An Improved Synthesis of Amphiphilic 4,4'-Disubstituted 2,2'-Bipyridines

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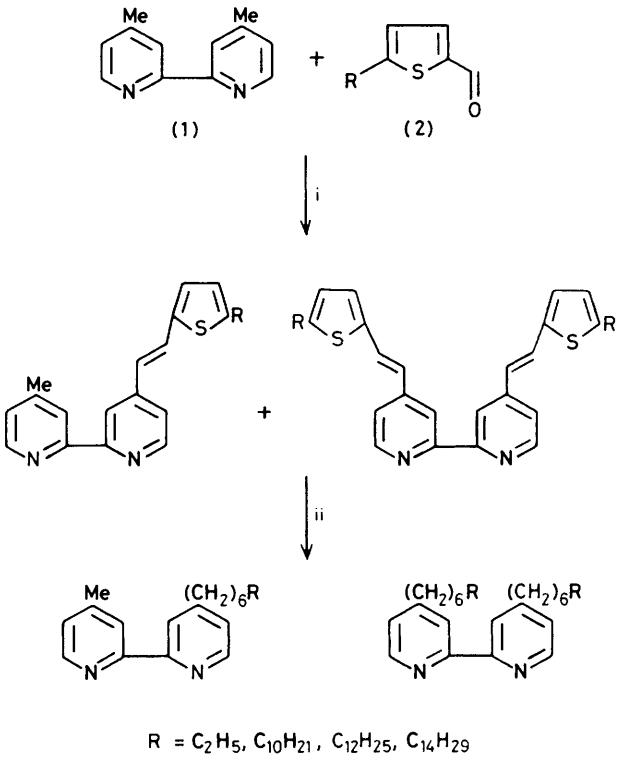
An expedient one step synthesis of 4-alkyl-4'-methyl- and 4,4'-dialkyl-2,2'-bipyridines has been developed. The desired products are obtained, in good yields, by reaction of alkyl bromides with either the mono- or dilithio-anion of 4,4'-dimethyl-2,2'-bipyridine.

Ruthenium(II) complexes containing the bipyridine ligand (bipy) have gained prominence as catalysts in photoinduced redox reactions.[1] $[Ru(2,2'\text{-bipyridine})_3]^{2+}$ in particular has been extensively studied for conversion of solar light into storable chemical energy, *via* photodecomposition of water.[2] Grätzel has recently reported that amphiphilic derivatives of $[Ru(bipy)_3]^{2+}$ exhibit higher activities in promoting the photolytic cleavage of water with light of wavelength >400 nm.[3] Specifically it has been found that stoichiometric volumes of hydrogen and oxygen are produced with a colloidal, bifunctional semiconductor in a heterogeneous system, using an aqueous solution of $[Ru(2,2'\text{-bipy})_2(L\text{-}L)]^{2+}$ (2,2'-bipy = 2,2'-bipyridine, L-L = 4-alkyl-4-methyl- or 4,4'-dialkyl-2,2-bipyridine). The enhanced catalytic activity of these amphiphilic ruthenium(II) complexes has been attributed to a hydrophobic interaction between the heterogeneous semiconductor and the ruthenium(II) photoexcited state.

The amphiphilic bipyridine ligands used in water photolysis were prepared as shown in Scheme 1.[4] Although seemingly straightforward, the steps shown are laborious and inspection of the experimental methods shows that felicitous conditions are required in a number of steps, *e.g.* the anhydride mediated condensation of the bipyridine (1) and the thiophen (2), the Raney-nickel desulphurisation–hydrogenation of the mono- and di-ethenyl adducts. In view of the synthetic methods shown in Scheme 1, we have developed, and report here, an efficient, one step synthesis of both 4-alkyl-4'-methyl- and symmetrical 4,4'-dialkyl-2,2'-bipyridines from 4,4'-dimethyl-2,2'-bipyridine, as shown in Scheme 2.



Scheme 1. *Reagents*: i, $(C_3H_7CO)_2O$, reflux; ii, W5 Raney Ni–DMF, reflux

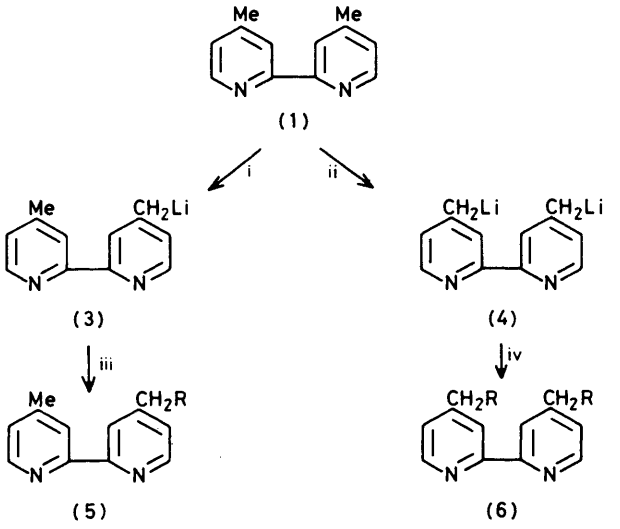
Results and Discussion

Reaction of 4,4'-dimethyl-2,2'-bipyridine and 1.0 equivalents of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) is known to generate the monolithio-species (3);[5] this compound reacts with formaldehyde gas to give 4-hydroxyethyl-4'-methyl-2,2'-bipyridine in 70% yield. However no further examples of alkylation have been reported. We found that the lithio-compound (3) is indeed generated under such conditions and can then be efficiently quenched with alkyl bromides, giving the 4-alkyl-4'-methyl-2,2'-bipyridines (5) in good to excellent yields. Furthermore, reaction of 4,4'-dimethyl-2,2'-bipyridine with an excess of LDA in THF has been found to generate the dilithio-species (4). This species can also be efficiently quenched with alkyl bromides to give the symmetrical 4,4'-dialkyl-2,2'-bipyridines (6).

Specifically, treatement of the dimethyl compound (1) with 1.0 equivalents of LDA in THF, at 0 °C for one hour affords the dark orange-red monolithio-compound (3). The dianion (4) is produced as a bright orange intermediate by reaction of 2.5 equivalents of LDA with compound (1) under the same conditions. In both instances, addition of the appropriate alkyl bromide, as a solution in THF, to the carbanion species yields the crude product; very little or no by-products are obtained. Column chromatography on neutral alumina of the crude product, followed by recrystallisation or bulb-to-bulb distillation, gives the desired products, as shown in the Table. The crude products often contain small amounts of alkyl bromide or 4,4'-dimethyl-2,2'-bipyridine. However, these materials are easily removed during the chromatographic purification step and can be subsequently recycled for further use. Previously 4,4'-dialkyl-2,2'-pyridines have been prepared using either alkylation techniques in liquid ammonia with sodium[6] or oxidative coupling of 4-alkylpyridines in the presence of a metal catalyst.[7] However, these methods are invariably laborious and, at best, give product yields of *ca.* 50%. Both of the above methods are not amenable to the preparation of 4-alkyl-4'-methyl-2,2'-bipyridine. Clearly the use of LDA in THF is a rapid and very convenient method for preparing the lithio-compounds (3) and (4), which can then be used for preparing various 4-alkyl-4'-methyl- and 4,4'-dialkyl-2,2'-bipyridines.

Experimental

All chemicals used were of reagent grade unless otherwise specified. 4,4'-Dimethyl-2,2'-bipyridine was purchased from



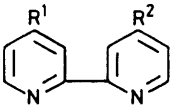
Scheme 2. *Reagents*: i, LDA in THF (1 equiv.); ii, LDA in THF (2.5 equiv.); iii, RBr; iv, excess of RBr

G. F. Smith Chemical Co. and used without further purification. Alkyl bromides were filtered through a short column of neutral alumina prior to use and were >99% pure by g.l.c. Anhydrous tetrahydrofuran (THF) was prepared by distillation from pulverised CaH_2 and then from sodium diphenylketyl under nitrogen. n-Butyl-lithium was purchased from Aldrich and its molarity determined by double titration.[8] Manipulations of air-sensitive materials and solutions were conducted using standard techniques.[9] Reactions and column chromatographic separations were monitored using Merck 60 F_{254} (Type E) pre-coated alumina t.l.c. plates. Column chromatography was carried out on alkaline alumina (activity 1), using flash chromatography [10] with the solvents specified. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer. 200 MHz ^{1}H N.m.r. spectra were recorded on a Jeol FX-200 spectrometer operating in the Fourier transform mode, in deuteriochloroform withtetramethylsilane as internal standard.

Reaction of 4-(*Methyl-lithio*)-4-*methyl*-2,2′-*bipyridine with Alkyl Bromides*: *General Procedure*.—To an anhydrous solution of di-isopropylamine (2 ml, 14.3 mmol) in THF (10 ml) at 0 °C, contained in a 300-ml Schlenck tube equipped with a magnetic stirrer and a rubber septum, was added 1.55M-n-butyl-lithium in hexane (9 ml, 14 mmol), *via* a syringe. The resulting pale yellow solution was stirred at 0 °C for 20 min, and then 4,4′-dimethyl-2,2′-bipyridine (2.5 g, 13.6 mmol) in THF (75 ml) was added *via* a cannula. On adding the solution of the bipyridine to the amide solution a dark orange-red solution was obtained. After 1 h at 0 °C, the orange-red solution containing (2) was treated with the required alkyl bromide (15 mmol) in THF (15 ml), *via* a syringe, during 5 min. The resulting solution was stirred at 0 °C for 30 min and at 25 °C overnight. The reaction was quenched by addition of methanol (2 ml) and the clear yellow solution obtained was poured into water (200 ml) before extraction with diethyl ether (3 × 100 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to give pale yellow oils. These oils solidified on standing at room temperature in those cases where long chain alkyl bromides were used as electrophiles. Only when allyl bromide was used as an electrophile was the product obtained as a liquid.

The crude products were chromatographed on alkaline alumina (activity 1), eluting with 2 : 1 v/v diethyl ether–hexane. After evaporation of the appropriate fractions, the products were recrystallised from absolute ethanol or bulb-to-bulb distilled.

Table Preparation of 4-alkyl-4′-methyl- and 4,4′-dialkyl-2,2′-bipyridines



RBr	R^1	R^2	M.p. (°C)	Yield (%)	R_F [e]
C_3H_5Br	Me	C_4H_7	Oil [a]	80	0.55
$C_{10}H_{11}Br$	Me	$C_{11}H_{23}$	61—63	67	0.68
$C_{11}H_{23}Br$	Me	$C_{12}H_{25}$	49—50.5 [b]	88 [d]	0.68
$C_{12}H_{25}Br$	Me	$C_{13}H_{27}$	65.5—67	64	0.70
$C_{14}H_{29}Br$	Me	$C_{15}H_{31}$	73—75.5	56	0.70
$C_{18}H_{37}Br$	Me	$C_{19}H_{39}$	72—74.5	70	0.72
$C_{11}H_{23}Br$	$C_{12}H_{25}$	$C_{12}H_{25}$	59—60	93	0.85

[a] B.p. 230 °C, 0.03 mmHg. [b] Lit.,[4] m.p. 47—48 °C. [c] Lit.,[4] m.p. 68—69 °C. [d] Yield based on consumed 4,4′-dimethyl-2,2′-bipyridine. [e] R_F values are for Al_2O_3, using 2 : 1 v/v diethyl ether–hexane as eluant.

The compounds listed in the Table, which were prepared by the above general method, had the following analytical data. 4-*But*-1-*enyl*-4′-*methyl*-2,2′-*bipyridine* (Found: C, 80.1; H, 7.5; N, 12.1. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5%); δ (200 MHz) 2.25—2.55 (m, 2-H, $C_3H_5CH_2$), 2.43 (s, 3 H, 4′-CH_3), 2.8 (t, 2 H, py-$CH_2C_4H_7$), 4.9—5.12 (m, 2 H, *J* 1.5, 6, and 17 Hz, CH_2=CHCH$_2$), 5.85 (m, 1 H, *J* 6, 10, and 17 Hz, CH_2=$CHCH_2$), 7.13 (dd, 2 H, $J_{3,5} = J_{3',5'} = 1.5$ Hz, $J_{5,6} = J_{5',6'} =$ 4.8 Hz, 5-, 5′-H), 8.23 (br s, 2 H, 3-, 3′-H), 8.53 (d, 1 H, $J_{5',6'}$ 4.8 Hz, 6′-H), and 8.56 (d, 1 H, $J_{5,6}$ 4.8 Hz, 6-H); $\nu_{max.}$ (film) 3 080, 3 070, 3 005, 2 990, 2 930m, 1 680m, 1 595s, 1 555s, 1 460s, 1 440sh, 1 380s, 995s, 915m, and 830 br cm^{-1}. 4-*Methyl*-4′-*undecyl*-2,2′-*bipyridine* (Found: C, 81.4; H, 10.1; N, 8.4. $C_{22}H_{32}N_2$ requires C, 81.5; H, 9.9; N, 8.6%); δ (200 MHz) [t, 3 H, *J* 5.5 Hz, $CH_3(CH_2)_{10}$], 1.1—1.5 [m, 16 H, $CH_3(CH_2)_8CH_2$], 1.6—1.8 (m, 2 H, $CH_2C_9H_9$), 2.43 (s, 3 H, 4-Me), 2.69 (t, 2 H, *J* 7.5 Hz, $CH_2C_{10}H_{21}$), 7.13 (dd, 2 H, $J_{3,5} = J_{3',5'} = 1.5$ Hz, $J_{5,6} = J_{5',6'} = 4.8$ Hz, 5-, 5′-H), 8.23 (br s, 2 H, 3-, 3′-H), and 8.56 (dd, 2 H, $J_{3,6} = J_{3',6'} = 0.7$ Hz, $J_{5,6} = J_{5',6'} = 4.8$ Hz, 6-, 6′-H). 4-*Dodecyl*-4′-*methyl*-2,2-*bipyridine*. The 200 MHz ^{1}H n.m.r. spectrum was identical with that of 4-methylundecyl-2,2′-bipyridine except for δ 1.1—1.5 [m, 18 H, $CH_3(CH_2)_9CH_2CH_2$]. 4-*Methyl*-4′-*tridecyl*-2,2′-*bipyridine* (Found: C, 81.4; H, 10.5; N, 7.7. $C_{24}H_{36}N_2$ requires C, 81.8; H, 10.3; N, 8.0%). The 200 MHz ^{1}H n.m.r. spectrum was identical with that of 4-methyl-4′-undecyl-2,2′-bipyridine except for δ 1.1—1.4 [m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2$]. 4-*Methyl*-4′-*pentadecyl*-2,2′-*bipyridine* (Found: C, 81.8; H, 10.7; N, 6.9. $C_{26}H_{24}N_6$ requires C, 82.0; H, 10.6; N, 7.4%). The 200 MHz ^{1}H n.m.r. spectrum was identical with that of 4-methyl-4′-undecyl-2,2′-bipyridine except for δ 1.1—1.5 [m, 24 H, $CH_3(CH_2)_{12}CH_2CH_2$]. 4-*Methyl*-4′-*nonadecyl*-2,2′-bipyridine (Found: C, 91.7; H, 11.4; N, 5.9%; M^+, 436.383. $C_{30}H_{48}N_2$ requires C, 82.6; H, 11.0; N, 6.4%; *M*, 436.3817.* The 200 MHz ^{1}H n.m.r. spectrum was identical with that of 4-methyl-4′-undecyl-2,2′-bipyridine except for δ 1.1—1.5 [m, 32 H, $CH_3(CH_2)_{16}CH_2CH_2$].

Preparation of 4,4′-*Didodecyl*-2,2′-*bipyridine* via *the Lithio-compound* (4).—To an anhydrous solution of di-isopropyl-

* Correct microanalytical data could not be obtained although a number of attempts were made with thrice recrystallised material.

amine (10 ml, 71.5 mmol) in THF (20 ml) at 0 °C, in a 300-ml Schlenck tube equipped with a magnetic stirrer and a rubber septum, was added 1.55M-n-butyl-lithium in hexane (45 ml, 70 mmol), *via* a syringe. The pale yellow solution was stirred at 0 °C for 20 min and then 4,4′-dimethyl-2,2′-bipyridine (5 g, 27 mmol) in THF (100 ml) was added *via* a cannula. On addition of the bipyridine a dark orange-red solution, indicative of the monoanion (2), was obtained. On further stirring at 0 °C (5—10 min) a bright orange solution was produced, signalling the formation of the desired dianion (3). The orange solution was stirred at 0 °C for 1 h before n-undecyl bromide (17 ml, 76 mmol) in tetrahydrofuran (20 ml) was added during 5 min *via* a syringe. The orange colour of the dianion (3) was discharged almost immediately and a dark red-brown solution was obtained which slowly turned green after 15 min at 0 °C. Stirring was continued for 30 min at 0 °C and overnight at 25 °C. The reaction was quenched by adding methanol (5 ml) and the clear, yellow solution was poured into water and the organic material extracted with diethyl ether (3 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow liquid, which solidified on standing at 25 °C. Recrystallisation of this solid from hot, absolute ethanol gave white crystals (12.3 g, 93%) of the product.

Acknowledgements

The authors thank the British Petroleum Company plc. for permission to publish this work.

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Received 24*th May* 1982; *Paper* 2/848