A Facile One-step Synthesis of Aromatic Indolizines by 1,3-Dipolar Cycloaddition of Pyridinium and Related Heteroaromatic Ylides with Alkenes in the Presence of TPCD [$Copy_4(HCrO_4)_2$]

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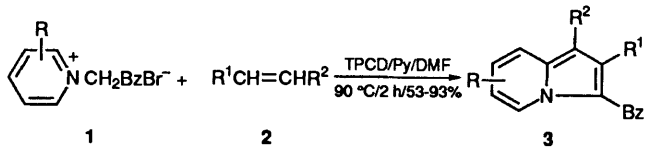
A facile and general one-step method is presented for the synthesis of aromatic indolizine compounds **3a–n** in moderate to high yields (53–99%) by reaction of the pyridinium *N*-ylides **1a–e**, the quinolinium *N*-ylide **1f** and the isoquinolinium *N*-ylide **1g** with various olefinic dipolarophiles, such as acrylonitrile **2a**, methyl acrylate **2b**, acrylamide **2c**, diethyl maleate **2d** and methyl crotonate **2e**, respectively, in the presence of a new oxidant TPCD [$Copy_4(HCrO_4)_2$, tetrapyridinecobalt(II) dichromate] at 90 °C for 2 h in DMF.

For both practical and theoretical reasons, a number of methods have been published for the synthesis of aromatic indolizines,[1–3] one of the most important, although usually low yielding, being the 1,3-dipolar cycloaddition of pyridinium and related heteroaromatic ylides with acetylenes.[4–12] Several modified methods have also been reported to lead to indolizines in relatively low yield or with relatively inaccessible materials.[12–16] The scope of all these procedures, however, have been limited by the acetylenes, few of which are commercially available. However, methods for the preparation of aromatic indolizines by 1,3-dipolar cycloaddition of pyridinium ylides with olefinic dipolarophiles replacing acetylenes are available for certain special cases (*e.g.* diphenylthiirene *S,S*-dioxide,[17] α-aminoethylene derivatives,[18] phenyl vinyl sulfoxide,[19] 2- or 4-vinylpyridines[20] and α-methoxyethylene derivatives);[21] also a two-step procedure is possible in which the initially formed tetrahydroindolizines or dihydroindolizines are dehydrogenated by treatment with suitable reagents.[5,6,18,22,23] All these procedures, however, suffer from drawbacks and limitations. Herein we report a simple and practical one-step method that affords aromatic indolizines in good to high yields starting from 1,3-dipolar cycloaddition of pyridinium ylides with olefinic dipolarophiles in the presence of a new oxidant TPCD [$Copy_4(HCrO_4)_2$, tetrapyridinecobalt(II) dichromate].

Results and Discussion

TPCD, a brown crystalline bi-metallic complex with pyridine, prepared easily by adding pyridine (4 equiv.) to aqueous chromium trioxide (2 equiv.) and cobalt(II) acetate (1 equiv.), has been found of value in the synthesis of aromatic five-membered ring nitrogen heterocycles.[24–26] In continuation of our studies of the chemical behaviour of TPCD, we found that the drawbacks in the synthesis of aromatic indolizines by 1,3-dipolar cycloaddition could be solved easily by its use.

N-Phenacylpyridinium bromide **1a** (1 equiv.) and acrylonitrile **2a** (4 equiv.), (the same starting materials as used in earlier work),[23] were treated with TPCD (0.65 equiv.) in DMF and pyridine at 90 °C under nitrogen for 2 h, after which the reaction mixture was worked up to give yellow crystals, m.p. 128–130 °C (Scheme 1) identical (IR, ^{1}H NMR and elemental analysis) with authentic 3-benzoyl-1-cyanoindolizines **3a** (m.p. 128 °C)[23] [*cf.* 3-benzoyl-1-cyano-1,2,3,8a-tetrahydroindolizine **4** (lit.,[22] m.p. 103–105 °C)]. The 1,3-dipolar cycloaddition and dehydrogenative aromatizations in this one-pot reaction gives an extraordinarily high yield (93%) not previously reported for similar procedures.



1 2 3

1	R	2	R^1	R^2
1a	H	2a	H	CN
1b	2-Me	2b	H	CO_2Me
1c	4-Me	2c	H	$CONH_2$
1d	3-CO_2Et	2d	CO_2Et	CO_2Et-*cis*
1e	4-CO_2Et	2e	Me	CO_2Me-*trans*
1f	2, 3-Benzo			
1g	3, 4-Benzo			

Scheme 1

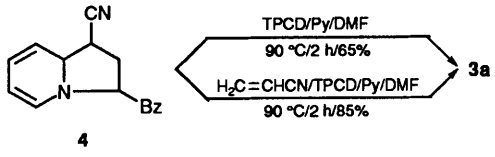
To demonstrate the scope of the reaction, several other olefinic dipolarophiles, *e.g.* methyl acrylate **2b**, acrylamide **2c**, diethyl maleate **2d** and methyl *trans*-crotonate **2e**, were allowed to react with *N*-phenacylpyridinium bromide **1a** under the same conditions to give the corresponding indolizines **3b–e**, respectively. It is interesting that the yields of products **3** decrease in the order **3a** to **3e** (see Table 1), the relative activity of the olefinic dipolarophiles changing with a change in the substituents on the ethylene. The monosubstituted ethylene with the strong electron-withdrawing group CN (in **2a**) gave the best yield and the 1,2-disubstituted ethylene with electron-withdrawing groups (in **2d**) gave a moderate yield. The activity of ethylene with an electron-donating group (**2e**), was reduced significantly.

The substituted pyridinium *N*-ylides **1b–e** were allowed to react with acrylonitrile **2a** to give **3f–j** also in high yield. The reaction between **1** and **2a** gave an isomeric mixture of **3h** and **3i** in a ratio of *ca.* 1:1.4 with a total yield of 84%. Results for non-regioselective reactions have already been reported[8,11,19] and here we observed that the reaction is non-specific with respect to the ratio of isomers. However, the reaction of isoquinolinium *N*-ylide **1g** with **2a** and **2b** gave the 1,2-cycloaddition products **3l** and **3m**, respectively. Quinolinium *N*-ylide **1f** gave **3k** in a relatively lower yield (79%).

Under the same reaction conditions, the reaction of **1a** with **2a** without TPCD, or in the presence of just one of the components of TPCD [CrO_3, pyridine or cobalt(II) acetate], gave none of the desired product **3a**. Further, none of the 2,3-dihydro-

Table 1 Indolizines **3** prepared

3	R	R^1	R^2	Yields (%)
3a	H	H	CN	93
3b	H	H	CO_2Me	88
3c	H	H	$CONH_2$	74
3d	H	CO_2Et	CO_2Et	70
3e	H	Me	CO_2Me	53
3f	5-Me	H	CN	99
3g	7-Me	H	CN	88
3h	6-CO_2Me	H	CN	35
3i	8-CO_2Me	H	CN	49
3j	7-CO_2Me	H	CN	95
3k	5,6-Benzo	H	CN	79
3l	7,8-Benzo	H	CN	98
3m	7,8-Benzo	H	CO_2Me	82



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Scheme 2

indolizine **5** or aromatic indolizine **3a** was obtained when 3-benzoyl-1-cyano-1,2,3,8a-tetrahydroindolizine **4**[22] was warmed with cobalt(II) acetate at 90 °C in DMF for 2 h.

Treatment of compound **4** by TPCD, with or without pyridine, at 90 °C in DMF for 2 h, led to the aromatization of **4** and formation of the indolizine **3a** (Scheme 2); the best yield (65%) in this reaction was obtained in only a few experiments. With a freshly prepared sample of **4** and addition of the acrylonitrile **2a** to the reaction the yield of **3a** increased to 85% (it is likely that the low yield is caused by partial dissociation of **4** at higher reaction temperatures), but it is still significantly lower than that in the one-step reaction (93%). In the light of the above results and the fact that no tetrahydroindolizine or dihydroindolizine could be detected as intermediates in quenched reactions, it seems unlikely that the system involved is a simple one-pot reaction consisting of two components. We suggest that the Co^{III} component is the 'real' and active entity in the dehydrogenative aromatization and that the Cr^{VI} is actually a reoxidation agent, ($Co^{II} \rightarrow Co^{III}$) in which it is converted into Cr^{III}. The experimental evidence to support such hypotheses is not, however, at present, to hand.

Experimental

All m.p.s are uncorrected and measured with a Yanaco MP-500 apparatus. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^1H NMR spectra were recorded on a JEOL JNM-PMX 60SI spectrometer at ambient temperature in $CDCl_3$ with TMS as an internal reference and elemental analyses were performed on a Perkin-Elmer 240-C instrument.

Preparation of 3-*Benzoyl*-1-*cyanoindolizine* **3a**: *Typical Procedure.*—A solution of *N*-phenacylpyridium bromide **1a** (2.78 g, 10 mmol), acrylonitrile **2a** (2.12 g, 40 mmol), TPCD (4.0 g, 6.5 mmol) and pyridine (2.0 cm^3) in DMF (40 cm^3) was stirred at 90 °C for 2 h. The mixture was then cooled to room temperature and poured into 5% aq. HCl (100 cm^3). The solution was extracted with diethyl ether (2 × 50 cm^3) and the combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to give a solid. This was purified by vacuum chromatography with a short column [silica gel G, 10 μm, 25 × 50 mm, eluted with 25% ethyl acetate in light petroleum (b.p. 60–90 °C)] to give **3a** as yellow crystals (2.29 g, 93%), m.p. 128–130 °C (from EtOH) (lit.,[23] 128 °C) (Found: C, 78.1; H, 4.0; N, 12.0. $C_{16}H_{10}N_2O$. Calc. for: C, 78.03; H, 4.09; N, 11.38%); ν_{max}/cm^{-1} 2200 and 1617; δ_H 7.05 (dd, *J* 1.0, 6.0, 1 H, ArH), 7.27 (dd, *J* 1.0, 6.0, 1 H, ArH), 7.40–7.90 (m, 9 H, ArH) and 9.95 (d, *J* 6.0, 1 H, ArH). Compounds **3b–m** were prepared by the same procedure (Table 1).

Methyl 3-*benzoylindolizine*-1-*carboxylate* **3b**. M.p. 160–162 °C (from EtOH) (lit.,[6] 161–162 °C) (Found: C, 73.3; H, 4.7; N, 4.8. Calc. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; 5.02%); ν_{max}/cm^{-1} 1615, 169; δ_H 3.69 (s, 3 H, CH_3), 7.05 (dd, *J* 1.0, 6.0, 1 H, ArH), 7.27 (dd, *J* 1.0, 6.0, 1 H, ArH), 7.43–7.95 (m, 6 H, ArH), 8.40 (d, *J* 8.0, 1 H, ArH) and 9.93 (d, *J* 6.0, 1 H, ArH).

3-*Benzoyl*-1-*carbamoylindolizine* **3c**. M.p. 183–184 °C (from EtOH) (lit.,[7] 193–194 °C) (Found: C, 72.6; H, 4.8; N, 10.5. Calc. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60%); ν_{max}/cm^{-1} 3350, 3170, 1670 and 1635; δ_H 3.20 (s, 2 H, NH_2), 7.00–7.95 (m, 7 H, ArH), 8.55 (d, *J* 9.0, 1 H, ArH) and 9.86 (d, *J* 7.0, 1 H, ArH).

Diethyl 3-*benzoylindolizine*-1,2-*dicarboxylate* **3d**. M.p. 107–109 °C (from EtOH) (Found: C, 69.1; H, 5.25; N, 3.6. $C_{21}H_{19}NO_5$ requires C, 69.09; H, 5.24; N, 3.64%); ν_{max}/cm^{-1} 1730, 1695 and 1600; δ_H 1.03 (t, *J* 7.0, 3 H, CH_3), 1.33 (t, *J* 7.0, 3 H, CH_3), 3.66 (q, *J* 7.0, 2 H, CH_2), 4.37 (q, *J* 7.0, 2 H, CH_2), 7.08 (dd, *J* 2.0, 7.0, 1 H, ArH), 7.30 (dd, *J* 2.0, 7.0, 1 H, ArH), 7.46–7.91 (m, 5 H, ArH), 8.40 (dd, *J* 1.0, 9.0, 1 H, ArH) and 9.70 (dd, *J* 1.0, 6.0, 1 H, ArH).

Methyl 3-*benzoyl*-2-*methylindolizine*-1-*carboxylate* **3e**. M.p. 116–117 °C (from EtOH) (Found: C, 73.7; H, 5.1; N, 4.6. $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.15; N, 4.60%); ν_{max}/cm^{-1} 1689 and 1602; δ_H 2.23 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 6.97 (m, 1 H, ArH), 7.23–7.89 (m, 6 H, ArH), 8.37 (d, *J* 9.0, 1 H, ArH) and 9.55 (d, *J* 7.0, 1 H, ArH).

3-*Benzoyl*-5-*methylindolizine*-1-*carbonitrile* **3f**. M.p. 160–162 °C (from EtOH) (Found: C, 78.4; H, 4.7; N, 10.6. $C_{17}H_{12}N_2O$ requires C, 78.44; H, 4.65; N, 10.76%); ν_{max}/cm^{-1} 2215 and 1625; δ_H 2.59 (s, 3 H, CH_3), 7.04 (d, *J* 8.0, 1 H, ArH), 7.35–7.98 (m, 7 H, ArH) and 8.17 (dd, *J* 2.0, 7.0, 1 H, ArH).

3-*Benzoyl*-7-*methylindolizine*-1-*carbonitrile* **3g**. M.p. 171–172 °C (from EtOH) (Found: C, 78.4; H, 4.4; N, 10.5. $C_{17}H_{12}N_2O$ requires C, 78.44; H, 4.65; N, 10.76%); ν_{max}/cm^{-1} 2210 and 1610; δ_H 2.67 (s, 3 H, CH_3), 7.10 (d, *J* 7.0, 1 H, ArH), 7.30–8.00 (m, 7 H, ArH) and 9.93 (d, *J* 7.0, 1 H, ArH).

Methyl 3-*benzoyl*-1-*cyanoindolizine*-6-*carboxylate* **3h**. M.p. 197–199 °C [EtOAc–light petroleum (60–90 °C)] (Found: C, 71.05; H, 3.8; N, 9.0. $C_{18}H_{12}N_2O_3$ requires C, 71.05; H, 3.97; N, 9.21%); ν_{max}/cm^{-1} 2215, 1720 and 1618; δ_H 4.00 (s, 3 H, CH_3), 7.10–8.15 (m, 8 H, ArH) and 10.45 (d, *J* 7.0, 1 H, ArH).

Methyl 3-*benzoyl*-1-*cyanoindolizine*-8-*carboxylate* **3i**. M.p. 206–209 °C [EtOAc–light petroleum (b.p. 60–90 °C)] (Found: C, 71.1; H, 3.7; N, 9.1. $C_{18}H_{12}N_2O_3$ requires C, 71.05; H, 3.97; N, 9.21%); ν_{max}/cm^{-1} 2220 and 1725; δ_H 4.07 (s, 3 H, CH_3), 7.10–8.14 (m, 8 H, ArH) and 10.10 (dd, *J* 1.0, 7.0, 1 H, ArH).

Methyl 3-*benzoyl*-1-*cyanoindolizine*-7-*carboxylate* **3j**. M.p. 212–214 °C (DMF) (Found: C, 71.0; H, 4.05; N, 9.3. $C_{18}H_{12}N_2O_2$ requires C, 71.05; H, 3.97; N, 9.21%); ν_{max}/cm^{-1} 2220, 1725 and 1625; δ_H 4.06 (s, 3 H, CH_3), 7.45–7.95 (m, 7 H, ArH), 8.53 (d, *J* 7.0, 1 H, ArH) and 9.93 (d, *J* 7.0, 1 H, ArH).

1-*Benzoylpyrrolo*[1,2-a]*quinoline*-3-*carbonitrile* **3k**. M.p. 180–182 °C (EtOAc–acetone) (lit.,[23] 177–179 °C) (Found: C, 81.0 H, 3.95; N, 9.3. Calc. for $C_{20}H_{12}N_2O$: C, 81.06; H, 4.08; N, 9.45%); ν_{max}/cm^{-1} 2225 and 1635; δ_H 7.33 (s, 1 H, ArH), 7.35–7.85 (m, 8 H, ArH), 7.86–8.15 (m, 3 H, ArH).

1-*Benzoylpyrrolo*[2,1-a]*isoquinoline*-3-*carbonitrile* **3l**. M.p. 192–193 °C ($CHCl_3$) (lit.,[23] 196–197 °C) (Found: C, 80.8; H, 4.0; N, 9.35. Calc. for $C_{20}H_{12}N_2O$: C, 81.06; H, 4.08; N, 9.45%); ν_{max}/cm^{-1} 2225 and 1630; δ_H 7.30 (d, *J* 7.0, 1 H, ArH), 7.40–7.95 (m, 9 H, ArH), 8.90 (m, 1 H, ArH) and 9.46 (d, *J* 7.0, 1 H, ArH).

Methyl 1-*benzoylpyrrolo*[2,1-a]*isoquinoline*-3-*carboxylate* **3m**. M.p. 183–184 °C ($CHCl_3$–acetone) (Found: C, 76.4; H, 4.35; N, 4.2. $C_{21}H_{15}NO_3$ requires C, 76.58; H, 4.59; N, 4.25%); ν_{max}/cm^{-1} 1705 and 1620; δ_H 3.90 (s, 3 H, CH_3), 7.22 (d, *J* 7.0, 1 H, ArH), 7.40–7.95 (m, 9 H, ArH), 9.60 (d, *J* 7.0, 1 H, ArH) and 9.85 (m, 1 H, ArH).

Dehydrogenation of 3-*Benzoyl*-1,2,3,8a-*tetrahydroindolizine*-1-*carbonitrile* **4a** *with TPCD*.—A solution of the 1,2,3,8a-tetrahydroindolizine **4a**[22] (2.50 g, 10 mmol), TPCD (4.0 g, 6.5 mmol) and pyridine (2.0 cm^3) in DMF (40 cm^3) was warmed at 90 °C for 2 h. The reaction was worked up and the product was purified by the procedure described above to give **3a** as yellow crystals (1.60 g, 65%), m.p. 128–129 °C.

When acrylonitrile **3a** (2.12 g, 40 mmol) was added to the reaction mixture as above under the same conditions, **3a** was obtained as yellow crystals (2.09 g, 85%), m.p. 128–129 °C.[23]

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