Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1007–1011

A one-pot synthesis of 1,4-dithiins and 1,4-benzodithiins from ketones using the recyclable reagent 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)

Siva Murru, Veerababurao Kavala, C. B. Singh and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, 781 039, Assam, India

Received 3 November 2006; revised 21 November 2006; accepted 1 December 2006
Available online 26 December 2006

Abstract—A novel access to 1,4-dithiins and 1,4-benzodithiins from the corresponding ketones in one-pot using the recyclable reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) is described. This method is mild, simple, environmentally benign and is applied successfully for the ring expansion of 1,3-dithiolane to 1,4-dithiins and the ring expansion associated with aromatisation of cyclic ketones with or without double bonds in the ring. The main feature of this method is that EDPBT acts as a promoter in the formation of 1,3-dithiolane and as a reagent in the ring expansion step. The spent reagent can be recovered, regenerated and reused.

We have been utilising tetrabutylammonium tribromide for bromination[1] and for various other organic transformations.[2] Recently we synthesised a new ditribromide reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and has several advantages over molecular bromine and other tribromides.[3] In addition to acting as an excellent brominating agent, it has been utilised as a catalyst for the acylation of alcohols[4] and for the synthesis of various thiazolidene-2-imine derivatives.[5] In this letter we describe the utility of this reagent for the synthesis of a variety of dihydro-1,4-dithiins and 1,4-benzodithiins from the corresponding ketones in one-pot. The syntheses of dihydro-1,4-dithiins and 1,4-benzodithiins have received much attention because of their applications in synthetic organic chemistry and medicinal chemistry. Derivatives of 1,4-dithiins show activities as non peptide antagonists of the human Galanin hGal-1 receptors.[6] They have also been used for the construction of larger rings containing sulfur atoms, for the 1,2-transposition of carbonyl compounds,[7] and as allylic alcohol anion and acyl β-anion equivalents for three carbon homologations.[8] Further, the 1,4-benzodithiin system is a useful intermediate for the synthesis of aromatic compounds and for the preparation of organic ferromagnets.[9,10] 1,4-Dithiins have also been transformed into derivatives of 5,6-dihydro-1,4-dithiin by reaction of butyllithium with various electrophiles.[8,11] The 5,6-dihydro-1,4-dithiin moiety has been shown to be a useful synthetic intermediate to mimic cis configured double bonds in the preparation of simple alkenes and other unsaturated compounds.[12] Derivatives of 2,3-dihydro-1,4-dithiins are reported to be easily oxidised affording dienophiles for use in Diels–Alder reactions.[13]

Although methods have been reported for ring expansion of 1,3-dithiolanes and a few for ring expansion combined with aromatisation, no method has been reported from ketones. Literature methods for the preparation of dihydro-1,4-dithiins are mostly from 1,3-dithiolanes using various reagents such as *N*-haloamides,[14a] PhSeCl,[14b] molecular bromine or chlorine in anhydrous CCl_4,[14c] $TeCl_4$,[14d,e] 2,4,6-trichloro-1,3,5-triazine in DMSO,[14f] WCl_6 in DMSO,[7b] SO_2Cl_2,[14g] 1,3-dibromo-5,5-dimethylhydantoin,[14h] *o*-iodoxybenzoic acid (IBX)-tetraethylammonium bromide (TEAB),[14i] 1,3-dibromo-5,5-dimethylhydantoin (DBH)[14j] and *tert*-butyl hypochlorite.[14k] Ring expanded monosubstituted 1,4-dithiins have been reported using (SiO_2Cl/DMSO)[15a] and N-substituted succinimides.[15b]

In spite of the several methods available in the literature, some of the procedures suffer due to the use of expensive

* Corresponding author. Tel.: +91 361 2582307; fax: +91 361 2690762; e-mail: patel@iitg.ernet.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.003

and toxic reagents, difficulty in handling and longer reaction times. Moreover, all the reported procedures involve two steps and the synthesis usually starts from the 1,3-dithiolane. Earlier we reported the thioacetalisation of various carbonyl compounds using a catalytic quantity of tetrabutylammonium tribromide (TBATB).[2f] We have utilised the acidic properties of EDPBT for the thioacetalisation of carbonyl compounds followed by ring expansion of the in situ generated thioacetal to give 1,4-dithiins in one-pot.[16]

In an initial reaction acetophenone **1** (5 mmol) was treated with 1,2-ethanedithiol (5.5 mmol), and a catalytic quantity of EDPBT (0.5 mmol) in acetonitrile (10 mL) and stirred for 0.5 h. During this time acetophenone was converted to the corresponding 1,3-dithiolane. Although the rate of 1,3-dithiolane formation for different ketones is different,[2e] we maintained a uniform time of 0.5 h for all the substrates. To the reaction mixture, a further quantity of EDPBT (2.5 mmol) was added and stirring was continued for 15 min. The desired ring expanded product, 1,4-dithiin **1a** was isolated in good yield. The structure of **1a** was unambiguously confirmed by single crystal X-ray diffraction analysis as shown in Figure 1. It should be mentioned here that when a similar reaction was performed with the 1,3-dithiane of ketones using methyltriphenylphosphonium tribromide, deprotection of the ketone without ring expansion was reported.[17f]

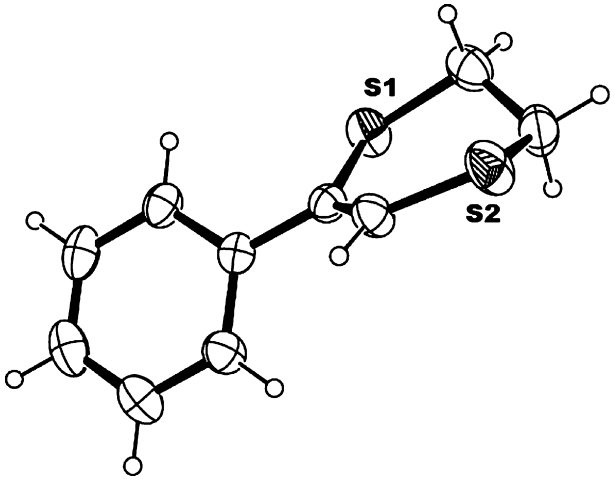
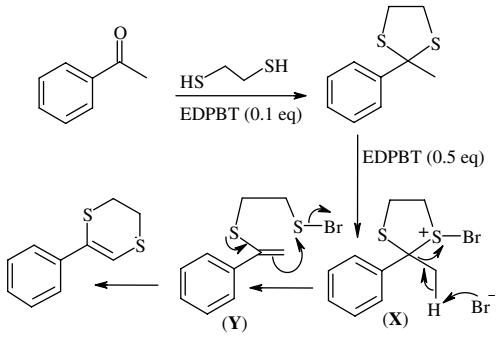


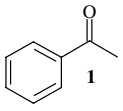
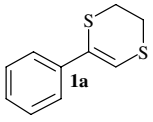
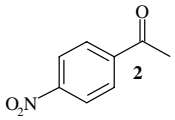
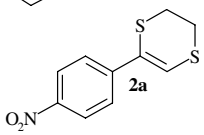
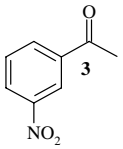
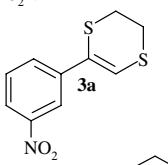
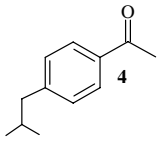
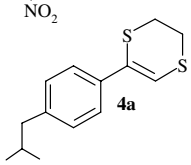
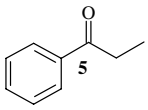
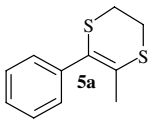
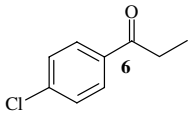
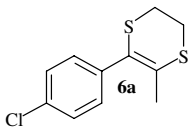
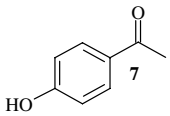
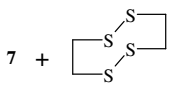
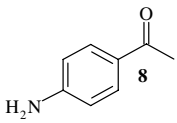
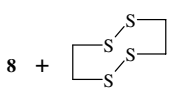
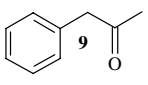
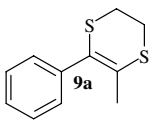
Figure 1. ORTEP diagram with atom numbering of **1a**.



Scheme 1. Proposed mechanism of formation of 1,4-dithiins.

A plausible mechanism for the ring expansion is proposed in Scheme 1. The first step of the reaction consists of 1,3-dithiolane formation.[2e] Consumption of a further equivalent of bromine forms bromosulfonium ion (**X**). The bromosulfonium ion (**X**) loses a molecule of HBr forming sulfanyl vinylbenzene intermediate (**Y**). Finally intramolecular nucleophilic attack leads to the desired product. This method was successfully applied to *p*-nitroacetophenone **2** and *m*-nitroacetophenone **3** both of which gave the corresponding ring expanded 1,4-dithiins **2a** and **3a**, respectively, in good yields (Table 1). 4-Isobutylacetophenone **4** gave 1,4-dithiin **4a** under identical

Table 1. Formation of 1,4-dithiins from ketones[a]

Substrate	Product[b]	Time[c] (min)	Yield[d] (%)
		15	85
		25	72
		25	68
		30	75
		20	73
		30	78
		25	50[e]
		25	55[e]
		30	70

[a] Reactions were monitored by TLC.
[b] Products were characterised by IR, ^{1}H and ^{13}C NMR.
[c] An additional 0.5 h for 1,3-dithiolane formation in the first step was required.
[d] Yield of isolated product.
[e] Yield refers to [1,2,5,6]-tetrathiocane, starting ketone was isolated in <90% yield.

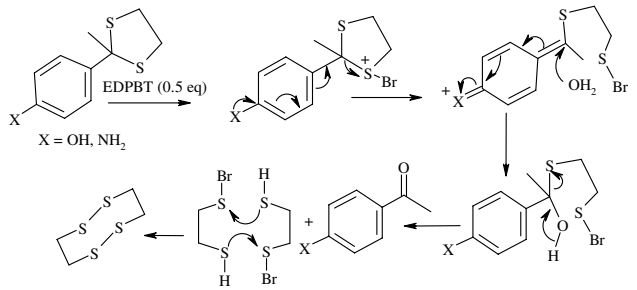
conditions. Propiophenone **5** and *p*-chloropropiophenone **6** yielded the ring expanded products **5a** and **6a**, respectively. However, when the reaction was performed with *p*-hydroxy acetophenone **7** and *p*-aminoacetophenone **8**, the ring expanded products were not obtained, instead the starting materials along with [1,2,5,6]-tetrathiocane were obtained. The formation of [1,2,5,6]-tetrathiocane is not due to oxidation of 1,2-ethanedithiol.

In the first step of the reaction of *p*-hydroxy and *p*-amino acetophenones with 1,2-ethanedithiol both were consumed forming the corresponding 1,3-dithiolanes. We have theoretically,[2a] as well as experimentally,[2f] proven that the presence of an electron donating substituent (OH, NH_2) on the aromatic ring favours thioacetalisation. Thus, recovery of the starting ketones **7** and **8** along with the formation of [1,2,5,6]-tetrathiocane can be explained by the following mechanism (Scheme 2). Due to the presence of OH and NH_2 substituents in the *para* position of the aromatic ring the quinone formation pathway is more favoured over proton abstraction returning the carbonyl compound along with [1,2,5,6]-tetrathiocane.

For ketones **1**–**6** the formation of the intermediate **Y** (Scheme 1) occurs via elimination of a methyl proton associated with C–S bond cleavage. In the case of phenylacetone **9** where the carbonyl group is flanked by a methyl and a methylene group, proton abstraction occurs from the methylene carbon because of its higher acidity, ultimately leading to the product **9a** regioselectively.

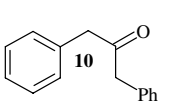
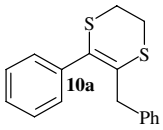
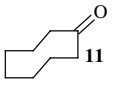
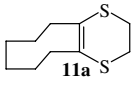
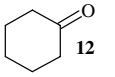
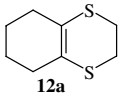
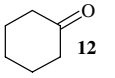
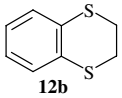
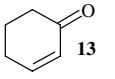
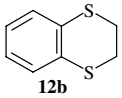
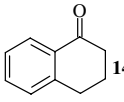
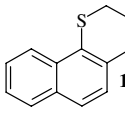
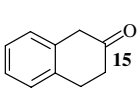
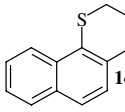
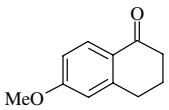
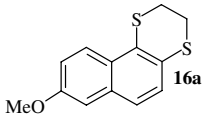
Symmetrical ketones such as dibenzyl ketone **10**, cyclooctanone **11** and cyclohexanone **12** were smoothly converted to 1,4-dithiins **10a**, **11a** and **12a**, respectively, with 0.6 equiv of EDPBT (Table 2). When cyclohexanone **12** was reacted with 1.6 equiv of EDPBT, it was converted into the 1,4-dithiin derivative with concomitant aromatisation of the cyclohexane ring, thus affording the valuable 1,4-benzodithiin heterocyclic ring system **12b**. In this transformation, a total of three bromine equivalents is needed, 1 equiv for the 1,4-dithiin ring formation and 2 equiv for aromatisation of the cyclohexane ring system as shown in Scheme 3. Literature revealed a few such ring expansions associated with aromatisation all starting from the corresponding 1,3-dithiolanes only.[9,17]

The first step of the 1,4-benzodithiin synthesis consists of the formation of dihydro-1,4-dithiin **12a** with the consumption of 1 equiv of bromine, that is, 0.5 equiv of EDPBT followed by two subsequent electrophilic attacks by bromine at one of the sulfur atoms with

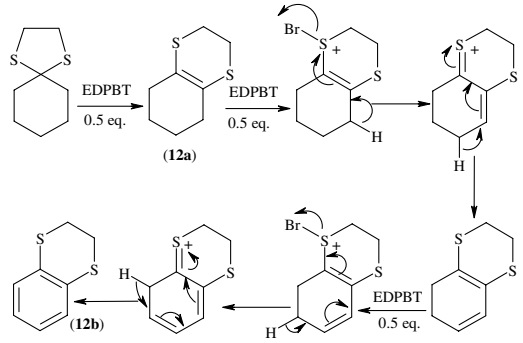


Scheme 2. Proposed mechanism for the formation of [1,2,5,6]-tetrathiocane and regeneration of the starting ketone.

Table 2. Formation of 1,4-dithiins and 1,4-benzodithiins from ketones[a]

Substrate	Product[b]	Time[c] (min)	Yield[d] (%)
 **10**	 **10a**	30	69
 **11**	 **11a**	40	63
 **12**	 **12a**	40	62
 **12**	 **12b**	60	70[e]
 **13**	 **12b**	60	70[e]
 **14**	 **14a**	60	75[f]
 **15**	 **14a**	60	67[f]
 **16** MeO	 **16a** MeO	60	72[f]

[a] Reactions were monitored by TLC.
[b] Products were characterised by IR, ^1H and ^{13}C NMR.
[c] An additional 0.5 h for 1,3-dithiolane formation in the first step was required.
[d] Yield of isolated product.
[e] 1.6 equiv of EDPBT was used.
[f] 1.1 equiv of EDPBT was used.



Scheme 3. A plausible mechanism for formation of 1,4-benzodithiins.

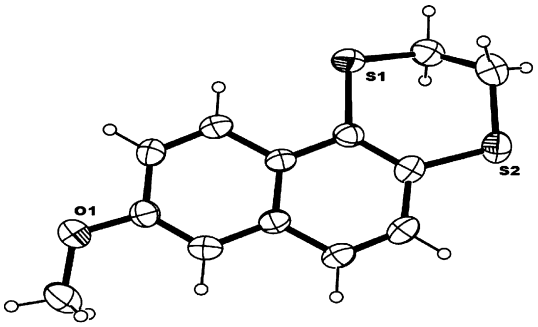


Figure 2. ORTEP diagram with atom numbering of **16a**.

two sequential losses of HBr. This process is associated with aromatisation leading to **12b**. Benzodithiin **12b** was also obtained from cyclohexenone **13** with just 1.1 equiv of EDPBT suggesting the requirement of two bromine equivalents for complete aromatisation as proposed in Scheme 3. Both α-tetralone **14** and β-tetralone **15** were converted to the same naphtho-1,4-dithiin **14a**. In the latter case, proton abstraction occurs from the benzylic carbon which is more acidic, whereas in the former, proton abstraction occurs from the only available β-carbon. Finally, 6-methoxytetralone **16** was converted into naphtho-1,4-dithiin derivative **16a**. The single crystal X-ray structure of **16a** is shown in Figure 2.

In conclusion, we have developed a one-pot transformation of acyclic ketones to 1,4-dithiins and cyclic ketones to 1,4-benzodithiins/1,4-naphthodithiins using the recyclable reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT).[18] This method is simple, convenient, mild and environmentally benign. An interesting aspect of this method is that EDPBT acts as a promoter in the formation of 1,3-dithiolane and as a reagent in the ring expansion step. The spent reagent can be recovered, regenerated and reused.[3,4]

Acknowledgements

B.K.P. and C.B.S. acknowledge the support for this research from DST (SR/S1/OC-15/2006) and CSIR (01/1946/04/EMR-II), New Delhi. S.M. and V.K. acknowledge financial support to the institute. Thanks are due to CIF IIT Guwahati, for NMR spectra and DST FIST for XRD facilities.

References and notes

1. (a) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163; (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.
2. (a) Roy, R. K.; Bagaria, P.; Naik, S.; Kavala, V.; Patel, B. K. *J. Phys. Chem. A* **2006**, *110*, 2181; (b) Roy, R. K.; Usha, V.; Patel, B. K.; Hairo, K. *J. Comp. Chem.* **2006**, 773; (c) Kavala, V.; Patel, B. K. *Eur. J. Org. Chem.* **2005**, 441; (d) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, 119; (e) Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, 1670; (f) Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842; (g) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679; (h) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.
3. (a) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267; (b) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 6556.
4. Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, 21.
5. Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397.
6. Scott, M. K.; Ross, T. M.; Lee, D. H. S.; Wang, H.-Y.; Shank, R. P.; Wild, K. D.; Davis, C. B.; Crooke, J. J.; Potocki, A. C.; Reitz, A. B. *Bioorg. Med. Chem.* **2000**, *8*, 1383.
7. (a) Larsen, L.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2311; (b) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, 413.
8. Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Org. Chem.* **1997**, *62*, 9369.
9. Caputo, R.; Ferreri, C.; Palumbo, G.; Russo, F. *Tetrahedron* **1991**, *47*, 4187.
10. Lapouyade, R.; Morand, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 223.
11. Caputo, R.; Ciriello, U.; Festa, P.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **2003**, 2617.
12. Caputo, R.; Palumbo, G.; Pedatella, S. *Tetrahedron* **1994**, *50*, 7265.
13. Nakayama, J.; Nakamura, Y.; Hoshino, M. *Heterocycles* **1985**, *23*, 1119.
14. (a) Yoshino, H.; Kawazoe, Y.; Taguchi, T. *Synthesis* **1974**, 713; (b) Fransisco, C. G.; Friere, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1621; (c) Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis* **1991**, 223; (d) Tani, H.; Inamasu, T.; Tamura, R.; Suzuki, H. *Chem. Lett.* **1990**, 1323; (e) Tani, H.; Inamasu, T.; Masumoto, K.; Tamura, R.; Shimizu, H.; Suzuki, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *67*, 261; (f) Karimi, B.; Hazarkhani, H. *Synthesis* **2003**, 2547; (g) Philip, C. B.; Ley, S. V.; Morton, J. A.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 457; (h) Jeko, J.; Timar, T.; Jaszberenyi, J. C. *J. Org. Chem.* **1991**, *56*, 6748; (i) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *Synlett* **2005**, 1483; (j) Jekö, J.; Timar, T.; Jaszberenyi, J. C. *J. Org. Chem.* **1991**, *56*, 6747; (k) Arote, N. D.; Telvekar, V. N.; Akamanchi, K. G. *Synlett* **2005**, 2935.
15. (a) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *J. Org. Chem.* **2002**, *67*, 2572; (b) Firouzabadi, H.; Iranpoor, N.; Garzan, A.; Shaterian, H. R.; Ebrahimzadeh, F. *Eur. J. Org. Chem.* **2005**, 416.
16. *Experimental procedure*: To a solution of carbonyl compound (5 mmol) in acetonitrile (10 mL) and 1,2-ethanedithiol (5.5 mmol) was added EDPBT (0.5 mmol). The reaction mixture was stirred at room temperature. After stirring for 30 min, an additional 2.5 mmol of EDPBT was added to the reaction mixture and stirring was continued at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, acetonitrile was evaporated and the reaction was quenched by adding saturated $NaHCO_3$ solution and the product was extracted with ethyl acetate (2×25 mL). The organic layer was separated and dried over anhydrous sodium sulfate and concentrated. Further purification was accomplished by column chromatography over a short column of silica gel using a mixture of hexane, ethyl acetate as eluent. The aqueous layer containing spent reagent was kept for regeneration.[3,4]

17. (a) Esteban, G.; Lopez, B.; Plumet, J.; del Valle, A. *Heterocycles* **1997**, *45*, 1921; (b) Hiroyuki, T.; Tokuo, I.; Rui, T.; Hitomi, S. *Chem. Lett.* **1990**, 1323; (c) Hiroyuki, T.; Shunsuke, I.; Kazunori, M.; Noboru, O. *Heterocycles* **1993**, *36*, 1783; (d) Benito, A.; Joaquin, P.; Rodriguez-Campos, I. M. *Heterocycles* **1986**, *24*, 141; (e) Verheijen, J. H.; Klossterziel, H. *Synthesis* **1975**, 451; (f) Cristau, H.-J.; Bazbouz, A.; Morand, P.; Torreilles, E. *Tetrahedron Lett.* **1986**, *27*, 2965.
18. *Selected Spectral data*. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (m, 2H), 3.32 (m, 2H), 6.54 (s, 1H), 7.30 (d, 1H, $J = 8$ Hz), 7.47 (t, 1H, $J = 8$ Hz), 7.80 (d, 1H, $J = 8$ Hz), 8.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 27.7, 116.0, 120.8, 122.3, 125.6, 129.4, 131.6, 141.8, 148.4; mass (EI): 239 (M^+). Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, 6H, $J = 6.4$ Hz), 1.83 (m, 1H), 2.44 (d, 2H, $J = 7.2$ Hz), 3.20 (m, 2H), 3.27 (m, 2H), 6.33 (s, 1H), 7.06 (d, 2H, $J = 8$ Hz), 7.31 (d, 2H, $J = 8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 27.1, 28.3, 30.5, 45.3, 111.8, 125.6, 128.1, 129.2, 137.7, 141.5. mass (EI): 250 (M^+). Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (s, 3H), 3.28 (s, 4H), 7.21 (d, 2H, $J = 8.4$ Hz), 7.29 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 29.5, 29.8, 121.2, 121.3, 128.5, 131.0, 133.5, 138.4; mass (EI): 242 (M^+). Compound **16a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (m, 4H), 3.90 (s, 3H), 7.05 (s, 1H), 7.16 (m, 2H) 7.39 (d, 1H, $J = 8.8$ Hz), 8.05 (d, 1H, $J = 9.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 30.3, 55.6, 107.0, 118.7, 119.5, 124.2, 124.8, 126.6, 127.6, 130.8, 132.9, 157.3; mass (EI): 248 (M^+). Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (m, 4H), 1.59 (m, 4H), 2.32 (t, 4H, $J = 6.4$ Hz), 3.14 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 29.5, 30.1, 34.3, 112.5; mass (EI): 200 (M^+). CCDC numbers for compounds **1a** and **16a** are CCDC 626301 and 626302, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.