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Synthesis of 5-(2-Phenylethenyl)indolizines by Selective Intermolecular 1,3-Dipolar Cycloaddition of 2-(2-Phenylethenyl)pyridinium *N*-Ylide with Alkenes Promoted by Tetrakis-pyridine Cobalt(II) Dichromate†

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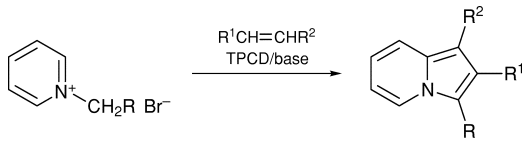
Intermolecular 1,3-dipolar cycloadditions of 2-(2-phenylethenyl)pyridinium *N*-ylides (**3a–d**) with electron-deficient alkenes (**5a–d**) were carried out selectively in the presence of tetrakis-pyridine cobalt(II) dichromate to yield 5-(2-phenylethenyl)indolizines (**6a–j**) in moderate yields (48–63%).

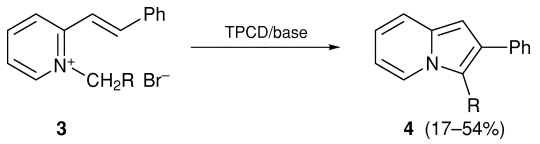
Synthetic indolizines have attracted special attention in past years mainly owing to their manifold practical utilities.[1–5] The methods for preparation of indolizines have been summarized in several reviews[6–9] and some new procedures have been reported.[10–18] Among them, intermolecular 1,3- and intramolecular 1,5-dipolar cyclization are very valuable.

To continue our research to find bioactive derivatives of indolizine as potential candidates in agricultural chemistry, some 5-(2-phenylethenyl)indolizines (**6**) were designed as target products for synthesis. Following the known procedures,[7] the 1,3-dipolar cycloaddition of 2-(2-phenylethenyl)pyridinium ylide (from salt **3a**, R = COPh) and dimethyl acetylenedicarboxylate yielded dimethyl 5-(2-phenylethenyl)indolizine-1,2-dicarboxylate (**6a**). However, the variety of functional groups on indolizines was limited seriously because the most electron-deficient acetylenes are not commercially available. The use of alkenes in place of acetylenes did not lead any desirable products under the same conditions. This is an expected result because the 1,3-dipolar cycloadditions of heteroaromatic *N*-ylides and alkenes usually give tetrahydroindolizines, which are generally not stable and are reversibly transformed into its components or ring-opened betaines.[19]



Scheme 1

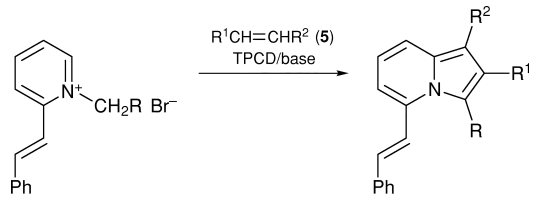
In our previous work, the first practical procedure to synthesise indolizines by intermolecular 1,3-dipolar cycloaddition of heteroaromatic *N*-ylides (from salts **1**) and alkenes (Scheme 1) has been reported.[20] Very recently, we have observed that intramolecular 1,5-dipolar cyclization of 2-(2-phenylethenyl)pyridinium *N*-ylides (from salts **3**) can also offer a synthetic entry to indolizines **4** (Scheme 2).[21] In both of reactions, a dehydrogenating reagent, tetrakis-pyridine cobalt(II) dichromate (TPCD), was employed and alkenes in place of acetylenes were used successfully as dipolarophiles. As most electron-deficient alkenes are more active dipolarophiles than phenylethene, it was assumed that a mixture of intermolecular 1,3- and intramolecular 1,5-dipolar cyclization products could be obtained and that the 1,3-cycloadduct 5-(2-phenylethenyl)indolizine (**6**) should



Scheme 2

be a major product when 2-(2-phenylethenyl)pyridinium *N*-ylide (from salt **3**) is treated with TPCD in the presence of an alkene. To our surprise, when a mixture of 2-(2-phenylethenyl)-*N*-(benzoylmethyl)pyridinium bromide (**3a**), dimethyl maleate (**5a**), triethylamine and TPCD was heated at 80–90 °C for 5 h, only the intermolecular 1,3-dipolar cycloadduct, dimethyl 5-(2-phenylethenyl)indolizine-1,2-dicarboxylate (**6a**), was obtained, as white crystals in 51% yield. No intramolecular 1,5-dipolar cyclization product was isolated or detected during the reaction. The experiment showed that intermolecular 1,3-dipolar cycloaddition of 2-(2-phenylethenyl)pyridinium *N*-ylide is preferred to intramolecular 1,5-dipolar cyclization under our conditions.

To test the scope of the reaction, three other alkenes, diethyl maleate (**5b**), methyl acrylate (**5c**) and acrylonitrile (**5d**), were used as dipolarophiles to react with pyridinium salt **3a** under the same conditions and gave indolizines **6b–d** smoothly in 49–63% yield. Using different pyridinium salts, **3b–d** (R = COMe in **3b**, R = CO_2Et in **3c**, R = 4-$NO_2C_6H_4$ in **3d**), the corresponding indolizines **6e–j**, were obtained in moderate yields (Scheme 3). Changing the bases (Et_3N or $NaHCO_3$) or solvents (toluene or DMF) has no noticeable effect on the product yields. But DMF does benefit the



	R	R^1	R^2
6a	COPh	CO_2Me	CO_2Me
b	COPh	CO_2Et	CO_2Et
c	COPh	H	CO_2Me
d	COPh	H	CN
e	COMe	H	CO_2Me
f	COMe	H	CN
g	CO_2Et	H	CO_2Me
h	CO_2Et	H	CN
i	4-$NO_2C_6H_4$	H	CO_2Me
j	4-$NO_2C_6H_4$	H	CN

Scheme 3

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

work-up procedure. It is noteworthy that no reactions occurred in the absence of TPCD.

In conclusion, a general and convenient procedure has been developed to synthesize 5-(2-phenylethenyl)indolizines in moderate yields. The method showed that alkenes are very good dipolarophiles in the 1,3-dipolar cycloaddition in the presence of TPCD and that intermolecular 1,3-dipolar cycloaddition of 2-(2-phenylethenyl)pyridinium *N*-ylides occurs in preference to intramolecular 1,5-dipolar cyclization under our conditions.

Experimental

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. The ^{1}H NMR spectra were recorded on a Bruker ACF-500 spectrometer with TMS as internal reference. The *J* values are given in Hz. MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. Elemental analyses were performed on a Perkin-Elmer 240C instrument.

General Procedure for the Preparation of 5-(2-*Phenylethenyl*)-*indolizines* **6a**–**j**.—A solution of 2-(2-arylethenyl)pyridinium salt **3** (10 mmol), alkene **5** (50 mmol), TPCD (10 mmol) and sodium hydrogen carbonate (15 mmol) in DMF (40 ml) was stirred at 80–90 °C. After 1 to 5 h (monitored by TLC), the mixture was cooled to room temperature and 5% aqueous hydrochloric acid (100 ml) was added. The precipitates were collected by centrifugal separation to give crude product **6**, which was purified by chromatography [silica gel, 25% EtOAc in light petroleum (bp 60–90 °C)].

Dimethyl 3-*Benzoyl*-5-(2-*phenylethenyl*)*indolizine*-1,2-*dicarboxylate* **6a**.—This compound was obtained as yellow crystals in 51% yield, mp 163–164 °C (Found: C, 73.7; H, 4.8; N, 3.2. $C_{27}H_{21}NO_5$ requires C, 73.8; H, 4.8; N, 3.2%); ν_{max}/cm^{-1} 1750, 1701, 1631, 1504, 1223, 793, 744, 695; δ_H (ppm) 8.36 (1 H, d, *J* 8.0), 7.69 (2 H, d, *J* 7.3), 7.49–7.16 (10 H, m), 6.99 (1 H, d, *J* 15.9), 6.65 (1 H, d, *J* 15.9), 3.90 (3 H, s), 3.55 (3 H, s); *m*/*z* (%) 439 (M$^+$, 19), 334 (25), 105 (100), 77 (23).

Diethyl 3-*Benzoyl*-5-(2-*phenylethenyl*)*indolizine*-1,2-*dicarboxylate* **6b**.—This compound was obtained as yellow plates in 49% yield, mp 120 °C (Found: C, 74.3; H, 5.3; N, 3.2. $C_{29}H_{25}NO_5$ requires C, 74.5; H, 5.4; N, 3.0%); ν_{max}/cm^{-1} 1729, 1694, 1623, 1511, 1223, 801, 733, 688; δ_H (ppm) 8.38 (1 H, d, *J* 8.8), 7.71 (2 H, d, *J* 7.6), 7.49–7.20 (9 H, m), 7.16 (1 H, d, *J* 7.1), 6.99 (1 H, d, *J* 15.9), 6.66 (1 H, d, *J* 15.9), 4.36 (2 H, q, *J* 7.1), 3.97 (2 H, q, *J* 7.1), 1.37 (3 H, t, *J* 7.1), 1.14 (3 H, t, *J* 7.1); *m*/*z* (%) 467 (M$^+$, 100), 422 (10), 362 (49), 105 (55).

Methyl 3-*Benzoyl*-5-(2-*phenylethenyl*)*indolizine*-1-*carboxylate* **6c**.—This compound was obtained as yellow crystals in 57% yield, mp 119–120 °C (Found: C, 78.6; H, 5.1; N, 3.7. $C_{25}H_{19}NO_3$ requires C, 78.7; H, 5.0; N, 3.7%); ν_{max}/cm^{-1} 1701, 1680, 1623, 1511, 1223, 794, 716, 680; δ_H (ppm) 8.36 (1 H, d, *J* 8.0), 8.01 (2 H, d, *J* 7.2), 7.76 (1 H, s), 7.55–7.28 (11 H, m), 7.00 (1 H, d, *J* 15.1), 3.89 (3 H, s); *m*/*z* (%) 381 (M$^+$, 35), 304 (16), 276 (100), 105 (12).

1-*Cyano*-3-*benzoyl*-5-(2-*phenylethenyl*)*indolizine* **6d**.—This compound was obtained as yellow needles in 63% yield, mp 159–160 °C (Found: C, 82.7; H, 4.8; N, 8.1. $C_{24}H_{16}N_2O$ requires C, 82.7; H, 4.6; N, 8.0%); ν_{max}/cm^{-1} 2221, 1631, 1518, 780, 730, 695; δ_H (ppm) 7.98 (2 H, d, *J* 7.4), 7.77 (1 H, d, *J* 8.7), 7.64 (1 H, t, *J* 7.5), 7.54–7.28 (11 H, m), 7.00 (1 H, d, *J* 15.9); *m*/*z* (%) 348 (M$^+$, 27), 243 (35), 105 (100), 77 (36).

Methyl 3-*Acetyl*-5-(2-*phenylethenyl*)*indolizine*-1-*carboxylate* **6e**.—This compound was obtained as yellow crystals in 61% yield, mp 124 °C (Found: C, 75.1; H, 5.4; N, 4.6. $C_{20}H_{17}NO_3$ requires C, 75.2; H, 5.4; N, 4.4%); ν_{max}/cm^{-1} 1722, 1638, 1518, 1223; δ_H (ppm) 8.33 (1 H, d, *J* 8.8), 8.09 (1 H, s), 7.64 (2 H, d, *J* 7.8), 7.45 (1 H, t, *J* 7.7), 7.38–7.29 (4 H, m), 7.26 (1 H, d, *J* 15.9), 7.07 (1 H, d, *J* 15.9), 3.94 (3 H, s), 2.66 (3 H, s); *m*/*z* (%) 319 (M$^+$, 56), 276 (71), 244 (59), 217 (100), 216 (15).

1-*Cyano*-3-*acetyl*-5-(2-*phenylethenyl*)*indolizine* **6f**.—This compound was obtained as yellow crystals in 56% yield, mp 147 °C (Found: C, 79.5; H, 5.0; N, 10.0. $C_{19}H_{14}N_2O$ requires C, 79.7; H, 4.9; N, 9.8%); ν_{max}/cm^{-1} 2214, 1645, 1511; δ_H (ppm) 7.85 (1 H, s), 7.71 (1 H, d, *J* 8.5), 7.54 (2 H, d, *J* 7.7), 7.48 (1 H, t, *J* 7.9), 7.40–7.31 (6 H, m), 7.26 (1 H, d, *J* 15.9), 7.07 (1 H, d, *J* 15.9), 2.65 (3 H, s); *m*/*z* (%) 286 (M$^+$, 25), 243 (100).

Methyl Ethyl 5-(2-*Phenylethenyl*)*indolizine*-1,3-*dicarboxylate* **6g**.—This compound was obtained as yellow crystals in 48% yield, mp 100–101 °C (Found: C, 72.0; H, 5.2; N, 4.1. $C_{21}H_{19}NO_4$ requires C, 72.2; H, 5.5; N, 4.0%); ν_{max}/cm^{-1} 1694, 1630, 1518, 1230; δ_H (ppm) 8.09 (1 H, d, *J* 8.8), 7.84 (1 H, s), 7.55–6.97 (9 H, m), 4.31 (2 H, q, *J* 7.2), 3.86 (3 H, s), 1.43 (3 H, t, *J* 7.2); *m*/*z* (%) 349 (M$^+$, 100), 276 (91), 244 (52), 217 (59).

Ethyl 1-*Cyano*-5-(2-*phenylethenyl*)*indolizine*-3-*carboxylate* **6h**.—This compound was obtained as yellow crystals in 57% yield, mp 123 °C (Found: C, 76.1; H, 4.95; N, 8.8. $C_{20}N_2O_2$ requires C, 75.9; H, 5.1; N, 8.9%); ν_{max}/cm^{-1} 2214, 1715, 1623, 1518, 1194; δ_H (ppm) 7.80 (1 H, s), 7.70 (1 H, d, *J* 8.7), 7.54 (2 H, d, *J* 7.8), 7.42–7.24 (7 H, m), 4.32 (2 H, q, *J* 7.1), 1.33 (3 H, t, *J* 7.1); *m*/*z* (%) 316 (M$^+$, 43), 243 (100).

Methyl 3-(4-*Nitrophenyl*)-5-(2-*phenylethenyl*)*indolizine*-1-*carboxylate* **6i**.—This compound was obtained as orange crystals in 59% yield, mp 246–248 °C (Found: C, 82.7; H, 4.8. $C_{24}H_{18}N_2O$ requires C, 82.7; H, 4.6; N, 8.0%); ν_{max}/cm^{-1} 1694, 1595, 1511, 1342, 1230; δ_H (ppm) 8.35 (1 H, d, *J* 8.9), 8.14 (2 H, d, *J* 8.7), 7.54 (2 H, d, *J* 8.7), 7.41 (1 H, s), 7.25–7.19 (4 H, m), 7.05 (2 H, m), 6.88 (2 H, d, *J* 7.3), 6.38 (1 H, d, *J* 16.0), 3.94 (3 H, s); *m*/*z* (%) 398 (M$^+$, 100), 367 (14), 292 (19).

1-*Cyano*-3-(4-*nitrophenyl*)-5-(2-*phenylethenyl*)*indolizine* **6j**.—The compound was obtained as orange crystals in 54% yield, mp 243–245 °C (Found: C, 75.5; H, 4.3; N, 11.5. $C_{23}H_{15}N_3O_2$ requires C, 75.6; H, 4.1; N, 11.5%); ν_{max}/cm^{-1} 2207, 1596, 1518, 1342; δ_H (ppm) 8.16 (2 H, d, *J* 8.5), 7.73 (1 H, d, *J* 8.8), 7.54 (2 H, d, *J* 8.5), 7.25–7.02 (7 H, m), 6.88 (2 H, d, *J* 7.2), 6.34 (1 H, d, *J* 15.9); *m*/*z* (%) 365 (M$^+$, 100), 319 (14), 243 (12).

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