Tetrahedron 68 (2012) 6146–6151

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Active methylene compounds in a very effective approach to 3-substituted isobenzofuranones through tandem aldol/lactonization reactions

Antonia Di Mola [b,*], Gianluca Croce [c], Vijaykumar More [a], Paolo De Caprariis [b], Rosanna Filosa [b], Antonio Massa [a,*]

[a] Dipartimento di Chimica e Biologia, Università di Salerno, Via Ponte Don Melillo, 84084 Fisciano (SA), Italy
[b] Dipartimento di Scienze Farmaceutiche e Biomediche, Via Ponte Don Melillo, 84084 Fisciano (SA), Italy
[c] DISIT-Universita' del Piemonte Orientale, Viale T. Michel 11, 15121 Alessandria, Italy

ARTICLE INFO

Article history:
Received 3 March 2012
Received in revised form 27 April 2012
Accepted 21 May 2012
Available online 27 May 2012

Keywords:
Phthalides
Tandem reactions
Aldol addition
Active methylene compounds

ABSTRACT

In this article we describe a new accessible methodology for the synthesis of isobenzofuran-1(3*H*)-ones. In this process we exploited an effective, economic, useful and environmentally benign K_2CO_3 catalyzed, solvent-free one-pot tandem aldol-lactonization reaction between active methylene compounds and methyl 2-carboxy benzaldehyde. A particularly simple work-up and purification procedure are additional advantages addressed to a general green chemistry approach to this important class of heterocyclic compounds.

1. Introduction

Phthalides [isobenzofuran-1(3*H*)-ones] are integral parts of many naturally occurring substances and they have a wide range of medicinal properties.[1] In particular, 3-substituted phthalides are vital heterocyclic motifs in many bioactive compounds, such as isocoumarins, anthraquinones, anthracyclines and several alkaloids.[2a] Typical examples are typhaphthalide,[2b] catalpalactone,[2c] vermistatin,[2d] isopestacin[2e] isoochracin and herbaric acid.[2f] They possess a wide range of biological activities, which include antibacterial, anticonvulsant and anti-HIV.[3a,b] Phthalides also serve as valuable synthetic intermediates into the synthesis of several alkaloids[4a] (e.g., the convulsant alkaloid biculline),[4b] and isoindolinones.[4c] In view of their importance, various methods have been developed for the synthesis of phthalides [isobenzofuran-1(3*H*)-ones]. These methods include cyclization reactions catalyzed by strong acids, such as trifluoroacetic acid[5a] and trifluoromethanesulfonic acid[5b] or strong bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[5c,d] sodium hydroxide and potassium hydroxide.[5e-g] Nucleophilic addition of alkyl or aryl organometallic compounds on appropriately substituted phthalaldehydic acids and its derivatives,[6a] photochemical rearrangements,[6b] intramolecular cyclization,[6c] Tischenko reaction[6d] and condensation reactions catalysed by $ZrOCl_2$[7a] are also used in the synthesis of 3-substituted phenylphthalides. Transition metal complexes yield 3-aryl and 3-alkenyl phthalides through catalyzed ketone hydroacylation and cascade addition/intramolecular cyclization processes.[8] Chiral rhodium catalysts provided an asymmetric version of this reaction,[8e] while one organo-catalytic approach has been described.[9] Conversely, due to the biological importance of chiral 3-substituted phthalides, chiral auxiliaries and resolutions of racemates have been intensively explored to develop asymmetric synthesis.[10]

Nevertheless relatively few methods focus on the synthesis of isobenzofuran-1(3*H*)-ones, substituted in the 3-position with 1,3-dicarbonyl groups. Although these derivatives are particularly useful in the synthesis of important bioactive compounds, such as isopestacin or herbaric acid,[5d] all these methods involve high temperature,[7b,c] the use of transition metals or harmful acids or bases, and show rather limited scope and selectivity.

Given the ever increasing necessity of new environmentally friendly methodologies for the synthesis of valuable compounds, herein we report a direct and efficient one-pot *tandem* aldol-lactonization reaction for the preparation of 3-substituted isobenzofuran-1(3*H*)-ones, reacting malonates, diketones, β-ketoesters and nitroalkanes as model nucleophiles under solvent free conditions and in the presence of catalytic amount of the inexpensive K_2CO_3.

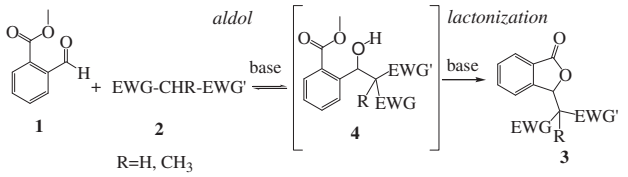
2. Results and discussion

The aldol addition of readily enolizable 1,3-dicarbonyl compounds to aldehydes is very difficult to achieve, and very few applications are

* Corresponding authors. Tel.: +39 089 969565; fax: +39 089 969603; e-mail address: amassa@unisa.it (A. Massa).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.05.079

available for these reactions: we recently demonstrated that the success of this challenging aldol addition is mainly related to the in situ trapping of the unstable aldol adducts by chlorosilane reagents[11,12] or by intramolecular trapping at the cyano group of 2-cyanobenzaldehyde.[13] In analogy to the reactivity of 2-cyanobenzaldehyde, that efficiently led to a series of 3-substituted isoindolinones,[13] we explored the reaction of methyl 2-carboxy benzaldehyde with several active methylene compounds in the synthesis of 3-substituted isobenzofuran-1(3*H*)-ones (Scheme 1).



Scheme 1. Synthesis of substituted isobenzofuran-1(3*H*)-ones from methyl 2-carboxy benzaldehyde and active methylene compounds.

In order to evaluate the effectiveness of our hypothesis, the reaction of methyl 2-carboxy benzaldehyde and di-*tert*-butyl malonate was performed under different conditions. First of all the mixture of these reagents was stirred for 24 h in the absence of base in DCM and no conversion was detected. Then we performed an experiment under similar conditions that led to 3-substituted isoindolinones, in the presence of Et_3N in DCM,[13] but unfortunately we recovered unreacted starting materials. However, since we believe that the lactonization is the limiting step of the tandem process, we thought that bases, such as K_2CO_3 could be more effective for both aldol and cyclization reactions. Thus, as shown in Table 1, in DMF, we finally obtained **3a** in almost quantitative yield at rt also in the presence of catalytic amount of base (Table 1, entries 1 and 2); however only traces of the final product were detected in acetone (Table 1, entry 6) and THF (Table 1, entry 7), while in 1,4-dioxane, dichloromethane and 1,2-dimethoxyethane the starting materials were recovered unreacted, even in the presence of 2 equiv of K_2CO_3 in a slurry mixture (Table 1, entries 3–5). Conversely a sufficient reactivity was also observed in DCM using a combination of K_2CO_3 and Et_3N probably due to the formation of a phase transfer system (Table 1, entry 8). Starting from these preliminary experiments we also explored the possibility to perform the reaction without the use of any solvent. Under these new conditions we were pleased to observe that in the presence of catalytic amount of K_2CO_3 at rt, **3a** was obtained in quantitative yield (Table 1, entry 9). Furthermore the observed high selectivity and the absence of byproducts gave us the possibility to obtain the final product without additional work-up, after only a quick filtration on a short pad of silica gel. This particular combination of conditions is an important goal for the atom economy philosophy and for a green approach to these isobenzofuranones, since the current methodologies require harsh conditions and more harmful reagents.[5–7]

Table 1
Reaction of methyl 2-carboxy benzaldehyde with di-*tert*-butyl malonate in the presence of **2** and 0.3 equiv of potassium carbonate in different solvents[a]

Entry	Solvent	Amount of K_2CO_3	Time (h)	Yield[b] (%)
1	DMF	2 equiv	24	93%
2	DMF	0.3 equiv	24	94%
3	CH_2Cl_2	2 equiv	24	0%
4	1,4-Dioxane	2 equiv	24	0%
5	1,2-Dimetoxy ethane	2 equiv	24	0%
6	Acetone	2 equiv	24	Traces
7	THF	2 equiv	24	Traces
8[c]	CH_2Cl_2	2 equiv	24	50%
9	Solvent free	0.3 equiv	5 h	99%

[a] Reaction conditions: methyl 2-carboxy benzaldehyde (0.31 mmol), di-*tert*-butyl malonate (0.34 mmol), K_2CO_3 rt, 1 mL solvent.
[b] Yields refer to chromatographically pure compounds.
[c] An additional 1 equiv of $^iPr_2NEt$ was used.

Interestingly, 0.3 equiv of Et_3N were also effective, giving the final product in 96% yield in 18 h, a result that can be particularly useful for future developments of asymmetric versions.

Conversely, under these new conditions, control experiments, without the use of any base, were unsuccessful and we recovered the starting materials unreacted.

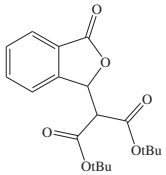
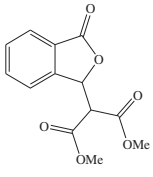
Considering the convenience to perform reactions under K_2CO_3 catalyzed, solvent-free conditions, we analyzed the scope of this protocol in the presence of different classes of active methylene compounds. Thus we were pleased to observe that this methodology is very general and gave the opportunity to synthesize an unprecedented variety of 3-substituted isobenzofuran-1(3*H*)-ones in quantitative yields and in reasonable reaction times with all the tested nucleophiles (Table 2).

In particular from the data reported in the Table 2, it is possible to note that whatever is the nature and the hindrance of the ester groups of malonates and β-ketoesters, this does not affect the reactivity of the tandem process (Table 2, entries 3–10).

The method was particularly simple and effective also on 2 mmol scale (Table 2, entry 2), opening the opportunity of further scale-up. Also nitro-compounds (Table 2, entries 11 and 12) and β-diketones (Table 2, entries 13 and 14) were particularly effective, giving **3** in quantitative yields, although 1,3-cyclohexanedione required a longer reaction time (Table 2, entry 14).

Very interestingly, products with contiguous tertiary and quaternary stereocenters (Table 2, entries 5, 9 and 10) were obtained in

Table 2
Synthesis of substituted isobenzofuran-1(3*H*)-ones by reacting methyl 2-carboxy benzaldehyde with active methylene compounds[a]

Entry	**2**		**3** Product		Time	Yield[b] (%)
1	**2a**	$CH_2(CO_2\text{-}tBu)_2$	**3a**		5 h	99
2[c]	**2b**	$CH_2(CO_2Me)_2$	**3b**		12 h	99

(*continued on next page*)

Table 2 (*continued*)

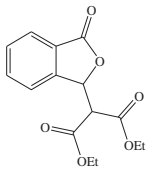
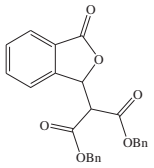
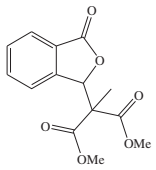
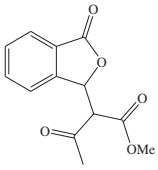
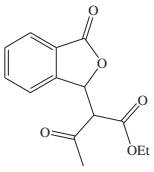
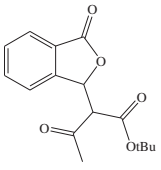
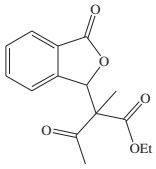
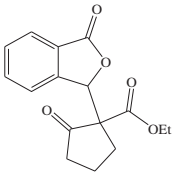
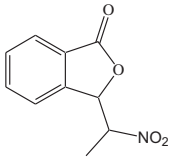
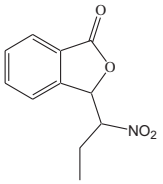
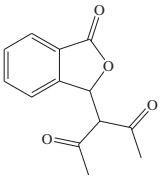
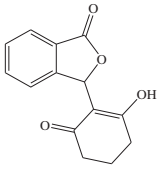
Entry	**2**		**3** Product	Time	Yield[b] (%)
3	**2c**	$CH_2(CO_2Et)_2$	**3c** 	8 h	98
4	**2d**	$CH_2(CO_2Bn)_2$	**3d** 	12 h	99
5	**2e**	$CH_3CH(CO_2Me)_2$	**3e** 	18 h	98
6	**2f**	Methyl acetoacetate	**3f** 	12 h	99 (dr 1.5/1)[d]
7	**2g**	Ethyl acetoacetate	**3g** 	7 h	99 (dr 1.3/1)[d]
8	**2h**	*tert*-Butyl acetoacetate	**3h** 	4 h	98 (dr 1.5/1)[d]
9	**2i**	2-Methyl ethyl acetoacetate	**3i** 	5 h	98 (dr 2/1)[d]
10	**2j**	Ethyl 2-oxocyclopentane carboxylate	**3j** 	15 h	98 (dr 2/1)[d,e]
11	**2k**	Nitroethane	**3k** 	2 h	99 (dr 1.3/1)[d]

Table 2 (*continued*)

Entry	**2**		**3** Product	Time	Yield[b] (%)
12	**2l**	Nitropropane	**3l** 	8 h	99 (dr 1/1)[d]
13	**2m**	Acetylacetone	**3m** 	12 h	96
14	**2n**	1,3-Cyclohexanedione[f]	**3n** 	48 h	98

[a] Reaction conditions: **1** (0.31 mmol), **2** (0.34 mmol), K_2CO_3 (30% mol), rt, solvent free.
[b] Yields refer to chromatographically pure compounds.
[c] Reaction performed on 2 mmol scale.
[d] Diastereomeric ratios were calculated on the basis of ^{1}H NMR spectrum of the crude product.
[e] The configuration of the major diastereomer is *RS*,*RS*.
[f] Reaction performed by adding a few drops of CH_3CN.

high yields by reacting **1** with a series of 2-substituted 1,3-dicarbonyl compounds. This is a further important goal that all the current methods for isobenzofuran-1(3*H*)-ones synthesis do not allow.[5–7] Usually low levels of diastereoselectivity were observed, although the diastereomers of **3j** and **3l** were easily separated by chromatography. **3j** was subsequently crystallized, with a hexane/ethyl acetate mixture, by slow evaporation in order to obtain suitable single crystals for X-ray diffraction measurement. This gave the possibility to further characterise the major diastereomer of **3j** confirming its structure with a relative configuration 3*RS*, 1*RS* (Fig. 1). It is worthy to note that the configuration of the already reported diastereomeric mixtures (**3g**, **3k** and **3l**) has never been described. For this reason we would be tempted to extend this assignation to the other mixtures for analogy. However, considering the possibility of interconversion of those compounds with the relatively acidic methine proton, the characterization of molecules like **3j** with contiguous tertiary and quaternary stereocenters is more relevant.

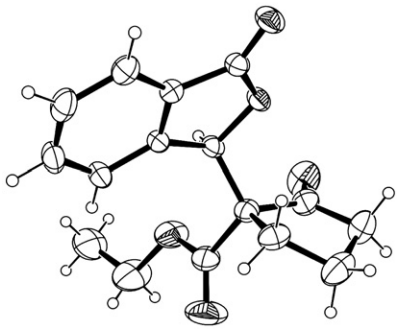


Fig. 1. Drawing of the asymmetric unit of **3j** compound with atomic displacement ellipsoids drawn at the 30% probability level.

On the basis of the obtained results we can confidently propose a catalytic tandem mechanism as described in Scheme 1, in which, after the reversible deprotonation of **2** and its subsequent nucleophilic addition to the aldehyde **1**, the unstable aldol intermediate **4** is entrapped by a regioselective intramolecular lactonization to give the title isobenzofuran-1(3*H*)-one. The possibility of using catalytic amounts of base is likely due to an autocatalysis pathway given that methoxide is generated during the lactonization step.

In conclusion a new method of isobenzofuran-1(3*H*)-ones synthesis has been developed. In this process we exploited an effective, economic, useful and environmentally benign K_2CO_3 catalyzed, solvent-free one-pot tandem aldol addition/lactonization reactions of active methylene compounds with methyl 2-carboxy benzaldehyde. Furthermore a particularly simple work-up and purification procedure are additional advantages addressed to a general green chemistry approach to this important class of heterocyclic compounds.

3. Experimental section

3.1. General remarks

Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The reagents (Aldrich and Across) were used without further purification. The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^{1}H; 100 MHz, 75 MHz, 62.5 MHz, ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Coupling constants *J* are reported in hertz. FT-IR spectra were recorded as thin films on KBr plates using Bruker Vertex 70 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro

quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS–O apparatus. Single crystal diffraction data were collected on a Oxford Xcalibur CCD area detector diffractometer, using graphite monochromatic Mo Kα (λ=0.71069Å) radiation. Data reduction and absorption correction were performed using CrysAlisPRO 171.34.44 (Oxford Diffraction). The structure was solved by direct methods using SIR2008[14] and refined by full-matrix least squares using SHELX-97.[15] Hydrogen atoms were generated in calculated position using SHELX-97. **3j** crystallized in the centrosymmetric [$P2_1/c$] space group and the crystal packing is driven at first by π–π contribution and the fine tuning of molecular unit docking is defined by short contacts (less than the sum of van der Waals radii) between the molecular units.

3.2. General procedure for the synthesis of isobenzofuranones

To a solution of aldehyde (50 mg, 0.31 mmol, 1 equiv) and potassium carbonate (12.6 mg, 0.093 mmol, 0.3 equiv) methylene active compounds (0.34 mmol, 1.1 equiv) were added dropwise. The mixture was stirred until starting material disappeared. Purification consists of a filtration on a short pad of silica gel with hexane/ethyl acetate mixtures to give the products **3**.

Compounds **3b**, **3g**, **3k**–**n** are known and have been characterized by comparing their spectroscopic data with those reported in Ref. 5d and 5i.

*3.2.1. Di-tert-butyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-malonate **3a**.* Filtration with hexane/ethyl acetate 8/2. Pale yellow oil (105 mg). Yield: 99%. IR (neat): 1762, 1747, 1056, 745 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): 7.89 (d, J=7.5 Hz, 1H, Ar), 7.65–7.53 (m, 3H, Ar), 5.96 (d, J=6.1 Hz, 1H, C*H*CH), 3.73 (d, J=6.1 Hz, 1H, CHC*H*), 1.43 (s, 9H, C(CH_3)$_3$), 1.32 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 169.6, 165.1, 164.9, 147.1, 133.9, 129.5, 126.6, 125.4, 123.4, 82.9, 82.8, 77.9, 57.5, 21.7, 21.6. ESI-MS: m/z=349 (M+1). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.36; H, 6.70.

*3.2.2. Dimethyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-malonate **3b**.* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (79 mg). Yield: 99%. Spectroscopic data are in agreement with those reported in literature.[5h] ESI-MS: m/z=265 (M+1). Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.24; H, 4.40.

*3.2.3. Diethyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-malonate **3c**.* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (88 mg). Yield: 98%. IR (neat): 1768, 1741, 1045, 765, 734 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (d, J=7.5 Hz, 1H, Ar), 7.66–7.51 (m, 3H, Ar), 6.02 (d, J=6.8 Hz, 1H, C*H*CH), 4.21 (q, J=7.05 Hz, 2H, $CO_2CH_2CH_3$), 4.13 (q, J=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.83 (d, J=6.8 Hz, 1H, CHC*H*), 1.22 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 166.9 (×2), 147.9, 135.5, 131.1, 127.6, 126.9, 124.4, 78.9, 63.4, 63.4, 57.1, 15.1, 15.0 ESI-MS: m/z=293 (M+1). Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.46; H, 5.40.

*3.2.4. Dibenzyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-malonate **3d**.* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (127 mg). Yield: 99%. IR (neat): 1759, 1743, 1034, 743 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): 7.81 (d, J=6.8 Hz, 1H, Ar), 7.56–7.48 (m, 3H, Ar), 7.33–7.21 (m, 10H, Ar), 6.07 (d, J=6.8 Hz, 1H, C*H*CH), 5.19 (d, J=12 Hz, 2H, C*H*HPh), 5.16 (d, J=12 Hz, 2H, CH*H*Ph), 5.11 (s, 2H, CH_2Ph), 3.96 (d, J=6.8 Hz, 1H, C*H*CH). ^{13}C NMR (75 MHz, $CDCl_3$): 169.21, 165.4, 165.3, 146.29, 134.66, 134.48, 134.14, 129.75, 128.55, 128.43, 128.30, 126.17, 125.69, 122.98, 67.85, 67.80, 55.86. ESI-MS: m/z=417 (M+1). Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.25; H, 4.70.

*3.2.5. Dimethyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-methylmalonate **3e**.* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (82 mg). Yield: 98%. IR (neat): 1761, 1747, 1026, 786 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (d, J=7.4 Hz, 1H, Ar), 7.63–7.51 (m, 3H, Ar), 6.19 (s, 1H, C*H*), 3.80 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 1.13 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 170.7, 170.0, 147.1, 135.5, 131.0, 128.1, 126.9, 125.1, 82.7, 58.6, 54.5, 54.3, 15.6. ESI-MS: m/z=279 (M+1). Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.56; H, 5.30.

*3.2.6. Methyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxobutanoate **3f** (mixture of diastereoisomers).* Filtration with hexane/ethyl acetate 7/3. White solid (75 mg). Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.87 (d, J=7.4 Hz, 1H+1H, Ar), 7.67–7.61 (m, 2H+1H, Ar), 7.57–7.42 (m, 1H+3H, Ar), 6.07 (d, J=8.4 Hz, 1H+1H), 3.89 (d, J=8.1 Hz, 1H, C*H*CH), 3.87 (d, J=8.3 Hz, 1H, C*H*CH), 3.78 (s, CO_2CH_3, 3H, minor), 3.72 (s, CO_2CH_3, 3H, major), 2.37 (s, $COCH_3$, 3H, major), 2.27 (s, $COCH_3$, 3H, minor). ^{13}C NMR (75 MHz, $CDCl_3$): 199.67, 199.04, 169.33, 169.23, 166.30, 166.03, 146.99, 146.78, 134.35, 129.82, 126.0, 125.87, 125.77, 123.24, 77.95, 63.47, 62.64, 53.05, 52.81, 30.55, 30.33. ESI-MS: m/z=249 (M+1). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.88. Found: C, 62.75; H, 4.79.

*3.2.7. Ethyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxobutanoate **3g**.* Filtration with hexane/ethyl acetate 7/3. White solid (75 mg). Yield: 99%. Spectroscopic data are in agreement with those reported in literature.[5d] ESI-MS: m/z=263 (M+1). Anal. Calcd for $C_{14}H_{12}O_4$: C, 64.12; H, 5.38. Found: C, 64.34; H, 5.23.

*3.2.8. tert-Butyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxobutanoate **3h** (mixture of diastereoisomers).* Filtration with hexane/ethyl acetate 7/3. White solid (72 mg). Yield: 98%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.86 (d, J=7.2 Hz, Ar), 7.63–7.26 (m, Ar), 6.22 (s, 1H, enol), 6.03 (d, J=7.2 Hz, 1H+1H), 3.90 (d, J=7.2 Hz, 1H, minor), 3.77 (d, J=7.2 Hz, 1H, major), 2.34 (s, 3H, $COCH_3$, minor), 2.28 (s, 3H, $COCH_3$, major), 2.23 (s, 3H, $COCH_3$, enol), 1.37 (s, 9H, C(CH_3)$_3$, major), 1.29 (s, 9H, C(CH_3)$_3$, minor), 1.03 (s, 9H, C(CH_3)$_3$, enol). ^{13}C NMR (75 MHz, $CDCl_3$): 201.51, 201.40, 170.87, 170.83, 166.29, 166.0, 148.62, 148.53, 135.49, 134.97, 130.96, 130.92, 129.80, 127.57, 126.95, 126.82, 126.49, 125.03, 124.29, 122.48, 84.79, 84.73, 79.35, 79.31, 65.82, 64.68, 31.57, 31.20, 28.93, 28.87, 20.57. ESI-MS: m/z=291 (M+1). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.34; H, 6.10.

*3.2.9. Ethyl-2-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-methyl-3-oxobutanoate **3i** (mixture of diastereoisomers).* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (82 mg). Yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, J=7.6 Hz, Ar), 7.66–7.65 (m, Ar), 7.55–7.47 (m, Ar), 6.26 (s, 1H, C*H*), 4.27 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$, minor), 4.18 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$, major), 2.35 (s, 3H, $COCH_3$, major), 2.20 (s, 3H, $COCH_3$, minor), 1.28 (t, J=7.2 Hz, $CO_2CH_2CH_3$, minor), 1.18 (t, J=7.2 Hz, $CO_2CH_2CH_3$, major), 1.16 (, 3H, CH_3, major), 1.07 (s, 3H, CH_3, minor), ^{13}C NMR (100 MHz, $CDCl_3$): 204.79, 203.19, 171.02, 170.81, 170.57, 169.78, 147.71, 147.50, 135.58, 135.51, 130.97, 130.92, 128.30, 127.87, 126.99, 126.92, 125.62, 125.13, 83.11, 82.79, 65.01, 64.50, 63.79, 63.42, 28.04, 27.69, 15.44, 15.20, 15.09, 14.95. ESI-MS: m/z=277 (M+1). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.14; H, 5.80.

*3.2.10. Ethyl-1-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-oxocyclopentane carboxylate **3j** (single diastereoisomer).* Filtration with hexane/ethyl acetate 75/25. (85 mg). Yield: 98%. White solid, recrystallised from hexane/ethyl acetate 8/2 for slow evaporation. IR (KBr): 1772, 1737, 1690, 1028, 756 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (d, J=7.6 Hz, 1H, Ar), 7.65 (t, J=7.6 Hz, 1H, Ar), 7.57–7.52 (m, 2H, Ar), 6.25 (s, 1H, C*H*), 4.29 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$),

2.52–2.43 (m, 2H, CH_2), 2.27–2.05 (m, 2H, CH_2), 1.98–1.92 (m, 1H, C*H*H), 1.44–1.38 (m, 1H, CH*H*), 1.31 (t, J=7.2 Hz, 2H, $CO_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 211.54, 170.89, 169.60, 147.98,135.79, 131.05, 128.32, 126.95, 124.63, 82.36, 64.14, 63.53, 39.24, 27.99, 21.08, 15.29. ESI-MS: m/z=289 (M+1). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.44; H, 5.60.

3.2.11. 3-(1-Nitroethyl)isobenzofuran-1(3H)-one ***3k****.* Filtration with hexane/ethyl acetate 7/3. Pale yellow oil (63 mg). Yield: 99%. Spectroscopic data are in agreement with those reported in literature.[5i] ESI-MS: m/z=208 (M+1). Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38. Found: C, 57.84; H, 4.50.

3.2.12. 3-(1-Nitropropyl)isobenzofuran-1(3H)-one ***3l****.* Filtration with hexane/ethyl acetate 8/2. White solid (66 mg). Yield: 99%. Spectroscopic data are in agreement with those reported in literature.[5i] The main diastereomer was easily recrystallised according to ref 5i. ESI-MS: m/z=222 (M+1). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01. Found: C, 59.84; H, 4.90.

3.2.13. 3-(2,4-Dioxopentan-3-yl)isobenzofuran-1(3H)-one ***3m****.* Filtration with hexane/ethyl acetate 8/2. Yield: 96%. Melting point and spectroscopic data are in agreement with those reported in literature.[5d] ESI-MS: m/z=233 (M+1). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.12; H, 5.37.

3.2.14. 3-(2-Hydroxy-6-oxocyclohex-1-enyl)isobenzofuran-1(3H)-one ***3n****.* Filtration with ethyl acetate/MeOH 98/2. White solid (72 mg). Yield: 98%. Melting point and spectroscopic data are in agreement with those reported in literature.[5d] ESI-MS: m/z=245 (M+1). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.74; H, 4.70.

Acknowledgements

Financial support from the MIUR (FARB 2011) is gratefully acknowledged.

Supplementary data

All the ^{1}H NMR and ^{13}C NMR spectra of the new compounds have been provided as additional material. Crystallographic table of compound **3j** is provided as additional material. CCDC 869877 contains the supplementary crystallographic data for compound **3j**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.079.

References and notes

1. Mukhopadhyay, R.; Kundu, N. G. *Tetrahedron* **2001**, *57*, 9475–9480.
2. (a) Kim, K. S.; Spatz, M. W.; Johnson, F. *Tetrahedron Lett.* **1979**, *20*, 331–334; (b) Shode, F. O.; Mahomed, A. S.; Rogers, C. B. *Phytochemistry* **2002**, *61*, 955–957; (c) Inouye, H.; Okuda, T.; Hirata, Y.; Nagakura, N.; Yoshizaki, M. *Chem. Pharm. Bull.* **1967**, *15*, 786–792; (d) Fuska, J.; Uhrin, D.; Proksa, B.; Voticky, Z.; Ruppeldt, J. *J. Antibiot.* **1986**, *39*, 1605–1608; (e) Strobel, G.; Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P. C. W.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179–183; (f) Jadulco, R.; Brauers, G.; Edrada, R. A.; Ebel, R.; Wray, V.; Sudarsono; Proksch, P. *J. Nat. Prod.* **2002**, *65*, 730–733.
3. (a) Brady, S. F.; Wagenaar, M. M.; Sing, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043–4046; (b) Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116–1117.
4. (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic: New York, NY, 1975; Vol. 1, pp 249–250; (b) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383–386; (c) Whelton, B. D.; Huitric, A. C. *J. Org. Chem.* **1970**, *35*, 3143–3144.
5. (a) Paradkar, M. V.; Gadre, S. Y.; Pujari, T. A.; Khandekar, P. P.; Kumbhar, V. B. *Synth. Commun.* **2005**, *35*, 471–474; (b) Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Klumpp, D. A. *J. Org. Chem.* **2004**, *69*, 2340–2347; (c) Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.* **2004**, *45*, 5109–5112; (d) Mal, D.; Pahari, P.; De, S. R. *Tetrahedron* **2007**, *63*, 11781–11792; (e) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2003**, *4*, 747–755; (f) Kolsaker, P.; Arukwe, J.; Barkoczy, J.; Wiberg, A.; Kristine Figerli, A. *Acta Chem. Scand.* **1998**, *52*, 490–498; (g) Bousquet, E. W.; Moran, M. D.; Harmon, J.; Johnson, A. L.; Summers, J. C. *J. Org. Chem.* **1975**, *40*, 2208–2211; (h) Kolsaker, P.; Arukwe, J.; Barcoczy, J.; Wiberg, A.; Fagerli, A. K. *Acta Chem. Scand.* **1998**, *52*, 490–498; (i) Hauser, F. M.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 4676–4681.
6. (a) Knepper, K.; Ziegert, R. E.; Brase, S. *Tetrahedron* **2004**, *60*, 8591–8603; (b) Kobayashi, K.; Itoh, M.; Sasaki, A.; Suginome, H. *Tetrahedron* **1991**, *47*, 5437–5452; (c) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653–2658; (d) Crimmin, M. R.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 331–333.
7. (a) Sangshetti, J. N.; Ansari, S. A. M. K.; Shinde, D. B. *Chin. Chem. Lett.* **2011**, *22*, 163–166; (b) Landge, S. M.; Berryman, M.; Török, B. *Tetrahedron Lett.* **2008**, *494*, 505–4508; (c) Heravi, M. M.; Rasmi, V.; Bamoharram, F. F.; Sadjadi, S.; Fotouhi, L.; Sadjadi, S.; Bakavoli, M. *Synth. Commun.* **2009**, *39*, 4109–4116.
8. (a) Yamamoto, Y.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631; (b) Trost, B. M.; Weiss, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664–7666; (c) Chang, H. T.; Jeganmohan, M.; Cheng, C. H. *Chem.—Eur. J.* **2007**, *13*, 4356–4363; (d) Lv, G.; Huang, G.; Zhang, G.; Pan, C.; Chen, F.; Cheng, J. *Tetrahedron* **2011**, *67*, 4879–4886; (e) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608–15609.
9. Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368–374.
10. (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992**, *57*, 782–784; (b) Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205–2208; (c) Kosaka, M.; Sekiguchi, S.; Naito, J.; Uemura, M.; Kuwahara, S.; Watanabe, M.; Harada, N.; Hiroi, K. *Chirality* **2005**, *17*, 218–232; (d) Pedrosa, R.; Sayalero, S.; Vicente, M. *Tetrahedron* **2006**, *62*, 10400–10407.
11. Massa, A. *Synlett* **2012**, 524–530.
12. (a) Massa, A.; Scettri, A.; Filosa, R.; Capozzolo, L. *Tetrahedron Lett.* **2009**, *50*, 7318–7321; (b) Massa, A.; Roscigno, A.; De Caprariis, P.; Filosa, R.; Di Mola, A. *Adv. Synth. Catal.* **2010**, *352*, 3348–3354; (c) More, V.; Di Mola, A.; Croce, G.; Tedesco, C.; Petronzi, C.; De Caprariis, P.; Peduto, A.; Filosa, R.; Massa, A. *Org. Biomol. Chem.* **2011**, *9*, 8483–8488.
13. More, V.; Di Mola, A.; Perillo, M.; De Caprariis, P.; Filosa, R.; Peduto, A.; Massa, A. *Synthesis* **2011**, 3027–3031.
14. Burla, C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Siliqi, D.; Spagna, R. *J. Appl. Crystallogr.* **2007**, *40*, 609–613.
15. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2007**, *64*, 112–122.