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Carbamoyl radicals from carbamoylxanthates: a facile entry into isoindolin-1-ones

Germán López-Valdez, Simón Olguín-Uribe and Luis D. Miranda*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior S.N., Ciudad Universitaria, Coyoacan, México D.F. 04510, Mexico

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Abstract—It has been found that carbamoylxanthates derived from secondary *t*-butyl amines are stable compounds which function as efficient sources of carbamoyl radicals. The carbamoylxanthates derived from *t*-butylbenzylamines can be efficiently transformed into 2-*t*-butylisoindolin-1-ones via an oxidative radical cyclization process. The carbamoylxanthates derived from *N*-*t*-butylamino olefins underwent the expected cyclization/xanthate-transfer process to afford the corresponding pyrrolidones and piperidones under thermally induced DLP fragmentation conditions and in the presence of catalytic Et_3B in air, at room temperature.

Acyl radicals can be grouped into three major classes: alkanoyl radicals **1**, alkoxycarbonyl radicals **2**, and carbamoyl radicals **3** (Fig. 1).[1] Alkanoyl radicals easily lose carbon monoxide to produce an alkyl radical, nevertheless this class of radicals is by far the most extensively studied, and has been used for synthetic purposes.[1] Alkoxylcarbonyl radicals also ought to be prone to fragmentation (loss of carbon dioxide), but these species have received little attention. Carbamoyl radicals **3**, which should be comparatively long lived species, since decarbonylation would afford high energy aminyl radicals, have been considerably less studied than have alkanoyl radicals **1**. Presumably, the paucity of convenient methods of generating **3** has been a factor contributing to this situation. Nevertheless, carbamoyl radical additions to double bonds,[2] aromatic systems,[3] and oxime ethers[4] have been reported. The synthetic potential of these radicals has been recently illustrated in the synthesis of the complex natural product stephacidin B.[5]

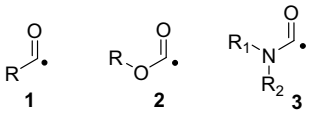

Figure 1. Acyl radicals.

In connection with our studies on the addition of alkyl and acyl radicals to aromatic and heteroaromatic systems,[6] it became of interest to examine the feasibility of effecting oxidative cyclization of carbamoyl radicals onto aromatic systems. Given the versatility of alkyl radical generation from dithiocarbonates, developed by Zard et al.[7] we entertained the possibility of using the related carbamoyl xanthates (carbamoyldithiocarbonates) as carbamoyl radical sources.[8] We fully recognized that such species might have stability problems and could lose carbon oxysulfide to generate thiocarbamates.[2g] Indeed, Grainger and Innocenti[2g] recently encountered this problem and resorted to the use of the more stable carbamoyldithiocarbamates as carbamoyl radical sources. Our endeavors in this area commenced with the reaction of the carbamoyl chlorides **5a–c** (Scheme 1) with potassium ethyl xanthate (0.9 equiv; see Ref. 7c for rationalization) in acetonitrile at room temperature. Whereas carbamoyl xanthates **6a** and **6b** were very unstable and rapidly decomposed to complex mixtures, the *N*-*t*-butyl substituted congener **6c** was isolated as a remarkably stable, crystalline compound, the structure of which was verified by X-ray crystallography (Fig. 2).[9] Indeed, **6c** remained unchanged after two hours in chlorobenzene at reflux temperature. When **6c** was, however, submitted to one of the typical Zard radical generation conditions, that is, portionwise addition of 1.2 equiv of lauroyl peroxide to a refluxing solution in 1,2-dichlorethane, isoindolinone **9** was isolated as the only product in good yield

* Corresponding author. Tel.: +52 55 56 22 44 40; fax: +52 55 56 16 22 17; e-mail: lmiranda@servidor.unam.mx

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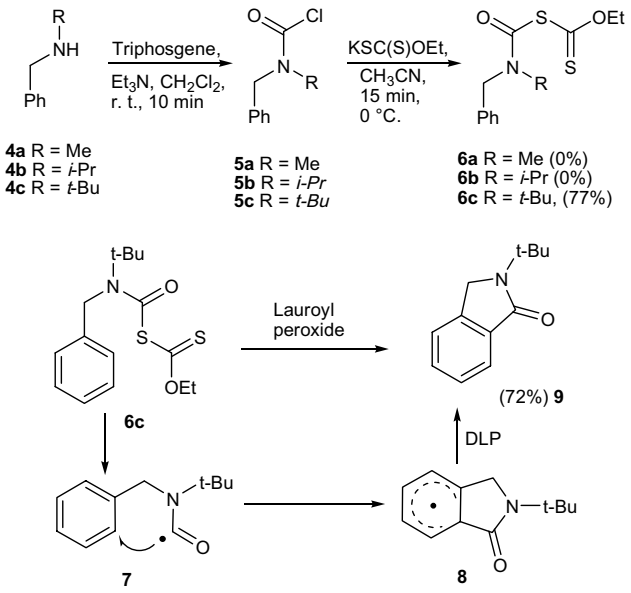


Scheme 1. Preparation and radical reaction of carbamoyl xanthate **6c**.

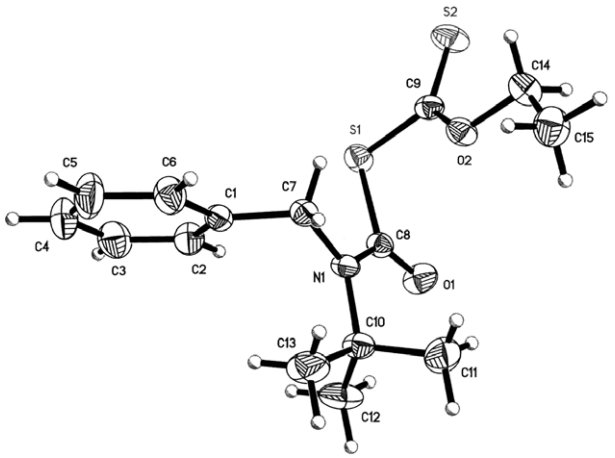


Figure 2. Computer generated perspective drawing of **6c**.

(Scheme 1).[10] Thus, the generation of carbamoyl radical **7**, its cyclization to **8**, and the dilauroyl peroxide (DLP) mediated oxidation[6a,b] of radical **8** to isoindolinone **9** all must take place with high efficiency.

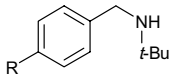
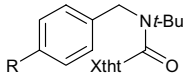
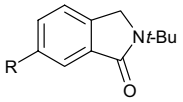
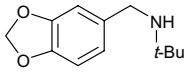
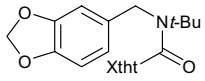
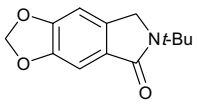
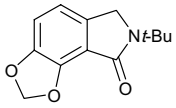
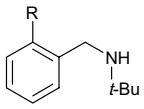
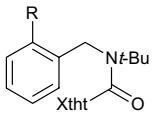
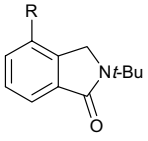
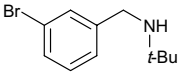
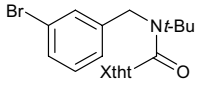
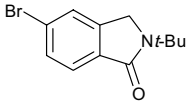
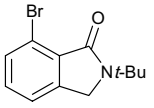
On the basis of this observation, several ring substituted *t*-butylbenzylamines were converted into the corresponding stable and isolable carbamoyl xanthates, which were then subjected to the above carbamoyl radical generation conditions. In every case the ring substituted *N*-*t*-butylisoindolinone was obtained in excellent yield (Table 1, entry 1), independent of the nature of the benzenoid substituent(s). Interestingly, 3,4-methylenedioxy compound **26** and 3-bromo compound **36** gave mixtures of isoindolinones in which the products derived from cyclization at C-6, the less hindered position (**27** and **37**, respectively), were only slightly favored over those derived from attack at C-2 (**28** and **38**, respectively). The data in Table 1 convincingly show that a variety of structurally diverse isoindolinones, a relatively rare class of compounds, are now readily available.

Furthermore, we realized that the *N*-unsubstituted congeners ought to be accessible by the removal of the *t*-butyl group in acidic media. One of the reported[11] conditions (catalytic trifluoromethanesulfonic acid; TFMSA) failed, however, to effect this transformation. Nevertheless, after some experimentation it was found that the removal of the *N*-*t*-butyl moiety from compounds **9** and **20**–**24** was accomplished simply by stirring solutions thereof in neat TFMSA at room temperature or neat trifluoroacetic acid (TFA) at reflux temperature. The trifluoroacetic acid procedure gave NH isoindolones **39**–**44** in excellent yields (Table 2) including compounds **43** and **44**, which were obtained somewhat less efficiently by the TFMSA procedure. It is worth pointing out that the NH isoindolinones are potential isoindole precursors whose utility in Diels–Alder reactions is well established.[12] In addition, many isoindolinone derivatives possess a variety of significant biological activities, including antidopaminergic and protein kinase inhibiting activities.[13]

How does the *N*-*t*-butyl group confer such notable stability upon the carbamoyl xanthates? This stability may be a consequence of conformational effects (fixed conformation and a high NCO rotational barrier) or steric hindrance in the vicinity of the NCO moiety, but at the present time we have no convincing data in this regard. Why do the *N*-*t*-butylcarbamoyl radicals derived from the above carbamoylxanthates undergo such efficient oxidative cyclization, which with one exception [3f] has not been observed before, even in substrates where it might have been expected to occur?[2c,g] In all of the previously reported substrates the carbamoyl radical could select between intramolecular addition to a double bond or to the *ortho* sites of a benzenoid nucleus. Radical addition to a double bond is generally a lower energy process and is expected to be favored over addition to an aromatic system. We are currently studying the synthetic consequences of, and the mechanistic questions which have been raised by the results described above.

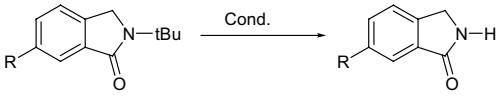
To further explore the potential utility of the *t*-butylcarbamoylxanthates, we examined the possibility of intramolecular addition of the derived carbamoyl radicals to a double bond. We were pleased to observe that the *N*-*t*-butylamino olefins **45** and **46** gave the thermally stable carbamoylxanthates **47** and **48,** respectively (Scheme 2). These compounds underwent the expected cyclization/xanthate-transfer process to afford the corresponding pyrrolidone **49** and piperidone **50** under thermally induced DLP fragmentation conditions. The γ-lactam **49** was obtained in slightly lower yield (76%) than that observed with the related dithiocarbamate reported before (80%).[2g] The reaction of xanthate **68** under the same conditions, afforded piperidone **50** in 62%, as the only product (Scheme 2). In contrast, in the similar reported experiment (using a related dithiocarbamate), a mixture (8.4:1) of the piperidone derivative and a seven-membered lactam (formed by a *7-endo* cyclization), was obtained in 65% yield.[2g] In addition, products **49** and **50** could also be generated at room temperature from xanthates **47** and **48**, albeit

Table 1. Synthesis of 2-*t*-butylisoindolin-1-ones from *t*-butylbenzylamines

Entry	Amine	Xanthate[a]	Product
1	 **10** R = Me **11** R = Cl **12** R = Br **13** R = OMe **14** R = COOMe	 **15** R = Me (81%) **16** R = Cl (71%) **17** R = Br (82%) **18** R = OMe (80%) **19** R = COOMe (85%)	 **20** R = Me (77%) **21** R = Cl (86%) **22** R = Br (92%) **23** R = OMe (72%) **24** R = COOMe (91%)
2	 **25**	 **26** (85%)	 **27** (44%)  **28** (36%)
3	 **29** R = Cl **30** R = F	 **31** R = Cl (84%) **32** R = F (65%)	 **33** R = Cl (85%) **34** R = F (90%)
4	 **35**	 **36** (60%)	 **37** (49%)  **38** (33%)

[a] Xtht = SC(S)OEt.

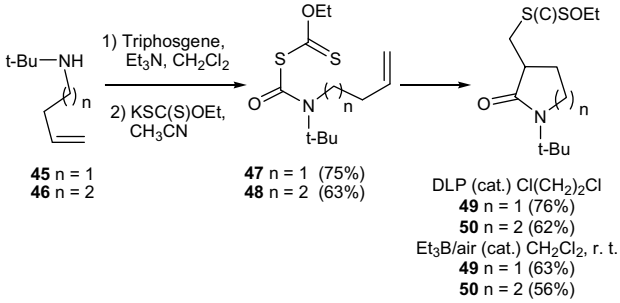
Table 2. Removal of the *t*-butyl group



	Subs.	R	Prod.	Cond. A		Cond. B	
				Time (h)	Yield	Time (h)	Yield
1	**9**	H	**39**	0.5	98	72	100
2	**20**	Me	**40**	0.5	97	72	100
3	**21**	Cl	**41**	24	100	72	100
4	**22**	Br	**42**	24	100	72	100
5	**23**	OMe	**43**	3	74	96	96
6	**24**	CO_2Me	**44**	0.5	42	96	95

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

in somewhat lower yields, by means of catalytic triethyl borane in an aerial atmosphere.



Scheme 2. Cyclization of carbamoyl radicals onto C–C double bonds.[2g]

In summary, we have demonstrated that carbamoylxanthates derived from secondary *t*-butyl-amines are stable compounds that serve as efficient sources of carbamoyl radicals both by thermally induced DLP

fragmentation and at room temperature in the presence of catalytic Et_3B in air. Carbamoylxanthates derived from *t*-butyl-benzylamines are transformed into 2-*t*-butylisoindolin-1-ones by oxidative radical cyclization of the derived carbamoyl radical onto the benzenoid system, a process scarcely exploited so far.

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References and notes

1. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
2. (a) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1989**, *30*, 3229; (b) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369; (c) Bella, A. F.; Jackson, L. V.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1839; (d) Bella, A. F.; Jackson, L. V.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 421; (e) Scanlan, E. M.; Slawin, A. M. Z.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 716; (f) Ribby, J. H.; Danca, D. M.; Horner, J. H. *Tetrahedron Lett.* **1998**, *39*, 8413; (g) Grainger, R. S.; Innocenti, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3445.
3. (a) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Gian, F. *Chem. Commun.* **2002**, 2496; (b) Biyouki, M. A. A.; Smith, R. A. J.; Bedford, J. J.; Leader, J. P. *Synth. Commun.* **1998**, *28*, 3817; (c) Nagata, K.; Itoh, T.; Okada, M.; Takahashi, O. A. *Heterocycles* **1991**, *32*, 2015; (d) Leardini, R.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3164; (e) Minisci, F.; Gardini, G. P.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, *1*, 15; (f) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430.
4. DiLabio, G. A.; Scanlan, E. M.; Walton, J. C. *Org. Lett.* **2005**, *7*, 155.
5. Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342.
6. (a) Osornio, Y. M.; Cruz-Almanza, R.; Jiménez-Montaño, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316; (b) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Osornio, Y. M.; Muchowski, J. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001; (c) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153.
7. (a) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201; (b) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley VCH: Weinhem, 2001; p 90; (c) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672.
8. For generation of alkoxycarbonyl radical from *S*-acylxanthates see: Forbes, J. E.; Saicic, R. N.; Zard, S. Z. *Tetrahedron* **1999**, *55*, 3791.
9. *General procedure for the preparation of carbamoylxanthates*. To a stirred solution of triphosgene (0.7 mmol) in CH_2Cl_2 (5.0 mL), at 5 °C the corresponding *t*-butylbenzylamine (1.0 mmol) was added, followed by dropwise addition of Et_3N (3.4 mmol). The mixture was stirred for 10 min at room temperature. 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 room temperature, 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. *Selected spectral data.* Compound (**6c**): A yellow oil; IR (film) cm^{-1} *v*: 2983, 2967, 2933, 1679; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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 (**15**): A yellow oil, IR (film) cm^{-1} *v*: 2978, 2927, 1691; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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 (**16**): A yellow oil; IR (film) cm^{-1} *v*: 2979, 2933, 1692; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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 (**17**): A yellow oil; IR (film) cm^{-1} *v*: 2976, 2932, 1692; ^1H NMR (200 MHz, $CDCl_3$): δ 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, CDCl3): δ 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 (**18**): IR (film) cm^{-1} *v*: 2978, 2934, 1690; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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 (**19**): A yellow oil; IR (film) cm^{-1} *v*: 2980, 2955, 2930, 1723, 1694; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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.
10. *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 residue was purified by a silica gel column chromatography (Hexanes/EtOAc, 90:10) to afford the corresponding isoindolin-1-one. *Selected spectral data.* Compound (**9**): A yellowish solid; IR (film) cm^{-1} *v*: 3013, 2956, 2923, 2854, 1660; ^1H NMR (200 MHz, $CDCl_3$): δ 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 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 (**20**): A yellowish solid; IR (film) cm^{-1} *v*: 3010, 2970, 2918, 2869, 1671; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 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 (**21**): A yellowish solid; IR (film) cm^{-1} *v*: 3065, 2982, 2958, 2869, 1672; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 167.4, 138.7, 136.2, 134.1, 131.0, 123.6, 123.3, 54.6, 48.1, 27.9; HRMS (CI+) calcd for $C_{12}H_{14}ClNO$: [M+] 223.0764, found: 223.0781. Compound (**22**): A yellowish solid; IR (film) cm^{-1} *v*: 3061, 2980, 1671; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 167.3, 139.2, 136.5, 133.8, 126.3, 123.9, 121.9, 54.6, 48.1, 27.9; HRMS (CI+) calcd for $C_{12}H_{15}BrNO$: [M+1] 268.0332, found: 268.0283. Compound (**23**): A yellowish solid; IR (film) cm^{-1} *v*: 3065, 2963, 2923, 2855, 1679; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 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 $C_{13}H_{18}NO_2$: [M+1] 220.1332, found: 220.1338. Compound (**24**): A yellowish solid; IR (film) cm^{-1} *v*: 2972, 2931, 1725, 1666; ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 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 $C_{14}H_{18}NO_3$: [M+1] 248.1281, found: 248.1287.

11. Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G. *Synlett* **1990**, 621.
12. For reviews in the field see: (a) Donohoe, T. J. *Sci. Synth.* **2001**, *10*, 653; (b) Bonnett, R.; North, S. A. *Adv. Hetrocycl. Chem.* **1981**, *29*, 341.
13. (a) Bellioti, T. R.; Wustrow, D. J. U.S. Patent 6,087,364, 2000; *Chem. Abstr.* **2000**, *133*, 89548; (b) Hudkins, R. L.; Reddy, D.; Singh, J.; Stripathy, R.; Underiner, T. L. PCT Int. Appl., WO 0047583, 2000; . *Chem. Abstr.* **2000**, *133*, 177158; (c) Duggan, M. E.; Hartman, G. D.; Hoffman, W. F. PCT Int. Appl., WO 9737655, 1997; *Chem. Abstr.* **1997**, *127*, 331749; (d) Sugimoto, H.; Tsuchiya, Y.; Sugumi, H.; Higurashi, K.; Karibe, N.; Iimura, Y.; Sasaki, A.; Araki, S.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1992**, *35*, 4542; (e) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1992**, *35*, 4613.