Synthesis of Functionalized 1-Benzoxepins by Tandem Ring-Opening/Cyclocondensation of 3-Bromoisoxazoles

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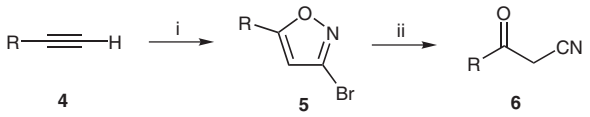
Abstract: A series of functionalized 1-benzoxepins were synthesized by way of a tandem ring-opening/cyclocondensation of aldehyde-containing 3-bromoisoxazoles.

Key words: benzoxepin, isoxazoles, reductive ring-opening, ferrous chloride, cyclocondensation

The construction of heterocycles occupies a central place in the synthesis of biologically interesting natural and unnatural products. In particular, interest in the synthesis of seven-membered oxacycles has steadily increased, in part due to their occurrence in a variety of natural and unnatural biologically active compounds.[1] An array of different methods have been employed for synthesis of this class heterocycles, these include reactions driven by anions, cations, radicals as well as metal-mediated ring-closures.[2] Of particular interest in our group are a number of biologically active compounds containing the seven-membered 2,3,4,5-tetrahydro-1-benzoxepin (**1**) ring skeleton. These natural products include pterulone (**2**) and related compounds,[3] which demonstrate antifungal and ubiquinone oxidoreductase inhibiting properties, as well as heliannuol C (**3**) (Figure 1).[4] Herein, we would like to report our initial investigations into the synthesis of the 1-benzoxepin ring system by way of a tandem ring-opening/cyclocondensation of 3-bromoisoxazoles.

Recently, we demonstrated that 3-bromoisoxazoles **5** can be reductively opened to give β-ketonitriles **6** in good to moderate yields by treatment with molybdenum hexacarbonyl or ferrous chloride tetrahydrate (Scheme 1).[5] These isoxazoles can be synthesized in good yields from the corresponding alkynes **4** and dibromoformaldoxime and have shown stability to a variety of reagents, making them versatile synthetic intermediates.[6]



4 5 6

Scheme 1 *Reagents and conditions*: i) Br_2CNOH, $NaHCO_3$, CH_2Cl_2, r.t.; ii) $FeCl_2{\cdot}4H_2O$, MeCN, r.t.

β-Cyanoketones have been shown to be useful synthetic precursors, as they readily undergo a variety of condensation reactions. With both our ring-opening and the reactivity of β-cyanoketones in mind, we envisioned the possibility of a tandem ring-opening/cyclocondensation sequence as shown in Figure 2. Ring-opening of the bromoisoxazole derivative **7**, substituted with a carbonyl tether, would initially give the β-ketonitrile **8**. This β-ketonitrile could then undergo an intramolecular condensation to give hydroxyketone **9**, which would readily undergo dehydration to give the cyclic unsaturated cyanoketone **10**. Unsaturated cyanoketones of this type have been shown to be versatile synthetic intermediates, as they readily undergo [4+2] cycloadditions[7] and Michael addition/oxidative cyclization.[8]

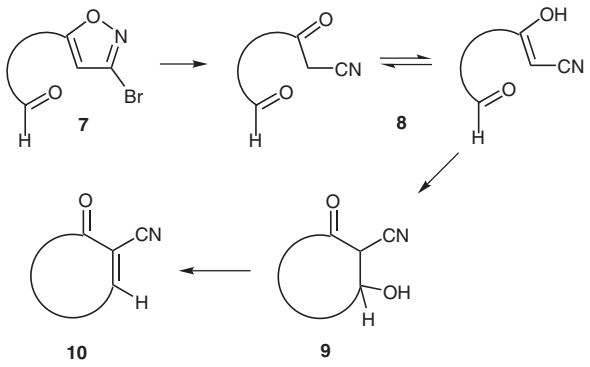


Figure 2 Tandem ring-opening/cyclocondensation sequence.

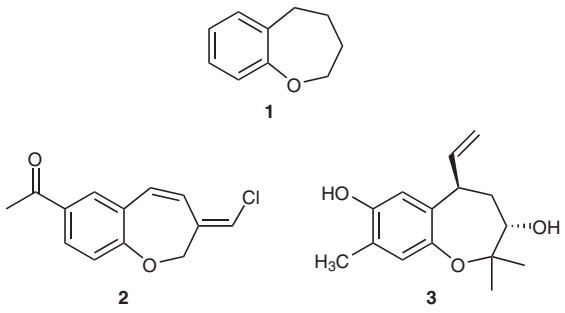


Figure 1 2,3,4,5-Tetrahydro-1-benzoxepin (**1**) and related natural products, pterlulone (**2**) and heliannuol C (**3**).

The use of intramolecular condensations of activated methylene compounds to construct carbocycles and heterocycles has been previously reported. The ozonolysis of unsaturated ketonitriles have been shown to give

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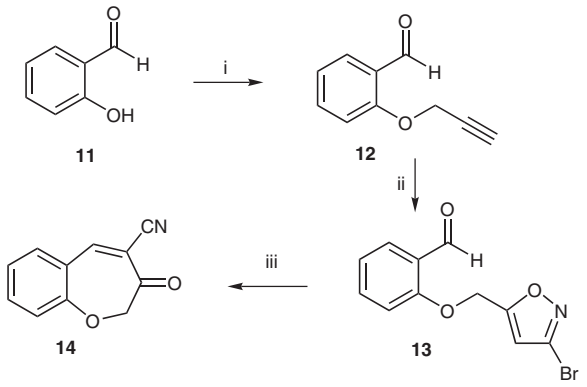
α-cyanoalkenones, by way of the aldehyde intermediate.[9] Similarly, the titanium-mediated intramolecular condensation between β-ketoesters and acetals has been reported.[10]

With our interest in the benzoxepin ring system in mind, we investigated the application of this tandem methodology to their synthesis. The synthesis of the desired 3-bromoisoxazole precursors was accomplished in two steps from the appropriately substituted salicylaldehydes. Initially, salicylaldehyde (**11**) was alkylated with a propargyl tosylate followed by reaction of resulting alkyne **12** with dibromoformaldoxime to give the desired 3-bromoisoxazole **13** in 86% yield. The tandem ring-opening/cyclocondensation sequence was then facilitated by treatment of the isoxazoles with ferrous chloride tetrahydrate to give 4-cyano-1-benzoxepin-3(2*H*)-one (**14**) in 76% yield (Scheme 2). Attempts to facilitate this tandem reaction with $Mo(CO)_6$, produced a mixture of products, the major being the ring-opened β-ketonitrile, with no evidence for the 1-benzoxepin.

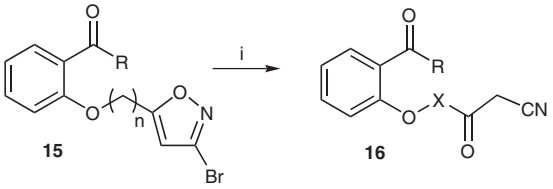


Scheme 2 *Reagents and conditions*: i) propargyl tosylate, K_2CO_3, DMF, r.t.; ii) Br_2CNOH, K_2CO_3, CH_2Cl_2, r.t.; iii) $FeCl_2{\cdot}4H_2O$, MeCN, r.t.

A series of bromoisoxazole precursors were synthesized as described above starting with substituted salicylaldehydes and the appropriate propargyl tosylates.[11] With the exception of **12b**, the propargyl ethers **12a–f** have been previously reported.[12] The compounds were then subjected to the ring-opening conditions with ferrous chloride, the results of which are shown in Table 1.[13] All the bromoisoxazoles and 1-benzoxepins gave satisfactory IR, ^{1}H NMR and elemental analysis.

In all cases, the compounds underwent tandem ring-opening/cyclocondensation to yield the benzoxepins in good yields. Substitution of the aromatic ring proved to have little effect on the cyclization as a number of substituted benzoxepins were synthesized. In addition, the synthesis of benzoxepins with substitution at the 2-position of the oxepin ring, **14e** and **14f**, was shown to proceed in good yields.

Attempts to apply this tandem reaction sequence to a ketone derivative **15a**, as well as compounds with longer tethers, **15b** and **15c**, proved unsuccessful. In the case of **15a**, the isoxazole opened cleanly giving ketonitrile **16a** in 70% yield, however, the condensation failed to take place under the reaction conditions. In the case of **15b** and **15c**, a mixture of products was formed, NMR analysis indicated the presence of the ketonitriles **16b** or **16c**, but none of the expected eight- or nine-membered cyclic ethers were observed (Scheme 3).



a R = CH_3; n = 1
b R = H; n = 2
c R = H; n = 3

Scheme 3 *Reagents and conditions*: i) $FeCl_2{\cdot}4H_2O$, MeCN, r.t.

In conclusion, we have demonstrated the facile synthesis of the 2,3-dihydroxy-1-benzoxepin ring system from salicylaldehyde derivatives, by way of a novel tandem ring-opening/cyclocondensation of 3-bromoisoxazoles. The versatility of this method is demonstrated by the synthesis of a number of substituted benzoxepin derivatives. The high degree of functionality in this unsaturated cyanoketone ring makes these compounds ideal precursors to highly functionalized benzoxepins. In addition, this short synthetic sequence has the advantage of starting with readily available salicylaldehyde derivatives. Further investigations will focus on the application of this methodology to natural products containing this ring system as well as applying it to carbocycles and other heterocyclic ring systems.

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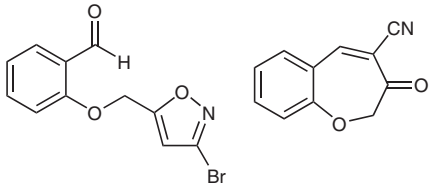
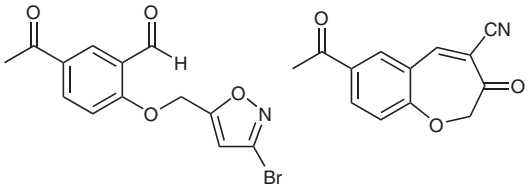
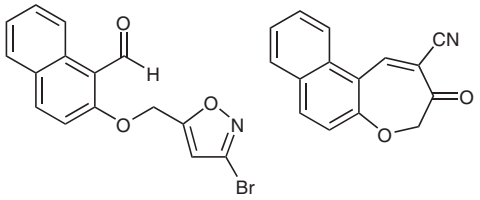
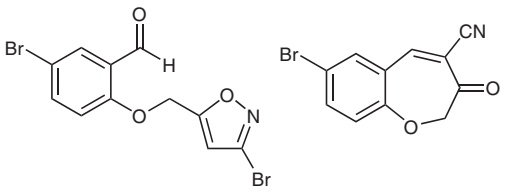
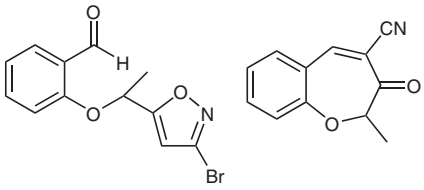
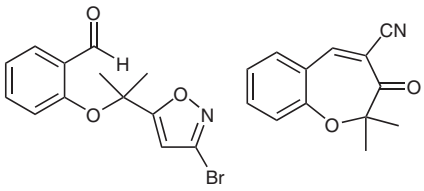
References

(1) For the isolation of some representative compounds see: (a) Kakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y.; Hirata, Y. *Chem. Lett.* **1985**, *6*, 713. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R. *J. Org. Chem.* **1982**, *47*, 1310. (c) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081. (d) Aydogmus, Z.; Imre, S.; Ersoy, L.; Wray, V. *Nat. Prod. Res.* **2004**, *18*, 43. (e) Guella, G.; Pietra, F. *Helv. Chim. Acta* **1991**, *74*, 47. (f) Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 303. (g) Suzuki, M.; Mizuno, Y.; Matsuo, Y.; Masuda, M. *Phytochemistry* **1996**, *43*, 121. (h) Aydogmus, Z.; Imre, S.; Ersoy, L.; Wray, V. *Nat. Prod. Res.* **2004**, *18*, 43.

Table 1 Synthesis of 3-Bromoisoxazoles **13** and Substituted Benzoxepins **14**

Entry	Bromoisoxazole **13**/Benzoxepin **14**	Yield of **13** (%)	Yield of **14** (%)
a		86	76
b		83	67
c		85	82
d		78	70
e		82	70
f		79	65

(2) (a) For a general review see: Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631. (b) For recent examples see: Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867. (c) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263. (d) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385. (e) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 6299. (f) Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867. (g) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385. (h) Lecornue, F.; Ollivier, J. *Org. Biomol. Chem.* **2003**, *1*, 3600.

(3) (a) Lemaire, P.; Balme, G.; Desbordes, P.; Vors, J. *Org. Biomol. Chem.* **2003**, *1*, 4209. (b) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203. (c) Gruijters, B. W. T.; Van Veldhuizen, A.; Weijers, C. A. G. M.; Wijnberg, J. B. P. A. *J. Nat. Prod.* **2002**, *65*, 558. (d) Huang, S. T.; Kuo, H. S.; Chen, C. T. *Tetrahedron Lett.* **2001**, *42*, 7473. (e) Kahnberg, P.; Sterner, O. *Tetrahedron* **2001**, *57*, 7181. (f) Engler, M.; Anke, T.; Sterner, O. *J. Antibiotics* **1997**, *50*, 330. (g) Engler, M.; Anke, T.; Sterner, O.; Brandt, U. *J. Antibiotics* **1997**, *50*, 325.

(4) (a) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 983. (b) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461. (c) Kishuku, H.; Yoshimura, T.; Kakehashi, T.; Shindo, M.; Shishido, K. *Heterocycles* **2003**, *61*, 125. (d) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 2047. (e) Kamei, T.; Shindo, M.; Shishido, K. *Synlett* **2003**, *15*, 2395. (f) Kamei, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2003**, *44*, 8505. (g) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron* **2003**, *59*, 8375. (h) Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350. (i) Doi, F.; Ogamino, T.; Sugai, T.; Nishiyama, S. *Tetrahedron Lett.* **2003**, *44*, 4877. (j) Doi, F.; Ogamino, T.;

Sugai, T.; Nishiyama, S. *Synlett* **2003**, 411. (k) Macias, F. A.; Chinchilla, D.; Molinillo, J. M. G.; Marin, D.; Varela, R. M.; Torres, A. *Tetrahedron* **2003**, *59*, 1679. (l) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Chem. Commun.* **2002**, 634. (m) Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309. (n) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807. (o) Grimm, E. L.; Levack, S.; Trimble, L. A. *Tetrahedron Lett.* **1994**, *35*, 6847.

(5) Kociolek, M. G.; Straub, N. G.; Marton, E. J. *Lett. Org. Chem.* **2004**, in press.

(6) For the synthesis of dibromoformaldoxime and its reaction with alkynes see: Rohloff, J. C.; Robinson, J. III; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113.

(7) Zhu, J.; Shia, K.; Liu, H. *Chem. Commun.* **2000**, 1599.

(8) Kung, L.; Tu, C.; Shia, K.; Liu, H. *Chem. Commun.* **2003**, 2490.

(9) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1999**, *64*, 2830.

(10) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849.

(11) **Typical Procedure:**
Propargyl tosylate (2.10 g, 10 mmol) and salicylaldehyde (**11**, 1.05 g, 10 mmol) were dissolved in dry DMF (15 mL) at r.t. K_2CO_3 (2.76 g, 20 mmol) was added and the reaction stirred at r.t. for 18 h. The reaction was poured into H_2O (50 mL) and extracted with Et_2O (3 × 25 mL). The combined ether layers were dried ($MgSO_4$) and evaporated giving propargyl ether **12a** as a white solid (1.36 g, 85%), which gave satisfactory ^{1}H NMR data and was used without further purification.
Compound **12b** previously unreported: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.51 (s, 1 H), 8.43 (d, *J* = 2.2 Hz, 1 H), 8.25 (dd, *J* = 2.2, 9.1 Hz, 1 H), 7.21 (d, *J* = 9.1 Hz, 1 H), 4.92 (d, *J* = 2.1 Hz, 2 H), 2.60 (m, 4 H).
Compound **12a** (1.36 g, 8.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and K_2CO_3 (42.5 mmol) was added. Dibromoformaldoxime (1.72 g, 8.5 mmol) dissolved in CH_2Cl_2 (30 mL) was added dropwise over 20 h via syringe pump. The reaction was poured into 1 M HCl (100 mL) and the layers separated. The aqueous layer was extracted with additional CH_2Cl_2 (50 mL) and the combined organic layers dried (Na_2SO_4) and evaporated leaving a yellow oil which was purified by column chromatography (silica gel; hexanes–EtOAc) giving **13a** as a light yellow solid (2.06 g, 86% yield).
Compound **13a**: light yellow solid; mp 95–96 °C. IR (KBr): 3139, 1688, 1597 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1 H), 7.92–6.97 (m, 4 H), 6.53 (s, 1 H), 5.30 (s, 2 H). Anal. Calcd for $C_{11}H_8BrNO_3$: C, 46.84; H, 2.86; N, 4.97. Found: C, 46.95; H, 2.99; N, 4.89.
Compound **13b**: white solid; mp 144–145 °C. IR (KBr): 3138, 1692, 1669, 1594 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.47 (s, 1 H), 8.43 (d, *J* = 2.2 Hz, 1 H), 8.25 (dd, *J* = 2.2, 9.1 Hz, 1 H), 7.21 (d, *J* = 9.1 Hz, 1 H), 6.55 (s, 1 H), 5.40 (s, 2 H), 2.61 (s, 3 H). Anal. Calcd for $C_{13}H_{10}BrNO_4$: C, 48.17; H, 3.11; N, 4.32. Found: C, 47.90; H, 3.20; N, 4.34.
Compound **13c**: white solid; mp 147–149 °C. IR (KBr): 3153, 1665, 1619, 1592 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.80 (s, 1 H), 9.25–9.09 (m, 1 H), 8.19–7.28 (m, 5 H), 6.64 (s, 1 H), 5.41 (s, 2 H). Anal. Calcd for $C_{15}H_{10}BrNO_3$: C, 54.24; H, 3.03; N, 4.22. Found: C, 53.96; H, 3.15; N, 4.19.
Compound **13d**: white solid; mp 119–120 °C. IR (KBr): 3146, 1687, 1589 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 7.95 (d, *J* = 2.3 Hz, 1 H), 7.66 (dd, *J* = 2.3, 9.2 Hz, 1 H), 6.92 (d, *J* = 2.3 Hz, 1 H), 6.48 (s, 1 H), 5.27 (s, 2 H). Anal. Calcd for $C_{11}H_7Br_2NO_3$: C, 36.60; H, 1.95; N, 3.88. Found: C, 36.72; H, 2.03; N, 3.88.
Compound **13e**: colorless oil. IR (KBr): 3129, 1687, 1598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.49 (s, 1 H), 7.93–6.90 (m, 4 H), 6.36 (s, 1 H), 5.62 (q, *J* = 6.7 Hz, 1 H), 1.78 (d, *J* = 6.7 Hz, 3 H). Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.74; H, 3.50; N, 4.75.
Compound **13f**: Colorless oil. IR (KBr): 3126, 1686, 1597 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1 H), 7.92–6.98 (m, 4 H), 6.42 (s, 1 H), 1.82 (s, 6 H). Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; N, 4.52. Found: C, 50.16; H, 4.16; N, 4.77.

(12) (a) Janietz, D.; Rudorf, W. D. *Tetrahedron* **1989**, *45*, 1661. (b) Mathur, S. S.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2479. (c) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44*, 8417. (d) Godrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.

(13) **Typical Procedure:**
Bromoisoxazole **13** (0.28 g, 1 mmol) was dissolved in MeCN (25 mL). Nitrogen was bubbled through the solution for 15 min after which $FeCl_2{\cdot}4H_2O$ (0.50 g, 2.5 mmol) was added and stirred at r.t. under nitrogen for 18 h. The reaction was then filtered through Celite and evaporated; the residue was purified by column chromatography (silica gel; hexanes–EtOAc) to give **14** as a yellow solid (0.14 g, 76%).
Compound **14a**: yellow solid; mp 162–163 °C. IR (KBr): 2227, 1676, 1603, 1559 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.15–7.60 (m, 4 H), 4.64 (s, 2 H). Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.63; H, 3.92; N, 7.49.
Compound **14b**: yellow solid; mp 186–187 °C. IR (KBr): 2225, 1677, 1601, 1565 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–8.25 (m, 3 H), 7.31 (d, *J* = 9.2 Hz, 1 H), 4.71 (s, 1 H), 2.63 (s, 3 H). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.60; H, 4.18; N, 6.14.
Compound **14c**: yellow solid; mp 150 °C (sub). IR (KBr): 2224, 1679, 1616, 1591, 1554 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 7.26–8.13 (m, 6 H), 4.71 (s, 2 H). Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.17; H, 4.07; N, 6.02.
Compound **14d**: yellow solid; mp 120–122 °C. IR (KBr): 2225, 1682, 1599, 1550 cm^{-1}. ^{1}H NMR (400 MHz, CD_3CN): δ = 7.75 (s, 1 H), 7.34–7.53 (m, 2 H), 6.89 (d, *J* = 9.1 Hz, 1 H), 4.41 (s, 2 H). Anal. Calcd for $C_{11}H_6BrNO_2$: C, 50.03; H, 2.29; N, 5.30. Found: C, 49.71; H, 2.41; N, 5.23.
Compound **14e**: yellow solid; mp 130–131 °C. IR (KBr): 2226, 1687, 1604, 1560 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.15–7.60 (m, 4 H), 4.45 (q, *J* = 6.7 Hz, 1 H), 1.56 (d, *J* = 6.7 Hz, 3 H). Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 71.98; H, 4.61; N, 6.95.
Compound **14f**: yellow solid; mp 105–106 °C. IR (KBr): 2228, 1674, 1604, 1563 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.08–7.61 (m, 4 H), 1.42 (s, 6 H). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.10; H, 5.21; N, 6.53.