Synthesis of a 7-(aminomethyl)indole and related bis-indole derivatives

Hakan Kandemir,[a,b] Ibrahim F. Sengul,[a,c] Naresh Kumar,[a] and David StC. Black*[a]

[a] *School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia*
[b] *Department of Chemistry, Faculty of Art and Science, Namık Kemal University, Tekirdag, Turkey*
[c] *Department of Chemistry, Faculty of Science, Gebze Technical University, Kocaeli, Turkey*
E-mail: d.black@unsw.edu.au

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.587

Abstract
A 7-(aminomethyl)indole is a useful precursor to form a new range of unsymmetrical and symmetrical 3-substituted amide-, imine-, and amine-linked 7,7′-bis-indoles. The reduction of an imine linked bis-indole leads to formation of the corresponding amine-linked bis-indole.

Keywords: Indoles, bis-indoles. 7-aminomethylindoles, 7-formylindoles, 7-cyanoindoles

Introduction

The aminomethyl moiety is found in many indole alkaloids which possess biological activity.[1] For example, brassinin **1** and cyclobrassinin **2**, are representative members of the phytoalexin family that have been isolated from cabbage and exhibit antitumor activity.[2] During the last two decades, approximately thirty phytoalexins have been isolated from cruciferous plants. The key intermediate for the synthesis of the phytoalexins is 3-aminomethylindole **3.**[3]

More complex indoles such as bis-indoles are also very important biologically active scaffolds as they are found in many pharmacologically active alkaloids.[4] Moreover, aminomethylindole based bis-indoles have been isolated from natural sources and demonstrate potential as biologically active compounds and useful synthetic targets. For example, bis-indole **4** has been isolated from the roots of *Antirhea lucida*, and synthesized from tryptamine derivatives through acid catalysed nucleophilic substitution of 1-hydroxytryptamine.[5]

Given the various potential applications of bis-indoles, it is important to develop new classes of natural and unnatural bis-indole derivatives. This development can be greatly facilitated by the use of activated indoles which are capable of undergoing reaction at the C7 position.

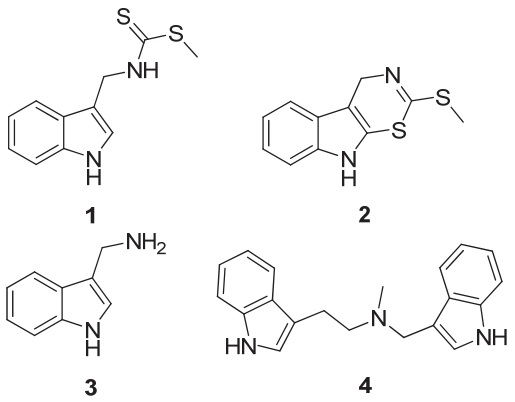
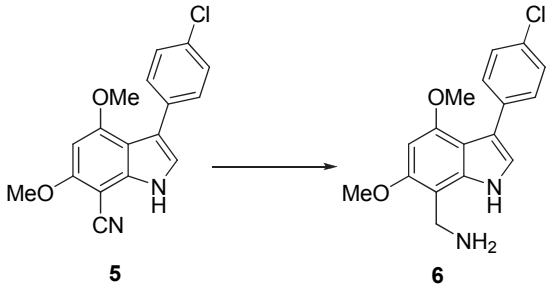


Figure 1. Examples of biologically active aminomethylindoles and derived compounds.

Results and Discussion

Reduction of the 7-cyanoindole[6] **5** was carried out using lithium aluminium hydride in tetrahydrofuran and gave exclusively the 7-aminomethylindole **6** in 73% yield (Scheme 1).

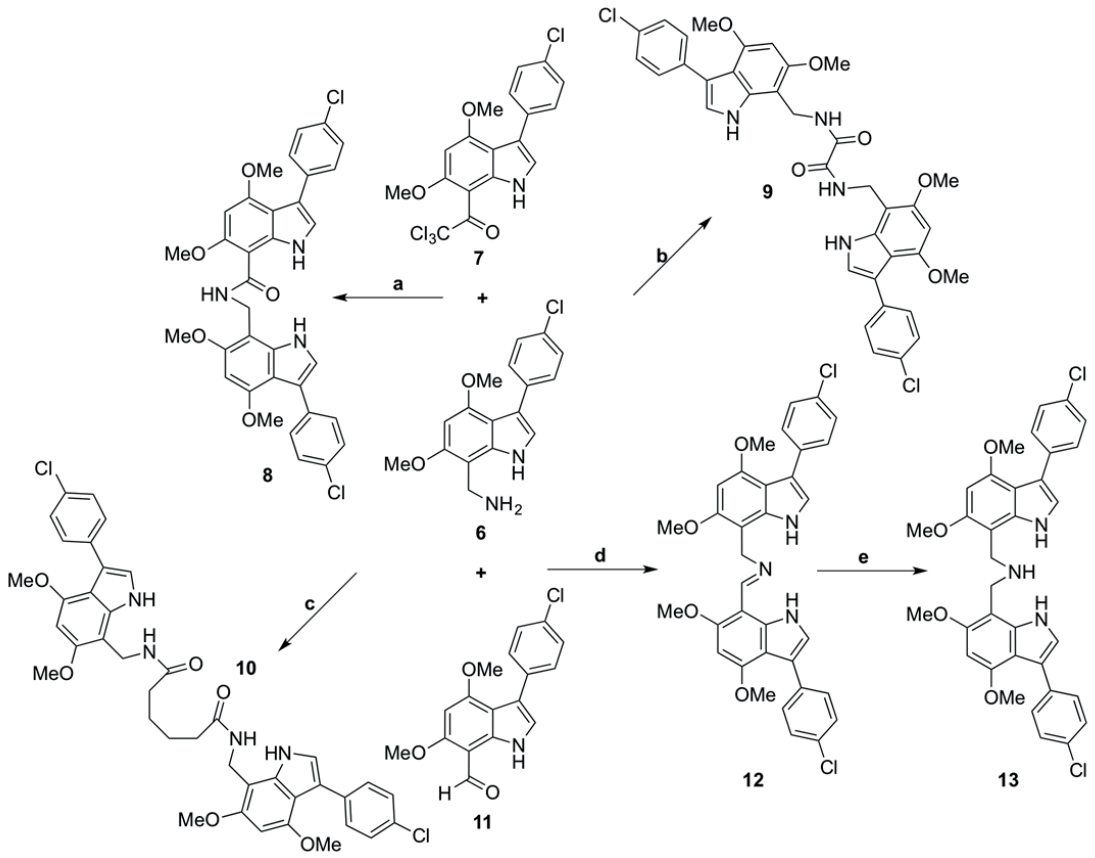


Scheme 1. *Reagent and conditions:* $LiAlH_4$, THF, rt.

The infrared spectrum of the amine **6** showed the characteristic absorptions of the primary amino group at 3368 and 3360 cm^{-1}. The formation of the amine was also deduced from the alkyl protons being present in the ^1H NMR spectrum at 4.15 ppm and a CH_2 signal appearing in the DEPT135 experiment. An *m/z* of 316.0973 was also obtained *via* high resolution mass spectrometry that was consistent with the target structure **6**.

For the construction of 7,7′-linked-bis-indoles two basic strategies have been used. The first involves the formation of symmetrical and unsymmetrical bis-indoles by joining the 7-aminomethyindole scaffold to mono- and bi-functional acyl chloride linkers such as 7-trichloroacetylindole, oxalyl chloride and adipoyl chloride. The amide functionality is one of the most prevalent structural moieties present in polymers, natural products and pharmaceuticals.[7] Accordingly, the first target 7,7′-bis-indole carboxamide **8** was prepared in 83% yield by the

reaction of equimolar amounts of 7-aminomethyindole **6** and 7-trichloroacetylindole **7**[8] in hot acetonitrile (Scheme 2).



Scheme 2. *Reagent and conditions*: (a) Et_3N, CH_3CN, reflux, overnight; (b) oxalyl chloride, Et_3N, DCM, r.t., 1 h; (c) adipoyl chloride, Et_3N, DCM, r.t., 1 h; (d) absolute ethanol, HCl, reflux; (e) $NaBH_4$, THF, absolute ethanol, reflux.

The construction of amide linked bis-indoles **9** and **10** was achieved by the treatment of the indole **6** with 0.5 equivalents of oxalyl chloride and adipoyl chloride respectively in the presence of triethylamine in dichloromethane. Both of the reactions were complete in an hour and the bis-indoles **9** and **10** were afforded in 81% and 86% yield respectively. In the ^{1}H NMR spectrum of compound **10**, for example, the amide NH appeared as a triplet at 8.27 ppm, while the indole NH resonance was observed at 10.91 ppm. The high chemical shift is indicative of strong intramolecular hydrogen bonding. Compound **10** also showed good solubility in deuterated dimethyl sulfoxide, allowing observation of a carbonyl resonance at 173 ppm in the ^{13}C NMR spectrum. Moreover, the CH_2 group resonance was determined both with ^{13}C DEPT135 NMR experiments.

The second strategy was to combine two different indole units which have different functionality, under suitable reaction conditions to form unsymmetrical bis-indoles.

Consequently, the condensation of 7-aminomethylindole **6** with indole-7-carbaldehyde[9] **11** in ethanol gave the imine bis-indole **12** in 75% yield (Scheme 2). The ^{1}H NMR spectrum showed the imine proton at 8.91 ppm and the indole NH resonances at 11.38 ppm and 11.49 ppm, indicating the presence of strong hydrogen bonding within the system. The protons of the four methoxy groups appeared at 3.82, 3.89, 3.90, 3.94 ppm and the H5 and H5′ protons at 6.46 ppm and 6.49 ppm confirming the unsymmetrical nature of the structure. A high resolution mass spectrum further confirmed the structure, showing a molecular ion at 614.1599 $(M+Na)^{+}$. In general, secondary amines have also been prepared from the imines *via* catalytic hydrogenation and reduction with sodium and alcohol.[10]

Following this, the desired amine **13** was prepared by heating the imine **12** with sodium borohydride at reflux in a mixture of ethanol and tetrahydrofuran (Scheme 2). The ^{1}H NMR spectrum of the compound **13** indicated an indole amine, as expected, in combination with the disappearance of the imine bond resonance and the presence of CH_2 resonance at 4.01 ppm, which clearly indicated that the reaction occurred across the double bond as anticipated. Also, ESI mass spectral analysis showed a molecular ion at 616.1768 $(M+H)^{+}$.

Conclusions

In summary, 7-aminomethylindole **6** was synthesised by reduction of the corresponding 7-cyanoindole **5**, and proved to be a useful precursor for a range of 7,7′-bis-indoles. The amide linked bis-indoles were obtained upon reaction of 7-aminomethylindole **6** with acyl chlorides, while an imine linked compound **12** was produced upon reaction with 7-formylindole **11**. The corresponding amine linked bis-indole **13** was obtained through reduction of the imine linkage with sodium borohydride. It is noteworthy that the bis-indoles all contain a nucleophilic unsubstituted C2 position that provides scope for further functionalisation. This rather limited study provides the basis for a simple and general route to a wide range of potentially interesting bis-indole compounds.

Experimental Section

General. All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Melting points were measured using a Mel-Temp melting point apparatus. Microanalyses were performed on a Carlo Erba Elemental Analyses EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX300 and Bruker DPX600 spectrometers. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI). Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Pressure column chromatography was carried out using Merck 230-400 mesh ASTM silica gel. Vacuum column

chromatography was performed using Merck 60H silica gel. Gravity column chromatography was conducted using Merck 70-230 mesh ASTM silica gel, whilst preparative thin layer chromatography was carried out using Merck silica gel 7730 60GF^{254}.

[3-(4-Chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl]methanamine (6). A suspension of lithium aluminium hydride (2.50 g, 65.8 mmol) in anhydrous tetrahydrofuran (30 mL) was cooled in an ice bath and stirred under argon while a solution of the 7-nitrile **5**[6] (2.58 g, 8.26 mmol) in anhydrous tetrahydrofuran (20 mL) was added via a dropping funnel over 30 min. Stirring was continued for 30 min with cooling, followed by stirring at room temperature for 4 h. The mixture was recooled in ice and cautiously treated sequentially with water (5 mL), 5M NaOH (10 mL) and water (10 mL). The resulting granular solid was filtered and washed with ethyl acetate. The combined organic filtrate was washed with brine, dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo*. Recrystallisation from acetonitrile afforded the title compound **6** (1.9 g, 73%) as brown crystals, Mp 179-181 ºC. IR (KBr): ν_{max} 3368, 3360, 1623, 1592, 1464, 1322, 1168, 1085, 938, 795 cm^{-1}. UV-vis (MeOH): λ_{max} 202 nm (ε 24,600 cm^{-1}M^{-1}), 228 (26,000), 281 (12,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.15 (s, 2H, CH_2), 6.24 (s, 1H, H5), 7.24, 7.46 (2d, *J* 8.8 Hz, 4H, aryl H), 7.98 (s, 1H, H2), 9.92 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.1 (CH_2), 55.5, 57.3 (OMe), 89.7 (C5), 123.1 (C2), 127.8, 130.84 (aryl CH), 108.0, 110.2, 116.0, 129.3, 130.0, 135.8, 138.0, 152.9, 153.4 (aryl C). HRMS (+ESI): $C_{17}H_{17}Cl_2N_2O_2$ $[M]^+$ requires 316.0979, found 316.0973.

3-(4-Chlorophenyl)-*N*-((3-(4-chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)-methyl)-4,6-dimethoxy-1*H*-indole-7-carboxamide (8). To a suspension of 7-aminomethylindole **6** (0.50 g, 1.57 mmol) and 7-trichloroacetylindole[8] **7** (0.68 g, 1.57 mmol) in acetonitrile (40 mL), triethylamine (15 drops) was added and the mixture was heated under reflux overnight. After cooling, the reaction mixture was poured into ice-water and the resulting precipitate was filtered, washed with water and recrystallised from ethanol to give the *title compound* **8** (0.82 g, 83%) as a white solid, Mp 234-236 ºC. IR (KBr): ν_{max} 3401, 3207, 2942, 2841, 1596, 1542, 1452, 1325, 1218, 981, 836, 796, 600 cm^{-1}. UV-vis (THF): λ_{max} 214 nm (ε 80,150 cm^{-1}M^{-1}), 284 (32,500). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 3.87 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.01 (s, 3H, OMe), 4.02 (s, 3H, OMe), 4.97 (d, *J* 6.7 Hz, 2H, CH_2), 6.26 (s, 1H, H5), 6.36 (s, 1H, H5′), 7.14 (d, *J* 2.31 Hz, 1H, H2), 7.19 (d, *J* 2.4 Hz, 1H, H2′), 7.31-7.56 (m, 8H, aryl H), 8.69 (m, 1H, NH), 10.65 (bs, 1H, NH), 11.30 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.9 (CH_2), 55.6, 55.8, 57.3, 58.0 (OMe), 87.8 (C5), 89.3 (C5′), 122.4 (C2), 122.7 (C2′), 128.0, 128.1, 131.0, 131.2, 132.6 (aryl CH), 97.8, 104.0, 111.0, 111.4, 117.2, 117.6, 131.6, 134.8, 135.3, 138.9, 139.9, 154.5, 154.6, 157.3, 157.9 (aryl C), 169.2 (C=O). HRMS (+ESI): $C_{34}H_{29}Cl_2N_3O_5$ $[M+Na]^+$ requires 652.1382, found 652.1373.

Bis-((3-(4-chlorophenyl)-4,6-dimethoxyindol-7-yl)-methyl)-oxalamide (9). Oxalyl chloride (0.05 mL, 0.60 mmol) in dry dichloromethane (10 mL) was added dropwise over 10 min to a solution of 7-aminomethylindole **6** (0.31 g, 0.97 mmol) in dry dichloromethane (18 mL) containing triethylamine (0.13 mL, 0.97 mmol) and the mixture was stirred at room temperature

for 1 h. The solvent was then evaporated and the residue was quenched with water. The resulting precipitate was filtered, dried and washed with hot methanol and *n*-hexane to yield the *title compound* **9** (0.27 g, 81%) as a pale yellow solid. Mp 278-280 ºC. IR (KBr): ν_{max} 3286, 2935, 1637, 1521, 1327, 1218, 1155, 1109, 798 cm^{-1}. UV-vis (THF): λ_{max} 215 nm (ε 101,600 $cm^{-1}M^{-1}$), 284 (42,450). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H, OMe), 3.85 (s, 6H, OMe), 4.64 (d, *J* 6.9 Hz, 4H, CH_2), 6.20 (s, 2H, H5), 6.93 (d, *J* 2.4 Hz, 2H, H2), 7.21, 7.39 (2d, *J* 8.6 Hz, 8H, aryl H), 7.95 (m, 2H, NH), 9.56 (bs, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.8 (CH_2), 55.5, 57.6 (OMe), 89.8 (C5), 123.2 (C2), 127.8, 130.9 (aryl CH), 101.6, 110.2, 116.2, 130.1, 135.5, 137.9, 153.9, 154.4 (aryl C), 160.2 (C=O). HRMS (+ESI): $C_{36}H_{32}Cl_2N_4O_6$ $[M]^+$ requires 686.1699, found 686.1693. (Found: C, 63.25; H, 4.95; N, 7.85; $C_{36}H_{32}Cl_2N_4O_6$ 0.1 C_6H_{14} requires C, 63.14; H, 4.84; N, 8.05%).

***N*1,*N*3-Bis{[3-(4-chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl]methyl}adipic diamide (10).** Adipoyl chloride (0.06 mL, 0.41 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of 7-aminomethylindole **6** (0.21 g, 0.65 mmol) in dry dichloromethane (10 mL) containing triethylamine (0.09 mL, 0.65 mmol) and the reaction mixture stirred at room temperature for 1 h. The solvent was then evaporated and the residue was quenched with water. The resulting precipitate was filtered, dried and recrystallised from methanol to yield the *title compound* **10** (0.19 g, 86%) as a white solid. Mp 258-260 ºC. IR (KBr): ν_{max} 3314, 2936, 2839, 1612, 1536, 1428, 1326, 1218, 1157, 788 cm^{-1}. UV-vis (THF): λ_{max} 229 nm (ε 83,300 $cm^{-1}M^{-1}$), 284 (37,770). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47 (s, 4H, CH_2), 2.10 (s, 4H, CH_2), 3.81 (s, 6H, OMe), 3.86 (s, 6H, OMe), 4.44 (d, *J* 5.4 Hz, 4H, CH_2-NH), 6.43 (s, 2H, H5), 7.28 (d, *J* 2.4 Hz, 2H, H2), 7.29-7.57 (m, 8H, aryl H), 8.27 (m, 2H, NH), 10.91 (d, *J* 2.1 Hz, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): *δ* 25.4, 35.2 (CH_2), 32.9 (CH_2-NH), 55.6, 57.4 (OMe), 89.6 (C5), 123.2 (C2), 127.8, 130.9 (aryl CH), 102.8, 110.0, 116.2, 130.9, 135.5, 138.3, 153.8, 154.1 (aryl C), 173.7 (C=O). HRMS (+ESI): $C_{40}H_{40}Cl_2N_4O_6$ $[M]^+$ requires 743.2403, found 743.2403. (Found: C, 64.03; H, 5.44; N, 7.39; $C_{40}H_{40}Cl_2N_4O_6$ 0.05 CH_2Cl_2 requires C, 64.32; H, 5.40; N, 7.49%).

1-(3-(4-Chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)-N-((3-(4-chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)-methylene)-methanamine (12). A mixture of 7-aminomethylindole **6** (0.14 g, 0.45 mmol) and 7-carbaldehyde **11** (0.14 g, 0.45 mmol) was heated under reflux in absolute ethanol (30 mL) for 24 h. The precipitate obtained was filtered, washed with water and dried. The crude product was purified by flash chromatography using dichloromethane/ethyl acetate (90:10) as eluent to yield the *title compound* **12** (0.21 g, 75%) as a white solid. Mp 221-223 ºC. IR (KBr): ν_{max} 3453, 1623, 1594, 1341, 1216, 1146, 1093, 788 cm^{-1}. UV-vis (THF): λ_{max} 225 nm (ε 85,430 $cm^{-1}M^{-1}$), 307 (35,430). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.02 (s, 1H, CH_2), 6.46 (s, 1H, H5), 6.49 (s, 1H, H5′), 7.30-7.59 (m, 10H H2+H2′, aryl H), 8.91 (s, 1H, CH), 11.38 (d, *J* 2.3 Hz, 1H, NH), 11.49 (bs, 1H, NH). HRMS (+ESI): $C_{34}H_{29}Cl_2N_3O_4$ $[M+H]^+$ requires 614.1569, found 614.1599. The sample was not soluble enough for ^{13}C NMR measurement.

Bis-((3-(4-chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)methyl)amine (13). To a solution of bis-indole **12** (0.08 g, 0.13 mmol) in a mixture of absolute ethanol/tetrahydrofuran (30 mL) (1:1), sodium borohydride (1.00 g, 26.3 mmol) was added and the mixture was heated under reflux for 8 h. The solvent was removed under reduced pressure, and the residue was treated with water and neutralized using dilute hydrochloric acid (2 M). The resulting precipitate was filtered, dried and recrystallised from dichloromethane/*n*-hexane to afford the *title compound* **13** (0.05 g, 65%) as a white solid. Mp 134-136 ºC. IR (KBr): ν_{max} 3307, 2933, 2836, 1622, 1597, 1540, 1518, 1463, 1329, 1201, 1123 cm^{-1}. UV-vis (THF): λ_{max} 305 nm (ε 29,800 $cm^{-1}M^{-1}$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H, OMe), 3.78 (s, 6H, OMe), 4.01 (s, 4H, CH_2) 6.23 (s, 2H, H5), 6.83 (s, 2H, H2), 7.22, 7.41 (2d, *J* 8.6 Hz, 8H, aryl H), 9.29 (bs, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.9 (CH_2), 55.3, 57.0 (OMe), 88.9 (C5), 121.7 (C2), 127.7, 130.6 (aryl CH), 110.6, 117.4, 131.4, 134.6, 138.5, 154.1, 154.5 (aryl C). HRMS (+ESI): $C_{34}H_{31}Cl_2N_3O_4$ $[M+H]^+$ requires 616.1770, found 616.1768.

Acknowledgements

We thank the University of New South Wales and the Turkish Government for their financial support.

References

1. Moron, J. A.; Campillo, M.; Perez, V.; Unzeta, M.; Pardo, L. *J. Med. Chem.* **2000**, *43*, 1684-1691.
2. http://dx.doi.org/10.1021/jm991164x
3. Csomos, P.; Fodor, L.; Sohar, P.; Bernath, G. *Tetrahedron* **2005**, *61*, 9257-9262. http://dx.doi.org/10.1016/j.tet.2005.07.068
4. Pedras, M. S. C.; Jha, M.; Ahiahonu, P. W. K. *Curr. Org. Chem*. **2003**, *7*, 1635-1647. http://dx.doi.org/10.2174/1385272033486242
5. Hollingsworth, M. D.; Ward, M. D. *Chem. Mater*. **1994**, *6*, 1087-1093. http://dx.doi.org/10.1021/cm00044a001
6. Somei, M.; Yamada, F.; Morikawa, H. *Heterocycles* **1997**, *46*, 91-94. http://dx.doi.org/10.3987/COM-97-S33
7. Wahyuningsih, T. D.; Kumar, N.; Nugent, S. J.; Black, D. StC. *Tetrahedron* **2005**, *61*, 10501-10506.
8. http://dx.doi.org/10.1016/j.tet.2005.08.049
9. Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev*. **1997**, *97*, 2243-2266. http://dx.doi.org/10.1021/cr950005s

10. Jones, A. W.; Purwono, B.; Bowyer, P. K.; Mitchell, P. S. R.; Kumar, N.; Nugent, S. J.; Jolliffe, K. A.; Black, D. StC. *Tetrahedron* **2004**, *60*, 10779-10786. http://dx.doi.org/10.1016/j.tet.2004.08.086
11. Bowyer, P. K.; Black, D. StC.; Craig, D. C.; Rae, A. D.; Willis, A. C. *J. Chem. Soc*., *Dalton Trans*. **2001**, 1948-1958. http://dx.doi.org/10.1039/b101350p
12. Sommers, A. H.; Aaland, S. E. *J. Org. Chem*. **1956**, *21*, 484-485. http://dx.doi.org/10.1021/jo01110a612

