Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 1335

www.rsc.org/greenchem

PAPER

Preparation of amides mediated by isopropylmagnesium chloride under continuous flow conditions†

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Received 9th January 2012, Accepted 20th February 2012
DOI: 10.1039/c2gc35037h

A safe, green and functional-group-tolerant flow version of the direct amide bond formation mediated by Grignard reagents (the Bodroux reaction) is described. The procedure can be applied to a wide variety of primary and secondary amines and anilines, as well as to aromatic and aliphatic esters. The flow approach leads to improved yields and selectivities in the reaction, which has a sustainable purification procedure and a simple scale-up. This reaction represents an efficient and green alternative to the use of alkylaluminium and metal-catalyzed procedures.

Introduction

The development of new and improved chemical processing techniques that are economically viable and have greater environmental compatibility is of great importance to the chemical industry. The ability to conduct complex and routine chemical transformations in a safe, reproducible and scalable way without recourse to costly route modification or redevelopment is highly desirable nowadays.

Amide bond formation is a common transformation in organic and medicinal chemistry.[1] An attractive procedure is the synthesis starting from esters, as they are stable and abundant in nature.[2] A three-step sequence of hydrolysis, activation and treatment with an amine is usually required to obtain the corresponding amide.

In an effort to avoid this three-step procedure, direct transformation has been widely studied. Among the alternative approaches, the use of trimethylaluminium has become the gold standard.[3] However, this reagent is highly pyrophoric, hazardous and potentially thermally unstable. With the aim of improving the safety of this transformation, especially on a large scale, a continuous flow procedure has recently been described.[4] Current alternatives involve more atom-economical catalytic syntheses. For instance, in a recent article a dearomatized ruthenium–pincer complex was described as a catalyst for the direct synthesis of amides from esters and amines with the liberation of H_2.[5] Although this procedure is environmentally benign, it is limited to the use of alkyl esters and alkyl amines.

Taking into consideration the precedents, it seems clear that more sustainable procedures are required to produce amides in a single step in a more general way. In fact, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable has labelled this transformation as a high priority research field.[6] In this sense, *tert*-butoxide-assisted amidation of esters has been lately described.[7] The procedure is general although it employs a high concentration of a strong base and, more important, oxygen is needed to complete the reaction, which may compromise its use at larger scales, because batch reactors are poorly equipped to ensure efficient gas–liquid mixing and high concentrations of dissolved O_2.[8]

Grignard-mediated amide formation, *i.e.* the Bodroux reaction,[9] can be considered as one of these procedures as all reagents involved in this reaction are inexpensive and environmentally inert. The enhanced reactivity of these magnesium reagents could be attributed to a 'push–pull' mechanism originating from the nucleophilicity of the magnesium amide coupled with the Lewis acid activation of the magnesium salt. Although this reaction has been known since the 1950s, its use has been limited by two main factors. On the one hand, the scope and limitations of this reaction have not been systematically studied. On the other hand, the high reactivity of Grignard reagents can compromise the selectivity of the reaction. These two drawbacks have restricted the use of this reaction over the alternatives mentioned above. For instance, in the synthesis of Weinreb's amide this approach has frequently been used as an alternative when trimethylaluminium-based conversion failed.[10] An efficient conversion of nitriles to amides using ethylmagnesium bromide has recently been described, although the procedure only works with aromatic nitriles.[11]

In recent years flow chemistry and microreactors have appeared as novel technologies that, among other advantages, allow much better control of reactions in which unstable and

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†Electronic supplementary information (ESI) available: Experimental procedures, GC/MS of representative crude mixtures, GC/MS of the selectivity assays and NMR spectra for all compounds. See DOI: 10.1039/c2gc35037h

highly reactive intermediates are involved, as these species are produced and reacted in line.[12] Microreactors have a high surface-to-volume ratio in microchannels and this permits very efficient heat transfer and, as a consequence, good control of the reaction temperature, thus avoiding the problems associated with highly exothermic reactions. Mass transfer is also enhanced and the use of dangerous or air- and moisture-sensitive compounds is improved due to the lower reaction volume. Optimization of reaction conditions is performed by control of residence time and the scalability of this kind of reaction is simply a matter of pumping, mixing and quenching the reagents continuously through the microreactor. This approach permits rapid experimentation and scale-up, thus shortening the time from research to development and production. From an environmental point of view, continuous flow reactors are considered as a sustainable alternative in chemical research and production as the levels of hazardous waste are reduced.[13] The use of Grignard reagents in flow conditions have been previously described in the literature.[14]

Results and discussion

Description of the instrument

As part of our efforts to apply flow approaches to typical medicinal chemistry problems, we considered the application of this technology to the Bodroux reaction as a greener alternative for the preparation of amides in a single step. In order to achieve this goal, a simple and inexpensive set up was built based on two 1 ml Sigma-Aldrich Starter Kit™ microreactors connected to two standard dual syringe pumps from Harvard Apparatus (Fig. 1). In the first microreactor, one line with isopropylmagnesium chloride and another with the amine, connected to the first syringe pump, were mixed to form the corresponding magnesium amide. The end of this line was fixed to the second microreactor, where the magnesium amide was mixed with the ester, coming from the second syringe pump. A 5 ml coil was added at the end of this second reactor in order to increase the residence time as this step was found to be the limiting one. Consequently, the time for the formation of the aminomagnesium chloride was adapted to the time set for the second reactor. All tubing, glass reactor and coils used have a 0.1 mm internal diameter. The reaction temperature can be monitored by sensors inserted into the glass microreactors.‡ The reaction mixture was finally connected to a column filled with Amberlyst A-15, thus enhancing the green character of the procedure. However, in order to facilitate the scalability of the process, quenching of the reaction can also be performed with 1 M HCl.

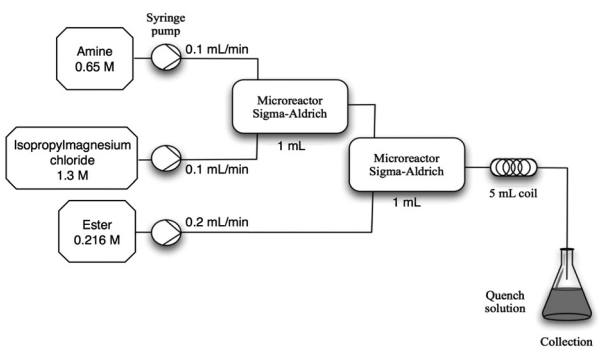


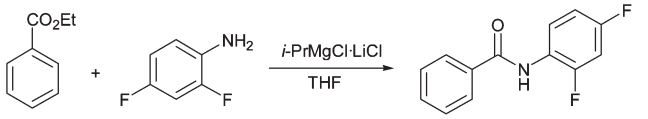
Fig. 1 Experimental set up of the flow system.

Reaction optimization

This simple set up outlined above was used to optimize the conditions for the reaction of 2,4-difluoroaniline **2a** with ethyl benzoate **1a** (Table 1). Aniline **2a** was selected due to its lower carcinogenicity in comparison to other analogues of this family. The procedure was first applied in batch (Table 1, entry 1) in order to assess the feasibility of the reaction in flow using an excess of amine and isopropylmagnesium chloride as described in the literature.[11] The presence of solid was not detected at any point of the reaction and the flow procedure was therefore tried using a 1 : 1 : 2 ratio of ester, aniline and Grignard reagents respectively (Table 1, entry 2). A higher yield was obtained in this flow procedure despite the lower excess of amine and the much shorter reaction time.

Following this promising result, yields were further improved by optimization of the reaction temperature, time and number of equivalents of aniline and alkylmagnesium chloride, always keeping the ester as the limiting reagent and adapting the concentration of amine and Grignard reagent to it. The use of longer retention times (*i.e.* reaction times) clearly improved the yield (entries 3 and 4), but the temperature could not be increased as the system became blocked by a black slurry observed in the magnesium amide line (entry 5). The use of 1.5 equivalents of aniline **1a** was required to complete the reaction (entry 6) but without reducing the aniline : Grignard reagent ratio. This

Table 1 Reaction optimization using ethyl benzoate **1a** and 2,4-difluoroaniline **2a**

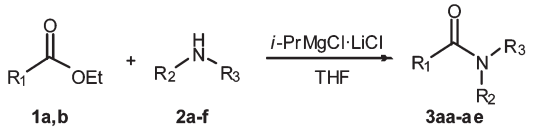


Entry	**2a**	i-PrMgBr	*T* (°C)	Rt_1 (min)	Rt_2 (min)	Yield[a] (%)
1	1.5	3	0, rt	60	60	45[b]
2	1	2	Rt	2	5	61
3	1	2	Rt	4	10	67
4	1	2	Rt	6	14	76
5	1	2	40	6	14	—[c]
6	1.5	3	Rt	6	14	90
7	1.5	1.5	Rt	6	14	88
8	1.5	3	Rt	6	20	87
9	1.5	3	Rt	6	14	95 (92%)[d]

[a] Yield by GCMS. [b] Batch reaction. [c] System blocked. [d] Reaction performed on an 18 mmol scale (isolated yield).

‡ For further information about elements used in the flow system set up the following web pages can be visited: microreactors (www.sigmaaldrich.com), syringe pumps (www.harvardapparatus.com) and 5 ml coil and tubing (www.vapourtec.co.uk).

Table 2 Combination of esters **1a** and **1b** with amines **2a–f**

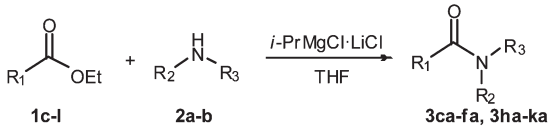


1a,b **2a-f** **3aa-ae** **3ba-bd, 3bf**

Entry	Ester	Amine	Compound[a]
1	$PhCO_2Et$ (**1a**)	2,4-diF-$C_6H_3NH_2$ (**2a**)	**3aa** (88%)
2	$PhCO_2Et$ (**1a**)	PhNHMe (**2b**)[b]	**3ab** (93%)
3	$PhCO_2Et$ (**1a**)	n-$BuNH_2$ (**2c**)	**3ac** (92%)
4	$PhCO_2Et$ (**1a**)	Piperidine (**2d**)[b]	**3ad** (83%)
5	n-$PrCO_2Et$ (**1b**)	2,4-diF-$C_6H_3NH_2$ (**2a**)	**3ba** (95%)
6	n-$PrCO_2Et$ (**1b**)	PhNHMe (**2b**)[b]	**3bb** (92%)
7	n-$PrCO_2Et$ (**1b**)	n-$BuNH_2$ (**2c**)	**3bc** (82%)
8	n-$PrCO_2Et$ (**1b**)	Piperidine (**2d**)[b]	**3bd** (80%)
9	$PhCO_2Et$ (**1a**)	2-Aminopyridine (**2e**)	**3ae** (65%)[c]
10	n-$PrCO_2Et$ (**1b**)	4-Br-aniline (**2f**)	**3bf** (88%)

[a] Compound number (isolated yield). [b] Ratio ester–amine–i-PrMgCl (1 : 1.5 : 1.5). [c] Reaction performed at 0.108 M of **1a**.

Table 3 General exploration of the scope



1c-l **2a-b** **3ca-fa, 3ha-ka** **3gb, 3lb**

Entry	R_1	Amine	Compound[a]
1	*p*-F-C_6H_4 (**1c**)	**2a**	**3ca** (92%)
2	*p*-MeO-C_6H_4 (**1d**)	**2a**	**3da** (90%)
3	*p*-NO_2-C_6H_4 (**1e**)	**2a**	**3ea** (52%)
4	*m*-CN-C_6H_4 (**1f**)	**2a**	**3fa** (95%)
5	$PhCH_2$ (**1g**)	**2b**[b]	**3gb** (84%)
6	2-Furyl (**1h**)	**2a**	**3ha** (91%)
7	2-Pyrrolyl (**1i**)	**2a**	**3ia** (61%)
8	5-Me-3-isoazolyl (**1j**)	**2a**	**3ja** (91%)
9	5-$ClCH_2$-2-furyl (**1k**)	**2a**	**3ka** (73%)
10	2-Br-5-thienyl (**1l**)	**2b**[b]	**3lb** (62%)

[a] Compound number (isolated yield). [b] Ratio ester–amine–i-PrMgCl (1 : 1.5 : 1.5).

reduction did not improve the yield and the crude product was less clean (entry 7). Similar results were observed on further extending the reaction time to 20 minutes (entry 8).

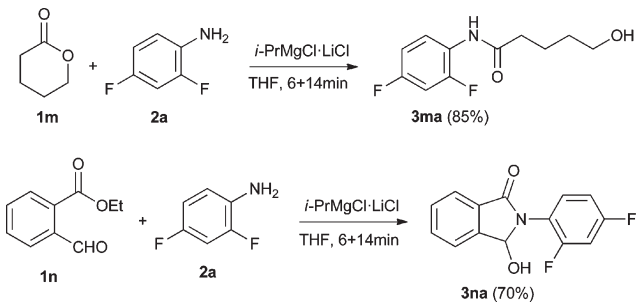
The optimized conditions shown in entry 6 can be easily scaled up by a factor of 22.5 (entry 9). Concentration of reagents and flow rates are given in Fig. 1. The higher yield obtained in this case can be explained by the longer steady state. Using this flow procedure up to 1.2 g h^{-1} of amide were produced. Quenching of the crude mixture was performed using 1 M HCl.

Scope of the reaction

The conditions reported in entry 6 (Table 1), with concentrations and flow rates given in Fig. 1, were selected to explore the scope of the reaction. Firstly, an alkyl and an aryl ester were selected in conjunction with alkyl, aryl, primary and secondary amines in order to test all possible combinations (Table 2, entries 1–8). All compounds were isolated in good to excellent yields. It is worth noting that for secondary amines a 1 : 1.5 : 1.5 ester–amine–Grignard reagent ratios were used. Two additional examples are included in Table 2 and these represent two potentially problematic situations: 2-aminopyridine **2e** as an example of a heterocyclic amine with low nucleophilicity and 4-bromoaniline **2f** to assess the potential interaction with the trans-metallation reaction. Both examples afforded the corresponding amides in good to excellent yields.

In a second approach, the reaction was performed with a wider range of amines and esters including heterocyclic systems and other functional groups. All of the examples were carried out using the same general conditions shown in Fig. 1. Excellent functional group tolerance was found (Table 3). Electron-donating and electron-withdrawing groups are compatible with the reaction, although strong electron-withdrawing groups conjugated with the ester function, such as the nitro group, led to a decrease in the yield of the reaction (Table 3, entries 1–4).

It is worth noting the high chemoselectivity of the reaction. For example, the reactivity of the ester group is higher than that



1m **2a** **3ma** (85%)

1n **2a** **3na** (70%)

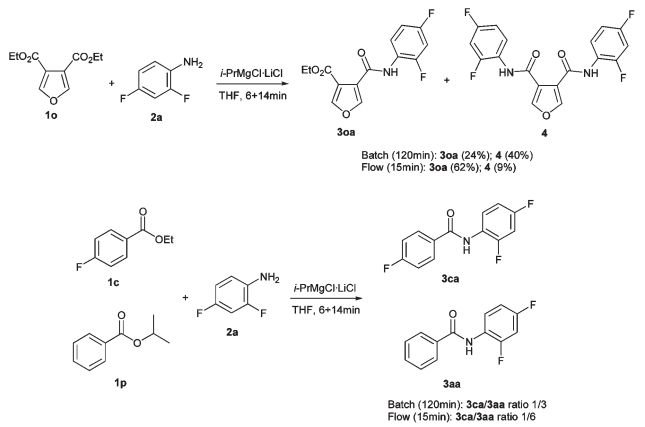
Scheme 1

of the cyano group in compound **1f**, despite the fact that both groups can react under the same conditions.[11] Benzylic and heterocyclic esters also provided the corresponding amides in good yield (entries 5–10). Pyrrolyl analogue **1i** reacted in the absence of a suitable protecting group on the nitrogen atom to give the desired product in good yield (entry 7). This is a clear improvement over the *tert*-butoxide procedure, very sensitive to hydrogen donating groups.[7]

The last two examples in Table 3 show chemoselective amide formation over nucleophilic aliphatic and aromatic substitution reactions. In both examples the expected amide was obtained in good yield and the substitution by-product was not found in the crude mixture. This represents an excellent example of chemoselectivity, especially considering the high reactivity of benzyl halides. In a third approach, ring opening and ring closure reactions were tried with esters **1m** and **1n** using the standard procedure as described in Table 1 entry 6 and shown in Fig. 1. These compounds provided amides **3ma** and **3na**, respectively, in good yields (Scheme 1).

Selectivity assays

Encouraged by the results obtained so far, two experiments were designed to explore further the selectivity of the reaction:



Scheme 2

Selective reaction of a single ester group in a diester compound and selective reaction between ethyl and isopropyl esters (Scheme 2).

In the first example, the selective reaction of one ester group in diester **1o**, was achieved easily in flow under the standard conditions shown in Fig. 1 using one equivalent of amine **2a**. The ratio between monosubstituted **3oa** and disubstituted product **4** was 6 : 1. In batch the selectivity was reversed, *i.e.* diamide **4** was the major product, in a 1 : 2 ratio.

In the second example, selectivity between ethyl and isopropyl esters, was tested with compounds **1c** and **1p**. To the best of our knowledge, selective amide formation between isopropyl and ethyl esters has not been described previously in the literature. Under Bodroux reaction conditions the isopropyl ester reacted faster to form amide **3aa**. This selectivity was enhanced under flow conditions, where the ratio between compounds **3aa** and **3ca** was 6 : 1, whereas in batch the ratio decreased to 3 : 1. In both examples the reaction in batch was only complete after 2 h whereas the flow reaction was complete in 15 min, thus demonstrating the efficiency of the flow approach.

Conclusions

In summary, acylation of amides using esters as acylating agents is effectively mediated by Grignard reagents. The reaction can be performed using a cheap, safe and environmentally benign reaction medium. The procedure proved to be very general, functional-group-tolerant, selective and easily scalable. The examples reported here cover many different situations that can be found typically in organic synthesis and medicinal chemistry. The use of microreactors in flow allows the Bodroux amide formation to be performed in a safer, more sustainable and selective manner that traditional batch approaches. These examples demonstrate the applicability of the reaction and show that this route may be considered as a primary approach in amide synthesis in academia and industrial processes instead of the use of alkylaluminium and metal-catalyzed procedures.

Experimental section

GC measurements were performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and autosampler, J&W HP-5MS column (20 m × 0.18 mm, 0.18 μm) from Agilent Technologies coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source/chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scan. The source temperature was maintained at 230 °C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 with standard pulse sequence, operating at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Reactions were performed in Sigma-Aldrich Starter Kit^{TM} microreactors connected to syringe pumps from Harvard Apparatus. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification.

General procedure for Bodroux reaction in flow

Two solutions, amine **2** (1.5 equiv) in THF and an isopropylmagnesium chloride lithium chloride complex solution 1.3 M in THF (3 equiv), were pumped at 0.1 mL min^{-1} (each solution) through a Sigma-Aldrich microreactor using a syringe pump. At the same time a third solution of ester **1** (1 equiv) in THF was pumped at 0.2 mL min^{-1} with a second syringe pump and mixed with the previous solution in a Sigma-Aldrich microreactor and then passed through a 5 mL coil (Rt = 14 min). The outlet solution was poured into 1 M HCl and extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents were evaporated *in vacuo* to yield the corresponding product.

On-line work-up

The output of the coil was directed to a 10 mm diameter Omnifit column filled with Amberlyst A-15 (2 g). The collected solution was evaporated to dryness to yield the product.

1-Benzamido-2,4-difluorobenzene (3aa).[15] White solid; m.p.: 170.1–171.1 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.88–6.96 (m, 2H), 7.49–7.54 (m, 2H), 7.58 (t, 1H, J = 7.4 Hz), 7.86–7.90 (m, 2H), 7.94 (br s, 1H), 8.38–8.45 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 104.0 (dd, J = 26.7, 23.5 Hz, CH), 118.8 (dd, J = 21, 3.5 Hz, CH), 122.7 (C), 122.9 (dd, J = 9, 2 Hz, CH), 127.5 (2 × CH), 129.3 (2 × CH), 132.6 (CH), 153.3 (dd, J = 246, 12 Hz, C–F), 134.7 (C), 159.0 (dd, J = 246, 12 Hz, C–F), 165.9 (C═O). m/z $C_{13}H_9F_2NO$ calc.: 233.06. Found (EI): 233.05.

***N*-Methyl-*N*-phenylbenzamide (3ab).**[16] Yellow oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 3.50 (s, 3H), 7.02–7.06 (m, 2H), 7.11–7.19 (m, 3H), 7.20–7.25 (m, 3H), 7.27–7.31 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ ppm): 38.7 (CH_3), 126.9 (CH), 127.3 (2 × CH), 128.1 (2 × CH), 129.1 (2 × CH), 129.5 (2 × CH), 130.0 (CH), 136.3, 145.3 (C), 170.6 (C═O). m/z $C_{14}H_{13}NO$ calc.: 211.10. Found (EI): 211.09.

***N*-Butylbenzamide (3ac).**[17] Pale yellow oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.96 (t, 3H, J = 7.4 Hz), 1.42 (qt, 2H, J = 7.2, 7.6 Hz), 1.61 (tt, 2H, J = 7.2, 7.2 Hz), 3.46 (dt, 2H, J = 6.8, 6.4 Hz), 6.14 (br s, 1H), 7.40–7.45 (m, 2H), 7.47–7.51 (m, 1H), 7.74–7.78 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ ppm): 13.8 (CH_3), 20.2 (CH_2), 31.8 (CH_2), 39.8 (CH_2), 126.8 (2 × CH), 128.5 (2 × CH), 131.3 (CH), 134.9 (C), 167.6 (C═O). *m/z* $C_{11}H_{15}NO$ calc.: 177.11. Found (EI): 177.11.

1-Benzoylpiperidine (3ad).[18] Colourless oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.52 (br s, 2H), 1.67 (br s, 4H), 3.34 (br s, 2H), 3.71 (br s, 2H), 7.39 (br s, 5H). ^{13}C-NMR ($CDCl_3$, δ ppm): 24.6 (CH_2), 25.7 (CH_2), 26.6 (CH_2), 43.1 (CH_2), 48.8 (CH_2), 126.8 (2 × CH), 128.4 (2 × CH), 129.3 (CH), 136.4 (C), 170.2 (C═O). *m/z* $C_{12}H_{15}NO$ calc.: 189.11. Found (EI): 189.10.

***N*-(2,4-Difluorophenyl)butyramide (3ba).** Pale yellow solid. m.p.: 112–113 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.02 (t, 3H, J = 7.4 Hz), 1.77 (qt, 2H, J = 7.2, 7.6 Hz), 2.38 (t, 2H, J = 7.6 Hz), 6.82–6.90 (m, 2H), 7.22 (br s, 1H), 8.22–8.31 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 13.7 (CH_3), 19.0 (CH_2), 39.6 (CH_2), 103.4 (dd, J = 26.8, 24.0 Hz, CH), 111.2 (dd, J = 21.2, 3.5 Hz, CH), 122.8 (dd, J = 9.0, 3.0 Hz, CH), 152.6 (dd, J = 246.0, 12.0 Hz, C–F), 158.4 (dd, J = 246.0, 12.0 Hz, C–F), 122.9 (C), 171.2 (C═O). *m/z* $C_{10}H_{11}F_2NO$ calc.: 199.08. Found (EI): 199.08.

***N*-Methyl-*N*-phenylbutyramide (3bb).**[19] Colourless oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.82 (t, 3H, J = 7.2 Hz), 1.55–1.65 (m, 2H), 2.05 (t, 2H, J = 6.6 Hz), 3.27 (s, 3H), 7.16–7.20 (m, 2H), 7.31–7.38 (m, 1H), 7.39–7.45 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ ppm): 13.8 (CH_3), 18.9 (CH_2), 35.9 (CH_2), 37.3 (CH_3), 127.3 (2 × CH), 127.6 (CH), 129.6 (2 × CH), 144.2 (C), 173.0 (C═O). *m/z* $C_{11}H_{15}NO$ calc.: 177.11. Found (EI): 177.11.

***N*-(n-Butyl)butyramide (3bc).**[20] Colourless oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, J = 7.2 Hz), 1.50–1.60 (m, 4H), 1.60–1.69 (m, 4H), 2.32 (t, 2H, J = 7.2 Hz), 3.45–3.55 (m, 4H). ^{13}C-NMR ($CDCl_3$, δ ppm): 13.7 (2 × CH_3), 19.3 (CH_2), 20.0 (CH_2), 31.6 (CH_2), 38.4 (CH_2), 39.4 (CH_2), 173.6 (C═O). *m/z* $C_8H_{17}NO$ calc.: 143.13. Found (EI): 143.12.

1-(Piperidin-1-yl)butan-1-one (3bd).[5] Colourless oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, J = 7.2 Hz), 1.50–1.60 (m, 4H), 1.60–1.69 (m, 4H), 2.32 (t, 2H, J = 7.2 Hz, 2H), 3.45–3.55 (m, 4H). ^{13}C-NMR ($CDCl_3$, δ ppm), 14.0 (CH_3), 18.9 (CH_2), 24.5 (3 × CH_2), 35.3 (CH_2), 40.4 (CH_2), 43.7 (CH_2), 171.4 (C═O). *m/z* $C_9H_{17}NO$ calc.: 155.13. Found (EI): 155.12.

***N*-Pyridin-2-yl-benzamide (3ae).**[21] Colourless oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 7.01 (ddd, 1H, J = 7.2, 4.9, 0.9 Hz), 7.44–7.49 (m, 2H), 7.52–7.57 (m, 1H), 7.71–7.76 (m, 1H), 7.91–7.94 (m, 2H), 8.09–8.12 (m, 1H), 8.41 (dt, 1H, J = 8.3, 0.9 Hz), 9.27 (br s, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 114.3 (CH), 119.8 (CH), 127.3 (2 × CH), 128.6 (2 × CH), 132.1 (CH), 134.3 (C), 138.4 (CH), 147.7 (CH), 151.7 (C), 166.0 (C═O). *m/z* $C_{12}H_{10}N_2O$ calc.: 198.08. Found (EI): 198.07.

***N*-(4-Bromophenyl)butanamide (3bf).**[22] White solid. m.p.: 125–126 °C (lit. 126 °C). ^{1}H-NMR ($CDCl_3$, δ ppm): 1.01 (t, 3H, J = 7.4 Hz), 1.71–1.78 (m, 2H), 2.33 (t, 2H, J = 7.4 Hz), 7.25 (br s, 1H), 7.42 (s, 4H); ^{13}C-NMR ($CDCl_3$, δ ppm): 13.7 (CH_3), 18.9 (CH_2), 39.6 (CH_2), 116.7 (C), 121.3 (2 × CH), 131.9 (2 × CH), 136.9 (C), 171.2 (C═O). *m/z* $C_{10}H_{12}BrNO$ calc.: 241.01. Found (EI): 241.01.

***N*-(2,4-Difluorophenyl)-4-fluorobenzamide (3ca).** White solid m.p.: 134.4–135.4 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.90–6.96 (m, 2H), 7.17–7.22 (m, 2H), 7.87 (br s, 1H), 7.88–7.93 (m, 2H), 8.37 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 103.6 (dd, J = 26.8, 24.0 Hz, CH), 111.4 (dd, J = 21.9, 3.5 Hz, CH), 115.9 (CH), 116.1 (CH), 123.0 (dd, J = 8.5, 2.1 Hz, CH), 129.4 (CH), 129.5 (CH), 130.4 (d, J = 3.5 Hz, C), 152.6 (dd, J = 245.8, 12 Hz, C–F), 158.6 (dd, J = 247.2, 12.0 Hz, C–F), 163.8 (C), 164.4 (C), 166.3 (C═O). *m/z* $C_{13}H_8F_3NO$ calc.: 251.06. Found (EI): 251.05.

***N*-(2,4-Difluorophenyl)-4-methoxybenzamide (3da).** White solid. m.p.: 132.7–133.7 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 3.88 (s, 3H), 6.88–6.94 (m, 2H), 6.97–7.01 (m, 2H), 7.83–7.87 (m, 3H), 8.37–8.43 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 55.5 (CH_3), 103.5 (dd, J = 26.8, 23.3 Hz, CH), 111.3 (dd, J = 21.9, 3.5 Hz, CH), 114.1 (2 × CH), 122.8 (dd, J = 9.2, 2.1 Hz, CH), 123.4 (C), 126.4 (Cq), 129.0 (2 × CH), 152.6 (dd, J = 245.1, 12 Hz, C–F), 158.3 (dd, J = 246.5, 12.0 Hz, C–F), 162.8 (C), 164.9 (C═O). *m/z* $C_{14}H_{11}F_2NO_2$ calc.: 263.08. Found (EI): 263.07.

***N*-(2,4-Difluorophenyl)-4-nitrobenzamide (3ea).** Pale yellow solid. m.p.: 159.4–160.4 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.93–6.99 (m, 2H), 7.95 (br s, 1H), 8.05–8.08 (m, 2H), 8.36–8.40 (m, 3H). ^{13}C-NMR ($CDCl_3$, δ ppm): 103.8 (dd, J = 26.8, 23.3 Hz, CH), 111.6 (dd, J = 21.9, 3.5 Hz, CH), 123.2 (d, J = 8.5 Hz, CH), 124.1 (2 × CH), 128.3 (2 × CH), 128.4 (C), 139.7 (C), 152.6 (dd, J = 245.1, 12 Hz, C–F), 158.3 (dd, J = 246.5, 12.0 Hz, C–F), 162.8 (C), 164.9 (C═O). *m/z* $C_{13}H_8F_2N_2O_3$ calc.: 278.05. Found (EI): 278.05.

3-Cyano-*N*-(2,4-difluorophenyl)-benzamide (3fa). White solid. m.p.: 146.7–147.7 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.92–6.99 (m, 2H), 7.67 (t, 1H, J = 7.9 Hz), 7.87 (dt, 1H, J = 7.9, 1.4 Hz), 7.92 (br s, 1H), 8.11 (dt, 1H, J = 8.1, 1.2 Hz), 8.19 (t, 1H, J = 0.9 Hz), 8.31–8.37 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 103.8 (dd, J = 26.8, 23.3 Hz, CH), 111.5 (dd, J = 21.9, 3.5 Hz, CH), 113.4 (C), 117.7 (C), 123.3 (dd, J = 9.2, 2.1 Hz, CH), 129.9 (CH), 130.9 (CH), 131.1 (CH), 135.3 (CH), 135.4 (C), 152.8 (dd, J = 246.5, 12.0 Hz, C–F), 159.2 (dd, J = 247.2, 12.0 Hz, C–F), 163.3 (C═O). *m/z* $C_{14}H_8F_2N_2O$ calc.: 258.06. Found (EI): 258.05.

***N*-Methyl-*N*-phenylphenylacetamide (3gb).**[23] Yellow oil. ^{1}H-NMR ($CDCl_3$, δ ppm): 3.28 (s, 3H), 3.46 (s, 2H), 7.05 (d, 2H, J = 7.2 Hz), 7.12 (d, 2H, J = 7.7 Hz), 7.17–7.26 (m, 3H), 7.32–7.43 (m, 3H). ^{13}C-NMR ($CDCl_3$, δ ppm): 37.6 (CH_3), 40.9 (CH_2), 126.5 (CH), 127.6 (2 × CH), 127.9 (CH), 128.3 (2 × CH), 129.0 (2 × CH), 129.7 (2 × CH), 135.4, 143.9 (C), 171.0 (C═O). *m/z* $C_{15}H_{15}NO$ calc.: 225.11. Found (EI): 225.10.

***N*-(2,4-Difluorophenyl)furan-2-carboxamide (3ha).** White solid. m.p.: 82.6–83.6 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.57–6.59 (dd, 1H, J = 3.5, 1.6 Hz), 6.85–6.94 (m, 2H), 7.26–7.28 (m, 1H), 7.54 (dd, 1H, J = 1.9, 0.9 Hz), 8.20 (br s, 1H), 8.37–8.42 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 103.6 (dd, J = 26.8, 23.3 Hz, CH), 111.3 (dd, J = 21.9, 4.24 Hz, CH), 112.6

(CH), 115.7 (CH), 122.6 (dd, J = 26.8, 23.3 Hz, CH), 144.6 (CH), 152.6 (dd, J = 245.8, 12 Hz, C–F), 158.6 (dd, J = 247.2, 12.0 Hz, C–F), 163.8 (C), 164.4 (C), 166.3 (C═O). m/z $C_{11}H_7F_2NO_2$ calc.: 223.04. Found (EI): 223.04.

***N*-(2,4-Difluorophenyl)-1*H*-pyrrole-2-carboxamide(3ia).** White solid. m.p.: 169.2–170.2 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.30–6.33 (m, 1H), 6.74–6.75 (m, 1H), 6.88–6.93 (m, 2H), 7.01 (dt, 1H, J = 1.4, 1.1 Hz), 7.64 (br s, 1H), 6.29–6.35 (m, 1H), 9.57 (br s, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 103.6 (dd, J = 26.8, 23.3 Hz, CH), 110.0 (CH), 110.4 (CH), 111.3 (dd, J = 21.9, 4.2 Hz, CH), 122.6 (dd, J = 8.5, 2.1 Hz, CH), 122.7 (CH), 125.4 (C), 155.4 (dd, J = 246.5, 12.0 Hz, C–F), 158.5 (dd, J = 246.1, 11.2 Hz, C–F), 158.7 (C), 161.3 (C═O). m/z $C_{11}H_8F_2N_2O$ calc.: 222.06. Found (EI): 222.05.

***N*-(2,4-Difluorophenyl)-5-methyl-1,2-oxazole-3-carboxamide (3ja).** White solid. m.p.: 97.6–98.6 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.53 (s, 3H), 6.53 (s, 1H), 6.92 (m, 2H), 8.31–8.37 (m, 1H), 8.64 (br s, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 12.4 (CH_3), 101.4 (CH), 103.8 (dd, J = 26.8, 23.3 Hz, CH), 111.3 (dd, J = 21.9, 4.2 Hz, CH), 121.8 (dd, J = 10.6, 4.2 Hz, C), 122.8 (dd, J = 9.2, 2.1 Hz, CH), 152.6 (dd, J = 247.9, 12.0 Hz, C–F), 156.9 (C), 158.2 (C), 158.8 (dd, J = 258.5, 11.3 Hz, C–F), 171.81 (C═O). m/z $C_{11}H_8F_2N_2O_2$ calc.: 238.05. Found (EI): 238.05.

1-[5-(Chloromethyl)fur-2-yl]-2-(2,4-difluorophenyl)ethanone (3ka). White solid. m.p.: 101.6–102.6 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 4.64 (s, 2H), 6.55 (d, 1H, J = 3.5 Hz), 6.89–6.96 (m, 2H), 7.21 (d, 1H, J = 3.5 Hz), 8.15 (br s, 1H), 8.32–8.38 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 37.7 (CH_2), 103.7 (dd, J = 26.8, 23.3 Hz, CH), 111.4 (dd, J = 21.9, 3.5 Hz, CH), 112.3 (CH), 116.6 (CH), 122.8 (dd, J = 9.2, 2.1 Hz, CH), 147.6 (C), 152.4 (C), 152.5 (dd, J = 246.5, 12.0 Hz, C–F), 155.5 (C), 158.8 (dd, J = 246.5, 11.3 Hz, C–F), 170.5 (C═O). m/z $C_{12}H_8ClF_2NO_2$ calc.: 271.02. Found (EI): 271.02.

2-Bromo-*N*-methyl-*N*-phenyl-1,3-thiazole-5-carboxamide (3lb). Yellow pale solid. m.p.: 97.4–98.4 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 3.50 (s, 3H), 7.31 (s, 1H), 7.35–7.37 (m, 2H), 7.57–7.56 (m, 3H). ^{13}C-NMR ($CDCl_3$, δ ppm): 38.7 (CH_3), 128.2 (2 × CH), 129.3 (CH), 130.3 (2 × CH), 136.7 (C), 141.1 (C), 142.5 (C), 146.7 (CH), 159.8 (C═O). m/z $C_{11}H_9BrN_2OS$ calc.: 295.96. Found (EI): 295.95.

***N*-(2,4-Difluorophenyl)-5-hydroxypentanamide (3ma).** White solid. m.p.: 45.4–46.4 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.55–1.75 (m, 2H), 1.75–1.90 (m, 2H); 2.12 (br s, 1H), 2.47 (t, 2H, J = 7 Hz), 3.70 (t, 2H, J = 6 Hz), 6.82–6.85 (m, 2H), 7.56 (br s, 1H), 8.15–8.26 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 21.8 (CH_2), 31.6 (CH_2), 36.9 (CH_2), 62.2 (CH_2), 103.5 (dd, J = 26.1, 23.3 Hz, CH), 111.1 (dd, J = 21.9, 3.5 Hz, CH), 122.5 (dd, J = 10.6, 4.2 Hz, C), 123.1 (dd, J = 9.2, 2.1 Hz, CH), 152.5 (dd, J = 245.8, 12.0 Hz, C–F), 158.4 (dd, J = 246.5, 11.3 Hz, C–F), 171.5 (C═O). m/z $C_{11}H_{13}F_2NO_2$ calc.: 229.05. Found (EI): 229.04.

2-(2,4-Difluorophenyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (3na). White solid. m.p.: 198–199 °C. ^{1}H-NMR ($CDCl_3$, δ ppm): 6.25 (d, 1H, J = 10.6 Hz), 6.97–7.02 (m, 2H), 7.45–7.51 (m, 1H), 7.58–7.62 (m, 1H), 7.67–7.69 (m, 2H), 7.89–7.91 (d, 1H, J = 7.63 Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 83.96 (CH), 105.5 (dd, J = 26.8, 23.3 Hz, CH), 112.3 (dd, J = 21.9, 4.2 Hz, CH), 122.6 (C), 123.9 (CH), 124.5 (CH), 130.7 (CH), 131.3 (dd, J = 9, 2 Hz, CH), 133.5 (CH), 152.4 (dd, J = 247.9, 12.0 Hz, C–F), 156.9 (C), 158.2 (C), 158.8 (dd, J = 258.5, 11.3 Hz, C–F), 171.81 (C═O). m/z $C_{14}H_9F_2NO_2$ calc.: 261.06. Found (EI): 261.05.

Ethyl 4-[(2,4-difluorophenyl)carbamoyl]furan-3-carboxylate (3oa). White solid. m.p.: 92.7–93.7 °C. ^{1}H-NMR (DMSO, δ ppm): 1.26 (t, 3H, J = 9.3 Hz), 4.23 (m, 2H), 7.09–7.13 (m, 1H); 7.32–7.38 (m, 1H); 8.14–8.20 (m, 1H), 8.47 (d, 1H, J = 1.62 Hz), 8.57 (d, 1H, J = 1.62 Hz), 11.11 (s, 1H). ^{13}C-NMR (DMSO, δ ppm): 21.4 (CH_3), 61.5 (CH_2), 104.1 (dd, J = 26.8, 24.0 Hz, CH), 111.2 (dd, J = 21.9, 3.53 Hz, CH), 115.3 (C), 117.8 (C), 122.6 (dd, J = 11.3, 3.5 Hz, C), 124.2 (dd, J = 9.2, 2.1 Hz, CH), 150.7 (CH), 151.6 (CH), 153.3 (dd, J = 247.9, 12.0 Hz, C–F), 158.4 (dd, J = 244.4, 12.0 Hz, C–F), 159.1 (C═O), 161.0 (C═O). m/z $C_{14}H_{11}F_2NO_4$ calc.: 295.06. Found (EI): 295.06.

***N*,*N*'-Bis(2,4-difluorophenyl)furan-3,4-dicarboxamide (4).** White solid. m.p.: 209.6–210.6 °C. ^{1}H-NMR (DMSO, δ ppm): 7.10–7.16 (m, 2H); 7.34–7.40 (m, 2H), 7.87–7.93 (s, 2H), 8.60 (s, 2H), 11.25 (s, 2H). ^{13}C-NMR (DMSO, δ ppm): 104.4 (dd, J = 26.8, 24.0 Hz, 2 × CH), 111.4 (dd, J = 21.9, 3.5 Hz, 2 × CH), 119.6 (2 × C), 121.87 (dd, J = 12.0, 3.53 Hz, 2 × Cq), 126.4 (dd, J = 9.9, 2.1 Hz, 2 × CH), 150.2 (2 × CH), 154.6 (dd, J = 249.4, 12.72 Hz, 2 × C–F), 159.1 (dd, J = 244.4, 11.3 Hz, 2 × C–F), 161.1 (2 × C═O). m/z $C_{18}H_{10}F_4N_2O_3$ calc.: 378.06. Found (EI): 378.06.

Acknowledgements

The authors acknowledge financial support from the Spanish Ministerio de Ciencia e Innovación (project CTQ2011-22410) and the Junta de Comunidades de Castilla-La Mancha (Program HITO 2010-54 and project PII2I09-0100).

Notes and references

1 V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–473.
2 R. C. Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989, pp. 989–990.
3 A. Basha, M. Lipton and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171–4174.
4 T. Gustafsson, F. Pontén and P. H. Seeberger, *Chem. Commun.*, 2008, 1100–1102.
5 B. Gnanaprakasam and D. Milstein, *J. Am. Chem. Soc.*, 2011, **133**, 1682–1685.
6 (*a*) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420.
7 B. R. Kim, H. G. Lee, S. B. Kang, G. H. Sung, J. J. Kim, J. K. Park, S. G. Lee and Y. J. Yoon, *Synthesis*, 2012, 42–50.
8 X. Ye, D. Johnson, T. Diao, M. H. Yates and S. S. Stahl, *Green Chem.*, 2010, **12**, 1180–1186.
9 H. L. L. Busset and C. R. Thomas, *J. Chem. Soc.*, 1954, 1188–1190.
10 J. Singh, N. Satyamurthi and I. S. Aidhen, *J. Prakt. Chem.*, 2000, **342**, 340–347.
11 A. Bhattacharya, R. E. Plata, V. Villarreal, S. Muramulla and J. Wu, *Tetrahedron Lett.*, 2006, **47**, 505–506.

12 (*a*) *Microreactors: New Technology for Modern Chemistry*, ed. W. Ehrfield, V. Hessel and H. Löwe, Wiley-VCH, Weinheim, 2000; (*b*) C. Wiles and P. Watts, *Eur. J. Org. Chem.*, 2008, 1655–1671; (*c*) T. Illg, P. Löb and V. Hessel, *Bioorg. Med. Chem.*, 2010, **18**, 3707–3719; (*d*) P. Watts and S. J. Haswell, *Drug Discovery Today*, 2003, **8**, 586–593; (*e*) *Microreactors in Organic Synthesis and Catalysis*, ed. T. Wirth, Wiley-VCH, Weinheim, 2008; (*f*) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300–2318; (*g*) H. R. Sahoo, J. G. Kralj and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5704–5708; (*h*) R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 7502–7519.
13 C. Wiles and P. Watts, *Green Chem.*, 2012, **14**, 38–54.
14 (*a*) H. Wakami and J. Yoshida, *Org. Process Res. Dev.*, 2005, **9**, 787–791; (*b*) H. Kim, A. Nagaki and J. Yoshida, *J. Nat. Commun.*, 2011, **2**, 1–6; (*c*) A. Nagaki, S. Yamada, M. Doi, Y. Tomida, N. Takabayashi and J. Yoshida, *Green Chem.*, 2011, **13**, 1110–1113; (*d*) T. Brodmann, P. Koos, A. Metzger, P. Knochel and S. V. Ley, *Org. Process Res. Dev.*, 2012, DOI: 10.1021/op200275d.
15 A. K. Prasad, V. Kumar, S. Malhotra, V. T. Ravikumar, Y. S. Sanghvib and V. S. Parmara, *Bioorg. Med. Chem.*, 2005, **13**, 4467–4472.
16 T. A. Dineen, M. A. Zajac and A. G. Myers, *J. Am. Chem. Soc.*, 2006, **128**, 16406–16409.
17 M. Zhang, P. Vedantham, D. L. Flynn and P. R. Hanson, *J. Org. Chem.*, 2004, **69**, 8340–8344.
18 S. C. Ghosh, S. Muthaiah, Y. Zhang, X. Xu and S. H. Honga, *Adv. Synth. Catal.*, 2009, **351**, 2643–2649.
19 K. Singh and K. Singh, *Tetrahedron*, 2009, **65**, 10395–10399.
20 C. L. Allen, S. Davulcu and J. M. J. Williams, *Org. Lett.*, 2010, **12**, 5096–5099.
21 L. H. Heitman, J. P. D. van Veldhoven, A. M. Zweemer, K. Ye, J. Brussee and A. P. Ijzerman, *J. Med. Chem.*, 2008, **51**, 4724–4729.
22 D. Mabire, S. Coupa, C. Adelinet, A. Poncelet, Y. Simonnet, M. Venet, R. Wouters, A. S. J. Lesage, L. V. Beijsterveldt and F. Bischoff, *J. Med. Chem.*, 2005, **48**, 2134–2153.
23 Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto and H. Nagashima, *Chem. Commun.*, 2009, 1574–1576.