,4-dicarboxylate (**4o**).* The crude material is purified by diethyl ether washing and filtration to give furan **4o** (61%) as a yellow solid; mp = 62–64 °C (found: C, 67.53; H, 6.90; N 3.30; $C_{24}H_{29}NO_6$ requires C, 67.43; H, 6.84; N 3.28%); ν_{max}(neat)/cm^{-1} 1740, 1700, 1560, 1216, 1192, 1087, 699; δ_H(300 MHz, $CDCl_3$) 7.22 (5 H, m), 4.37 (2 H, q, *J* 7.1), 4.18 (2 H, q, *J* 7.1), 3.57 (4 H, m), 2.96 (4 H, m), 1.66 (4 H, m), 1.36 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1); δ_C(75 MHz, $CDCl_3$) 186.8, 164.9, 162.6, 161.5, 141.9 (2C), 139.0, 129.3, 129.2, 126.9, 94.3, 62.8, 61.2, 50.2, 40.8, 30.5, 26.4, 24.7, 14.9, 14.8; *m/z* 450 (M + Na)$^+$.

Di-tert-*butyl 2-hexanoyl-5-pyrrolidin-1-ylfuran-3,4-dicarboxylate (**4p**).* The crude material is purified by diethyl ether washing and filtration to give furan **4p** (55%) as a light yellow solid; mp = 98–100 °C (found: C, 66.00; H, 8.40; N 3.11; $C_{24}H_{37}NO_6$ requires C, 66.18; H, 8.56; N 3.22%); ν_{max}(neat)/cm^{-1} 1734, 1697, 1559, 1242, 1160, 1140, 749, 668; δ_H(300 MHz, $CDCl_3$) 3.60 (4 H, m), 2.62 (2 H, t, *J* 7.4), 1.95 (4 H, m), 1.60 (9 H, s), 1.49 (9 H, s), 1.29 (6 H, m), 0.87 (3 H, t, *J* 6.3); δ_C(75 MHz, $CDCl_3$) 188.4, 164.0, 163.2, 159.4, 139.8, 130.9, 95.1, 84.3, 82.7, 51.1, 39.7, 32.9, 29.7, 29.6, 26.8, 25.2, 23.8, 15.3; *m/z* 458 (M + Na)$^+$.

Notes and references

1 (*a*) F. M. Dean, *Advances in Heterocyclic Chemistry*, ed. A. R. Katrizky, Academic Press, New York, 1982, vol. 30, pp. 167–238; (*b*) F. M. Dean and M. V. Sargent, in *Comprehensive Heterocyclic Chemistry*, ed. C. W. Bird and G. W. H. Cheeseman, Pergamon Press, New York, 1984, vol. 4, part 3, pp. 531–598.

2 (*a*) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795–819; (*b*) H. N. C. Wong, P. Yu and C. Y. Yick, *Pure Appl. Chem.*, 1999, **71**, 1041–1044; (*c*) H. K. Lee, K. F. Chan, C. W. Hui, H. K. Yim, X. W. Wu and H. N. C Wong, *Pure Appl. Chem.*, 2005, **77**, 139–143; (*d*) J. Raczko and J. Jurczak, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, 1995, vol. 16, pp. 639–685.

3 For an overview on recent developments in furan synthesis, see: (*a*) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076–2080; (*b*) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955; (*c*) R. C. D. Brown, *Angew. Chem.,*

Int. Ed., 2005, **44**, 850–852; (*d*) X. L. Hou, Z. Yang, K. S. Yeung and H. N. C. Wong, *Prog. Heterocycl. Chem.*, 2009, **21**, 179–223.
4 G. Balme, D. Bouyssi and N. Monteiro, *Heterocycles*, 2007, **73**, 87–124.
5 (*a*) N. Nair and A. U. Vinod, *Chem. Commun.*, 2000, 1019–1020; (*b*) A. Alizadeh, S. Rostamnia and M. L. Hu, *Synlett*, 2006, 1592.
6 (*a*) V. Nair, R. S. Menon, A. U. Vinod and S. Viji, *Tetrahedron Lett.*, 2002, **43**, 2293–2295; (*b*) A. Alizadeh, S. Rostamnia, N. Zoreh and Q. Oskueyan, *Synlett*, 2007, 1610–1612; (*c*) A. Alizadeh, S. Rostamnia and L. G. Zhu, *Synthesis*, 2008, 1788–1792.
7 (*a*) G. C. Tron and J. Zhu, *Synlett*, 2005, 532–534; (*b*) P Janvier, H. Bienaymé and J. Zhu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4291–4294; (*c*) D Bonne, M. Dekhane and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 2485–2488; (*d*) A. Fayol and J. Zhu, *Angew. Chem., Int. Ed.*, 2002, **41**, 3633–3635; (*e*) A. Fayol and J. Zhu, *Org. Lett.*, 2004, **6**, 115–118.
8 R. Mossetti, T. Pirali, G. C. Tron and J. Zhu, *Org. Lett.*, 2010, **12**, 820–823.
9 To the best of our knowledge, the only dialkyl 2-acyl-5-aminofuran-3,4-dicarboxylates reported to date have been described by the Doyle and Padwa group. This skeleton was synthesized by reacting a rhodium-catalyzed cycloaddition between DMAD and an isomunchnone dipole. See: M. P. Doyle, R. J. Pieters, J. Taunton, H. Q. Pho, A. Padwa, D. L. Hertzog and L. Precedo, *J. Org. Chem.*, 1991, **56**, 820.
10 H. König, F. Graf and V. Weberndörfer, *Liebigs Ann. Chem.*, 1981, 668–682.
11 A. Dömling, B. Beck, T. Fuchs and A. Yazback, *J. Comb. Chem.*, 2006, **8**, 872–880.
12 C. Housseman and J. Zhu, *Synlett*, 2006, **11**, 1777–1779.