Simple and facile synthesis of tetralone-spiro-glutarimides and spiro-bisglutarimides from Baylis–Hillman acetates†

Deevi Basavaiah* and Raju Jannapu Reddy

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A simple and convenient synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides from Baylis–Hillman acetates *via* an interesting biscyclization strategy involving facile C–C and C–N bond formation is described. Also, one-pot multistep transformation of the Baylis–Hillman acetates into di(*E*)-arylidene-spiro-bisglutarimides is presented.

Introduction

Tetralone and spiro-tetralone derivatives[1] continue to occupy an important place in organic and medicinal chemistry because of the presence of this moiety in a number of natural products such as palmarumycins[1a–d] (possess antifungal, antibacterial, and herbicidal activites), humicolone[1e] (possesses cytotoxic activity), daldinone A,[1f] and aristelegones A–C[1g] *etc.* The glutarimide framework[2] represents yet another important structural organization present in a number of bioactive molecules such as thalidomide[2a–c] (sedative and hypnotic), migrastatin[2d] (antitumor), sesbanimide[2e] (antitumor), aminoglutethimide[2f] (antineoplastic), cinperene[2g] (antipsychotic and neuroleptic) and phenglutarimide[2h] (antiparkinsonian and anticholinergic) *etc.* Recently, certain spiro-glutarimides[2i] have been investigated for selective antagonists at the α_{1d} adrenergic receptor. It occurred to us that the development of a simple and facile synthesis of an interesting and aesthetically appealing spiro molecular architecture containing both the tetralone framework and glutarimide structural unit linked by an appropriate spiro bridge as in the case of alonimid (**I**), *i.e.* [1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′, 6′-dione] (well known for sedative and hypnotic activities),[3] would certainly provide an easy access to the different derivatives of alonimid (Fig. 1) and hence represents an attractive and challenging endeavor in organic and medicinal chemistry. In continuation of our interest in developing simple and useful methodologies for the synthesis of spiro and hetero/carbocyclic molecules,[4] we herein report a convenient synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonimids, **II**] *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (acetates of Baylis–Hillman adducts) followed by an interesting biscyclization strategy involving successive C–C and C–N bond formation through an intramolecular Friedel–Crafts reaction and hydrolysis of the nitrile group with subsequent formation of a glutarimide ring. We also herein report one-pot multistep transformation of the Baylis–Hillman acetates into spiro-bisglutarimide derivatives.[5]

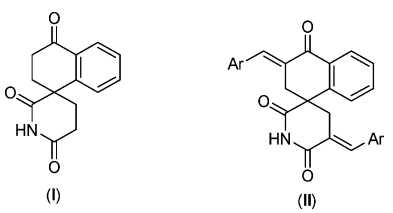


Fig. 1 Alonimid (**I**) and di(*E*)-arylidene alonimids (**II**).

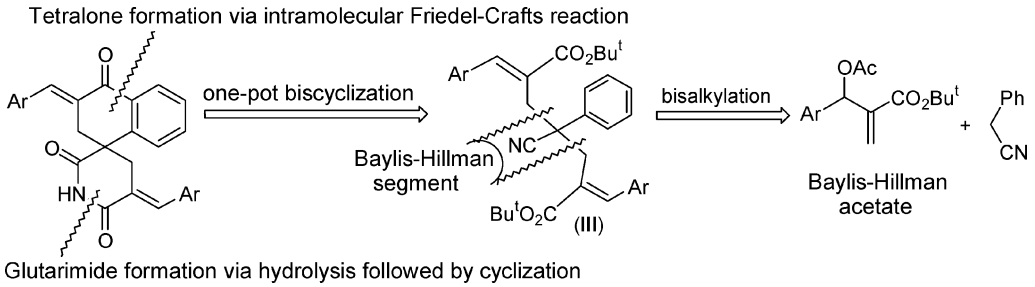
School of Chemistry, University of Hyderabad, Hyderabad 500 046, India. E-mail: dbsc@uohyd.ernet.in; Fax: 91-40-23012460

† Electronic supplementary information (ESI) available: Representative experimental procedures, with all spectral data of **2a–i**, **3a–i** and **4a–e**, crystal data and ORTEP diagrams of **2e**, **3a**, **3f** and **4d**. See DOI: 10.1039/b717843c

Results and discussion

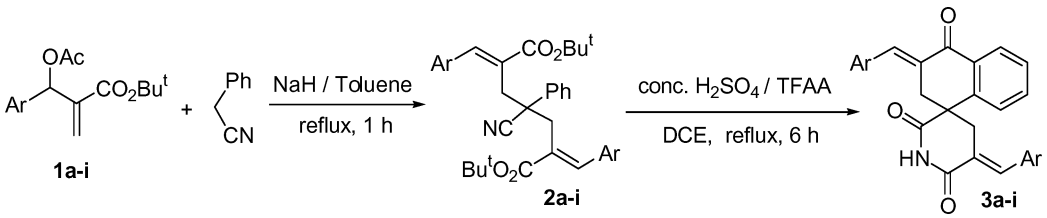
In recent years, the Baylis–Hillman reaction[6] has become a powerful atom-economical carbon–carbon bond forming reaction in organic chemistry because it provides a simple and facile method for the synthesis of interesting classes of densely functionalized molecules that have been used in a variety of interesting organic transformation methodologies.[4,6–8] We have been working on the applications of Baylis–Hillman adducts[4c,e–g,k,n,7s] and acetates[4a,h,j,m,7r] with a view to developing Baylis–Hillman chemistry as a useful source for the synthesis of various structural frameworks that ultimately would lead to the production of important molecules of medicinal relevance. During our ongoing research program on the synthesis of spiromolecues,[4b,d] it occurred to us that the carbon linking phenyl and nitrile groups in benzyl cyanide would be easily projected as the spiro-carbon, as the phenyl ring would be converted into the tetralone moiety while the nitrile group would be transformed into the glutarimide skeleton (Scheme 1). We also envisaged that Baylis–Hillman (B–H) acetates *i.e. tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates, would serve as good alkylating agents for bisalkylation of benzyl cyanide, as one of the ester groups in the bisadduct (**III**) would be used for an intramolecular Friedel–Crafts reaction while the other ester group would serve in the formation of the glutarimide framework thus leading to the generation of the spiro molecule with an appropriate substitution profile (Scheme 1).

Accordingly, we first selected *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) as an alkylating agent for bisalkylation of benzyl cyanide. The best results were achieved when benzyl cyanide (2 mmol) was treated with B–H acetate **1a** (5 mmol)



Scheme 1 Schematic representation of a retro-synthetic strategy for di(*E*)-arylidene alonimids.

Table 1 Synthesis of bisadducts (**2a–i**)[a] and di(*E*)-arylidene-tetralone-spiro-glutarimides (**3a–i**)[b] from B–H acetates (**1a–i**)



Entry	B–H acetate	Ar	Product[c]	Yield[d] (%)	Product[c]	Yield[d] (%)
1	**1a**	C_6H_5	**2a**	73	**3a**[e]	80
2	**1b**	2-MeC_6H_4	**2b**	81	**3b**	75
3	**1c**	4-MeC_6H_4	**2c**	80	**3c**	77
4	**1d**	4-EtC_6H_4	**2d**	78	**3d**	78
5	**1e**	4-(i-Pr)C_6H_4	**2e**[e]	72	**3e**	75
6	**1f**	2-ClC_6H_4	**2f**	70	**3f**[e]	82
7	**1g**	3-ClC_6H_4	**2g**	65	**3g**	67
8	**1h**	4-ClC_6H_4	**2h**	66	**3h**	77
9	**1i**	4-BrC_6H_4	**2i**	63	**3i**	71

[a] All reactions were carried out on a 2 mmol scale of benzyl cyanide with 5 mmol of B–H acetate (**1a–i**) in the presence of excess NaH (10 mmol) in anhydrous toluene under reflux for 1 h in N_2 atm. [b] All reactions were carried out on a 0.5 mmol scale of bisadducts (**2a–i**) in 1,2-dichloroethane (DCE, 3 mL) with conc. H_2SO_4 (2.5 mmol) and TFAA (2.5 mmol) under reflux for 6 h. [c] All the products (**2a–i** and **3a–i**) were obtained as colorless solids, and fully characterized (see ESI†). [d] Isolated yields of the pure products **2a–i** (based on benzyl cyanide) and **3a–i** (based on bisadducts). [e] The structures of these molecules were also established from the single crystal X-ray data (see Fig. 2 and 3 and ESI†,‡).[10]

in the presence of excess NaH (10 mmol) in anhydrous toluene under reflux for 1 h to provide the desired bisadduct, di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**2a**) in 73% isolated yield after column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization[9] (from 3% EtOAc in hexanes at 0 °C) (Scheme 2, Table 1 and entry 1). Subsequent treatment of this bisadduct **2a** (0.5 mmol) with conc. H_2SO_4 (2.5 mmol)–trifluoroacetic anhydride (TFAA) (2.5 mmol) in 1,2-dichloroethane (DCE, 3 mL) under reflux for 6 h provided the desired 2,5′-di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (**3a**) as a colorless solid in 80% isolated yield after column chromatography using silica gel (30% EtOAc in hexanes) (Scheme 2, Table 1 and entry 1). This result is indeed very interesting and encouraging in the sense that the Baylis–Hillman acetate (**1a**) is transformed into 2,5′-di[(*E*)-benzylidene] alonimid (**3a**) in two steps in 58% overall yield. We then successfully extended this methodology to representative B–H acetates (**1b–i**) to provide di(*E*)-arylidene alonimids (**3b–i**) in good yields (Scheme 2, Table 1 and entries 2–9). In fact, we obtained single crystals in the case of bisadduct **2e**, di(*E*)-arylidene alonimids **3a** and **3f**, and established the structures of these molecules by single crystal X-ray data analyses (see Fig. 2 and 3 and ESI†,‡).[10]

After successfully developing a simple and convenient methodology for the synthesis of di(*E*)-arylidene alonimids, we directed our attention towards the synthesis of spiro-bisglutarimides *via* bisalkylation of malononitrile with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates, followed by the hydrolysis of nitrile groups and subsequent cyclization in a one-pot operation (Scheme 3). In this direction, we first selected *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) as a substrate for bisalkylation. Thus, the treatment of **1a** (2 mmol) in acetonitrile (3 mL) with malononitrile (1 mmol) in the presence of triethylamine (1 mmol) at room temperature for 1 h provided the bisadduct, which, on subsequent reaction (after removing acetonitrile and triethylamine under reduced pressure) with conc. H_2SO_4 (2 mmol) and TFAA (2 mmol) (addition at 0 °C) at room temperature for 24 h in dichloromethane

‡ CCDC reference numbers 656194–656197. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b717843c

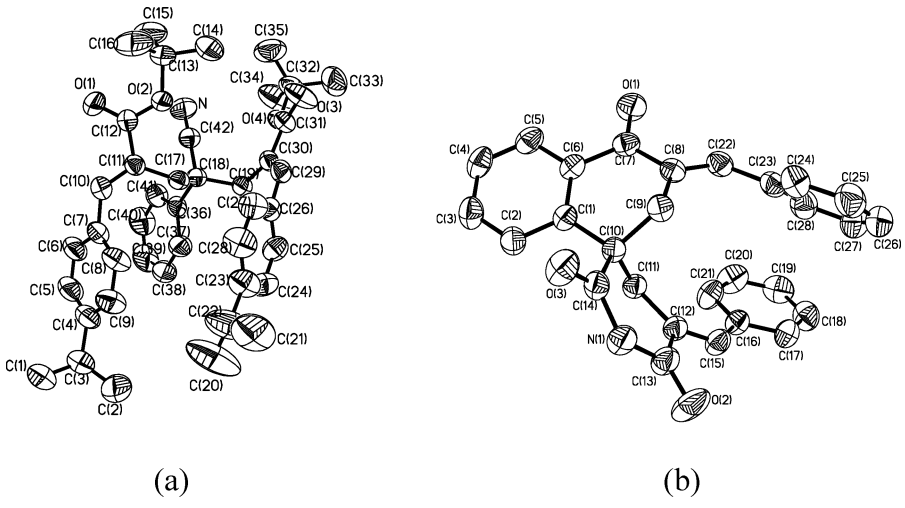


Fig. 2 ORTEP diagrams (50% probability) of compounds (a) **2e** and (b) **3a** (hydrogen atoms are omitted for clarity).

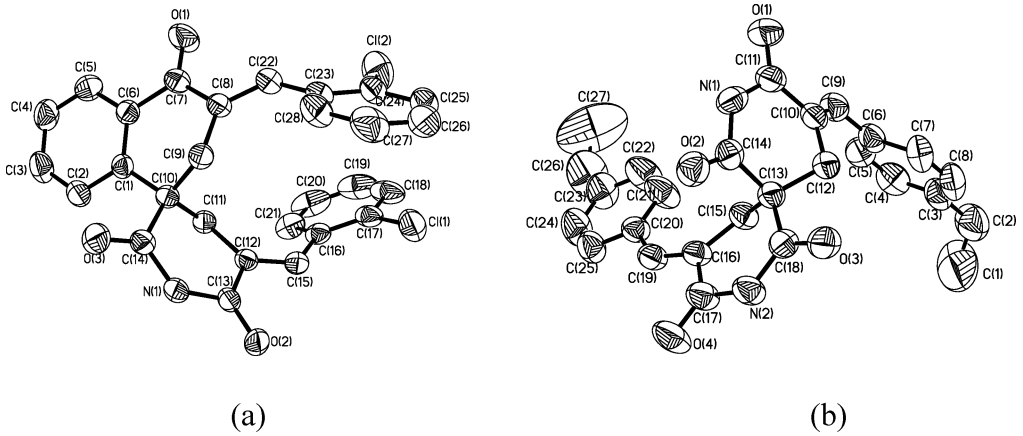
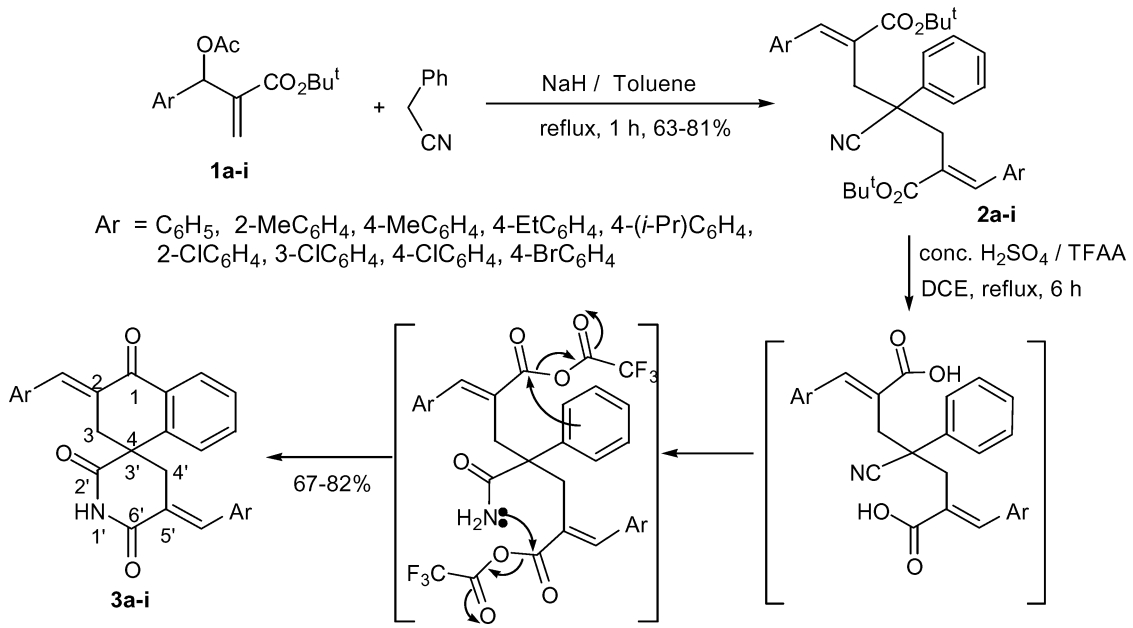
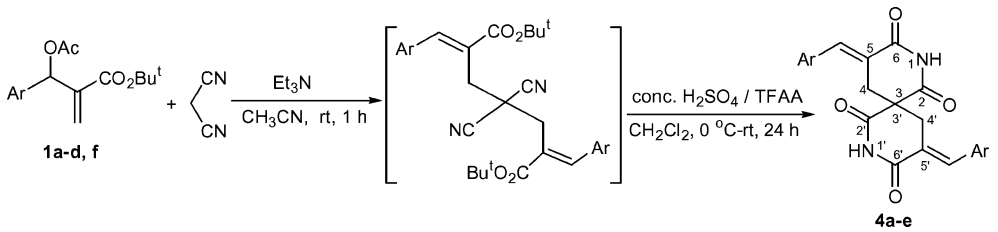


Fig. 3 ORTEP diagrams (50% probability) of compounds (a) **3f** and (b) **4d** (hydrogen atoms are omitted for clarity).



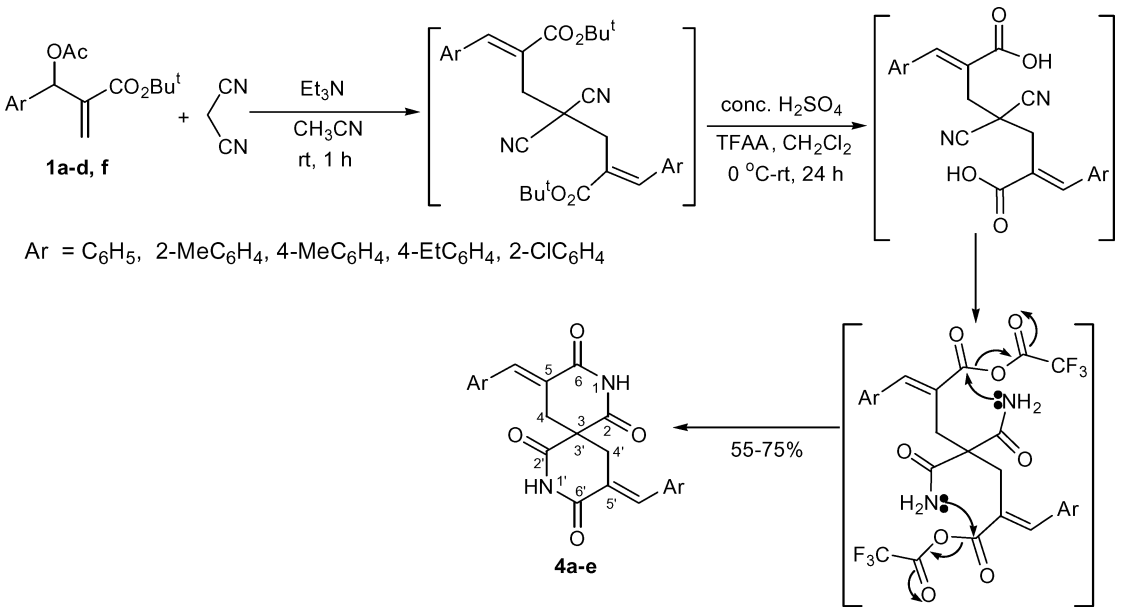
Scheme 2 Synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonimids].

Table 2 One-pot multistep synthesis of di(*E*)-arylidene-spiro-bisglutarimides (**4a–e**)[a] from B–H acetates (**1a–d**, **f**)



Entry	B–H acetate	Ar	Product[b]	Yield[c] (%)
1	**1a**	C_6H_5	**4a**	75
2	**1b**	2-MeC_6H_4	**4b**	56
3	**1c**	4-MeC_6H_4	**4c**	64
4	**1d**	4-EtC_6H_4	**4d**[d]	59
5	**1f**	2-ClC_6H_4	**4e**	55

[a] All reactions were carried out on a 1 mmol scale of malononitrile with 2 mmol of B–H acetate (**1a–d**, **f**) in the presence of Et_3N in acetonitrile at room temperature for 1 h and then subsequent treatment with conc. H_2SO_4 (2 mmol)–TFAA (2 mmol) in dichloromethane (5 mL) at room temperature for 24 h. [b] All the pure products **4a–e** were obtained as colorless solids [with (*E*)-stereochemistry as evidenced by the ^{1}H NMR spectral analysis and also in analogy with that of **4d**] and fully characterized (see ESI†). [c] Yields of the pure products based on B–H acetates. [d] The structure of this molecule [with (*E*)-stereochemistry] was also established from the single crystal X-ray data (see Fig. 3 and ESI†,‡).[10]



Scheme 3 One-pot multistep synthesis of di(*E*)-arylidene-spiro-bisglutarimides.

(5 mL) followed by usual work-up, provided the desired 3,3′-spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (**4a**) in 75% yield (Scheme 3, Table 2 and entry 1).

With a view to understanding the generality of this methodology, we extended this strategy to the Baylis–Hillman acetates (**1b–d**, **f**), which provided the resulting spiro-bisglutarimides (**4b–e**) in moderate to good yields in an operationally simple one-pot procedure (Scheme 3, Table 2 and entries 2–5). In fact, we obtained a single crystal for compound **4d** and established the structure of this molecule by single crystal X-ray data (see Fig. 3 and ESI‡).[10]

Conclusions

In conclusion, we have successfully developed a convenient and operationally simple two-step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonimids] and also described a one-pot multistep synthesis of di(*E*)-arylidene-spiro-bisglutarimides from Baylis–Hillman acetates (*tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates).

Experimental

General methods

Melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT-IR model 5300 spectrometer using solid samples as KBr plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (50/100 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) or deuterodimethyl sulfoxide (DMSO-d_6) or in deuterochloroform

($CDCl_3$) containing deuterodimethyl sulfoxide (DMSO-d_6), on a Bruker-AVANCE-400 and Bruker-AC-200 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard. Elemental analyses were recorded on a Thermo-Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on a Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å).

Di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (2a). To a stirred suspension of oil-free excess NaH (10 mmol, 0.24 g) in anhydrous toluene were added benzyl cyanide (2 mmol, 0.234 g) and *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) (5 mmol, 1.38 g) at room temperature, and the mixture was heated under reflux for 1 h under a N_2 atmosphere. Then the reaction mixture was allowed to come to room temperature and was cooled to 0 °C. Excess NaH was carefully quenched with the very slow addition of water at 0 °C. The reaction mixture was extracted with ether (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue, thus obtained, was purified by column chromatography (5% ethyl acetate in hexanes) followed by crystallization (from 3% ethyl acetate in hexanes at 0 °C) to afford di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**2a**), as a colorless solid in 73% (0.80 g) yield; mp: 118–120 °C; IR (KBr): ν 2235, 1711, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 18H), 3.09 and 3.34 (ABq, 4H, $J = 13.6$ Hz), 6.98–7.38 (m, 15H), 7.62 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.00, 35.95, 48.28, 81.34, 120.39, 126.53, 127.50, 128.04, 128.16, 128.42, 128.84, 130.27, 135.60, 137.54, 142.01, 166.94; LCMS (m/z): 548 $(M - H)^-$; Anal. Calcd. for $C_{36}H_{39}NO_4$: C, 78.66; H, 7.15; N, 2.55; Found: C, 78.67; H, 7.11; N, 2.64%.

2,5′-Di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (3a). To a stirred solution of di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**2a**) (0.5 mmol, 0.275 g) in 1,2-dichloroethane (DCE, 3 mL) were added conc. H_2SO_4 (2.5 mmol, 0.245 g, 0.13 mL) and trifluoroacetic anhydride (TFAA, 2.5 mmol, 0.525 g, 0.35 mL) at room temperature. The reaction mixture was heated under reflux for 6 h and was then allowed to cool to room temperature. The reaction mixture was poured into aqueous K_2CO_3 solution and extracted with EtOAc (3 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue thus obtained was purified by column chromatography (30% ethyl acetate in hexanes) to provide 2,5′-di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (**3a**) as a colorless solid in 80% (0.168 g) yield; mp: 184–186 °C; IR (KBr): ν 3300–2800 (multiple bands), 1711, 1693, 1651, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.08 (s, 2H), 3.38 and 3.48 (ABq, 2H, $J = 14.8$ Hz), 6.88 (d, 2H, $J = 6.6$ Hz), 7.13–7.41 (m, 9H), 7.43–7.51 (m, 1H), 7.53–7.62 (m, 1H), 7.72 (s, 1H), 7.85 (s, 1H), 8.20 (d, 1H, $J = 7.2$ Hz), 8.68 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.23, 36.15, 48.25, 124.07, 126.64, 128.64, 128.67, 129.10, 129.17, 129.42, 129.55, 129.74, 129.87, 132.58, 133.63, 133.90, 134.60, 140.29, 142.49, 166.30, 174.45, 185.72; LCMS (m/z): 420 $(M + H)^+$; Anal. Calcd. for $C_{28}H_{21}NO_3$: C, 80.17; H, 5.05; N, 3.34; Found: C, 80.27; H, 5.00; N, 3.35%; Crystal data for **3a**: empirical formula, $C_{28}H_{21}NO_3$; formula weight, 419.46; crystal color, habit: colorless, block; crystal dimensions, $0.44 \times 0.28 \times 0.22$ mm^3; crystal system, monoclinic; lattice type, primitive; lattice parameters, $a = 9.0369(18)$ Å, $b = 25.751(5)$ Å, $c = 9.2740(18)$ Å; $\alpha = 90.00$; $\beta = 96.108(3)$; $\gamma = 90.00$; $V = 2145.9(7)$ $Å^3$; space group, $P21/n$ (International Table No. 14); $Z = 4$; $D_{calcd} = 1.298$ g cm^{-3}; $F_{000} = 880$; λ(Mo-K_α) = 0.71073 Å; $R\,(I \geq 2\sigma_1) = 0.0427$; $wR^2 = 0.1031$.‡

3,3′-Spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (4a). To a stirred solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) (2 mmol, 0.552 g) in acetonitrile (3 mL) were added malononitrile (1 mmol, 0.066 g, 0.06 mL) and triethylamine (1 mmol, 0.131 mL). After stirring at room temperature for 1 h, solvent acetonitrile and Et_3N were evaporated under reduced pressure. The resulting residue was diluted with dichloromethane (5 mL) and cooled to 0 °C. To this solution at 0 °C, conc. H_2SO_4 (2 mmol, 0.192 g, 0.10 mL) and trifluoroacetic anhydride (TFAA, 2 mmol, 0.42 g, 0.28 mL) were added. Then the reaction mixture was allowed to warm to room temperature. After stirring for 24 h at room temperature, the reaction mixture was poured into aqueous K_2CO_3 solution. The solid separated was filtered and well washed with water followed by ethyl acetate. Thus the obtained solid was dried *in vacuo* to provide pure 3,3′-spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (**4a**) as a colorless solid in 75% (0.289 g) yield; mp: 255 °C (dec.); IR (KBr): ν 3200–2830 (multiple bands), 1711, 1680, 1610 cm^{-1}; ^1H NMR (400 MHz, 50% DMSO-d_6 in $CDCl_3$): δ 2.86 and 3.34 (ABq, 4H, $J = 15.2$ Hz), 7.19–7.41 (m, 10H), 7.72 (s, 2H), 11.08 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.02, 50.84, 125.59, 128.88, 129.34, 129.87, 134.34, 138.90, 165.97, 170.54; LCMS (m/z): 387 $(M + H)^+$; Anal. Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25; Found: C, 71.33; H, 4.71; N, 7.17%.

Acknowledgements

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10 Detailed X-ray crystallogaphic data is available from the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK for compounds **2e** (CCDC # 656194), **3a** (CCDC # 656195), **3f** (CCDC # 656196) and **4d** (CCDC # 656197).