Improved Synthesis of Cationic Pyridinium-Substituted Indolizines

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Received 24 February 2006; revised 18 April 2006

Abstract: This paper describes the optimization of the synthesis of pyridinium-substituted indolizines. Different conditions, solution and solid-phase synthesis were used for the key step of [3+2] cycloaddition. The best yields and shortest reaction time were obtained by microwave-assisted solid-phase synthesis.

Key words: cycloadditions, fused-ring systems, heterocycles, solid-phase synthesis, ylide

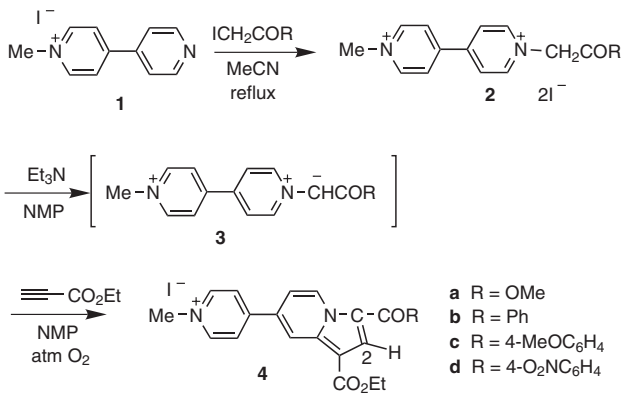
A literature survey reveals that indolizines have a special place in the field of heterocycles, a large number of these compounds being biologically active molecules, potential antioxidants, inhibitors of 15-lypoxygenase, or ligands for the estrogen receptors.[1–5] Considering also the well known fluorescence properties of indolizines and the increasing importance of fluorescence spectroscopy in both biological and environmental analyses, we are interested in the synthesis of this class of compounds, as systems suitable for use in fluorometric analysis.[6–10] We[11] and others[12,13] have previously described the synthesis of indolizines from pyridinium salts using a [3+2] cycloaddition reaction. The mono- or bisindolizines thus formed are fluorescent but display a low solubility in water that precludes their use as fluorescent indicators in biological systems. The present paper describes the synthesis of water-soluble pyridinium-substituted indolizines from asymmetric diquaternary salts of 4,4′-bipyridine (Scheme 1). The novelty of this paper resides in the functionalization as methylpyridinium at an early stage of the synthesis, prior to the ylide formation and subsequent cycloaddition, combined with the use of solvent-free microwave reaction.

The asymmetric diquaternary salts **2a–d** were prepared by alkylation of *N*-methyl-4-pyridyl pyridinium iodide (**1**), which in turn was prepared by controlled monomethylation of bipyridine with methyl iodide. The iodo alkylating agents (iodo acetophenones and iodo methyl acetate) were prepared from the commercial bromo derivatives following the methods described in the literature.[14,15] The diquaternary salts **2a–d** were thus obtained in good yields (88–98% yields). To form the indolizine nucleus, the intermediate formation of pyridinium ylides **3a–d** was required for reaction with the alkynes by a cycloaddition process. The 'salt method'[16] has been applied to this reaction in order to form in situ, the pyridinium ylides, that react with the dipolarophile (ethyl propiolate) to directly give the indolizines **4a–d** (Scheme 1). As pointed out previously,[17] formation of the indolizines **4a–d** probably proceeds via unstable intermediates, which due to the tendency of stabilization spontaneously undergo an aromatization, possibly through an oxidative dehydrogenating reaction under ambient conditions. The best results in solution were obtained when the asymmetric diquaternaty salts **2a–d** were treated with a slight excess of ethyl propiolate (1.4 equiv) in the presence of triethylamine in *N*-methyl-2-pyrrolidone as solvent (Scheme 1). The mixture was allowed to react at moderate temperature (50–60 °C) for about 6–9 hours to complete the conversion. After a conventional workup the indolizine derivatives **4a–d** were obtained in yields ranging from 53% (**4b**) to 71% (**4c**). Following our previous work on the use of microwave irradiation to achieve [3+2] cycloaddition,[17] we performed the reaction under similar conditions. The reactions were carried out at atmospheric pressure in a multimode microwave reactor (700 W). The reagents, **2a–d** and ethyl propiolate, were first adsorbed on KF–Al_2O_3. The resulting solids were subsequently irradiated for ten minutes. The temperature was measured at 95 °C at the end of the microwave irradiation by introducing a glass thermometer into the reaction mixture. After workup, compounds **4a–d** were isolated in 77–85% yields. To assess the influence of the microwave irradiation on the reaction, we performed control reactions by heating the reaction mixtures adsorbed on KF–Al_2O_3 at 95 °C, under vigorous mechanical stirring without microwave irradiation. As shown in Table 1, a significant increase of the yields was observed under microwave irradiation.

The structures of the new compounds were assessed by spectral analysis (NMR, MS) and elemental analysis. In particular heteronuclear 2D NMR experiments (GHMBC) were used to confirm the regioselectivity of the reaction. Two $^3J_{HC}$ couplings between proton H-2 and both the carbonyl and carboxylate carbon atoms were identified. This result confirms that the cycloaddition of the ylides with the unsymmetrical ethyl propiolate is regioselective as previously described for the synthesis of bisindolizines.[11]

In conclusion, we report the efficient synthesis of asymmetric diquaternary salts of 4,4′-bipyridine. We successfully reacted these salts as starting materials in a cycloaddition reaction with ethyl propiolate under basic

SYNTHESIS 2006, No. 16, pp 2640–2642
Advanced online publication: 12.07.2006
DOI: 10.1055/s-2006-942482; Art ID: T02806SS



Scheme 1

conditions. The presence of the cationic methyl pyridinium substituent does not prevent the formation and reactivity of the ylide. The prolonged reaction time of the reaction performed in solution is due to the low solubility of the starting bipyridium salts. The solvent-free solid-phase synthesis is an answer to this problem. The use of microwave irradiation to perform the cycloaddition step is very successful and has major advantages, namely yield improvement, lower reaction time and easier workup.

Melting points were obtained on a Reichert Thermovar instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer with DMSO as internal standard. Mass spectra were recorded on a Polarisq Thermo Finnigan spectrometer. Elemental analyses were performed at 'Service de microanalyse, Université Joseph Fourier'. All starting materials were commercially available.

Preparation of Asymmetric Diquaternary Salts of 4,4′-Bipyridine (2a–d); General Procedure

Compound **1** (1 mmol) and reactive iodo derivatives (iodoacetophenones or iodomethyl acetate, 1.50 mmol) were suspended in MeCN (10 mL). The mixture was heated at reflux, under vigorous stirring, for 15–20 h. The reaction product was separated by filtration of the hot reaction mixture, washed with boiling MeCN (15 mL) and dried under vacuum at r.t.

***N*-Methyl-*N*′-carbomethoxymethyl-4,4′-bipyridinium Diiodide (2a)**

Red crystals; yield: 88%; mp > 350 °C (decomp.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.34–9.40 (m, 4 H), 8.92 (d, J = 6.9 Hz, 2 H), 8.82 (d, J = 6.6 Hz, 2 H), 5.84 (s, 2 H, CH_2), 4.47 (s, 3 H, NCH_3), 3.80 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.9, 150.0, 148.3, 147.4, 146.9, 126.6, 126.5, 60.5, 53.5, 48.3.

MS (electrospray): m/z = 243 [M^{2+} – H^+].

Anal. Calcd for $C_{14}H_{16}I_2N_2O_2$: C, 33.76; H, 3.24; N, 5.63. Found: C, 33.78; H, 3.33; N, 5.56.

***N*-Methyl-*N*′-phenacyl-4,4′-bipyridinium Diiodide (2b)**

Red-orange crystals; yield: 89%; mp 248–250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.30–9.36 (m, 4 H), 8.93 (d, J = 6.5 Hz, 2 H), 8.82 (d, J = 6.5 Hz, 2 H), 8.10 (d, J = 7.9 Hz, 2 H), 7.79–7.84 (m, 1 H), 7.66–7.71 (m, 2 H), 6.63 (s, 2 H, CH_2), 4.47 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.9, 149.9, 148.8, 147.7, 147.2, 135.4, 134.0, 129.7, 128.8, 126.9, 126.8, 66.8, 48.6.

MS (electrospray): m/z = 289 [M^{2+} – H^+].

Anal. Calcd for $C_{19}H_{18}I_2N_2O$: C, 41.94; H, 3.34; N, 5.15. Found: C, 41.85; H, 3.23; N, 5.13.

***N*-Methyl-*N*′-(*p*-methoxyphenacyl)-4,4′-bipyridinium Diiodide (2c)**

Red-orange crystals; yield: 98%; mp 260–262 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.25–9.33 (m, 4 H), 8.93 (d, J = 6.6 Hz, 2 H), 8.84 (d, J = 6.6 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2 H), 6.59 (s, 2 H, CH_2), 4.48 (s, 3 H, NCH_3), 3.91 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 188.8, 164.6, 149.5, 148.4, 147.4, 146.9, 131.0, 126.6, 126.5, 114.7, 66.2, 56.1, 48.3.

MS (electrospray): m/z = 319 [M^{2+} – H^+].

Anal. Calcd for $C_{20}H_{20}I_2N_2O_2$: C, 41.84; H, 3.52; N, 4.88. Found: C, 41.87; H, 3.45; N, 4.80.

***N*-Methyl-*N*′-(*p*-nitrophenacyl)-4,4′-bipyridinium Diiodide (2d)**

Red crystals; yield: 88%; mp 235–236 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.34 (d, J = 6.7 Hz, 2 H), 9.29 (d, J = 7.0 Hz, 2 H), 8.92 (d, J = 7.1 Hz, 2 H), 8.81 (d, J = 6.9 Hz, 2 H), 8.51 (d, J = 8.9 Hz, 2 H), 8.33 (d, J = 9.0 Hz, 2 H), 6.65 (s, 2 H, CH_2), 4.47 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.3, 151.2, 150.1, 148.7, 147.7, 147.2, 138.7, 130.4, 127.0, 126.8, 124.8, 67.1, 48.6.

MS (electrospray): m/z = 334 [M^{2+} – H^+].

Anal. Calcd for $C_{19}H_{17}I_2N_3O_3$: C, 38.74; H, 2.91; N, 7.14. Found: C, 38.68; H, 2.95; N, 7.14.

Preparation of *N*-Methyl-4-(1-ethoxycarbonyl-3-substituted-indolizin-7-yl)pyridinium Iodide (4a–d); General Procedure

Compound **2a–d** (1 mmol) and ethyl propiolate (1.40 mmol) were suspended in *N*-methylpyrrolidinone (10 mL). Then Et_3N (2 mmol diluted in 3 mL *N*-methylpyrrolidinone) was added dropwise under

Table 1 Comparative Yields and Reaction Conditions

Compound	Solution			Solid-phase			Microwave irradiation		
	Time (min)	Temp (°C)	Yield (%)	Time (min)	Temp (°C)	Yield (%)	Time (min)	Temp (°C)	Yield (%)
4a	480	50	63	10	95	57	10	95	84
4b	480	50	61	10	95	50	10	95	77
4c	360	55	71	10	95	52	10	95	85
4d	540	60	53	10	95	47	10	95	71

vigorous stirring. The solution was slowly heated for 6–9 h at 50–60 °C. The desired product (**4b–d**) precipitated after adding EtOAc (50 mL) to the solution. The precipitate was separated by filtration and washed with EtOAc (30 mL) and Et_2O (20 mL). For purification of products **4a–d**, the crude precipitate was suspended in H_2O (10 mL) and extracted with $CHCl_3$ (500 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Compounds **4a–d** were separated as yellow crystals by precipitation with Et_2O and filtration.

Preparation of *N*-Methyl-4-(1-ethoxycarbonyl-3-substituted-indolizin-7-yl)pyridinium Iodide (4a–d) Using Microwave Irradiation; General Procedure

To a solution of diquaternary salts **2a–d** (1 mmol) and ethyl propiolate (1.40 mmol) in acetone (5 mL) was added KF–Al_2O_3 (4 g KF–Al_2O_3/1 g **2a–d**) under vigorous stirring. After solvent evaporation, the resulting solid was irradiated for 10 min in a multimode microwave reactor (700 W). The reaction mixture was then cooled to r.t., washed with $CHCl_3$ (50 mL) and filtered. The resulting filtrate was evaporated under vacuum. The crude residue was treated as described above for the reaction in solution.

***N*-Methyl-4(1-ethoxycarbonyl-3-methoxycarbonylindolizin-7-yl)pyridinium Iodide (4a)**

Yellow crystals; mp 233–235 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.57 (dd, *J* = 0.9, 7.5 Hz, 1 H), 9.10 (d, *J* = 6.9 Hz, 2 H), 8.76 (d, *J* = 1.1 Hz, 1 H), 8.59 (d, *J* = 7.0 Hz, 2 H), 7.85 (s, 1 H), 7.83 (dd, *J* = 2.0, 7.5 Hz, 1 H), 4.39 (s, 3 H, NCH_3), 4.34 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.2, 160.9, 151.9, 146.5, 137.5, 131.0, 128.7, 124.9, 124.4, 119.2, 116.1, 113.6, 108.0, 60.6, 52.4, 47.9, 14.8.

MS (electrospray): *m*/*z* = 339 [M$^+$].

Anal. Calcd for $C_{19}H_{19}N_2O_4I·0.5H_2O$: C, 48.02; H, 4.32; N, 6.10. Found: C, 48.26; H, 4.35; N, 5.81.

***N*-Methyl-4-(1-ethoxycarbonyl-3-benzoylindolizin-7-yl)pyridinium Iodide (4b)**

Yellow crystals; mp 215–219 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.88 (dd, *J* = 0.7, 7.4 Hz, 1 H), 9.16 (d, *J* = 6.5 Hz, 2 H), 8.84 (d, *J* = 1.2 Hz, 1 H), 8.64 (d, *J* = 6.7 Hz, 2 H), 7.91 (dd, *J* = 2.0, 7.4 Hz, 1 H), 7.80–7.84 (m, 2 H), 7.67–7.72 (m, 2 H), 7.58–7.63 (m, 2 H), 4.42 (s, 3 H, NCH_3), 4.35 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.34 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 185.5, 163.2, 151.8, 146.6, 139.3, 138.4, 132.8, 132.7, 129.7, 129.3, 129.2, 128.5, 125.0, 123.5, 119.0, 114.3, 108.5, 60.7, 47.9, 14.8.

MS (electrospray): *m*/*z* = 385 [M$^+$].

Anal. Calcd for $C_{24}H_{21}N_2O_3I·1.5H_2O$: C, 53.39; H, 4.55; N, 5.38. Found: C, 53.10; H, 4.40; N, 4.95.

***N*-Methyl-4-[1-ethoxycarbonyl-3-(*para*-methoxy)benzoylindolizin-7-yl]pyridinium Iodide (4c)**

Yellow crystals; mp 238–240 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.82 (d, *J* = 7.9 Hz, 1 H), 9.13 (d, *J* = 6.2 Hz, 2 H), 8.86 (s, 1 H), 8.64 (d, *J* = 6.4 Hz, 2 H), 7.85–7.89 (m, 3 H), 7.72 (s, 1 H), 7.15 (d, *J* = 8.7 Hz, 2 H,), 4.34–4.40 (m, 5 H, NCH_3, CH_2), 3.89 (s, 3 H, OCH_3), 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 184.0, 163.1, 162.9, 151.7, 143.3, 137.9, 132.1, 131.5, 131.3, 129.5, 127.5, 124.8, 123.6, 118.9, 114.3, 113.7, 108.0, 60.4, 55.9, 47.7, 14.6.

MS (electrospray): *m*/*z* = 415 [M$^+$].

Anal. Calcd for $C_{25}H_{23}N_2O_4I·H_2O$: C, 53.53; H, 4.56; N, 5.18. Found: C, 53.51; H, 4.36; N, 4.91.

***N*-Methyl-4[1-ethoxycarbonyl-3-(*para*-nitro)benzoylindolizin-7-yl]pyridinium Iodide (4d)**

Yellow crystals; mp 237–238 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.97 (d, *J* = 7.5 Hz, 1 H), 9.14 (d, *J* = 5.2 Hz, 2 H), 8.92 (s, 1 H), 8.68 (d, *J* = 5.2 Hz, 2 H), 8.44 (d, *J* = 8.8 Hz, 2 H), 8.08 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 7.1 Hz, 1 H), 7.76 (s, 1 H), 4.33–4.40 (m, 5 H, NCH_3, CH_2), 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 183.3, 162.4, 151.0, 148.9, 145.8, 143.9, 138.1, 132.6, 129.8, 129.2, 128.3, 124.4, 123.6, 122.5, 118.3, 113.9, 108.1, 60.0, 47.1, 14.0.

MS (electrospray): *m*/*z* = 430 [M$^+$].

Anal. Calcd for $C_{24}H_{20}N_3O_5I$: C, 51.73; H, 3.62; N, 7.54. Found: C, 51.69; H, 3.88; N, 7.47.

Acknowledgment

We thank partial financial support from Romanian CNCSIS grant AT81.

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