Aust. J. Chem., 1995, **48**, 1425–1436

Synthesis of 4-[ω-(3-Thienyl)alkyl]pyridines and 4-[ω-(3-Thienyl)alkyl]-2,2′-bipyridines

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Abstract

The synthesis is reported of 4-[ω-(3-thienyl)alkyl]pyridine (2), 4-[ω-(3-thienyl)alkyl]-2,2′-bipyridine (3) and 4-methyl-4′-[ω-(3-thienyl)alkyl]-2,2′-bipyridine (4), where the length of the alkyl chain is varied (n = 2, 5, 7, 9, 11). The synthetic methodology involved the reaction of the 3-(ω-bromoalkyl)thiophen with the anions derived from 4-methylpyridine, 4-methyl-2,2′-bipyridine or 4,4′-dimethyl-2,2′-bipyridine by lithiation. The n.m.r. (^{1}H and ^{13}C) and electronic spectral characteristics of the compounds are discussed.

Introduction

The formation of adherent polymer films on electrode surfaces by electropolymerization of stable monomers is an important means of electrode modification.[1,2] The resultant films may vary widely in character, and be conducting (as in the case where they are derived from heterocycles such as pyrrole or thiophen) or non-conducting (for example, when they are based on a polyvinyl framework).[2] The incorporation of redox-active centres within films of both types has been achieved, with the aim of inducing specific catalytic activity, and also of probing of factors which affect the electron and ion transfer processes within the films themselves.[3–7]

Of interest in the present study was the incorporation of metallated redox-active centres in polymer-coated electrodes formed from monomers with an appended

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Manuscript received 2 February 1995 0004-9425/95/081425$05.00

N-heterocyclic group that may act as a ligand for metal coordination. Earlier work on the introduction of redox-active centres into polymers utilized pyrrole as the basic monomer unit, and many examples of alkylated pyrroles bearing pyridyl-based ligands have been reported.[8–15] Pyrrole has proved itself to be a convenient synthetic starting point, the ease of alkylation at the nitrogen being one reason for its early popularity.

An alternative monomer unit, thiophen, has received more limited attention presumably because of the greater difficulties associated with its derivatization. Although there are a significant number of examples in the literature of thiophens alkylated at the 3-position,[16–18] there are few reports of the attachment of *N*-heterocycles to the thiophen moiety. Mirrazaei *et al.* have reported the synthesis of two 3-substituted thiophens attached to tris(2,2′-bipyridine)iron redox centres through vinyl or ether linkages between the thiophen and bipyridyl groups in the 5-position.[19] Thiophen attached to pyridine with methine and ethine linkages has recently been reported.[20]

A recent publication by Bäuerle *et al.*[21] reported the synthesis of a series of 3-(ω)-haloalkyl)thiophens (1) for $n = 4$–6, 8 and 10. These species provide access to a range of 3-substituted thiophens, including functionalization by potentially ligating species which may be attached to metal centres. We undertook the synthesis of such thiophen derivatives with *N*-heterocyclic substituent groups, where the length of the alkyl linkage between the thiophen and pyridyl (or bipyridyl) moieties was systematically varied from 2 to 11, with the ultimate aim of investigating the electrochemical characteristics of their electropolymerized films and the metallated analogues. A particular interest was the effect exerted on those properties as the alkyl bridge between the two entities was systematically lengthened. New synthetic procedures were required to produce the desirable monomers, containing either pyridyl or bipyridyl ligands attached from the 4-position of the *N*-heterocycle through a saturated alkyl chain to the 3-position of thiophen. This paper reports the synthesis of 4-[ω-(3-thienyl)alkyl]pyridine (2), 4-[ω-(3-thienyl)alkyl]-2,2′-bipyridine (3) and 4-methyl-4′-[ω-(3-thienyl)nonyl]-

[8] Mao, H., and Pickup, P. G., *J. Am. Chem. Soc.*, 1990, **112**, 1776.
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[13] De Giovani, W. F., and Deronzier, A., *J. Electroanal. Chem.*, 1992, **337**, 285.
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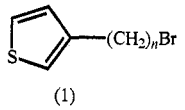
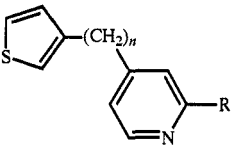
[21] Bäuerle, P., Würthner, F., and Heid, S., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 419.

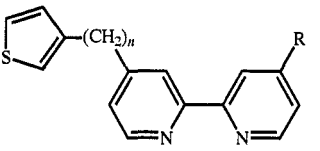
2,2′-bipyridine (4). Detailed electrochemical studies of the polymerized films will be reported subsequently.



(1)



(2a–e; n = 2, 5, 7, 9, 11)



(3a–e; n = 2, 5, 7, 9, 11) R = H
(4; n = 9) R = CH_3

Results and Discussion

The key step in the syntheses of the target molecules (2)–(4) was seen to be the coupling of the thiophen and *N*-heterocyclic moieties through an alkyl chain. The decision was made to extend the chain from thiophen rather than the *N*-heterocycles after some unsuccessful preliminary Grignard and Wittig reaction trials using 4-(ω-bromoalkyl)-4′-methyl-2,2′-bipyridine. Three possible strategies were considered: (i) Wittig coupling using the triphenyl phosphonium salt derived from a ω-bromoalkyl chain extended from thiophen; (ii) catalysed coupling of Grignard reagents formed from (ω-bromoalkyl)thiophens; and (iii) coupling of (ω-bromoalkyl)thiophens with the anion formed from 4-methyl-*N*-heterocycles by lithiation.

Of these, (iii) ultimately proved the most tractable and was the preferred synthetic route. As all three strategies involved the use of a family of 3-(ω-bromoalkyl)thiophens (1) as precursors, the synthesis of (1) was an initial goal before an investigation of the coupling step was undertaken.

Synthesis of 3-(ω-Bromoalkyl)thiophen (1)

The production of (1) used the three-step synthetic pathway described by Bäuerle *et al.*[21] (Scheme 1), which allowed access to a series of homologues where the length of the alkyl chain varied with $n = 4$, 6, 8 or 10. Attempts were made to eliminate the protection/deprotection steps [Scheme 1, (i) and (iv)] by using α-bromo-ω-chloroalkanes in the catalysed Grignard coupling reaction [(ii) and (iii)]. It is known[22] that in haloalkanes where both bromide and chloride substituents are present, mono-Grignard formation can occur exclusively at the bromide, leaving the chloride intact, provided the alkyl chain between the halides has more than two carbon atoms. Unfortunately in the present case, the consumption of both halides was found to occur, reinforcing the utility of the protection step (i)[23] of Scheme 1 to produce (1). Both protection and deprotection steps generally proceeded with good yields (65–80%, except where $n = 4$), and products were easy to purify by either distillation or chromatography. A yield of 35% was obtained in the deprotection to produce 3-(ω-bromobutyl)thiophen, lower than that reported (51%) in earlier work done by Bäuerle *et al.*[21]

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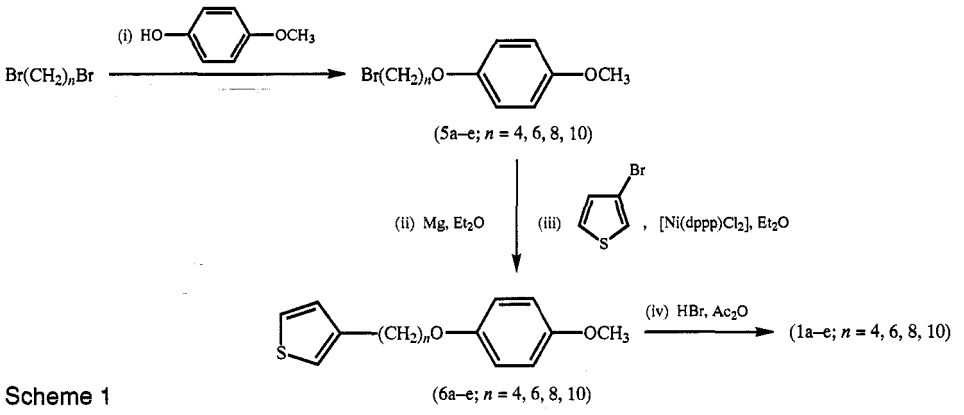
[23] Ashley, J. N., Collins, R. F., Davis, M., and Sirett, N. E., *J. Chem. Soc.*, 1958, 3298.



Scheme 1

The second step in Scheme 1 [the formation of the Grignard reagent (ii) and its catalysed coupling with 3-bromothiophen (iii)][21,24] gave excellent yields. Quantitative production of the Grignard reagent (based on unused magnesium) was possible as long as the magnesium had been sufficiently activated.[25] The method of activation was to rinse magnesium turnings in distilled diethyl ether, heat under vacuum to ensure dryness, and then stir overnight under an atmosphere of dry nitrogen. Slow, controlled addition of monoprotected alkyl bromide to the magnesium with constant reflux was essential to eliminate Wurtz-type[22] coupling. The second stage of the reaction (the catalysed coupling of 3-bromothiophen with the alkylmagnesium bromides) was achieved by refluxing the reagents overnight in diethyl ether in the presence of 0·1–1 mol % 1,3-bis(diphenylphosphino)propanenickel(II) chloride [Ni(dppp)Cl_2],[26] which produced the compounds (6b; $n = 4$), (6c; $n = 6$), (6d; $n = 8$) and (6e; $n = 10$) in high yields (80–97%). The lowest yield (80%) was observed for 3-[ω-(4-methoxyphenoxy)butyl]thiophen (6b), where there was a small amount of a by-product formed [ω-(4-methoxyphenoxy)but-1-ene].

The ^{1}H n.m.r. spectral data ($CDCl_3$ solvent) for the compounds (5), (6) and (1) are given in supplementary Tables S1–S3, respectively.†

It is noted that in these reactions where $n = 3$ and $n = 2$ (i.e. starting with 1,3-dibromopropane[21] and 1,2-dibromoethane), elimination was extensive during the Grignard step (ii).

An alternative strategy was used to produce the shortest alkyl chain ($n = 1$) homologue of (1). A photochemically initiated free-radical bromination of 3-methylthiophen with *N*-bromosuccinimide[27] produced the desired product (1; $n = 1$) in 78% yield. The reaction was undertaken in CCl_4, in which solvent succinimide, formed as the reaction proceeds, is insoluble and was removed by filtration. The product was found to be unstable, with slow decomposition over several days, and so was immediately used in the next stage of the synthesis.

† Copies of the supplementary Tables (Tables S1–S5) are available from the Australian Journal of Chemistry, P.O. Box 89, East Melbourne, Vic. 3002.

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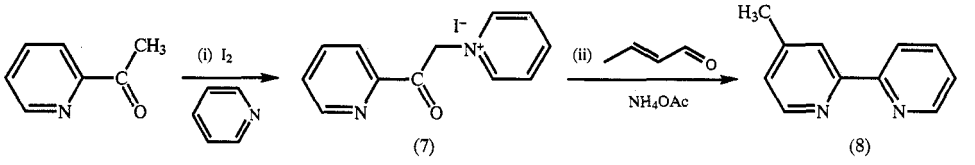
[25] Baker, K. V., Brown, J. M., Hughes, N., Skarnulis, A. J., and Sexton, A., *J. Org. Chem.*, 1991, **56**, 698.
[26] Wecke, G. R. V., and Horrocks, W. D., *Inorg. Chem.*, 1966, **5**, 1968.
[27] Futurama, S., and Zong, Z. M., *Bull. Chem. Soc. Jpn*, 1992, **65**, 345.

Synthesis of 4-Methyl-2,2'-bipyridine (Mebpy) (8)

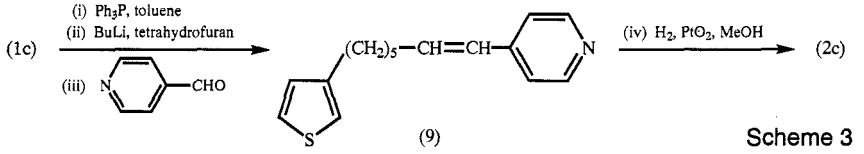
The synthetic procedure for 4-methyl-2,2'-bipyridine (8) is shown in Scheme 2.[28–30] The principle of the method has been discussed by Kröhnke.[28] A modified method was used here, involving isolation and purification of the iodide intermediate (7)[29] as well as the addition of some water in the second step. The addition of water elevated the reflux temperature from 64 to 75–85°C and this may be a key factor in improving the yield from 10%[29] to over 50%. A further improvement was also possible for the final purification procedure through the formation of the $[Fe(Mebpy)_3]^{2+}$ complex, this facilitating the elimination of organic impurities that were otherwise difficult to remove.[30]



Scheme 2

Wittig Coupling of 3-(ω-Bromoalkyl)thiophens with Pyridine-4-carbaldehyde and 4'-Methyl-2,2'-bipyridine-4-carbaldehyde

Mirrazaei *et al.*[19] have utilized a Wittig coupling to produce an unsaturated bridge between thiophen and a bipyridyl moiety. In the present work, the methodology had the immediate drawback of requiring a hydrogenation step to reach the target molecule from the Wittig product. The method is shown in Scheme 3, the reaction of (1c) with pyridine-4-carbaldehyde being used as an example. Although the synthetic route was successful, yields were poor (less than 20%). The phosphonium salts proved almost intractable as they adhered to the walls of the reaction flasks, making isolation very difficult. Interestingly, in the n.m.r. spectra, the resonances for the olefinic protons were observed relatively downfield of normal olefinic protons. The proximity to the aromatic system presumably allowed delocalization of the electrons, thus causing pseudo-aromatic behaviour. Proton shifts in the n.m.r. spectra indicated that only one geometric isomer had formed, this being tentatively assigned as the *cis* isomer on the basis of the coupling values of 12 Hz.[31]



Scheme 3

[28] Kröhnke, F., *Synthesis*, 1976, 1.
[29] Treffert-Ziemelis, S. M., Golus, J., Strommen, D. P., and Kincaid, J. R., *Inorg. Chem.*, 1993, **32**, 3890.
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Catalysed Coupling of the Grignard Reagent Formed from 3-(ω-Bromoalkyl)thiophens with 3-Bromopyridine

The reaction was investigated in which the Grignard reagents generated from 3-(ω-bromoalkyl)thiophens were reacted with 3-bromopyridine, in an analogous procedure to the catalysed Grignard coupling reaction in Scheme 1 [(ii) and (iii)]. Unfortunately, this method was not totally successful; ^{1}H and ^{13}C n.m.r. spectra confirmed the generation of the desired product after purification by chromatography, but the yield was very low (less than 10%) and the purification was difficult. This result was not entirely unexpected because the reactions of halopyridines with Grignard reagents generally occur in rather low yields.[32,33] Tamao *et al.* have reported the preparations of 3-butylpyridine with a yield of 47%,[24] but in the present case significantly lower yields were observed in the synthesis of 3-[ω-(3-pyridyl)butyl]thiophen. This reaction scheme was not pursued further.

Coupling of 3-(ω-Bromoalkyl)thiophens with the Carbanion Formed from 4-Methylpyridine, 4-Methyl-2,2′-bipyridine or 4,4′-Dimethyl-2,2′-bipyridine by Lithiation (Scheme 4)

This strategy proved to be the best method for coupling (1) with 4-methylpyridine, 4-methyl-2,2′-bipyridine and 4,4′-dimethyl-2,2′-bipyridine. Carbanions may be formed in high yield by deprotonation of a methyl substituent in *N*-heterocyclic ring systems by using a lithium salt of an amine anion (such as lithium diisopropylamide).[34,35] Such anions have been used extensively[35–38] for the elaboration of alkyl substituents on these systems. They react smoothly with electrophiles, and bromides are known[36] to react readily and cleanly with the lithiated methyl groups, following the mechanism of nucleophilic substitution. The highly coloured carbanions are stable for moderate periods at low temperatures. In the case of the 4,4′-dimethyl-2,2′-bipyridine, monolithiation at only one methyl group can be successfully achieved by an addition of 1 equiv. of base,[35] and allowing the reaction to stir over about 30 min. Lithiated methyl intermediates reacted readily with (1) to produce the target series of compounds.

The relative stabilities of the generated carbanions varied with the number of pyridyl rings. Whereas the 4-methylpyridine anion was stable at 0°C (orange solution), the dark purple/deep red 4-methyl-2,2′-bipyridine anions were found to require lower temperatures (−78°C) to minimize losses by adventitious quenchers before the reaction with the 3-(ω-bromoalkyl)thiophens was complete. The reaction rates of these larger carbanions were considerably slower than those of the methylpyridines. This is consistent with steric considerations[39] in a nucleophilic substitution process. There was no evidence to indicate dependence of reaction

[32] Ryang, H. S., and Sakurai, H., *J. Chem. Soc., Chem. Commun.*, 1972, 594.
[33] Wynberg, H., Van Bergan, T. J., and Kellogg, R. M., *J. Org. Chem.*, 1969, **34**, 3175.
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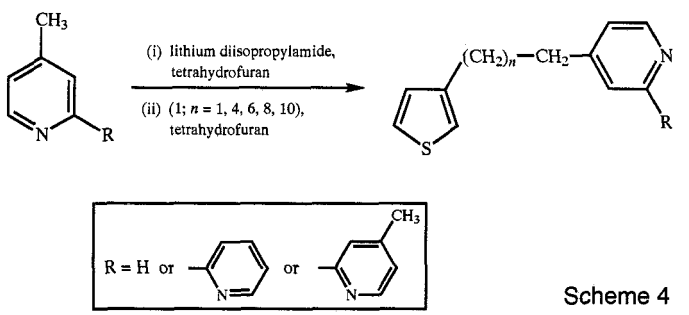
[39] Hartshorn, S. R., 'Aliphatic Nucleophilic Substitution' p. 33 (Cambridge University Press: London 1973).

rate on the length of the alkyl chains attached to the thiophen, again consistent with the mechanism of substitution at a primary alkyl halide. As an exception, the coupling of 3-bromomethylthiophen was markedly more rapid than the longer chained thiophens. This may be indicative of the benzylic bromide producing a cation sufficiently stabilized to allow an S_N1-type mechanism.[39] The formation of the target monomers was completed by this coupling strategy in yields that ranged from 40 to 75%.

The chemical structures of 4-[ω-(3-thienyl)alkyl]pyridines (2) and 4-[ω-(3-thienyl)alkyl]-2,2′-bipyridines (3) were analysed by ^1H and ^{13}C n.m.r. spectra; the resonances and their assignments are available in supplementary Tables S4 and S5. Representative data are given for the respective species with $n = 2$ and 11 in the Experimental section. The spectra of 4-[ω-(3-thienyl)undecyl]pyridine (2e; $n = 11$) are summarized as an illustrative example. In the ^1H spectrum, resonances at δ 8·47 and 7·07 arise from protons on the pyridine ring, and at δ 7·21, 6·92 and 6·90 from protons on the thiophen ring. In the aliphatic region, evidence of connection of thiophen to pyridine by the undecyl chain is provided by the resonances at δ 2·61 and 2·57: two close triplets are assigned to the protons attached to C 1′ (attached to thiophen) and C 11′ (attached to pyridine) of the undecyl chain, respectively. The four protons connected to C 2′ and C 10′ of the alkyl chain appear as a multiple peak centred at δ 1·61. In the ^{13}C spectrum, resonances at δ 151·5 and 143·0 are assigned to C 4″ of pyridine and C 3 of thiophen. In the undecyl chain, the C 11′ connected to pyridine ring is observed at δ 35·1, and C 1′ (connected to the thiophen ring) at δ 30·4. Signals arising from the other carbon atoms of the undecyl chain are in the range δ 29–30·1.



Scheme 4

In the ^1H n.m.r. spectrum of the analogous bipyridine derivative, (3e; $n = 11$) two protons at 6-positions of the pyridine rings appear at δ 8·69 and 8·55, downfield of the α-protons of the pyridine ring in (2e). The signal at δ 8·40, with coupling constants $^3J_{3''',4'''}$ 8·1 and $^4J_{3''',5'''}$ 0·9 Hz, is assigned to the proton at the 3‴-position. A simple peak with an insignificant split at δ 8·23 corresponds to the proton at the 3″-position of the bipyridine. These two protons are downfield of the β-protons of pyridine in (2e) because of the effect of the second pyridine ring. The resonances of the protons of the thiophen ring are similar to those observed for the 4-[ω-(3-thienyl)alkyl]pyridines. In the aliphatic region, four protons connected to C 2′ and C 10′ of the alkyl chain show a larger separation of the peaks (δ 2·69 and 2·61 respectively) compared with the equivalent protons in 4-[ω-(3-thienyl)alkyl]pyridines. The other assignments are listed in Table S4.

The ^1H and ^{13}C n.m.r. spectra of the other 4-[ω-(3-thienyl)alkyl]pyridines and 4-[ω-(3-thienyl)alkyl]-2,2′-bipyridines may be rationalized in a similar manner. $^1H,^1H$-COSY two-dimensional and $^1H,^{13}C$-correlated two-dimensional n.m.r. spectra confirmed the connectivities given in supplementary Tables S4 and S5.

Ultraviolet Spectroscopic Analysis of 4-[ω-(3-Thienyl)alkyl]pyridines (2) and 4-[ω-(3-Thienyl)alkyl]-2,2′-bipyridines (3)

In 4-[ω-(3-thienyl)alkyl]pyridines (2), absorptions arising from $\pi \rightarrow \pi^*$ transitions occur with λ_{max} at 194–196, 204–210 and 238 nm, with a shoulder at 264 nm, in acetonitrile solution. For (3), λ_{max} are observed at 212, 240 and 275 nm, with two shoulders at 194–196 and 286–288 nm. Thiophen has been reported to have λ_{max} at 204–220 and 221–260 nm (in hexane),[40–42] and pyridine at 256 and 281 nm (shoulder) in cyclohexane.[43] Because of the effect of the alkyl chain, the $\pi \rightarrow \pi^*$ bands of (2) and (3) are shifted to longer wavelengths, consistent with a previous report.[43] There do not appear to be significant dependencies of λ_{max} on the length of alkyl chain for either series, particularly (3).

Conclusions

A methodology has been developed for the synthesis of (2)–(4) with different alkyl chain lengths in the range $n = 2$–11, involving the reaction of the appropriate 3-(ω-bromoalkyl)thiophen with the carbanions derived from 4-methylpyridine, 4-methyl-2,2′-bipyridine or 4,4′-dimethyl-2,2′-bipyridine by lithiation. The products have been characterized by ^1H and ^{13}C n.m.r. spectroscopy.

Experimental

Materials

For Grignard reactions, magnesium turnings (AJAX) were washed sequentially with 1 M HCl (twice), H_2O, ethanol and dry diethyl ether (Et_2O), dried overnight under vacuum at 100°C, then stirred for 2 days under dry nitrogen at room temperatures.[25] Dry Et_2O was refluxed and distilled from sodium benzophenone ketyl prior to use. 1,3-Bis(diphenylphosphino)propanenickel(II) chloride ([Ni(dppp)Cl_2]; Strem) and ω-(*p*-methoxyphenoxy)alkyl bromides were dried under vacuum. 3-Bromothiophen (Aldrich) and 4-methylpyridine (Aldrich) were distilled and stored over 4 Å molecular sieves. *N*-Bromosuccinimide (Fluka) was recrystallized from hot water and dried under vacuum. Pyridine (AJAX; L.R.) was freshly distilled under nitrogen from KOH onto 5 Å molecular sieves. All the solvents used for recrystallization and chromatography were distilled prior to use. The light petroleum used had a boiling point range of 40–60°C. All solvents for synthesis, except CCl_4 (M & B; A.R. grade), were of laboratory grade and used without further purification. Acetonitrile (Fluka; for u.v. spectroscopy) was used without further purification. 2-Acetylpyridine (Aldrich; 99+%), crotonaldehyde (Aldrich; 99+%), iodine (Aldrich; 99·8%), ammonium acetate (BDH; A.R.), acetic anhydride (Aldrich; 99+%) and hydrobromic acid (Aldrich; 48%) were used without further purification. Butyllithium (Aldrich) and lithium diisopropylamide mono(tetrahydrofuran) (Aldrich) were purchased as solutions in cyclohexane, and the concentrations checked by titration against 2,2,2′-trimethylpropionanilide. Aluminium oxide (Fluka Type 507C, neutral; Aldrich activated basic Brockmann 1) and silica gel (Merck; Kieselgel 60H) were used for chromatography.

4-Methyl-2,2′-bipyridine (Mebpy) (8) was synthesized as described elsewhere.[29,30]

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Spectroscopic Measurements

^{1}H (300 MHz) and ^{13}C (75 MHz) n.m.r. spectra were recorded on a Bruker AM300 Fourier-transform spectrometer. U.v./vis. spectra were recorded by using an HP 8452A Diode Array spectrophotometer.

Syntheses

ω-(4-Methoxyphenoxy)alkyl Bromides (5b–e; n = 4, 6, 8, 10)

The syntheses followed literature procedures.[21,23] The compounds (5b) [73% yield, b.p. 129–130°C/0·3 mm, m.p. 41–42°C (lit.[23] 42–44°C)] and (5c) [80% yield, b.p. 148–150°C/0·3 mm, m.p. 49–50°C (lit.[44] 47°C)] were purified by distillation. The reaction mixtures for (5d,e) were distilled to remove the dibromides, and the residues recrystallized from n-hexane (A.R.). Filtration realized white crystals which were dried under high vacuum at 45°C for several days: (5d), yield 67%, m.p. 54–55°C; (5e), yield 72%, m.p. 62–63°C (lit.[45] 61–62°C). The ^{1}H n.m.r. spectral data of (5b–e) are available in supplementary Table S1.

3-[ω-(4-Methoxyphenoxy)alkyl]thiophens (6b–e; n = 4, 6, 8, 10)

All glassware was dried at 130° overnight and cooled in a desiccator prior to use. Reactions were performed under high purity nitrogen. Compound (5) (0·11 mol) in dry Et_2O (300 cm^3) was added to magnesium turnings (5·4 g, 0·22 mol) in dry Et_2O (50 cm^3) over 5–6 h, with stirring and gentle refluxing of the solution. The reaction mixture was then refluxed for 1 h. The Grignard solution of (5) was subsequently transferred via cannula to another dried apparatus and added dropwise at 0°C to a mixture of [Ni(dppp)Cl_2] (0·3 g, 0·5 mol %) and 3-bromothiophen (19·5 g, 0·12 mol) over 1 h. The reaction mixture was refluxed for 12–15 h. The resultant solution was hydrolysed with an iced aqueous solution of 0·2 M HCl (200 cm^3) at 0°C followed by extraction with several portions of Et_2O. The organic phase was washed to neutrality with water and dried with anhydrous sodium sulfate before the solvent was removed under vacuum giving a yellowish-white material which was recrystallized from hexane or methanol to give (6). Yields: (6b) (77%), (6c) (90%), (6d) (96%), (6e) (97%). The low melting point compounds were characterized by comparison of their ^{1}H n.m.r. spectra (supplementary Table S2) with those reported in the literature.[21]

3-(ω-Bromoalkyl)thiophens (1b–e; n = 4, 6, 8, 10)

The syntheses followed a method modified from that described by Bäuerle *et al.*[21] Acetic anhydride (112 g, 1·1 mol) was added to 48% HBr (76 cm^3, 0·67 mol) dropwise with stirring at 0°C. This mixture was then added to (6) (0·112 mol) under nitrogen, and the reaction mixture was heated at 100°C for 20–25 h. After dilution with water, the mixture was extracted with Et_2O. The combined organic phase was washed to neutrality with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After removal of solvent, a mixture of Et_2O and light petroleum was added until a dark green precipitate formed. After cooling, the precipitate was filtered off, and the filtrate reduced to a small volume. The crude product was purified by column chromatography [silica gel (7×10 cm); eluent light petroleum]. Removal of solvent provided white crystals [(1b) yield 35%] or colourless oils [(1c) (65%), (1d) (70%), (1e) (71%)] as the product. The compounds were characterized by comparison of their ^{1}H n.m.r. spectra (supplementary Table S3) with those reported in the literature.[21]

3-Bromomethylthiophen (1a; n = 1)

A mixture of *N*-bromosuccinimide (4·45 g, 25 mmol) and CCl_4 (80 cm^3) was added gradually over 0·5 h to a vigorously refluxed solution of 3-methylthiophen (2·03 g, 21 mmol) in CCl_4 (10 cm^3) with irradiation by a 100 W sun lamp and under an inert atmosphere. The mixture was refluxed under irradiation for 40 min until no more precipitate formed. The resultant solution was cooled in an ice bath before the succinimide was filtered off and the filtrate was dried with calcium carbonate. The product was distilled under N_2 from calcium carbonate and collected (yield 78%) at 96–99°C/2·3 mm (lit.[46] 75–78°C/1 mm). The ^{1}H

[44] Korte, H., Schumacher, H., Klein, W., and Daffertshofer, *Tetrahedron*, 1968, **24**, 5601.
[45] Ziegler, K., and Weber, H., *Chem. Ber.*, 1937, **70**, 1275.
[46] Rabjohn, N., (Ed.) *Org. Synth.*, 1963, Coll. Vol. 4, 921.

and ^{13}C n.m.r. spectra are available in supplementary Table S3. The pure product (colourless oil) may be stored under N_2 in a refrigerator for only 2–3 days.

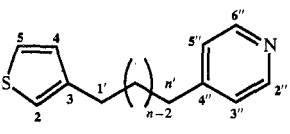
4-[ω-(3-Thienyl)heptyl]pyridine (2c)

A solution of Ph_3P (10·1 g, 41 mmol) in toluene (30 cm^3) was added to (1c) (1·03 g, 4·2 mmol) in toluene (10 cm^3) under nitrogen. The mixture was heated to reflux overnight. The sticky phosphonium salt (1·07 g, 51%) was filtered off, washed with cold toluene and light petroleum (b.p. 60–80°C), and dried under vacuum. To a solution of this salt (0·87 g, 1·71 mmol) in dry tetrahydrofuran (40 cm^3) was added butyllithium (1·13 cm^3 of 1·2 M solution in cyclohexane; 1·71 mmol) via syringe under nitrogen at −78°C. The mixture was stirred for about 30 min, then 0·163 cm^3 (1·71 mmol) of pyridine-4-carbaldehyde was added via syringe and the reaction mixture was stirred for 1 h at −78°C before the temperature was allowed to rise to room temperature and the reaction was stirred for a further 5 h. The reaction mixture was quenched with water (40 cm^3) at 0°C and extracted with Et_2O. The organic phases were combined and dried over anhydrous Na_2SO_4 before removal of the solvent provided yellow crystals as a crude product. The crystals were purified by column chromatography (alumina, $CHCl_3$/light petroleum, 1:1). Removal of solvent provided 4-[ω-(3-thienyl)hept-1-enyl]pyridine (9) (90 mg) as a light yellow powder (19%).

A reaction flask, charged with this compound (46 mg, 0·17 mmol) and PtO_2 (1 mg) in MeOH (15 cm^3), was evacuated, purged with hydrogen and maintained under a slight positive pressure of hydrogen by using a balloon. The reaction mixture was stirred at room temperature for 10 h before being filtered through a pad of Celite to remove the catalyst. Evaporation of solvent under vacuum gave 43 mg (95%) of (2c) as light yellow crystals. The ^1H n.m.r. spectrum is reported in supplementary Table S4.

4-[ω-(3-Thienyl)alkyl]pyridines (2a,b,d,e; n = 2, 5, 9, 11)

All glassware was dried at 130°C overnight and cooled in a desiccator prior to use. To a stirred solution of lithium diisopropylamide mono(tetrahydrofuran) (10 cm^3 of 1·5 M; 15 mmol) in dry tetrahydrofuran (14 cm^3) at 0°C, 4-methylpyridine (1·4 cm^3, 14·3 mmol) was added dropwise under nitrogen over 10 min. The resultant orange mixture was stirred over 50 min at 0°C. To this solution, 3-(ω-bromoalkyl)thiophen, (1), (8·0 mmol; dried under high vacuum) in tetrahydrofuran (12 cm^3) was added dropwise at 0°C over 15 min. The resultant darker mixture was stirred at 0°C for 3–6 h before the temperature was allowed to rise gradually to room temperature. The reaction was stopped for (2a) after 3 h reaction at 0°C. With long chain 3-(ω-bromoalkyl)thiophens the solution was allowed to remain stirring at room temperature under nitrogen for longer periods (e.g. overnight). The resultant solution was hydrolysed with water (30 cm^3) added dropwise at 0°C, followed by extraction with Et_2O. The organic phases were dried with anhydrous sodium sulfate and the solvent was removed under vacuum to afford yellowish-white solids. Crude products were purified by column chromatography (neutral alumina; $CHCl_3$/light petroleum, 2:5). The R_F of the products was *c.* 0·6 on t.l.c. (alumina) with the same eluent. Removal of solvent gave yellow pure liquids of (2b) (70%), (2d) (81%) and (2e) (60%). Following solvent removal, (2a) (61%) was further purified by distillation (b.p. 102–104°C/0·2 mm) to give a yellow crystalline *solid* (m.p. 74–75°C) (Found for (2a): C, 69·7; H, 5·9; N, 7·2. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·9; N, 7·4%. Found for (2b): C, 72·7; H, 7·3; N, 5·5. $C_{14}H_{17}NS$ requires C, 72·7; H, 7·4; N, 6·0%. Found for (2d): C, 75·7; H, 7·9; N, 4·5. $C_{18}H_{25}NS$ requires C, 75·2; H, 8·8; N, 4·9%. Found for (2e): C, 76·2; H, 9·3; N, 3·9. $C_{20}H_{29}NS$ requires C, 76·1; H, 9·3; N, 4·4%).



For (2a): δ_H (300 MHz, $CDCl_3$) 8·48, 2H, dd, $J_{2'',3''}$ 4·51, $J_{2'',5''}$ 1·46 Hz, H2'',6''; 7·24, 1H, dd, $J_{5,4}$ 4·81, $J_{5,2}$ 2·91 Hz, H5; 7·08, 2H, d, $J_{3'',2''}$ 5·89 Hz, H3'',5''; 6·92, 1H, dd, $J_{4,5}$ 4·98, $J_{4,2}$ 1·23 Hz, H4; 6·90, 1H, dd, $J_{2,5}$ 2·50, $J_{2,4}$ 1·28 Hz, H2'; 2·95, 2H, t, $J_{1,2}$ 3·41 Hz, H1'; 2·93, 2H, t, $J_{2,1}$ 3·35 Hz, H2'.

For (2e): δ_H (300 MHz, $CDCl_3$) 8·47, 2H, d, $J_{2'',3''}$ 5·28 Hz, H2″,6″; 7·21, 1H, dd, $J_{5,4}$ 4·77, $J_{5,2}$ 3·08 Hz, H5; 7·07, 2H, d, $J_{3'',2''}$ 5·54 Hz, H3″,5″; 6·92, 1H, dd, $J_{4,5}$ 5·03, $J_{4,2}$ 1·10 Hz, H4; 6·90, 1H, dd, $J_{2,5}$ 2·51, $J_{2,4}$ 1·61 Hz, H2; 2·61, 2H, t, $J_{1',2'}$ 7·59 Hz, H1′; 2·57, 2H, t, $J_{11',10'}$ 8·09 Hz, H11′; 1·61, 4H, m, $J_{2',1'}$ 6·45, $J_{10',11'}$ 7·02 Hz, H2′,10′; 1·35–1·20, 14H, m, H3′,4′,5′,6′,7′,8′,9′. δ_C (75 MHz, $CDCl_3$) 151·6, C4″; 149·4, C2″, 6″; 143·0, C3; 128·1, C4; 124·9, C5; 123·7, C3″,5″; 119·6, C2; 35·1, C11′; 30·4, C1′; 30·1, C2′,10′; 29·4, C3′,4′,5′,7′,8′,9′; 29·0, C6′. The ^1H and ^{13}C n.m.r. spectra of (2a–e) are given in supplementary Table S4.

1-[2-Oxo-2-(2-pyridyl)ethyl]pyridinum Iodide (7)

This compound was synthesized by using a modification of literature procedures.[28] To a solution of 2-acetylpyridine (8·4 g, 0·4 mol) in dry pyridine (100 cm^3) was added a solution of iodine (101·5 g, 0·4 mol) in the same solvent (300 cm^3) at 20°C. The reaction mixture was refluxed for 3 h under nitrogen, then the heating bath was removed and the reaction mixture was allowed to stand overnight. The crude crystals were filtered off, washed with pyridine, and dried under suction. The crude crystals were recrystallized from ethanol (2·7 litre), to which active charcoal (40 g) was added; after the mixture was refluxed for 1 h, it was filtered through Celite and the filtrate was cooled (4°C) overnight, producing light yellow shining crystals (yield 58·5 g, 45%), m.p. 197–198°C (lit.[47] 198–199°C). δ_H (300 MHz, CD_3CN) 8·79, 1H, dt, $J_{6',5'}$ 4·6, $J_{6',4'}$ 1·1 Hz, H6′; 8·73, 2H, dd, $J_{2,3}$ 5·5, $J_{2,4}$ 1·2 Hz, H2,6; 8·64, 1H, tt, $J_{4,3}$ 7·8, $J_{4,5}$ 7·6, $J_{4,6}$ 1·2 Hz, H4; 8·13, 2H, t, $J_{3,2}$ 7·2, $J_{3,4}$ 7·1 Hz, H3,5; 8·06, 1H, t, $J_{4',3'}$ 2·5, $J_{4',2'}$ 1·3 Hz, H4′; 8·04, 1H, d, $J_{3',4'}$ 1·6 Hz, H3′, 7·72, 1H, m, H5′; 6·41, 2H, s, CH_2. δ_C (75 MHz, CD_3CN) 192·0, C=O; 151·4, C2′; 150·6, C6′; 147·6, C4; 147·0, C2,6; 138·9, C4′, 130·1, C5′; 129·0, C3,5; 123·2, C3′; 67·6, CH_2.

4-Methyl-2,2′-bipyridine (Mebpy) (8)

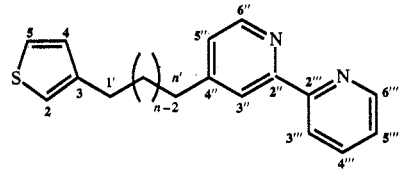
The title compound was synthesized from (7) by using literature procedures.[29,30] The crude solid was sublimed at 80°C/0·1 mm to give a white crystalline solid (yield 51%), m.p. 65·5–66°C (lit.[29] 63–64°C) (Found: C, 77·6; H, 6·0; N, 16·6. $C_{11}H_{10}N_2$ requires C, 77·7; H, 5·9; N, 16·5%). δ_H (300 MHz, $CDCl_3$) 8·66, 1H, dt, $J_{6',5'}$ 4·96, $J_{6',4'}$ 1·15 Hz, H6′; 8·53, 1H, d, $J_{6,5}$ 4·9 Hz, H6, 8·39, 1H, dt, $J_{3',4'}$ 8·0, $J_{3',5'}$ 1·0 Hz, H3′, 8·23 1H, t, $J_{3,5}$ 0·9 Hz, H3, 7·82; 1H, dt, $J_{4',3'}$ 7·7, $J_{4',5'}$ 7·6, $J_{4',6'}$ 1·7 Hz, H4′; 7·33–7·26, 1H, m, H5′; 7·15, 1H, dd, $J_{5,6}$ 4·8, $J_{5,3}$ 1·1 Hz, H5; 2·44, 3H, s, CH_3. δ_C (75 MHz, $CDCl_3$) 156·5, C2′; 155·9, C2; 149·1, C6′; 140·0, C6; 148·1, C4; 136·9, C4′; 124·7, C3; 123·6, C3′; 121·9, C5; 121·2, C5′; 21·2, CH_3.

4-[ω-(Thienyl)alkyl]-2,2′-bipyridines (3a–e; n = 2, 5, 7, 9, 11)

Butyllithium (6·74 cm^3 of 1·9 M solution in cyclohexane, 12·8 mmol) was added dropwise via syringe to diisopropylamide (1·79 cm^3, 12·8 mmol) in dry tetrahydrofuran (15 cm^3) at −78°C under nitrogen. The mixture was stirred for 10 min at −78°C before a solution of (8) (2·0 g, 11·76 mmol) in dry tetrahydrofuran (10 cm^3) was added dropwise via syringe to the reaction mixture at −78°C. The resultant dark purple solution was stirred for 50 min at −78°C before (1a–e) (13·0 mmol) in dry tetrahydrofuran (10 cm^3) was added over 10 min. The mixture was stirred for a further 1 h at −78°C, after which the temperature was allowed to rise gradually to room temperature. After stirring for a further 1–3 days (until the mixture changed colour to yellow or light brown), the reaction was quenched with 5% aqueous NH_4Cl solution at 0°C then extracted with Et_2O (3×50 cm^3). The organic layers were combined and dried over anhydrous Na_2SO_4. Removal of solvent provided a yellow oil as the crude product, which was purified by column chromatography on basic alumina (eluent chloroform/light petroleum, 2:5). The R_F of the products was 0·58 (3c) on t.l.c. (alumina) with the same eluent. Following removal of solvent, the residue was found to contain some of the starting material (7), which was readily removed by sublimation. The pure products were obtained as crystalline materials [light yellow for (3a) (yield 71%), m.p. 72–73°C; white for (3e) (yield 59%), m.p. 41–42°C)] or colourless oils [(3b) (yield 52%), (3c) (yield 69%), (3d) (yield 74%)] (Found for (3a): C, 71·8; H, 5·0; N, 10·1. $C_{16}H_{14}N_2S$ requires C, 72·2; H, 5·3; N, 10·5%. Found for (3b): C, 74·3; H, 6·2; N, 9·4. $C_{19}H_{20}N_2S$ requires C, 74·0; H, 6·5; N, 9·5%.

[47] Kröhnke, F., and Gross, K. F., *Chem. Ber.*, 1959, **92**, 22.

Found for (3c): C, 75·2; H, 7·3; N, 7·8. $C_{21}H_{34}N_2S$ requires C, 75·0; H, 7·2; N, 8·3%. Found for (3d): C, 75·6; H, 7·8; N, 7·4. $C_{23}H_{28}N_2S$ requires C, 75·8; H, 7·70; N, 7·7%. Found for (3e): C, 76·4; H, 8·6: N, 6·9. $C_{25}H_{32}N_2S$ requires C, 76·5; H, 8·2; N, 7·1%).



For (3a): δ_H (300 MHz, $CDCl_3$) 8·70, 1H, dt, $J_{6''',5'''}$ 4·9, $J_{6''',4'''}$ 1·1 Hz, H6'''; 8·56, 1H, d, $J_{6'',5''}$ 4·9 Hz, H6''; 8·40, 1H, dt, $J_{3''',4'''}$ 8·2, $J_{3''',5''}$ 1·0 Hz, H3'''; 8·28, 1H, t, $J_{3'',5''}$ 0·9 Hz, H3''; 7·82, 1H, td, $J_{4''',3'''}$ 7·7, $J_{4''',5'''}$ 7·7, $J_{4''',6'''}$ 1·8 Hz, H4'''; 7·34–7·29, 1H, m, H5'''; 7·28–7·25, 1H, m, H5; 7·10, 1H, dd, $J_{5'',6''}$ 4·9, $J_{5'',3''}$ 1·7 Hz, H5''; 6·96, 1H, dd, $J_{4,5}$ 4·8 Hz, H4; 6·94, 1H, dd, $J_{2,5}$ 2·8 Hz, H2; 3·03, 4H, t, H1′,2′. δ_C (75 MHz, $CDCl_3$) 156·2, C2'''; 156·1, C2''; 151·5, C4''; 149·1, C6'''; 149·1, C6''; 141·2, C3; 136·9, C4'''; 128·0, C4; 125·6, C5; 123·9, C2; 123·7, C3'''; 121·2, C5'''; 121·0, C3''; 120·6, C5''; 36·4, C2′; 31·0, C1′.

For (3e): δ_H (300 MHz, $CDCl_3$) 8·69, 1H, dt, $J_{6''',5'''}$ 4·9, $J_{6''',4'''}$ 1·0 Hz, H6'''; 8·55, 1H, dd, $J_{6'',5''}$ 5·0 Hz, H6''; 8·40, 1H, dt, $J_{3''',4'''}$ 8·1, $J_{3''',5'''}$ 0·9 Hz, H3'''; 8·23, 1H, t, H3''; 7·81, 1H, td, $J_{4''',3'''}$ 7·6, $J_{4''',5'''}$ 7·5, $J_{4''',6'''}$ 1·7 Hz, H4'''; 7·33–7·28, 1H, m, H5'''; 7·22, 1H, dd, $J_{5,4}$ 4·9, $J_{5,2}$ 3·0 Hz, H5; 7·15, 1H, dd, $J_{5'',6''}$ 4·9, $J_{5'',3''}$ 1·4 Hz, H5''; 6·94, 1H, dd, $J_{4,5}$ 6·2, $J_{4,2}$ 0·9 Hz, H4; 6·92, 1H, dd, $J_{2,5}$ 2·4, $J_{2,4}$ 1·0 Hz, H2; 2·69, 2H, t, $J_{1',2'}$ 7·5 Hz, H1′; 2·61, 2H, t, $J_{11',10'}$ 7·6 Hz, H11′; 1·70, 2H, m, H2′; 1·61, 2H, m, H10′; 1·40–1·20, 14H, m, H3′–9′. δ_C (75 MHz, $CDCl_3$) 156·3, C2'''; 155·9, C2''; 152·9, C4''; 149·1, C6'',6'''; 143·2, C3; 136·9, C4'''; 128·3, C4; 125·0, C5; 124·0, C2; 123·6, C3'''; 121·2, C5'''; 121·1, C3''; 119·7, C5''; 35·5, C11′; 30·5, C1′; 30·4, C10′; 30·2, C2′; 29·5, C6′; 29·5, C3′,9′; 29·4, C4′,8′; 29·3, C5′,7′.

The ^1H and ^{13}C n.m.r. data for (3a–e) are given in supplementary Table S5.

4-Methyl-4′-[ω-(3-thienyl)]nonyl]-2,2′-bipyridine (4)

A solution of butyllithium in hexane (11·9 cm^3, 1·5 M, 1 equiv.) was added to diisopropylamine (2·52 cm^3, 1·1 equiv.) in tetrahydrofuran (20 cm^3) at −78°C and the mixture was stirred for 10 min before being transferred slowly via cannula to a solution of 4,4′-dimethyl-2,2′-bipyridine (3·3 g, 1 equiv.) in tetrahydrofuran (100 cm^3) at −78°C. After 30 min, (1d) (5 g) dissolved in tetrahydrofuran (50 cm^3) was added, and the reaction was allowed to gradually rise to room temperature. Stirring was continued for 2 days before the reaction mixture was quenched with 10% $NaHCO_3$ solution and extracted with Et_2O. The organic extracts were washed with a saturated solution of $NaHCO_3$ before being dried with anhydrous sodium sulfate. Removal of solvent afforded a light yellow solid which was purified by column chromatography on neutral alumina (ethyl acetate eluent). Recrystallization from acetonitrile gave (4) as a white *powder* (3·3 g, 49%), m.p. 45·5–46·0°C (Found: C, 76·4; H, 7·80; N, 7·8. $C_{24}H_{30}N_2S$ requires C, 76·1; H, 8·00; N, 7·4%). δ_H (300 MHz, $CDCl_3$) 8·54, 2H, t, J 4·6 Hz; 8·2, 2H, s; 7·22, 1H, br m, J 1 Hz; 7·13, 2H, d, J 4·6 Hz; 6·93, 1H, d, $J < 1$ Hz; 6·90, 1H, d, $J < 1$ Hz; 2·68, 2H, d, J 3·5 Hz; 2·60, 2H, t, J 7·6 Hz; 2·44, 3H, s; 1·72, 2H, br t, J 6·4 Hz; 1·65, 2H, br t, J 7·3 Hz, 1·23, 10H, br m. δ_C (75 MHz, $CDCl_3$) 156·1; 152·9; 148·9; 148·1; 143·0; 128·2; 125·0; 124·6; 123·9; 122·0; 121·3; 119·7; 35·5; 30·5; 30·4; 30·2; 29·4; 29·3; 21·2.

Acknowledgments

This research was supported by the Australian Research Council. We thank Dr George Meehan and Mr Laurie Kelso for their assistance, and Dr Tom Boussie (University of North Carolina) for providing details of the improved synthesis of Mebpy (8) prior to publication. J.W. wishes to acknowledge the Australian International Development Assistance Bureau for an Australian Development Cooperation Scholarship Scheme scholarship and James Cook University for a postgraduate research award for overseas students.