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Convenient access to isoindolinones via carbamoyl radical cyclization. Synthesis of cichorine and 4-hydroxyisoindolin-1-one natural products

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ABSTRACT

An efficient and convenient access to 2-*tert*-butylisoindolin-1-ones via an oxidative radical cyclization process from stable carbamoylxanthates, derived from secondary *tert*-butylamines, is described. The proposed mechanism for this transformation involves, the generation of a carbamoyl radical, its cyclization to the aromatic system, and the dilauroyl peroxide (DLP) mediated rearomatization to generate the isoindolinone ring system. Additionally, the syntheses of cichorine and 4-hydroxyisoindolin-1-one natural products were carried out to underscore the synthetic potential of this xanthate-based carbamoyl radical-oxidative cyclization.

1. Introduction

Isoindolin-1-ones are a common moiety in a variety of natural products including magallanesine **1**,[1] lennoxamine **2**,[2] stachybotrin C **3**,[3] and also in some pharmacologically important synthetic compounds, such as zopiclone **4**[4] and pagoclone **5** (Fig. 1).[2d,e,5] Numerous synthetic and natural molecules containing the isoidolin-1-one framework have been reported to display significant biological activities including antimicrobials,[6] anti-viral drugs for the treatment of the common cold,[7] HIV-1 inhibitors,[8] TACE inhibitors,[9] antitumor activity,[10] sedative, hypnotic agents,[11] antidopaminergic agents, and also protein kinase inhibiting activities.[12] Their utility in Diels–Alder reactions is well established and these heterocycles frequently serve as a building block for asymmetric synthesis.[13,14] Recently these heterocyclic scaffolds were also reported to have special fluorescent properties.[15]

Several methodologies have been developed for the construction of the isoindolinone ring system[1b,16] including cyclizations of aryl lithium species of different *N*-acyl-benzylamine derivatives such as *N*′-benzyl-*N*,*N*-dimethylureas.[16b] However, such methodologies require the use of strong basic organo-lithium regents, which are normally incompatible with functional groups sensitive to nucleophilic attack. More recently, several metal-catalyzed approaches have been described for the synthesis of isoindolinones. Leading examples include carbonylation of benzylamines under CO atmosphere using the catalytic system $Pd(OAc)_2$–$Cu(OAc)_2$,[16c] a tandem elimination–cyclization–Suzuki approach,[16d] a Heck–Suzuki–Miyaura domino reaction involving ynamides,[16e] and a Sonogashira reaction of 2-halobenzamides with terminal alkynes. Other approaches to the isoindolinone system involve electrophilic cyclization,[1b] and an intramolecular cyclization of acyl radicals onto an azide group.[16f] Importantly, the majority of the aforementioned approaches require the preparation of haloarene starting materials, which sometimes involves multistep synthetic sequences (Fig. 1).

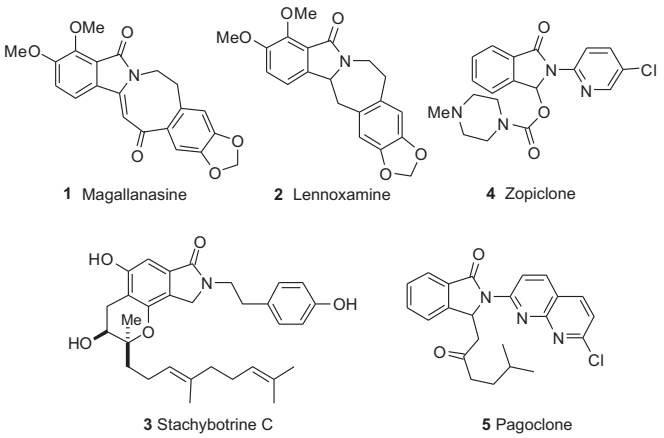

Fig. 1. Natural products containing the isoindolin-1-one ring system.

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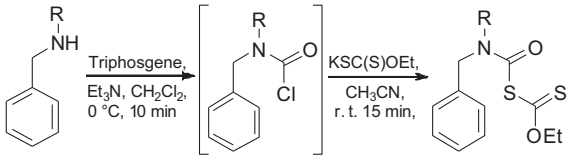
We have been interested in the use of the addition of alkyl and acyl radicals to aromatic and heteroaromatic systems.[17] In this context, we examined the feasibility of implementing the oxidative cyclization of carbamoyl radicals onto aromatic systems as an innovative and easy access to the isoindolin-1-one ring system.[18] The application of the cyclization of carbamoyl radicals to a benzenoid system to prepare the isoindolinone ring system entails several advantages: in this free radical-based process, the use of strong bases is avoided; no high pressure of CO is required; and it occurs through a substitution at a C–H bond of the aromatic ring, obviating the complications associated with the synthesis of haloarene starting materials. Addition processes of carbamoyl radicals to double bonds,[19] aromatic systems,[20] and oxime ethers[21] have been reported. More recently the powerful synthetic potential of these radicals has been illustrated in the synthesis of the complex natural product stephacidin B.[22] Given the efficiency of generation of alkyl and acyl radicals from dithiocarbonates, developed by Zard and co-workers,[23] we envisioned the possibility of using the related carbamoylxanthates (carbamoyldithiocarbonates) as the carbamoyl radical source.[24] Previously, while preparing carbamoyldithiocarbonates, Grainger and Innocenti[19g] observed that these species are unstable and lost a CS or a CO molecule, affording poor yields of the desired dithiocarbonate. This drawback was resolved by using[19g] the more stable carbamoyldithiocarbamates as the carbamoyl radical source and this methodology was used to construct several lactams of different sizes via an intermolecular carbamoyl addition/xanthate transfer radical process onto a double bond. Despite these advances, the synthesis of carbamoylxanthates, their use as a source of carbamoyl radicals and their oxidative cyclization to an aromatic system has remained elusive.[19]

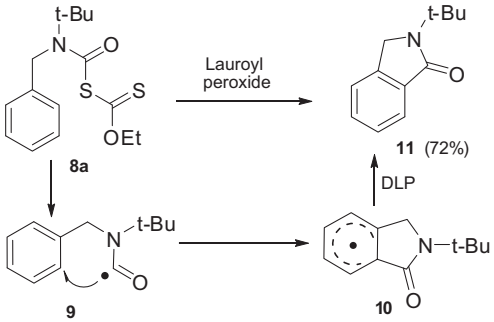
2. Results and discussion

In contrast with the report of Grainger and Innocenti regarding the instability of carbamoyldithiocarbonates, our initial studies showed that the corresponding carbamoyldithiocarbonate **8a** could be isolated as a remarkably stable, crystalline compound in gratifying 77% yield, from the reaction of the *N*-*tert*-butylbenzylamine **6a** and triphosgene, reacting the carbamoyl chloride intermediate **7a** with commercial potassium ethyl xanthate in acetonitrile at rt (Scheme 1). The structure of this compound **7a** was verified by X-ray crystallography. We further observed that the stability of **8a** relied on the steric hindrance in the amine moiety since the putative carbamoylxanthates **8b** and **8c** were unstable and rapidly decomposed to complex mixtures during their preparation under the same conditions. Remarkably, **8a** remained unchanged after 2 h in chlorobenzene at reflux temperature. This stability may be a consequence of conformational effects of the *N*-*tert*-butyl group either through fixing a specific conformation, engendering a high NCO rotational barrier, or simply by steric hindrance in the vicinity of the NCO moiety, preventing further decomposition (CO/CS loss)[19g] of the carbamoylxanthate. However, at the present time we have no convincing data to support these speculations. Previously, Zard and co-workers had observed that an excess of potassium ethyl xanthate itself in the reaction media might be responsible for the fast decomposition of related congener *S*-acylxanthates.[24] It is noteworthy that the use of an excess of the potassium xanthate had no significant effect on the isolated yield of **8a**.



Scheme 1.

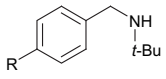
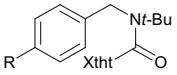
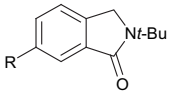
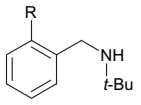
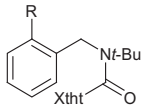
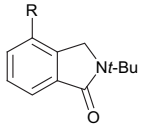
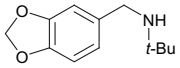
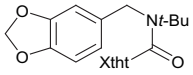
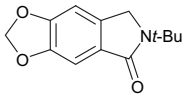
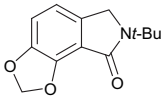
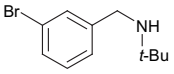
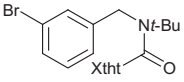
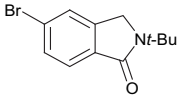
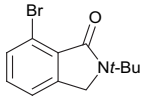
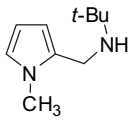
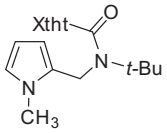
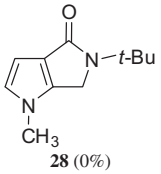
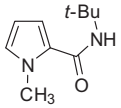
With the desired carbamoylxanthate **8a** in hand, its ability to undergo carbamoyl radical-mediated cyclization to the isoindolinone **11** was then evaluated under typical free radical conditions. We were gratified to observe that the isoindolinone **11** was obtained in good yield, upon the portionwise addition of a stoichiometric amount of dilauroyl peroxide (DLP) (1.2 equiv over 1.5 h) to a boiling solution of **8a** in dichloroethane (2 mL/mmol) (Scheme 2). The proposed mechanism for this transformation involves the DLP-induced generation of the carbamoyl radical **9** by a mechanism similar to that observed in related alkylxanthates, then the cyclization of this latter radical to generate the radical **10**, which might undergo a DLP-mediated oxidative rearomatization[23] to the isoindolinone **11**. According to the proposed mechanism, the DLP acts as both initiator and oxidant, and thus, stoichiometric amounts of this reagent are needed for the completion of the reaction.



Scheme 2. Proposed mechanism.

To investigate the scope of this practical entry into isoindolin-1-one scaffolds, several ring substituted *tert*-butylbenzylamines were prepared from the corresponding aldehydes by reductive amination with *N*-*tert*-butylamine. Then, all these latter benzylamines were converted into the corresponding stable and isolable carbamoylxanthates, under the aforementioned conditions. Furthermore, independently of the electronegative nature of the benzenoid substituent(s), in every case but one the ring substituted *N*-*tert*-butylisoindolinone was obtained in excellent yield when the carbamoylxanthates were subjected to the above carbamoyl radical generating conditions. Isoindolinones **14a**,**b** were isolated from the reaction of the electron-rich substrates carbamoylxanthates **13a**,**b** in good yield. Electron-deficient substrates **13c**–**e** underwent carbamoyl radical cyclization in similar good yield (Table 1, entry 1). Comparable good yields were observed with *para*- and *ortho*-substituted substrates (Table 1, entries 1 and 2). However, for reasons that are not completely clear, the nitro derivatives **13f** (4-NO_2) and **16c** (2-NO_2) were obtained in only low yields and did not afford the desired isoindolinone under the same radical-oxidative conditions. It was observed that **13f** and **16c** decomposed spontaneously after a careful purification. Interestingly, the carbamoylxanthate **13e**, also bearing an electron withdrawing ester group, afforded the corresponding isoindolinone **14e** in very good yield. The 3,4-methylenedioxy compound **19** gave a mixture of isoindolinones in which the product derived from cyclization at C-6 (**20**), the less hindered position, was only slightly favored (5.5:4.5) over that derived from attack at C-2 (**21**). The 3-bromo compound **23** gave a 3:2 mixture of products derived from cyclization at C-2 (**25**) and C-6 (**24**), respectively. The data collected in Table 1 convincingly show that

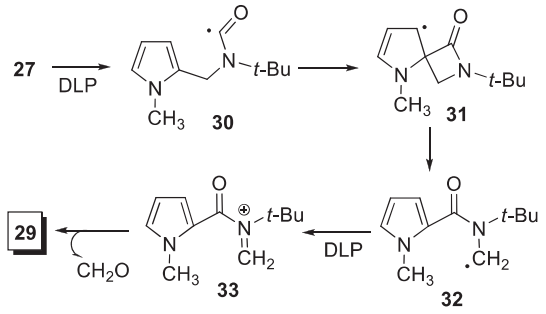
Table 1
Synthesis of 2-*tert*-butylisoindolin-1-ones from *tert*-butylbenzylamines

Entry	Amine	Xanthate[a]	Product
1	 **12a** R = Me **12b** R = OMe **12c**R = Br **12d** R = Cl **12e** R = COOMe **12f** R = NO_2	 **13a** R = Me (81%) **13b** R = OMe (80%) **13c** R = Br (82%) **13d** R = Cl (71%) **13e** R = COOMe (85%) **13f** R = NO_2 (42%)	 **14a** R = Me (77%) **14b** R = OMe (72%) **14c**R = Br (92%) **14d** R = Cl (86%) **14e** R = COOMe (91%) **14f** R = NO_2 (0%)
2	 **15a** R = Cl **15b** R = F **15c** R = NO_2	 **16a** R = Cl (84%) **16b** R = F (65%) **16c** R = NO_2 (31%)	 **17 a**R = Cl (85%) **17b** R = F (90%) **17c** R = NO_2 (0%)
3	 **18**	 **19** (85%)	 **20**  **21** (80%)
4	 **22**	 **23** (60%)	 **24**  **25** (82%)
5	 **26**	 **27** (51%)	 **28** (0%)  **29** (85%)

[a] Xtht=SC(S)OEt.

a variety of substituted isoindolinones can be readily prepared using this technology.

To expand the scope of the methodology, we applied the carbamoyl radical cyclization methodology to the pyrrole derivative **27** in an attempt to obtain the pyrrolo-pyrrolidone system **28** (Table 1, entry 5). Thus, 1-methyl-2-formylpyrrole, afforded the corresponding amine **26** through a reductive amination process with *N*-*tert*-butylamine. Then, amine **26** was converted into the corresponding carbamoylxanthate **27** in good yield, under the conditions described above. Interestingly, under the optimized radical conditions, xanthate **27** afforded the *tert*-butylamide derivative **29** as the sole product in good yield, instead of the desired pyrrolo-pyrrolidone ring system **28** (Table 1, entry 5). Mechanistically, this transformation might be a result of a Smiles-type rearrangement mechanism similar to those reported previously (Scheme 3).[25] Accordingly, the carbon-centered carbamoyl

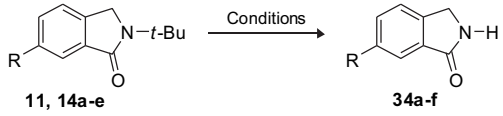


Scheme 3.

radical **30**, formed from the xanthate precursor **27**, presumably adds at the *ipso* C-2 position of the pyrrole nucleus to produce the spiro-β-lactam intermediate **31**. The reversible fragmentation of the strained four-membered ring would afford the stabilized radical **32** (alpha to the nitrogen atom), which could be oxidized to the iminium ion **33** by the action of the dilauroyl peroxide, which is present in a stoichiometric amount in the reaction medium.[26] Hydrolysis of the iminium ion would yield the isolated amide **29** and a formaldehyde molecule.

We fully recognized the requisite elimination of the *N*-*tert*-butyl moiety in order to validate the synthetic scope of the methodology. After considerable experimentation, we found that the deprotected isoindolinones **34a**–**f** could be obtained in excellent yields when **11** and **14a**–**e** were heated in refluxing neat trifluoroacetic acid (TFA) (Table 2).[27] The *N*-*tert*-butyl moiety could also be removed from **11** and **14b**,**d**,**e** compounds in excellent yields simply, by stirring solutions in neat trifluoromethanesulfonic acid (TFMSA) at rt; however, under these conditions, the more sensitive substrates **14b** and **14e** afforded low yields of the corresponding deprotected isoindolinones **34c** and **34f** (Table 2, entries 3 and 6).

Table 2
Removal of the *tert*-butyl group



11, 14a-e **34a-f**

	Subs.	R	Prod.	Cond. A		Cond. B	
				Time h	Yield	Time h	Yield
1	**11**	H	**34a**	0.5	98	72	100
2	**14a**	Me	**34b**	0.5	97	72	100
3	**14b**	OMe	**34c**	24	74	72	96
4	**14c**	Br	**34d**	24	100	72	100
5	**14d**	Cl	**34e**	3	100	96	100
6	**14e**	CO_2Me	**34f**	0.5	42	96	95

Conditions: (A) neat TFMSA, rt. (B) neat TFA, reflux.

3. Synthesis of the natural products cichorine and 4-hydroxyisoindolin-1-one

The naturally occurring molecules cichorine **35** and 4-hydroxyisoindolin-1-one **37** (Fig. 2) have a similar isoindolin-1-one core bearing an unsubstituted hydroxyl group in the benzenoid ring. Cichorine **35** and its prenylated derivative zinnimidine **36** are natural phytotoxins that have been isolated from cultures of several fungi of the genus *Alternaria*.[28] These phytotoxins have been implicated in diseases of commercially important plants.[28] As a result, this class of isoindol-1-ones has recently attracted considerable attention in the scientific community.[28,29] Certainly, constructing the pentafunctionalized aromatic nucleus of the cichorine framework represents an interesting synthetic challenge.[29] The

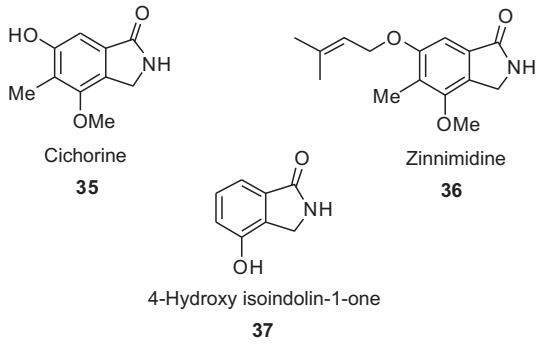
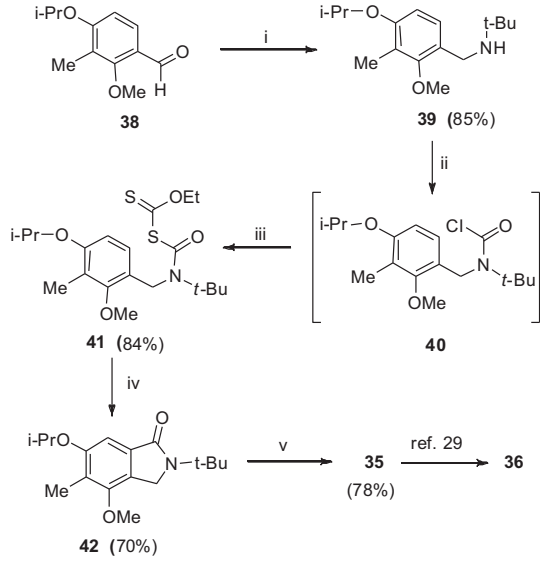


Fig. 2. Cichorine, zinnimidine, and 4-hydroxy isoindolin-1-one natural products.

4-hydroxyisoindolin-1-one **37**, on the other hand, has been isolated from the dried bodies of ant lions (the larvae of Myrmeleontidae species), which are used as a traditional Chinese medicine to treat malaria and childhood convulsions.[30] Compound **37** has been shown to have anti-HIV[31] and anti-inflammatory[32] activities, making this small molecule also an important synthetic target.

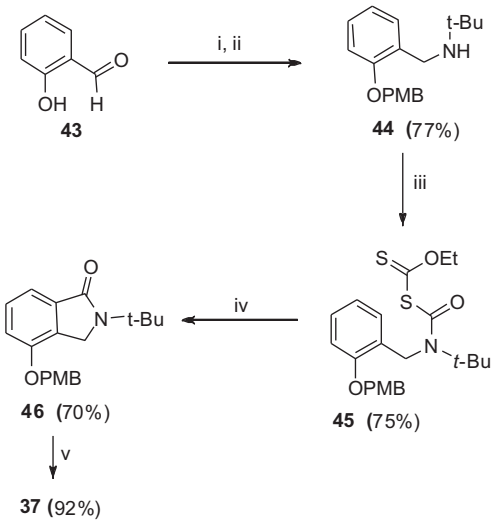
Therefore, we realized that the penta-substituted system of **35** might be prepared from the corresponding tetra-substituted *tert*-butylbenzylamine **39**. Thus, this later substrate was prepared by reductive amination of the aldehyde **38** with *tert*-butylamine (the aldehyde **38** was readily available from 2-methylresorcinol).[28] Both the transformation of the amine **39** into the corresponding carbamoyl chloride **40** using triphosgene as an acylating agent, and the subsequent conversion of **40** into the carbamoylxanthate **41**, under the conditions described previously,[18] proceeded in good yield (Scheme 4). It was gratifying to observe that the isoindolinone **42** was obtained in good yield when the xanthate **41** was reacted with DLP in refluxing dichloroethane. Thus, exposure of **42** to neat refluxing TFA fortuitously induced removal of both the *tert*-butyl and isopropyl groups to afford the expected cichorine **35** directly in 76% yield (in 38% overall yield from the benzaldehyde **38**). The ^1H and ^{13}C NMR spectra of **35** were identical to the published data.[28,29] Given that the OH prenylation process of **36** has been reported,[29] this scheme thus represents a formal synthesis of zinnimidine **36**. The synthetic sequence described herein also represents one of the most



Scheme 4. Synthesis of cichorine. Reagents and conditions: (i) *tert*-butylamine (4.0 equiv), anhydrous MeOH, molecular sieves, 12 h, then $NaBH_4$ 0.5 h (1.2 equiv), (ii) triphosgene (0.7 equiv), Et_3N (3.4 equiv), CH_2Cl_2, 0 °C, 10 min, (iii) CH_3CN, KSC(S)OEt (0.85 equiv), 15 min, rt (iv) DLP added portionwise (1.2 equiv), 1,2-dichloroethane, reflux, 4 h (v) TFA, neat, reflux. 96 h.

efficient and shortest syntheses reported to date for these natural phytotoxins.

Synthesis of 4-hydroxyisoindolin-1-one **37** started from the readily available salicylaldehyde **43**, as depicted in Scheme 5. The *p*-methoxybenzyl group was chosen to protect the OH of the salicylaldehyde in the first step because this group could be easily removed using acidic conditions in the last step of the synthesis. The subsequent reductive amination process produced **44** in 77% yield over the two steps. Reaction of **44** with triphosgene followed by trapping the intermediate carbamoyl chloride with the potassium ethyl xanthate afforded the radical precursor **45**. Cyclization of the xanthate **45** under the aforementioned radical conditions proceeded efficiently to afford the isoindolinone **46**. Finally, exposure of **46** to acidic conditions secured the removal of both the *t*-Bu and *p*-methoxybenzyl groups. Thus, this protocol directly furnished the natural product 4-hydroxyisoindolin-1-one **37** in 41% overall yield from the readily available salicylaldehyde **43**. The ^{1}H and ^{13}C NMR spectra of **37** were identical to published data.[30]



Scheme 5. Synthesis of 4-hydroxyisoindolin-1-one. Reagents and conditions: (i) 4-methoxybenzyl bromide (2.0 equiv), K_2CO_3 (1.2 equiv), acetone, reflux, 12 h. 91%. (ii) *tert*-butylamine (4.0 equiv), anhydrous MeOH, molecular sieves, 12 h. Then, $NaBH_4$ 0.5 h (1.2 equiv), 85%, (iii) (a) Triphosgene (0.7 equiv), Et_3N (3.4 equiv), CH_2Cl_2, 0 °C, 10 min (b) KSC(S)OEt (0.85 equiv), CH_3CN, 15 min, rt (iv) DLP (1.2 equiv), 1.2-dichloroethane, reflux, 4 h (v) neat TFA, reflux 48 h.

4. Conclusions

In this work we have demonstrated that carbamoylxanthates derived from secondary *tert*-butyl-amines are stable compounds that serve as efficient sources of carbamoyl radicals by thermally induced DLP-fragmentation. Carbamoylxanthates derived from *tert*-butylbenzylamines are transformed into 2-*tert*-butylisoindolin-1-ones by oxidative radical cyclization of the corresponding carbamoyl radical onto the benzenoid system, a process scarcely exploited so far. In this metal-free approach to isoindolin-1-ones the use of strong bases is avoided; no high pressure of CO is required; and the transformation occurs through a substitution on a C–H bond of the aromatic ring, avoiding synthesis of haloarene starting materials. The synthesis of cichorine and 4-hydroxyisoindolin-1-one underscores the synthetic potential of this xanthate-based carbamoyl radical-oxidative cyclization. Moreover, the synthesis of cichorine **35** described herein represents the shortest method reported to date and to our knowledge, our synthesis of 4-hydroxyisoindolin-1-one **37** is the first ever reported for this natural product. The use of TFA to remove the *t*-Bu group from the isoindolinones also proved to be very efficient and general.

5. Experimental section

5.1. General procedure for the preparation of carbamoylxanthates

To a stirred solution of triphosgene (0.7 mmol) in CH_2Cl_2 (5.0 mL), at 0 °C the corresponding *tert*-butylbenzylamine (1.0 mmol) was added, followed by dropwise addition of Et_3N (3.4 mmol). The mixture was stirred for 10 min at rt. The solvent was removed under reduced pressure to give the crude carbamoyl chloride. This compound was used in the next step without further purification. A solution of the crude carbamoyl chloride in acetonitrile (5.0 mL) was treated with the *O*-ethylxanthic acid, potassium salt (0.95 mmol). The reaction was stirred for 15 min, at rt, quenched with water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The carbamoylxanthate was purified by a silica gel column chromatography (hexanes/EtOAc, 98:2) to afford the pure xanthate.

Compound **8a**: IR (film) ν_{max}/cm^{-1}: 2983, 2967, 2933, 1679; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.44 (s, 9H), 1.46 (t, 3H), 4.66 (q, 2H), 4.78 (s, 2H), 7.18–7.40 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 207.3, 160.2, 138.2, 128.7, 127.3, 125.8, 70.6, 60.7, 51.1, 28.3, 13.5; HRMS (FAB^+) calcd for $C_{15}H_{22}NO_2S_2$: [M+1] 312.1092, found: 312.1091.

Compound **13a**: IR (film) ν_{max}/cm^{-1}: 2978, 2927, 1691; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.42 (s, 9H), 1.45 (t, 3H), 4.65 (c, 2H), 4.73 (s, 2H), 7.14 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 207.3, 160.1, 136.9, 135.1, 129.3, 125.7, 70.5, 60.6, 50.8, 28.3, 20.9, 13.5; HRMS (FAB^+) calcd for $C_{16}H_{24}O_2NS_2$: [M+1] 326.1248, found: 326.1247.

Compound **13b**: IR (film) ν_{max}/cm^{-1}: 2978, 2934, 1690; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.45 (t, 3H), 3.79 (s, 3H) 4.66 (c, 2H), 4.71 (s, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 7.12 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 207.3, 160.0, 158.8, 130.0, 127.0, 114.0, 70.5, 60.5, 55.2, 50.4, 28.3, 13.5; HRMS (CI^+) calcd for $C_{16}H_{23}NO_3S_2$: [M^+] 341.1119, found: 341.1111.

Compound **13c**: IR (film) ν_{max}/cm^{-1}: 2976, 2932, 1692; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.46 (t, 3H), 4.63 (c, 2H), 4.71 (s, 2H), 7.09 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.7, 160.2, 137.3, 131.8, 127.5, 121.1, 70.7, 60.7, 50.4, 28.3, 13.5; HRMS (FAB^+) calcd for $C_{15}H_{21}O_2NBrS_2$: [M+1] 390.0197, found: 390.0196.

Compound **13d**: IR (film) ν_{max}/cm^{-1}: 2979, 2933, 1692; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.45 (t, 3H), 2.33 (s, 3H), 4.65 (c, 2H), 4.73 (s, 2H), 7.08 (d, *J*=8.2 Hz, 2H), 7.15 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.6, 160.0, 136.7, 132.9, 128.7, 127.1, 70.6, 60.6, 50.3, 28.2, 13.4; HRMS (FAB^+) calcd for $C_{15}H_{21}O_2NClS_2$: [M+1] 346.0702, found: 346.0704.

Compound **13e**: IR (film) ν_{max}/cm^{-1}: 2980, 2955, 2930, 1723, 1694; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.46 (t, 3H), 3.92 (s, 3H) 4.66 (c, 2H), 4.82 (s, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 8.03 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.7, 166.5, 160.1, 143.5, 130.0, 129.2, 125.7, 70.6, 60.7, 52.0, 50.8, 28.2, 13.4; HRMS (FAB^+) calcd for $C_{17}H_{24}NO_4S_2$: [M+1] 370.1147, found: 370.1150.

Compound **13f**: IR (film) ν_{max}/cm^{-1}: 2984, 2964, 2933, 1694; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.42 (s, 9H), 1.43 (t, 3H), 4.63 (c, 2H), 4.85 (s, 2H), 7.40 (d, *J*=8.6 Hz, 2H), 8.20 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.0, 159.8, 149.5, 145.8, 128.4, 123.1, 70.6, 60.6, 50.3, 28.8, 13.2; HRMS (FAB^+) calcd for $C_{15}H_{20}N_2O_4S_2$: [M^+] 356.4603, found: 356.4603.

Compound **16a**: IR (film) ν_{max}/cm^{-1}: 2979, 2935, 1738, 1695; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.45 (s, 9H), 1.46 (t, 3H), 4.66 (c, 2H), 4.80 (s 2H), 7.20–7.40 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.8, 160.6, 135.5, 131.4, 129.6, 128.5, 127.2, 127.0, 70.6,.60.7, 48.7, 28.1, 13.5; HRMS (FAB^+) calcd for $C_{15}H_{21}ClNO_2S_2$: [M+1] 346.0702, found: 346.0710.

Compound **16b**: IR (film) ν_{max}/cm^{-1}: 2978, 2935, 1738, 1694; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.44 (s, 9H), 1.46 (t, 3H), 4.66 (c, 2H), 4.81 (s 2H), 7.00–7.29 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.9, 161.7, 160.3, 156.8, 128.9, 128.8, 127.6, 127.5, 125.5, 125.3, 124.3, 124.2, 115.5, 115.1, 70.6, 60.6, 44.8, 44.6, 28.1, 13.5; HRMS (FAB^+) calcd for $C_{15}H_{21}FNO_2S_2$: [M+1] 330.0998, found: 330.0997.

Compound **16c**: IR (film) ν_{max}/cm^{-1}: 2964, 2934, 2871, 1689; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.46 (s, 9H), 1.46 (t, 3H), 4.66 (c, 2H), 5.15 (s 2H), 7.46–7.57 (m, 2H), 7.72 (td, *J*=8.0, 1.2 Hz, 1H), 8.14 (dd, *J*=8.2, 1.2 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.0, 160.6, 146.5, 134.4, 133.8, 128.2, 128.0, 125.4, 70.6, 60.6, 48.5, 27.9, 13.3; HRMS (FAB^+) calcd for $C_{15}H_{20}N_2O_4S_2$: [M^+] 356.4603, found: 356.4603.

Compound **19**: IR (film) ν_{max}/cm^{-1}: 2978, 2929, 1690; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.44 (s, 9H), 1.46 (t, 3H), 4.66 (c, 2H), 4.67 (s 2H), 5.96 (s, 2H), 6.62–6.80 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 207.2, 160.1, 148.1, 146.8, 132.0, 118.9, 108.4, 106.4, 101.1, 70.3,.60.7, 50.8, 28.3, 13.5; HRMS (FAB^+) calcd for $C_{16}H_{22}NO_4S_2$: [M+1] 356.0990, found: 356.0995.*Compound* **23**: IR (film) ν_{max}/cm^{-1}: 2979, 2933, 1734, 1692; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.46 (t, 3H), 4.66 (c, 2H), 4.74 (s 2H), 7.12–7.42 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 206.6, 159.9, 140.6, 130.3, 130.2, 128.7, 124.3, 122.8, 70.2, 60.7, 50.4, 28.2, 13.5; HRMS (FAB^+) calcd for $C_{15}H_{21}BrNO_2S_2$: [M+1] 390.0197, found: 390.0199.

Compound **27**: IR (film) ν_{max}/cm^{-1}: 2978, 2935, 1690; ^1H NMR (200 MHz, acetone-d_6) δ/ppm: 1.42 (t, 3H), 1.47 (s, 9H), 3.57 (s, 3H) 4.62 (c, 2H), 4.76 (s, 2H), 5.88 (d, *J*=2.8 Hz, 1H), 5.95 (dd, *J*=3.4 Hz, 2.8, 1H), 5.88 (d, *J*=2.2, 1H);[13] C RMN (50.3 MHz, acetone-d_6) δ/ppm: 209.7, 159.6, 130.3, 123.0, 107.6, 107.4, 71.3, 60.8, 45.1, 33.7, 28.2, 13.7; $EMAR_{FAB}$ Calcd. For $C_{14}H_{23}N_2O_2S_2$: [M+1] 315.1201. Found: 315.1182.

5.2. General procedure for the synthesis of isoindolin-1-ones

A deaerated solution of the corresponding xanthate (1.0 mmol) in 1,2-dichloroethane (10 mL) was heated at reflux, and 1.2 mmol of dilauroyl peroxide was added portionwise (0.3 mmol/h). After completion (4 h) the solution was cooled and the 1,2-dichloroethane evaporated under reduced pressure. In order to precipitate the by-products derived from DLP, the reaction crude was suspended in acetonitrile (10 mL). The reaction mixture was then filtered and acetonitrile was removed under reduced pressure. The residue concentrated and purified by a silica gel column chromatography (hexanes/EtOAc, 90:10) to afford the corresponding isoindolin-1-one.

Compound **11**: IR (film) ν_{max}/cm^{-1}: 3013, 2956, 2923, 2854, 1660; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.57 (s, 9H), 4.45 (s, 2H), 7.37–7.54 (m, 3H), 7.78 (dt, *J*=6.8, 1.6 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 168.8, 140.6, 134.4, 130.8, 127.7, 123.0, 122.2, 54.2, 48.4, 27.9; HRMS (FAB^+) calcd for $C_{12}H_{16}NO$: [M+1] 190.1232, found: 190.1236.

Compound **14a**: IR (film) ν_{max}/cm^{-1}: 3010, 2970, 2918, 2869, 1671; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.56 (s, 9H), 2.42 (s, 3H), 4.41 (s, 2H), 7.29 (2H), 7.58 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 169.0, 137.9, 137.7, 134.5, 131.8, 123.3, 122.0, 54.3, 48.2, 27.9, 21.3; HRMS (FAB^+) calcd for $C_{13}H_{18}NO$: [M+1] 204.1383, found: 204.1388.

Compound **14b**: IR (film) ν_{max}/cm^{-1}: 3065, 2963, 2923, 2855, 1679; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.56 (s, 9H), 3.84 (s, 3H), 4.38 (s, 2H), 7.06 (dd, *J*=8.2, 2.4 Hz, 2H), 7.29 (dd, *J*=6.0, 0.6 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 159.8, 135.7, 132.8, 123.1, 119.4, 105.7, 55.5, 54.3, 48.0, 29.6, 27.9; HRMS (FAB^+) calcd for C13H18NO2: [M+1] 220.1332, found: 20.1338.

Compound **14c**: IR (film) ν_{max}/cm^{-1}: 3061, 2980, 1671; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.56 (s, 9H), 4.41 (s, 2H), 7.29 (dd, *J*=7.4, 0.6 Hz, 1H), 7.61 (dd, *J*=8.0, 2.0 Hz, 1H) 7.90 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 167.3, 139.2, 136.5, 133.8, 126.3, 123.9, 121.9, 54.6, 48.1, 27.9; HRMS (Cl^+) calcd for $C_{12}H_{15}BrNO$: [M+1] 268.0332, found: 268.0283.

Compound **14d**: IR (film) ν_{max}/cm^{-1}: 3065, 2982, 2958, 2869, 1672; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.56 (s, 9H), 4.43 (s, 2H), 7.33 (dd, *J*=8.0, 0.6 Hz, 1H), 7.46 (dd, *J*=8.0, 2.0 Hz, 1H) 7.74 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 167.4, 138.7, 136.2, 134.1, 131.0, 123.6, 123.3, 54.6, 48.1, 27.9; HRMS (Cl^+) calcd for $C_{12}H_{14}ClNO$: [M^+] 223.0764, found: 223.0781.

Compound **14e**: IR (film) ν_{max}/cm^{-1}: 2972, 2931, 1725, 1666; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.58 (s, 9H), 3.94 (s, 3H), 4.51 (s, 2H), 7.48 (dd, *J*=7.8, 0.6 Hz, 1H), 8.20 (dd, *J*=8.2, 1.8 Hz, 1H), 8.44 (dd, *J*=0.8 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 168.1, 166.5, 145.1, 132.1, 130.3, 124.7, 122.5, 54.5, 52.2, 48.5, 27.9; HRMS (FAB^+) Calcd for C14H18NO3: [M+1] 248.1281, found: 248.1287.

Compound **17a**: IR (film) ν_{max}/cm^{-1}: 2962, 2923, 2869, 1673; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.58 (s, 9H), 4.43 (s, 2H), 7.39 (t, *J*=8.2 Hz, 1H), 7.46 (dd, *J*=8.0, 1.6 Hz, 1H), 7.68 (dd, *J*=8.0, 1.6 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 167.7, 138.6, 136.3, 130.7, 129.4, 128.6, 121.5, 54.6, 47.5, 27.9; HRMS (Cl^+) calcd for $C_{12}H_{15}ClNO$: [M+1] 224.0837, found: 224.0855.

Compound **17b**: IR (film) ν_{max}/cm^{-1}: 3072, 2970, 2924, 2868, 1676; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.57 (s, 9H), 4.50 (s, 2H), 7.17 (td, *J*=8.2, 1.0 Hz, 1H), 7.36–7.47 (m, 1H), 7.59 (dt, *J*=7.6, 1.0 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 159.7, 154.8, 130.0, 129.9, 126.8, 126.4, 119.1, 119.0, 117.6, 117.2, 54.6, 45.2, 27.9; HRMS (Cl^+) calcd for $C_{12}H_{15}FNO$: [M^+] 207.1059, found: 207.1044.

Compound **20**: IR (film) ν_{max}/cm^{-1}: 3069, 2974, 2911, 2871; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.54 (s, 9H), 4.33 (d, *J*=0.6 Hz, 2H), 6.03 (s, 2H), 6.80 (d, *J*=0.6 Hz, 1H), 7.16 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 168.5, 150.8, 147.9, 135.8, 128.3, 102.9, 102.5, 101.6, 54.3, 48.1, 28.0; HRMS (FAB^+) calcd for $C_{13}H_{16}NO_3$: [M+1] 234.1125, found: 234.1144.

Compound **21**: IR (film) ν_{max}/cm^{-1}: 2968, 2913, 2789; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.54 (s, 9H), 4.41 (d, *J*=0.8 Hz, 2H), 6.10 (s, 2H), 6.80 (dt, *J*=8.0, 1.0 Hz, 1H), 6.93 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 168.3, 148.0, 142.8, 134.0, 117.1, 114.6, 110.6, 102.4, 54.4, 48.6, 27.8; HRMS (FAB^+) calcd for $C_{13}H_{16}NO_3$: [M+1] 234.1125, found: 234.1144.

Compounds **24** and **25** mixture: IR (film) ν_{max}/cm^{-1}: 3069, 2970, 2925, 2856, 1683; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.562 (s, 9H), 1.569 (s, 9H), 4.404 (s, 2H), 4.435 (s, 2H), 7.28–7.38 (m, 3 H), 7.52–7.67 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 143.3, 142.3, 132.8, 131.7, 131.2, 125.6, 125.4, 124.5, 121.5, 118.2, 54.6, 54.5, 47.9, 47.1, 27.9; HRMS (Cl^+) calcd for $C_{12}H_{15}BrNO$: [M+1] 268.0332, found: 268.0354.

Compound **29**: IR (film) ν_{max}/cm^{-1}: 3392, 3101, 2998, 2966, 2929, 1637; ^1H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.42 (s, 9H), 3.91 (s, 3H), 6.045 (dd, *J*=4.0, 2.6 Hz, 1H), 6.432 (dd, *J*=4.0, 1.8 Hz, 1H), 6.671 (t, *J*=2.2 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 161.6, 127.4, 126.8, 110.7, 106.7, 51.1, 36.6, 29.0; $EMAR_{FAB}$ calcd for $C_{14}H_{18}NO_3$: [M+1] 180.1263. Found: 180.1282.

5.3. General procedure for the removal of the *N-tert*-butyl group

The corresponding *N-tert*-butylisoindolin-1-one was dissolved in neat trifluoroacetic acid and refluxed until the starting material was consumed indicated by TLC. The trifluoroacetic acid was then removed under reduced pressure and the residue was purified by column chromatography (hexanes/AcOEt).

Compound **34a**. A mixture of isoindolin-1-ona **11** (0.04 g, 0.211 mmol) and TFA (0.53 mL, 28 mmol) refluxed for 30 min. Product **34a** as an oil (0.028 g, 100%); IR (KBr), ν_{max} cm^{-1}: 3481, 3209, 3080, 3024, 2928, 2862, 1682; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.47 (s, 2H), 7.45 (br s, 1H, N–H), 7.45–7.60 (m, 3H), 7.88 (d, *J*=8.1, Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 171.8, 132.1, 131.8,

143.6, 131.8, 128.0, 123.8, 123.1, 45.6; HRMS (FAB^+) calcd for C_8H_8NO: [M+1] 134.0606, found: 134.0609.

Compound **34b**. A mixture of the isoindolin-1-ona **14a** (0.05 g, 0.246 mmol), and TFA (0.60 mL, 28 mmol) refluxed for 30 min. Product **34b** as a white solid (0.036 g, 100%); IR (KBr), ν_{max} cm^{-1}: 3452, 3207, 3080, 3024, 2927, 2862, 1682; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.44 (s, 3H), 4.42 (s, 2H), 7.33–7.66 (m, 2H), 7.92 (br s, 1H, N–H), 7.88 (d, J=8.1, Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 172.3, 140.9, 137.9, 132.7, 132.2, 123.8, 122.8, 45.5, 21.2; HRMS (FAB^+) calcd for $C_9H_{10}NO$: [M+1] 148.0762, found: 148.0763.

Compound **34c**. A mixture of the isoindolin-1-ona **14b** (0.031 g, 0.141 mmol), and TFA (0.35 mL, 28 mmol) refluxed for 2.5 h. Product **34c** as a white solid (0.017 g, 74%); IR (KBr), ν_{max} cm^{-1}: 3328, 3215, 3085, 3018, 2932, 2864, 1681; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.85 (s, 3H), 4.38 (s, 2H), 7.13 (dd, J=8.4, 2.34 Hz, 1H), 7.34 (d, J=7.34 Hz, 1H), 7.35 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 171.8, 160.0, 135.7, 123.9, 120.4, 106.3, 55.6, 45.3, 29,6; HMRS (FAB^+) Calcd for $C_9H_{10}NO_2$: [M+1] 164.0712, found: 164.0713.

Compound **34d**. A mixture of the isoindolin-1-ona **14c** (0.025 g, 0.093 mmol), and TFMSA (0.60 mL, 28 mmol) was refluxed for 24 h. Product **34d** as oil (0.019 g, 100%); IR (KBr), ν_{max} cm^{-1}: 3201, 3079, 2959, 2928, 2863, 1684; ^1H NMR (300 MHz, DMSO-d_6) δ/ppm:4.33 (s, 2H), 7.54 (d, J=7.8 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.77 (s, 1H) 8.70 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ/ppm: 168.4, 143.2, 134.9, 131.7, 126.0, 125.4, 120.8, 44.8; MS m/z (%): [M+2] 213 (65), [M^+] 211 (63), 167 (30), 132 (100). HMRS (FAB^+) Calcd for C_8H_6NBrO: [M+1] 211.9605, found: 211.9687.

Compound **34e**. A mixture of the isoindolin-1-ona **14d** (0.05 g, 0.246 mmol), and TFMSA (0.60 mL, 28 mmol) was refluxed for 3 h. Product **34e** (0.041 g, 100%); IR (KBr), ν_{max} cm^{-1}: 3201, 3078, 2929, 2862, 1684; ^1H NMR (300 MHz, DMSO-d_6) δ/ppm: 4.36 (s, 2H), 7.58–7.64 (m, 3H), 8.71 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ/ppm: 168.5, 142.7, 134.6, 132.6, 131.2, 125.6, 122.4, 44.7; MS m/z (%): [M+2] 169 (19), [M^+] 167 (60), 139 (26), 132 (100). HMRS (FAB^+) Calcd for C_8H_6NClO: [M+1] 168.0112, found: 168.0124.

Compound **34f**. A mixture of the isoindolin-1-ona **14e** (0.04 g, 0.161mmol), and TFMSA (0.35 mL, 28 mmol) was refluxed for 30 min. Product **34f** as a white solid (0.012 g, 42%); IR (KBr), ν_{max} cm^{-1}: 3422, 3217, 3084, 2932, 2859, 1726, 1684; ^1H NMR (300 MHz, DMSO-d_6) δ/ppm: 3.87 (s, 3H), 4.45 (s, 2H), 7.72 (d, J=8.7 Hz, 1H), 8.15 (d, J=1.8 Hz, 1H), 8.16 (dd, J=8.4, 1.6 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ/ppm: 168.9, 165.8, 149.9, 131.9, 131.6, 128.6, 124.4, 123.4, 52.4, 45.2; MS m/z (%): [M^+] 191 (48), [M–15] 176 (11), 160 (34), 132 (100). HMRS (FAB^+) Calcd for $C_{10}H_9NO_3$: [M+1] 192.0322, found: 192.0326.

*5.3.1. tert-Butylbenzylamine (**39**).* *tert*-Butylamine (0.74 mL, 14.7 mmol) was added to a solution of aldehyde **38** (1.53 g, 7.35 mmol) in anhydrous methanol (10 mL) containing molecular sieves, and the resulting mixture was stirred for 12 h at rt. The reaction mixture was then cooled in an ice bath, after which $NaBH_4$ (0.42 g, 11.0 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was filtered through a layer of Celite, the solvent was removed under reduced pressure, and the organic residue was suspended in water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the pure *tert*-butylbenzylamine **53** (1.64 g, 85%); IR (film) ν_{max}/cm^{-1}: 3316, 2970, 2870, 2743, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.18 (s, 9H), 1.30 (d, J=6.0 Hz, 6H),1.76 (N–H), 2.13 (s, 3H), 3.68 (s, 2H), 3.75 (s, 3H), 4.45 (m, 1H), 6.60 (d, J=8.4 Hz, 1H), 7.08 (d, J=8.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 157.6, 156.3, 127.2, 125.8, 121.0, 109.4, 70.5, 60.8, 50.7, 42.1, 28.9, 22.2, 9.3; $HRMS_{FAB}$ calcd for $C_{16}H_{28}NO_2$: [M+1] 266.2120, found: 266.2124.

*5.3.2. Carbamoylxanthate (**41**).* *tert*-Butylbenzylamine **39** (0.5 g, 1.88 mmol) was added to a solution at 0° C of triphosgene (0.39 g, 1.32 mmol) dissolved in CH_2Cl_2 (10.0 mL), after which Et_3N (0.89 mL, 6.41 mmol) was added dropwise. The reaction mixture was stirred for 10 min at rt and the solvent was removed under reduced pressure to give the crude carbamoyl chloride. The crude carbamoyl chloride was dissolved in acetonitrile (5.0 mL) and *O*-ethylxantic acid potassium salt (0.27 g, 0.90 mmol) was added to the resulting solution. The reaction mixture was stirred for 15 min at rt. The solvent was evaporated to dryness and the residue was treated with distilled water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude carbamoylxanthate as an oil, which was then purified by column chromatography (hexane/EtOAc, 98:2) to give the pure carbamoylxanthate **41** (0.65 g, 84%); IR (film) ν_{max}/cm^{-1}: 3369, 2977, 2934, 1692, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.33 (d, J=6.0 Hz, 6H), 1.44 (s, 9H), 1.46 (t, J=7.2 Hz, 3H), 2.21 (s, 3H), 3.70 (s, 3H), 4.50 (m, 1H), 4.66 (q, J=7.2 Hz, 2H), 4.74 (s, 2H), 6.64 (d, J=8.4 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 207.6, 160.3, 156.5, 155.6, 123.9, 122.7, 120.9, 108.7, 70.5, 70.4, 60.5, 60.2, 45.9, 28.2, 22.2, 13.5, 9.1; $HRMS_{FAB}$ calcd for $C_{20}H_{32}NO_4S_2$: [M+1] 414.1773, found: 414.1770.

*5.3.3. Isoindolin-1-one (**42**).* The carbamoylxanthate **41** (0.61 g, 1.47 mmol) was dissolved in 1,2-dichloroethane (10 mL), and the solution was warmed to reflux. DLP (0.70 g, 1.77 mmol) was added in portions of 0.3 equiv each hour to a total of 1.2 equiv After the addition of peroxide was complete, the solution was cooled and the 1,2-dichloroethane was removed under reduced pressure. To precipitate by-products derived from the DLP, the crude reaction was suspended in acetonitrile (10 mL). The reaction mixture was then filtered and acetonitrile was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 90:10) to afford the pure isoindolin-1-one **42** (0.30 g, 70%): IR (CH_3Cl) ν_{max}/cm^{-1}: 3207, 2976, 2930, 2872, 1673, 1619; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.34 (d, J=6.0 Hz 6H), 1.56 (s, 9H), 2.16 (s, 3H), 3.86 (s, 3H), 4.45 (s, 2H), 4.58 (m, 1H), 7.02 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 168.9, 157.5, 153.3, 133.5, 123.4, 123.0, 102.0, 70.6, 59.7, 54.2, 46.4, 27.9, 22.0, 9.5; $HRMS_{FAB}$ calcd for $C_{17}H_{26}NO_3$: [M+1] 292.1913, found: 292.1905.

*5.3.4. Cichorine (**35**).* Isoindolin-1-one **42** (0.047 g, 0.16 mmol) was dissolved in neat trifluoroacetic acid (5 mL) and warmed to reflux for 96 h. The trifluoroacetic acid was then removed under reduced pressure and the residue was purified by column chromatography using hexane/EtOAc (50:50) as eluent to produce the pure cichorine (0.025 g, 78%) as withe crystals, mp 216–218° (lit.[35] 215–216°): the ^1H and ^{13}C NMR spectra of **35** were identical to the published data.[28,29] ^1H NMR (300 MHz, DMSO-d_6) δ/ppm: 2.04 (s, 3H), 3.83 (s, 3H), 4.40 (s, 2H), 6.81 (s, 1H), 8.43 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ/ppm: 9.29, 43.18, 58.87, 103.05, 119.15,123.19, 132.07, 153.67, 156.55, 170.03.

*5.3.5. tert-Butylbenzylamine (**44**).* Protection of salicylaldehyde: a mixture of salicylaldehyde **43** (1.0 g, 8.19 mmol), 4-methoxybenzyl bromide (1.41 mL, 9.80 mmol), K_2CO_3 (1.13 g, 8.18 mmol), and acetone (10 mL) was refluxed for 12 h. After cooling to rt, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc/acetone (80:10:10) as eluent to produce pure the desired product (1.81 g, 91%): IR (film) ν_{max}/cm^{-1}: 3007, 2958, 2873, 2763, 1687, 1596; ^1H NMR (300 MHz, acetone-d_6) δ/ppm: 3.80 (s, 3H), 5.22 (s, 2H), 6.96 (d, J=8.7 Hz, 2H), 7.06 (t,

J=7.5 Hz, 1H), 7.30 (d, J=8.4 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 7.61 (td, J=7.2, 2.0, Hz, 1H), 7.75 (dd, J=7.8, 1.8, Hz, 2H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ/ppm: 55.51, 71.00, 114.69, 114.76, 121.60,126.09, 128.41, 129.37, 130.26, 136.75, 160.64, 162.08, 189.45; HRMS$_{FAB}$ calcd for $C_{15}H_{15}O_3^+$: [M+1] 243.1021, found: 243.1023.

tert-Butylamine (1.22 mL, 11.62 mmol) was added to a solution of the protected salicylaldehyde (1.41 g, 5.82 mmol) in anhydrous methanol (10 mL) containing molecular sieves and the resulting mixture was stirred for 12 h at rt. The reaction mixture was then cooled in an ice bath and $NaBH_4$ (0.33 g, 8.72 mmol) was added, after which the solution was stirred for 30 min. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The organic residue was suspended in water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford the pure *tert*-butylbenzylamine **44** (1.5 g, 86%): IR (film) ν_{max}/cm^{-1}: 3065, 2961, 2836, 1610, 1587, 1619; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.09 (s, 9H), 3.72 (s, 2H), 3.81 (s, 3H), 5.00 (s, 2H), 6.88–6.93 (m, 4H), 7.19 (td, J=7.8, 1.8 Hz, 1H), 7.30 (dd, J=7.2, 1.8 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 159.3, 156.8, 130.1, 129.7, 129.1, 129.0, 127.9, 120.9, 113.8, 111.6, 69.8, 55.2, 42.9, 28.9; HRMS$_{FAB}$ calcd for $C_{19}H_{26}NO_2$: [M+1] 300.1964, found: 300.1966.

*5.3.6. Carbamoylxanthate (**45**).* *tert*-Butylbenzylamine **44** (1.0 g, 3.34 mmol) was added to a solution at 0° C of triphosgene (0.39 g, 1.32 mmol) in CH_2Cl_2 (10.0 mL), and then Et_3N (1.57 mL, 11.28 mmol) was added dropwise. The reaction mixture was then stirred for 10 min at rt, after which the solvent was removed under reduced pressure to afford the crude carbamoyl chloride. The crude carbamoyl chloride was dissolved in acetonitrile (5.0 mL), and *O*-ethylxanthic acid potassium salt (0.45 g, 2.81 mmol) was added to the solution. The reaction mixture was stirred for 15 min at rt. The solvent was then evaporated to dryness and the residue was treated with distilled water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford the crude carbamoylxanthate, which was purified by column chromatography (hexane/EtOAc, 98:2) to give the pure carbamoylxanthate **45** (1.12 g, 75%); IR (KBr) ν_{max}/cm^{-1}: 2965, 2930, 2877, 2838, 1685; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.46 (t, 3H), 3.82 (s, 3H), 4.64 (c, 2H), 4.74 (s, 2H), 5.01 (s, 2H), 6.91–7.00 (m, 4H), 7.18–7.35 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ/ppm: 207.7, 160.4, 159.5, 155.0, 129.1, 128.8, 128.1, 126.7, 120.9, 120.7, 114.0, 111.6, 70.5, 69.8, 60.4, 55.2, 46.1, 28.1, 13.5; HRMS$_{FAB}$ calcd for $C_{23}H_{30}NO_4S_2$: [M+1] 448.1616, found: 448.1610.

*5.3.7. Isoindolin-1-one (**46**).* The carbamoylxanthate **45** (1.05 g, 2.34 mmol) was dissolved in 1,2-dichloroethane (10 mL) and the solution was warmed to reflux. DLP (0.10 g, 2.76 mmol) was added in portions of 0.3 equiv every hour to complete a total of 1.2 equiv After the addition of peroxide was completed, the solution was cooled and 1,2-dichloroethane was removed under reduced pressure. To precipitate by-products derived from the DLP, the crude reaction mixture was suspended in acetonitrile (10 mL). The reaction mixture was then filtered and acetonitrile was removed under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (90:10) as eluent, affording the pure isoindolin-1-one **46** (0.58 g, 78%); IR (solution) ν_{max}/cm^{-1}: 2968, 2929, 2868, 1725, 1681; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.54 (s, 9H), 3.82 (s, 3H), 4.38 (s, 2H), 5.06 (s, 2H), 6.91–7.04 (m, 4H), 7.33–7.40 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ/ppm: 168.7, 159.6, 153.5, 136.2, 129.3, 129.2, 128.4, 115.4, 114.0, 113.0, 69.9, 55.2, 54.3, 46.3, 28.0; HRMS$_{FAB}$ calcd for $C_{20}H_{24}NO_3$: [M+1] 326.1756, found: 326.1766.

*5.3.8. 4-Hydroxyisoindolin-1-one (**37**).* Isoindolin-1-one **46** (0.123 g, 0.37 mmol) was dissolved in neat trifluoroacetic acid (5 mL) and refluxed for 48 h. The trifluoroacetic acid was then removed under reduced pressure and the residue was purified by column chromatography using hexane/EtOAc (50:50) as eluent, affording the pure 4-hydroxyisoindolin-1-one **37** (0.82 g, 92%); the ^{1}H and ^{13}C NMR spectra of **37** were identical to the published data.[30] ^{1}H NMR (300 MHz, CD_3OD) δ/ppm: 4.34 (s, 2H), 6.98 (dd, J=7.5, 1.2 Hz, 1H), 7.26 (dd, J=7.5, 1.2 Hz, 1H), 7.31 (t, J=7.5, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ/ppm: 174.0, 154.1, 134.8, 131.5, 130.5, 119.0, 115.3, 44.6.

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.003. These data include MOL files and InChiKeys of the most important compounds described in this article.

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