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Combinatorial synthesis of indolizines on solid support

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Abstract

A solid phase synthesis of trisubstituted aromatic indolizines utilizing a formal [3+2] dipolar cycloaddition of a resin-bound pyridinium salt with chalcones followed by oxidation has been achieved. The utility of this procedure for the synthesis of combinatorial libraries is also demonstrated.

While searching for interesting molecular frameworks to use for the synthesis of combinatorial libraries on solid support our attention was drawn to the formal [3+2] cycloaddition of pyridinium ylides with electron deficient alkenes. This chemistry has ample precedent in solution and is particularly attractive due to the high yields and mild conditions typically involved.[1] The work of Tsuge and co-workers using maleimides as dipolarophiles and that of Katritzky with chalcones seemed particularly relevant.[2,3] The indolizine nucleus created by this reaction is not just a scaffold for other functionality but has well recognized biological activity. For example, indolizines have antiarrhythmic and anti-inflammatory activity.[4,5]

Initially isonicotinic acid was coupled to deprotected Rink amide resin and then quaternized by treatment with 2-bromoacetophenone in DMF. The resin bound pyridinium salt was simply washed with DMF and dichloromethane and then treated with (2,4-dichlorophenyl)but-1-en-3-one in the presence of triethylamine in DMF for 1 h at 60°C to give resin bound tetrahydroindolizine **2a** (Scheme 1). Higher temperatures or longer reaction times were found to give Diels–Alder adducts between **2a** and the excess α,β-unsaturated ketone. When the resin was treated with 95:5 TFA:H_2O a major product (HPLC retention time 26.0 min, 80% pure) with m/e 456 (as required) was obtained.[6] There was also a small peak at 26.6 min (11%), presumed to be a diastereomer. However, ^{1}H NMR of the crude product of this reaction showed that the major product was not a tetrahydroindolizine but rather an open-chain pyridinium salt **3a**.[7] Ring opening undoubtedly occurs upon acidic cleavage of **2a** from the resin since Katritzky and co-workers have observed ring opening of closely related tetrahydroindolizines under even brief exposure to acetic acid.[3b]

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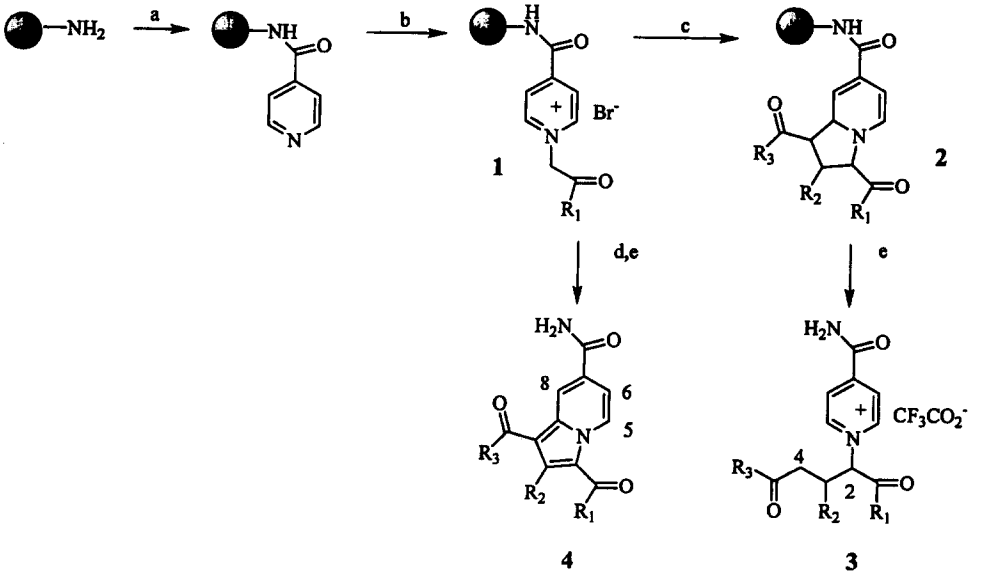

Scheme 1. Conditions: (a) PyBrop., DIEA, isonicotinic acid, 1,2-dichloroethane, rt, o.n.; (b) $BrCH_2COR_1$, DMF, 45°C, 1 h; (c) $R_2CHCHCOR_3$, Et_3N, DMF, 60°C, 1 h; (d) $R_2CHCHCOR_3$, TPCD, Et_3N, DMF, 80°C, 2 h; (e) 95:5 TFA:H_2O, 20 min

In order to preserve the bicyclic ring structure an oxidative strategy was adopted. Hu and co-workers have recently developed the bimetallic complex TPCD [Co(pyridine)$_4$($HCrO_4$)$_2$] as a reagent for the one-pot synthesis of aromatic indolizines from phenacylpyridinium bromide and alkenes.[8,9] When the dipolar cycloaddition with (2,4-dichlorophenyl)but-1-en-3-one was repeated in the presence of TPCD at 80°C clean reaction occurred to give the aromatic indolizine **4a**. The aromatic indolizine is much less polar than the open chain pyridinium salt **3a** (HPLC retention time of 33 min).[6] The ^{1}H NMR of **4a** shows a complete loss of the two aliphatic resonances present in **3a**. The pyridine ring protons now come as a doublet at 9.41 ppm (H-5, J=7.3 Hz) coupled to H-6 (dd, 7.62 ppm, J=7.3, 1.6 Hz) while H-8 comes as a broadened singlet at 8.94 ppm. The ms parent ion for the indolizine is 5 daltons less than the pyridinium salt, which is consistent with the assigned structure, taking into account that M^+ is observed for **3a** while MH^+ is observed for **4a**.

In order to test this chemistry pyridinium salts **3a–g** and the corresponding indolizines **4a–g** were prepared (Scheme 1 and Table 1).[10] The crude **4a–g** were passed over a short Grade V neutral alumina column to remove residual metal salts. The assigned structures were confirmed by ^{1}H NMR, and low and high resolution mass spectrometry. It was clear that a wide variety of functionality such as nitrile, ketone, amide, halogen, or ether as well as heterocyclic rings could be tolerated in this synthesis and that a reasonably complex molecular scaffold could be constructed rapidly in good purity.

Since the goal of this chemistry is combinatorial library synthesis we decided to construct a small library. Reasoning that the reactivity of the bromomethylketone part would be almost independent of the attached aryl moiety, an equimolar mixture of nine α-bromoketones was reacted with the resin bound isonicotinamide. The resulting mixture of pyridinium salts was then reacted with 1-[3-(trifluoromethyl)phenyl]but-1-en-3-one in DMF with triethylamine and TPCD at 80°C for 2 h, followed by cleavage with 95:5 TFA:H_2O and passage through alumina to give indolizines **5a–i**. The structures and HPLC trace of the library are shown in Fig. 1. Assignments were subsequently made by HPLC–mass spectrometry. All of the expected indolizines are present and the purity appears good.

In conclusion, the formal [3+2] cycloaddition reaction of resin bound pyridinum ylides with chalcones

Table 1
Preparation of aromatic indolizines **4** and pyridinium salts **3**

R_1	R_2	R_3	Cpd	Yield[a]	Purity[b]	MS[c]	Cpd	Yield	Purity	MS
Ph	2,4-Di-chloroPh	Me	3a	83	87	420	4a	54	70	416
6-(2-Oxo-1,2,3,4-tetrahydroquinolyl)	3-CF_3Ph	Me	3b	36	83	524	4b	66	82	520
4-Biphenylyl	3-CF_3Ph	Me	3c	58	95	531	4c	69	85	527
4-OCF_3Ph	3-Br-2-OMePh	c-C_3H_7	3d	99	83	605	4d	71	88	601
4-CNPh	3-Br-2-OMePh	c-C_3H_7	3e	89	85	546	4e	61	80	542
1-(3,4-Trimethylene-dioxy)Ph	Ph	Ph	3f	90	94	521	4f	57	80	517
2-(5-Chloro-3-methylbenzothienyl)	Ph	Ph	3g	69	84	553	4g	34	83	549

a) Crude product, lyophilized 3 times
b) Determined by C-18 RP HPLC at 220 nm
c) Electrospray M^+ for 3, MH^+ for 4

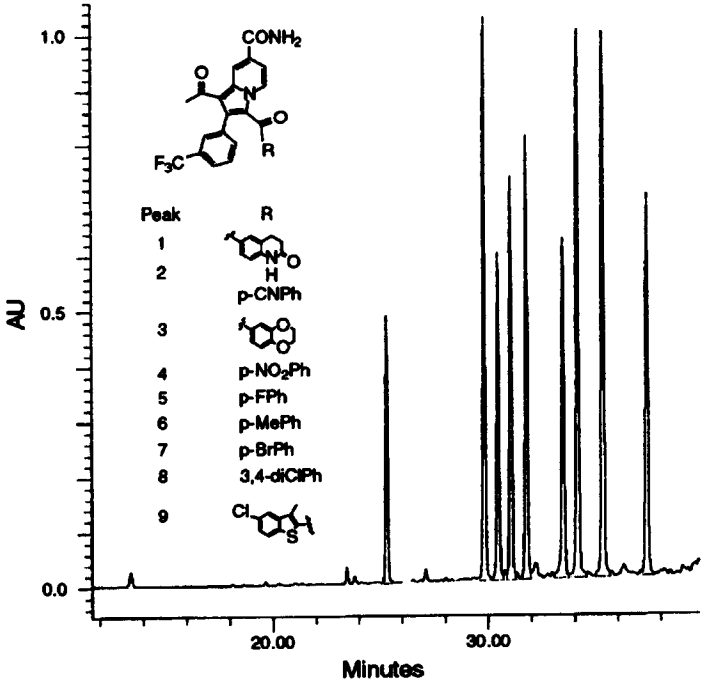

Figure 1. Preparation of an indolizine combinatorial mixture

followed by oxidation is a viable route to combinatorial libraries of indolizines. The mildness of the reaction conditions allows a wide variety of substituents on the carbonyl components, hence allowing for further modification of the indolizines while still attached to the resin.

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6. HPLC utilized a Vydac analytical C-18 RP column with a gradient of 0–80% acetonitrile with water containing 0.1% trifluoroacetic acid over 40 min. Detection was at 214 nm, flow rate=1.0 mL/min.
7. The major diastereomer **3a** was separated by semi-preparative C-18 RP HPLC. Diagnostic in the ^{1}H NMR are the two doublets at 8.45 and 9.36 ppm (J=6.0 Hz) for the symmetrical 4-carboxamidopyridinium ring. The protons in the aliphatic chain are readily assigned. H-2 is deshielded by the pyridinium ring and appears as a doublet at 6.80 ppm (J=10.5 Hz), H-3 appears as a complex multiplet at 4.7 ppm, while the H-4 methylene protons occur as two dd, 3.34 ppm (J=10.1, 18.1 Hz) and 2.65 ppm (J=18, <1 Hz). These assignments were confirmed by a DQ COSY experiment (2:1 CD_3CN:D_2O). Interestingly, when the NMR sample was concentrated to dryness in vacuo at approx. 60°C and then redissolved in DMSO-d_6 the percentage of minor diastereomer in the mixture has increased from <5% to 28% [major diastereomer: 4.60 (m, H-3), 3.28 (dd, J=17.4, 10.4, H-4b), 2.64 (dd, J=17.8, 3.7, H-4a), 1.88 (s, $COCH_3$); minor diastereomer: 4.70 (m, H-3), 3.08 (AB q, 4-CH_2), 1.76 (s, $COCH_3$)]. These assignments were confirmed by a DQ COSY experiment on the mixture of diastereomers. H-2 of both diastereomers overlap at 6.95 ppm. These results indicate that **3a** readily epimerizes upon heating. **3b–g** were purified by HPLC. In all of the purified samples variable amounts of a minor diastereomer could be seen in the ^{1}H NMR. This could be due to incomplete HPLC separation or re-equilibration. ^{1}H NMR of several of the crude mixtures gave the following ratio of diastereomers: **3a** (20:1), **3e** (4:1), **3f** (5:1) and **3g** (1:1).
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9. After this work had been completed, Wei and co-workers reported the first direct synthesis of 1-acylindolizines using α,β-unsaturated ketones. See: Zhang, X.; Cao, W.; Wei, X.; Hu, H. *Synth. Comm.* **1997**, *27*, 1395–1403.
10. Typical experimental procedure: Rink amide resin (4.1 g) was deprotected by treatment with 20% piperidine in DMF (50 mL) (1×5 min, 1×20 min). The resin was washed well with DMF and dichloromethane and then mixed overnight (wrist shaker) at room temperature with a solution of PyBrop® (3.3 g), diisopropylethylamine (4.2 mL) and isonicotinic acid (0.90 g) in 1,2-dichloroethane (25 mL). The resin was again washed, then dried in vacuo. A 50 mg aliquot was cleaved with 95:5 TFA:H_2O and the yield of crude lyophilized isonicotinamide was determined. This gave a loading of 0.27 mmol/g of resin. The resin (120 mg) was treated with a solution of 2-bromo-4′-cyanoacetophenone (1.5 mmol) in DMF (3 mL) for 1 h at 45°C. The resin was washed with DMF and dichloromethane and air dried, then divided into two equal portions. The first portion was treated with a solution of 3-(5-bromo-2-methoxyphenyl)-1-cyclopropyl-2-propen-1-one (1.5 mmol) and triethylamine (0.21 mL, 1.5 mmol) in DMF (3 mL) at 60°C for 1 h. The resin was washed with DMF

and dichloromethane and then treated with 95:5 TFA:H_2O (20 min) at room temperature. The resin was washed with acetic acid, diluted with water and lyophilized. The crude product was re-lyophilized from acetonitrile/H_2O to give **3d** as a solid (15.1 mg). HPLC (gradient 0–80% acetonitrile in water with 0.1% TFA over 40 min) rt=26.4 min. The remainder of the resin was treated as above except that 50 mg of TPCD was included and the reaction was run for 2 h at 80°C. After the initial lyophilization the crude product was dissolved in acetonitrile and passed down a short column of Grade V neutral alumina. After concentration in vacuo, the material was lyophilized to give a light green solid **4d** (8.8 mg). HPLC rt=33.0 min.