Tetrahedron Letters 49 (2008) 7352–7354

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple synthesis of 2,2′-bipyrroles from pyrrole

Liangfeng Fu, Gordon W. Gribble *

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

ARTICLE INFO

Article history:
Received 28 August 2008
Revised 7 October 2008
Accepted 8 October 2008
Available online 14 October 2008

Keywords:
2,2′-Bipyrroles
Oxidation
Paal-Knorr pyrrole Synthesis

ABSTRACT

2,2′-Bipyrroles, which are obvious precursors for the synthesis of 2,2′-bipyrrole-based natural products, are synthesized in three steps from pyrrole employing known pyrrolyl ketoalcohols by a sequential alcohol oxidation and Paal-Knorr pyrrole synthesis.

Bipyrroles are attractive and obvious precursors for the synthesis of various polyhalogenated 1,2′-[1] and 1,3′-bipyrroles[2] found in marine organisms and in several 2,2′-bipyrrole-based natural products[3] (Fig. 1). Several new syntheses of 1,2′-, 1,3′-, and 2,2′-bipyrroles have been achieved in our laboratory in the context of approaches to the environmentally significant and ubiquitous naturally occurring polyhalogenated analogs (e.g., **1** and **2**).

Unlike the relatively little studied 1,2′- and 1,3′-bipyrroles, syntheses of 2,2′-bipyrroles have attracted the attention of a number of different research groups since the beginning of the last century. Previous syntheses of 2,2′-bipyrroles include metal-catalyzed coupling of halogenated pyrroles,[4–11] such as palladium-[4] and copper-catalyzed[5] coupling of iodopyrroles. 2,2′-Bipyrroles can also be synthesized by Suzuki coupling of boronopyrroles and pyrrolyltriflate,[6] Paal-Knorr condensation,[7] aza-Nazarov reaction,[8] Trofimov reaction,[9] phenyliodine bis(trifluoroacetate)-mediated oxidative coupling of pyrroles,[10] nickel-catalyzed coupling of pyrroles,[3d] and by other methods.[11]

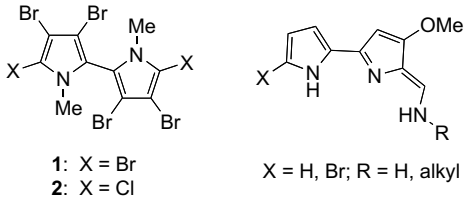
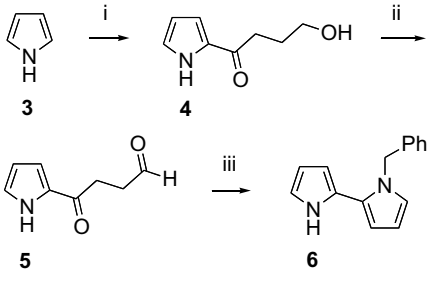


Figure 1.

Our recent work[12] describing the Paal-Knorr reductive pyrrolylation of nitropyrroles in the presence of 1,4-diketones for the synthesis of 1,2′- and 1,3′-bipyrroles prompted us to explore a new and simple synthesis of 2,2′-bipyrroles.

In the initial study, the known pyrrolyl ketoalcohol **4**, which was prepared by magnetization of pyrrole and reaction with butyrolactone, was oxidized with pyridine chlorochromate (PCC)[13] in methylene chloride to give the desired ketoaldehyde **5**[15] in 92% yield. After exploration of this Paal-Knorr reaction under various conditions, we found that treatment of ketoaldehyde **5** with benzylamine and acetic acid in methanol led to the desired 1-benzyl-2,2′-bipyrrole[16] (**6**) in 81% yield (Scheme 1).

The same reaction of ketoaldehyde **5** with benzylamine and a 1:1 mixture of acetic acid and sodium acetate in toluene provides bipyrrole **6** in a lower 68% yield.



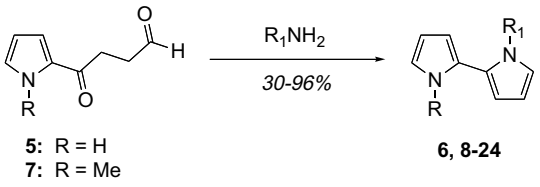
Scheme 1.

* Corresponding author. Tel.: +1 603 646 3118; fax: +1 603 646 3946.
E-mail address: GGribble@dartmouth.edu (G. W. Gribble).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.034

With these intial results in hand, other amines were allowed to react with **5** and the *N*-methylpyrrole analog **7**, and our results are summarized in Scheme 2 and in Table 1. Both conditions A and B give good results of 75% and 65% of product **8**,[16] respectively, when *p*-methoxybenzylamine was employed (entries 3 and 4). Allylamine gave the best yield of 96% of **9**[16] when the reaction was conducted in acetic acid and methanol (entry 5), while only 51% of **9** is obtained using acetic acid and sodium acetate in toluene (entry 6). Methylamine affords excellent yields of **10** (81% and 89%) under conditions A and B. During our efforts to prepare the parent bipyrrole **11**,[16–18] no **11** was obtained when ketoaldehyde **5** was treated with ammonium acetate, acetic acid, and potassium acetate in toluene. However, this reaction worked well when **5** was treated with ammonium acetate in a 1:25 solution of 28% ammonium hydroxide and ethanol (conditions C) (entry 9).

Bipyrrole **14** is an important intermediate for the synthesis of the natural products **1** and **2**. Therefore, *N*-methylketoaldehyde **7** was targeted for the synthesis of bipyrrole **14**. Thus, **7**[15] was prepared in two steps from *N*-methylpyrrole by lithiation[14] with *n*-butyllithium and TMEDA followed by quenching with butyrolactone to give the corresponding ketoalcohol **15**[15] (not shown), and subsequent oxidation with pyridinium chlorochromate (PCC)[13] in methylene chloride.



Scheme 2.

Table 1
Paal-Knorr condensation of **5** and **7** for the synthesis of 2,2′-bipyrroles **6, 8–24**

Entry	R	R_1	Condition	Product	Yield (%)
1	H	$PhCH_2$	A	**6**	81
2	H	$PhCH_2$	B	**6**	68
3	H	*p*-$MeOPhCH_2$	A	**8**	75
4	H	*p*-$MeOPhCH_2$	B	**8**	65
5	H	$CH_2CH{=}CH_2$	A	**9**	96
6	H	$CH_2CH{=}CH_2$	B	**9**	51
7	H	Me	A	**10**	81
8	H	Me	B	**10**	89
9	H	H	C	**11**	53
10	Me	$PhCH_2$	B	**12**	30
11	Me	$CH_2CH{=}CH_2$	A	**13**	47
12	Me	$CH_2CH{=}CH_2$	B	**13**	49
13	Me	Me	A	**14**	40
14	Me	Me	B	**14**	57
15	Me	H	C	**10**	49

Conditions A: amine, AcOH, MeOH, 40 °C; *Conditions B*: amine, AcOH, NaOAc, toluene, 60 °C; *Conditions C*: NH_4OAc, 28% NH_4OH, EtOH, 40 °C.

Methylamine in acetic acid and sodium acetate in toluene give the best result for the preparation of bipyrrole **14**[3d,16] (57% yield, entry 14). Other amines such as benzylamine and allylamine give bipyrroles **12**[16] and **13**[16] in lower yields (entries 10–13). A 49% yield of **10**[11a,16] was obtained when **7** was treated with ammonium acetate in ammonium hydroxide and ethanol.

Our results indicate that ketoaldehyde **5** is invariably superior to **7** under these reaction conditions. For a synthesis of natural bipyrrole **1**, intermediate **14** was most efficiently obtained from known ketoalcohol **4** in three steps (Scheme 3). Bipyrrole **14** was generated in 91% yield from **10** by alkylation with iodomethane. Exhaustive bromination of bipyrrole **14** with *N*-bromosuccinimide in THF gave **1**[3d] in 78% yield.

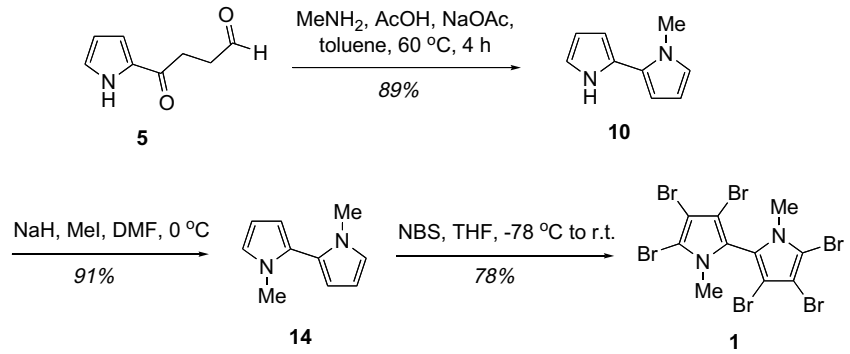
In summary, a relatively efficient and simple synthesis of 2,2′-bipyrroles using a modified Paal-Knorr condensation was developed, which is potentially useful for the synthesis of 2,2′-bipyrrole-based natural products, and is particularly attractive for the synthesis of 2,2′-bipyrroles with different N-substituents.

Acknowledgments

This work was supported by the Donors of the Petroleum Research Fund (PRF), administrated by the American Chemical Society, and by Wyeth.

References and notes

1. (a) Pangallo, K.; Nelson, R. K.; Teuten, E. L.; Pedler, B. E.; Reddy, C. M. *Chemosphere* **2008**, *71*, 1557–1565; (b) Teuten, E. L.; Reddy, C. M. *Environ. Pollut.* **2007**, *145*, 668–671; (c) Vetter, W.; Gaul, S.; Olbrich, D.; Gaus, C. *Chemosphere* **2007**, *66*, 2011–2018; (d) Teuten, E. L.; Pedler, B. E.; Hangsterfer, A. N.; Reddy, C. M. *Environ. Pollut.* **2006**, *144*, 336–344; (e) Vetter, W. *Rev. Environ. Contam. Toxicol.* **2006**, *188*, 1–57; (f) Vetter, W.; Hahn, M. E.; Tomy, G.; Ruppe, S.; Vatter, S.; Chahbane, N.; Lenoir, D.; Schramm, K.-W.; Scherer, G. *Arch. Environ. Contam. Toxicol.* **2005**, *48*, 1–9; (g) Kurt, W.; Helmut, G. *Chemosphere* **2003**, *53*, 667–678; (h) Vetter, W.; Wu, J. *Chemosphere* **2003**, *52*, 423–431; (i) Vetter, W.; Wu, J.; Gerhard, A. *Chemosphere* **2003**, *52*, 415–422; (j) Wu, J.; Vetter, W.; Gribble, G. W., ; Schneekloth, J. S., Jr.; Blank, D. H.; Gorls, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1740–1743; (k) Vetter, W.; Stoll, E. *Eur. Food Res. Technol.* **2002**, *215*, 523–528; (l) Vetter, W. *Organohalogen Compd.* **2002**, *59*, 271–274; (m) Vetter, W. *Chemosphere* **2002**, *46*, 1477–1483; (n) Vetter, W.; Scholz, E.; Gaus, C.; Muller, J. F.; Haynes, D. *Arch. Environ. Contam. Toxicol.* **2001**, *41*, 221–231; (o) Vetter, W. *Organohalogen Compd.* **1999**, *43*, 433–436.
2. Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629–631.
3. (a) Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 5127–5130; (b) Jolicoeur, B.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 6107–6110; (c) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *Aust. J. Chem.* **2001**, *54*, 355–359; (d) Gribble, G. W.; Blank, D. H.; Jasinski, J. P. *Chem. Commun.* **1999**, 2195–2196.



Scheme 3.

4. (a) Nikitin, E. B.; Nelson, M. J.; Lightner, D. A. *J. Heterocycl. Chem.* **2007**, *44*, 739–743; (b) Jiao, L.; Hao, E.; Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **2007**, *72*, 8119–8122; (c) Dairi, K.; Tripathy, S.; Attardo, G.; Lavallee, J.-F. *Tetrahedron Lett.* **2006**, *47*, 2605–2606.
5. (a) Matsumoto, S.; Kobayashi, T.; Ogura, K. *Heterocycles* **2006**, *68*, 283–294; (b) Matsumoto, S.; Kobayashi, T.; Ogura, K. *Heterocycles* **2005**, *66*, 319–332; (c) Gavalda, A.; Borrell, J. I.; Teixido, J.; Nonell, S.; Arad, O.; Grau, R.; Canete, M.; Juarranz, A.; Villanueva, A.; Stockert, J. C. *J. Porphyrins Phthalocyanines* **2001**, *5*, 846–852; (d) Hayashi, T.; Nakashima, Y.; Ito, K.; Ikegami, T.; Aritome, I.; Suzuki, A.; Hisaeda, Y. *Org. Lett.* **2003**, *5*, 2845–2848; (e) Skowronek, P.; Lightner, D. A. *Monatsh. Für. Chem.* **2003**, *134*, 889–899; (f) Shevchuk, S. V.; Davis, J. M.; Sessler, J. L. *Tetrahedron Lett.* **2001**, *42*, 2447–2450; (g) Guilard, R.; Aukauloo, M. A.; Tardieux, C.; Vogel, E. *Synthesis* **1995**, 1480–1482; (h) Sessler, J. L.; Cyr, M.; Burrell, A. K. *Tetrahedron* **1992**, *48*, 9661–9672; (i) Sessler, J. L.; Hoehner, M. C. *Synlett* **1994**, 211–212; (j) Oda, K.; Sakai, M.; Ohno, K.; Machida, M. *Heterocycles* **1999**, *50*, 277–282; (k) Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689–702; (l) Sessler, J. L.; Cyr, M. J.; Lynch, V. *J. Am. Chem. Soc.* **1990**, *112*, 2810–2813; (m) Burger, U.; Dreier, F. *Helv. Chim. Acta* **1980**, *63*, 1190–1197.
6. (a) Regourd, J.; Ali, A. A.; Thompson, A. *J. Med. Chem.* **2007**, *50*, 1528–1536; (b) Shevchuk, S. V.; Lynch, V. M.; Sessler, J. L. *Tetrahedron* **2004**, *60*, 11283–11291; (c) D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513–514; (d) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, *5*, 254–255; (e) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1980**, *2*, 49–50.
7. (a) Johnson, M. R. *J. Org. Chem.* **1997**, *62*, 1168–1172; (b) Hinz, W.; Jones, R. A.; Patel, S. U.; Karatza, M.-H. *Tetrahedron* **1986**, *42*, 3753–3758. For a recent review, see: (c) Gribble, G. W. Knorr and Paal-Knorr Pyrrole Syntheses. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, New Jersey, 2004; pp 79–88.
8. Dieker, J.; Frohlich, R.; Wurthwein, E.-U. *Eur. J. Org. Chem.* **2006**, 5339–5365.
9. Zaitsev, A. B.; Schmidt, E. Yu.; Vasil'tsov, A. M.; Mikhaleva, A. I.; Petrova, O. V.; Afonin, A. V.; Zorina, N. V. *Chem. Heterocycl. Compd.* **2006**, *42*, 34–41.
10. Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007–2010.
11. (a) Spaggiari, A.; Vaccari, D.; Davoli, P.; Prati, F. *Synthesis* **2006**, 995–998; (b) Sessler, J. L.; Aguilar, A.; Sanchez-Garcia, D.; Seidel, D.; Kohler, T.; Arp, F.; Lynch, V. M. *Org. Lett.* **2005**, *7*, 1887–1890; (c) Yu, M.; Pantos, D.; Sessler, J. L.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057–1059; (d) Wasserman, H. H.; Xia, M.; Wang, J.; Petersen, A. K.; Jorgensen, M.; Power, P.; Parr, J. *Tetrahedron* **2004**, *60*, 7419–7425; (e) Flogel, O.; Reissig, H.-U. *Synlett* **2004**, 895–897; (f) Wasserman, H. H.; Petersen, A. K.; Xia, M.; Wang, J. *Tetrahedron Lett.* **1999**, *40*, 7587–7589; (g) Tamao, K.; Ohno, S.; Yamaguchi, S. *Chem. Commun.* **1996**, 1873–1874; (h) van Haare, J. A. E. H.; van Boxtel, M.; Janssen, R. A. J. *Chem. Mater.* **1998**, *10*, 1166–1175; (i) Barluenga, J.; Tomas, M.; Rubis, E.; Lopez-Pelegrin, J. A.; Garcia-Granda, S.; Priede, M. P. *J. Am. Chem. Soc.* **1999**, *121*, 3065–3071; (j) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725–1728; (k) Brown, D.; Griffiths, D.; Rider, M. E.; Smith, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, *3*, 455–463; (l) Bordner, J.; Rapoport, H. *J. Org. Chem.* **1965**, *30*, 3824–3828.
12. Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 3545–3548.
13. Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, *5*, 235–240.
14. Bergauer, M.; Hubner, H.; Gmeiner, P. *Tetrahedron* **2004**, *60*, 1197–1204.
15. Compound **5**: White solid; mp: 67–69 °C; ^{1}H NMR ($CDCl_3$): δ 10.0 (br s, 1H), 9.87 (s, 1H), 7.04 (m, 1H), 6.99 (m, 1H), 6.28 (m, 1H), 3.17 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 201.1, 188.5, 131.5, 125.4, 116.9, 111.0, 38.1, 30.4; MS (EI): m/z (%) = 151 ([M^+]), 123, 94 (100), 66; HRMS (EI): m/z calcd for $C_8H_9NO_2$: 151.0633, found: 151.0632.
Compound **15**: Yellow oil; ^{1}H NMR ($CDCl_3$): δ 6.97 (m, 1H), 6.77 (m, 1H), 6.08 (m, 1H), 3.89 (s, 3H), 3.65 (t, J = 6.1 Hz, 2H), 3.10 (br s, 1H), 2.89 (t, J = 7.1 Hz, 2H), 1.89–1.92 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 191.8, 131.5, 130.7, 119.8, 108.2, 62.4,38.0, 36.0, 28.0; MS (EI): m/z (%) = 167 ([M^+]), 150, 123, 108 (100), 85; HRMS (EI): m/z calcd for $C_9H_{13}O_2N$: 167.0946, found: 167.0946.
Compound **7**: Yellow oil; ^{1}H NMR ($CDCl_3$): δ 9.88 (s, 1H), 7.02 (m, 1H), 6.81 (m, 1H), 6.13 (m, 1H), 3.92 (s, 3H), 3.16–3.19 (t, J = 6.5 Hz, 2H), 2.83 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 201.4, 188.6, 131.4, 130.3, 119.5, 108.4, 38.1, 37.9, 31.5; MS (EI): m/z (%) = 165 ([M^+]), 137, 108 (100), 80; HRMS (EI): m/z calcd for $C_9H_{11}O_2N$: 165.0790, found: 165.0791.
16. *Representative procedure* (**9**) (*conditions A*): To a solution of pyrrolyl ketoaldehyde (**5**) (118.9 mg, 0.79 mmol) in methanol (8 mL) were added allylamine (228.0 mg, 4.0 mmol) and acetic acid (240 mg, 4.0 mmol). The resulting mixture was heated to 40 °C under stirring for 48 h (the progress of the reaction was monitored by TLC). After the completion of the reaction, it was cooled to room temperature and poured into 1 M aqueous HCl (20 mL). It was extracted with methylene chloride (4 × 20 mL), and the combined organic extracts were washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent and flash column chromatography over silica gel with hexane/EtOAc (4:1) gave the desired 1-allyl-1H,1′H-2,2′-bipyrrole (**9**) (129.5 mg, 96%) as a brown oil: ^{1}H NMR ($CDCl_3$): δ 8.29 (br s, 1H), 6.74–6.84 (m, 2H), 6.24–6.31 (m, 4H), 5.99–6.14 (m, 1H), 5.23–5.27 (m, 1H), 5.00–5.14 (m, 1H), 4.61 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 135.5, 127.0, 124.2, 122.2, 118.1, 116.9, 109.5, 108.3, 107.7, 49.8; MS (EI): m/z (%) = 172 ([M^+]), 157, 145, 131 (100), 117, 104, 98, 91, 85, 76, 63, 58; HRMS (EI): m/z calcd for $C_{11}H_{12}N_2$: 172.1001, found: 172.1001.
Compound **6**: white solid (turns black upon standing); mp: 70–72 °C; ^{1}H NMR ($CDCl_3$): δ 8.01 (br s, 1H), 7.20–7.32 (m, 3H), 7.00 (m, 2H), 6.71 (m, 2H), 6.23 (m, 2H), 6.16 (m, 1H), 6.03 (m, 1H), 5.16 (s, 2H); ^{13}C NMR ($CDCl_3$): 139.2, 129.1, 127.7, 126.6, 126.5, 126.4, 122.8, 118.1, 109.5, 108.6, 108.0, 107.7, 51.0; MS (EI): m/z (%) = 222 ([M^+]), 205, 191, 168, 145, 131 (100), 104, 91, 58; HRMS (EI): m/z calcd for $C_{15}H_{14}N_2$: 222.1157, found: 222.1158.
Compound **8**: Brown solid; mp: 69–70 °C; ^{1}H NMR ($CDCl_3$): δ 8.19 (br s, 1H), 6.98 (m, 2H), 6.85 (m, 2H), 6.77 (m, 1H), 6.73 (m, 1H), 6.24 (m, 3H), 6.10 (m, 1H), 5.14 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.1, 131.0, 127.9, 127.1, 124.2, 122.6, 118.1, 114.4, 109.4, 108.4, 108.0, 107.7, 55.5, 50.5; MS (EI): m/z (%) = 252 ([M^+]), 180, 121 (100), 104, 76; HRMS (EI): m/z calcd for $C_{16}H_{16}ON_2$: 252.1263, found: 252.1263.
Compound **12**: Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.25–7.29 (m, 3H), 6.93 (m, 2H), 6.83 (m, 1H), 6.67 (m, 1H), 6.28 (m, 1H), 6.24 (m, 1H), 6.17 (m, 1H), 6.12 (m, 1H), 5.02 (s, 2H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.9, 128.7, 127.5, 127.2, 125.1, 124.9, 122.8, 122.3, 111.4, 110.9, 108.1, 107.6, 51.0, 34.3; MS (EI): m/z (%) = 236 ([M^+]), 195, 159, 145 (100), 117, 91; HRMS (EI): m/z calcd for $C_{16}H_{16}N_2$: 236.1314, found: 236.1312.
Compound **13**: Yellow oil; ^{1}H NMR ($CDCl_3$): δ 6.73–6.80 (m, 2H), 6.18–6.27 (m, 4H), 5.84–5.96 (m, 1H), 5.13–5.16 (m, 1H), 4.95–4.99 (m, 1H), 4.42 (m, 2H), 3.51 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 135.1, 125.0, 124.9, 122.9, 121.7, 116.9, 110.9, 110.8, 107.9, 107.6, 49.5, 34.6; MS (EI): m/z (%) = 186 ([M^+], 100), 171, 145, 117, 91, 71; HRMS (EI): m/z calcd for $C_{12}H_{14}N_2$: 186.1157, found: 186.1157.
Compound **14**:[3d] Yellow oil; ^{1}H NMR ($CDCl_3$): δ 6.74 (m, 2H), 6.18–6.23 (m, 4H), 3.54 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 125.3, 122.9, 110.7, 107.6, 34.7.
17. *Representative procedure* (**10**) (*conditions B*): To a solution of ketoaldehyde **5** (66.5 mg, 0.44 mmol) in toluene (5 mL) were added methylamine (1.1 mL, 2 M solution in methanol, 2.2 mmol), sodium acetate (37.0 mg, 0.44 mmol), and acetic acid (27.0 mg, 0.44 mmol). The resulting mixture was heated to 60 °C under stirring for 4 h (the progress of the reaction was monitored by TLC). The mixture was cooled to room temperature and poured into 1 M aqueous HCl. It was extracted with methylene chloride (4 × 20 mL), and the combined organic extracts were washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent and flash column chromatography over silica gel with hexane/EtOAc (4:1) gave the desired product **10**[11a] (57.0 mg, 89%) as a brown oil (solid upon standing); ^{1}H NMR ($CDCl_3$): δ 8.25 (br s, 1H), 6.84 (m, 1H), 6.73 (m, 1H), 6.35 (m, 1H), 6.30 (m, 1H), 5.24 (m, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 127.4, 124.6, 123.3, 118.0, 109.5, 107.9, 107.2, 107.0, 35.4.
18. *Representative procedure* (**11**) (*conditions C*): To a solution of ketoaldehyde **5** (91.5 mg, 0.61 mmol) in a prepared solution of 28% NH_4OH in ethanol (1:25, 20 mL) was added ammonium acetate (470 mg, 6.1 mmol). The resulting mixture was heated to 40 °C under stirring for 48 h (the progress of the reaction was monitored by TLC). The mixture was cooled to room temperature, and poured into saturated NaCl (20 mL). It was extracted with EtOAc (4 × 20 mL), and the combined organic extracts were dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel with hexane/EtOAc (4:1) gave the desired product **11**[10] (42.4 mg, 53%) as a white solid: white solid; mp 186–187.5 °C (lit.[19] mp 187–189 °C); ^{1}H NMR ($CDCl_3$): δ 8.44 (br s, 2H), 6.77 (m, 2H), 6.21–6.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 126.2, 117.7, 109.6, 103.7.
19. Dohi, T.; Morimoto, K.; Ito, M.; Kita, Y. *Synthesis* **2007**, 2913–2919.