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A CONVENIENT SYNTHESIS OF 1-ACYL INDOLIZINES BY 1,3-DIPOLAR CYCLOADDITION REACTIONS OF PYRIDINIUM YLIDES AND α,β-UNSATURATED ALDEHYDES OR KETONES IN THE PRESENCE OF TETRAKIS-PYRIDINE COBALT DICHROMATE

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Abstract: In the presence of tetrakispyridine cobalt dichromate ($CoPy_4(HCrO_4)_2$), pyridinium ylides and α,β-unsaturated aldehydes or ketones undergo 1,3-dipolar cycloaddition reactions followed by *in situ* aromatization to give 1-acyl substituted indolizines in moderate to good yields.

1,3-Dipolar cycloaddition reaction of pyridinium ylides and dipolarophilic alkenes is an efficient and important way of constructing the indolizine ring.[1] For the synthesis of aromatic indolizines, acetylenes were often chosen as the dipolarophile because the dihydroindolizines formed can be aromatized *in situ* to indolizines.[2] The use of some specific olefins has also been reported.[3] With simple dipolarophilic alkenes, the reaction terminates at the 1,2,3,8a-tetrahydroindolizine and a second aromatization step is required.[4] However, to the best of our knowledge and a little bit surprisingly, a direct synthesis of 1-acylindolizines using simple α,β-unsaturated aldehydes or ketones as dipolarophiles has not been described. In fact, reactions of α,β-unsaturated aldehydes or ketones and pyridinium ylides gave the simple 1,4-addition

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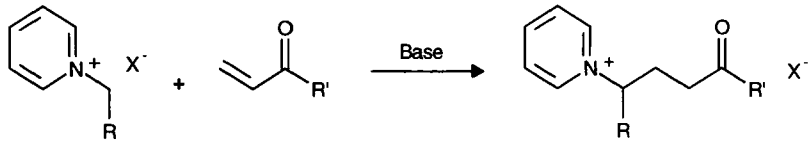
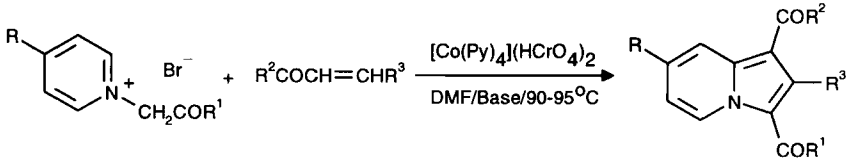
products as shown in scheme 1.[5] A survey of the literature revealed the following methods of synthesising 1-acyl indolizines: the 1,3-dipolar cycloaddition reaction of pyridinium ylides with acyl acetylenes,[6-8] the thermal reaction of pyridinium 3,3-diacyl-1-carbonyl-allides prepared from pyridinium N-ylides with 2,2-diacyl-1-ethoxyethylenes,[9-10] the reaction of pyridinium salts and acyl methoxyethylene,[11] the reaction of 2-halopyridinium salts with β-keto esters and β-diketones in the presence of DBU[12] and, as a single example for the preparation of 1,3-diacetylindolizine, the reaction of 2-methylpyridine with acetic anhydride at 200-220 °C.[13] Many of these methods, however, have the serious drawback that the starting materials are not easily available.

In previous work, we developed a facile one-step method for the synthesis of indolizines by the 1,3-dipolar cycloaddition reaction of pyridinium ylides and alkenes which used a mild oxidant tetrakispyridinecobalt(II) dichromate (TPCD) as the reagent.[14] This method is very efficient and allows alkenes to be used as dipolarophiles instead of the corresponding acetylenes because the 1,2,3,8a-tetrahydroindolizines generated during the reaction can be aromatized immediately by the oxidant to drive the reaction equilibrium towards the product. Recently, because we had begun working on a related coordination chemistry project and because of the fact that simple α,β-unsaturated aldehydes or ketones have not been used to synthesise 1-acylindolizine derivatives, we studied their reaction with pyridinium ylides under our reaction conditions using TPCD as the oxidant. Herein we report that 1-acylindolizine derivatives can be prepared efficiently in this way.

The operation is easy and simple. Pyridinium salts (**1a-e**), alkenes (α,β-unsaturated aldehydes or ketones **2a-e**), TPCD and a base ($NaHCO_3$ or pyridine) are allowed to react in DMF at 90-95 °C for about four hours to complete the reaction. After the usual workup and column chromatography, indolizines **3a-m** can be obtained in moderate to good yields (40-88%). In a crude NMR analysis we couldn't find any traces of regioisomers or 1,2,3,8a-tetrahydroindolizines so the 1,3-dipolar



Scheme 1



1

1a: R=H, R¹=Ph
1b: R=H, R¹=Me
1c: R=H, R¹=OEt
1d: R=Me, R¹=Ph
1e: R=Me, R¹=Me

2

2a: R²=Me, R³=H
2b: R²=Ph, R³=H
2c: R²=H, R³=Ph
2d: R²=Me, R³=Ph
2e: R²=CH=CHPh, R³=Ph

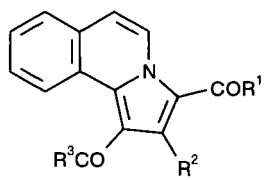
3

3a: R=H, R¹=Me, R²=Ph, R³=H
3b: R=H, R¹=Me, R²=Me, R³=H
3c: R=H, R¹=OEt, R²=Ph, R³=H
3d: R=H, R¹=OEt, R²=Me, R³=H
3e: R=H, R¹=Ph, R²=Ph, R³=H
3f: R=H, R¹=Ph, R²=Me, R³=H
3g: R=H, R¹=Ph, R²=H, R³=Ph
3h: R=H, R¹=Ph, R²=Me, R³=Ph
3i: R=H, R¹=Ph, R²=CH=CHPh, R³=Ph
3j: R=Me, R¹=Ph, R²=Ph, R³=H
3k: R=Me, R¹=Ph, R²=Me, R³=H
3l: R=Me, R¹=Ph, R²=Me, R³=Ph
3m: R=Me, R¹=Ph, R²=CH=CHPh, R³=Ph

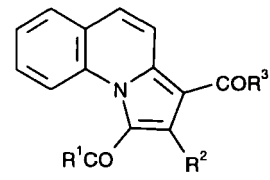
Scheme 2

cycloaddition reaction must be regioselective and the following aromatization must be fast and complete.

The reactions of isoquinolinium and quinolinium N-ylides and α,β-unsaturated aldehydes or ketones have also been studied. The corresponding indolizines **4a-h, 5a-b** were obtained in 46-86% yields (Scheme 3). Again no regioisomer was observed.



4



5

4a: R^1=Me, R^2=H, R^3=Me
4b: R^1=Me, R^2=H, R^3=Ph
4c: R^1=Ph, R^2=H, R^3=Me
4d: R^1=Ph, R^2=H, R^3=Ph
4e: R^1=Ph, R^2=Ph, R^3=H
4f: R^1=Ph, R^2=Ph, R^3=Me
4g: R^1=OEt, R^2=H, R^3=Me
4h: R^1=OEt, R^2=H, R^3=Ph

5a: R^1=Ph, R^2=H, R^3=Me
5b: R^1=Ph, R^2=H, R^3=Ph

Scheme 3

All compounds have been characterized by ^{1}H-NMR, IR and microanalysis. Physical data of the known compounds have also been compared with those in the literature.

In summary, by using TPCD as the reagent, 1,3-dipolar cycloaddition reactions of pyridinium N-ylides and α,β-unsaturated aldehydes or ketones followed by *in situ* aromatization have been achieved. This provides a simple and practical one-pot method for the synthesis of the 1-acylindolizines. Our method has two important advantages: the operation is easy and the starting materials are readily available.

Experimental

Melting points are uncorrected. IR spectrum were recorded on a Nicolet FT-IR 5DX spectrometer (KBr). ^{1}H-NMR were recorded using either a JNMFX-90Q, a Bruker ACF-300 or Bruker AM-500 spectrometer using $CDCl_3$ or DMSO as solvent and TMS as internal standard. Mass spectra were recorded using a VG-ZAB-MS spectrometer. A Perkin-Elmer 240C instrument was used for microanalysis. All

chemicals were of reagent grade and used as purchased without any further purification. TPCD was prepared by the literature method.[15]

Preparation of 1-Acylindolizines; General Procedure:

To a solution of pyridinium salt (5 mmol) in DMF (35 mL) was introduced alkene (25 mmol), TPCD (3.5 g) and $NaHCO_3$ (1 g) or pyridine (1 mL). The reaction mixture was heated to 90-95 °C (80 °C in the case of 6a) and stirred at this temperature for 4 hours. After cooling down to room temperature the reaction mixture was poured onto a 5% HCl solution (80 mL). The precipitated solid was collected by suction or centrifugal separation, dried under vacuum and further purified by flash column chromatography on silica gel using petrol-ether(60-90 °C)-ethyl acetate (V:V=4:1) as eluant to give the indolizine product.

3a, yellow solid, yield 40%. Mp 110-2 °C (Found: C, 77.83; H, 4.98; N, 5.49. Calc. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.97; N, 5.31%); ν_{max}/cm^{-1}: 1641, 1633, 1620; δ_H: 2.55(s, 3 H, Me), 7.76(s, 1 H, ArH),7.10-7.89(m, 7 H, ArH), 8.61(d, J 9.0, 1 H, ArH), 9.95(d, J 7.0, 1 H, ArH). m/z: 263(M^+, 15%), 186(100%).

3b, yellowish plates, yield 70%. Mp 174-6 °C (Literature[13]: 176 °C) (Found: C, 71.66; H, 5.67; N, 7.39. Calc. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96%); ν_{max}/cm^{-1}: 1631; δ_H: 2.56(s, 3H, MeCO), 2.59(s, 3 H, MeCO), 7.03-7.42(m, 2 H, ArH), 7.84(s, 1H, ArH), 8.55(d, J 9.0, 1H, ArH), 9.85(d, J 7.0, 1H, ArH). m/z: 201(M^+, 48%), 186(100%). This compound was not fully characterized in literature.

3c, yellow solid, yield 52%. Mp110-1 °C (Literature[8,11]: 115-6 °C). Spectroscopic data were consistent with those in literature.[8,11]

3d, yellow solid, yield 41%. Mp 147-9 °C (Literature[10,11]: 145-6 °C). Spectroscopic data were consistent with those in literature.[10,11]

3e, bright yellow needles, yield 68%. Mp 214-6 °C (Literature[4b]: 205-6 °C). Spectroscopic data were consistent with those in literature.[4b]

3f, yellow solid, yield 73%. Mp: 143-5 °C (Literature[6,9]: 141-4 °C). Spectroscopic data were consistent with those in literature.[9]

3g, bright yellow needles, yield 45%. Mp 165-7 °C (Found: C, 81.03; H, 4.82; N, 3.88. Calc. for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31%); ν_{max}/cm^{-1}: 1644, 1595; δ_H: 7.24-7.99(m, 12H, ArH), 8.67(m, 1H, ArH), 8.92(s, 1H, CHO), 9.67(d, J 8.0, 1H, ArH). m/z: 325(M^+, 100%).

3h, bright yellow needles, yield 71%. Mp 186-8 °C (Literature[12] gave a mixture of this compound and its isomer) (Found: C, 81.71; H, 5.15; N, 3.80. Calc. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.12%); ν_{max}/cm^{-1}: 1620; δ_H: 1.84(s, 3H, Me), 6.98-7.46(m, 12H, ArH), 8.63(d, J 9.0, 1H, ArH), 9.64(d, J 7.2, 1H, ArH). m/z: 339(M^+, 95%), 105(100%).

3i, bright yellow solid, yield 88%. Mp 169-71 °C (Found: C, 84.21; H, 5.20; N, 3.27. Calc. for $C_{30}H_{21}NO_2$: C, 84.29; H, 4.95; N, 3.28%); ν_{max}/cm^{-1}: 1644, 1595; δ_H: 6.31(d, J 15.3, 1H, -C=CH-), 6.92-7.33(m, 17H, ArH), 7.31(d, J 15.3, 1H, -CH=C), 8.70(d, J 9.0, 1H, ArH), 9.65(d, J 7.0, 1H, ArH). m/z: 427(M^+, 100%).

3j, orange needles, yield 61%. Mp 201-3 °C (Found: C, 81.08; H, 5.27; N, 4.07. Calc. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13%); ν_{max}/cm^{-1}: 1649, 1606, 1575; δ_H: 2.53(s, 3H, Me), 7.01(d, J 7.0, ArH), 7.25-7.83(m, 11H, ArH), 8.47(s, 1H, ArH), 9.89(d, J 7.0, 1H, ArH). m/z: 339(M^+, 100%).

3k, bright yellow needles, yield 61%. Mp180-2 °C (Literature[9]: 175-6 °C). Spectroscopic data were consistent with those in literature.[9]

3l, orange plates, yield 47%. Mp 152-4 °C (Found: C, 81.56; H, 5.41; N, 3.58. Calc. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96%); ν_{max}/cm^{-1}: 1647, 1606, 1576; δ_H: 1.81(s, 3H, Me), 2.49(s, 3H, COMe), 6.86-7.34(m, 11H, ArH), 8.45(s, 1H, ArH), 9.53(d, J 7.0, 1H, ArH). m/z: 353(M^+, 50%), 43(100%).

3m, red solid, yield 77%. Mp 181-3 °C (Found: C, 84.38; H, 5.43; N, 2.96. Calc. for $C_{31}H_{23}NO_2$: C, 84.33; H, 5.25; N, 3.17%); ν_{max}/cm^{-1}: 1638, 1584; δ_H: 2.51(s, 3H, Me), 6.28(d, J 16.0, 1H, C=CH-), 6.94(d, J 7.0, 1H, ArH), 7.05-7.37(m, 15H, ArH), 7.50(d, J 16.0, 1H, -CH=C), 8.53(s, 1H, ArH), 9.58(d, J 7.0, 1H, ArH). m/z: 441(M^+, 100%).

4a, bright yellow crystals, yield 60%. Mp 162-4 °C (Found: C, 76.27; H, 5.29; N, 5.67. Calc. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57%); ν_{max}/cm^{-1}: 1661, 1641, 1631; δ_H: 2.53(s, 3H, COMe), 2.63(s, 3H, COMe), 7.07(d, J 7.0, 1H, ArH), 7.49-7.62(m, 3H, ArH), 7.75(s, 1H, ArH), 9.48(d, J 7.0, 1H, ArH), 9.68(m, 1H, ArH). m/z: 251(M^+, 47), 236(100%).

4b, yellowish crystals, yield 72%. Mp 159-61 °C (Found: C, 80.06; H, 4.75; N, 4.75. Calc. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.78; N, 4.76%); ν_{max}/cm^{-1}: 1518, 1448, 1368, 963, 728; δ_H: 2.48(s, 3H, COMe), 7.14(d, J 7.0, 1H, ArH), 7.37-7.97(m, 8H, ArH), 7.90(s, 1H, ArH), 8.98(m, 1H, ArH), 9.59(d, J 7.0, 1H, ArH). m/z: 313(M^+, 100%).

4c, yellowish plates, yield 86%. Mp 200-1 °C (Found: C, 80.51; H, 4.85; N, 4.52. Calc. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47%); ν_{max}/cm^{-1}:1660, 1623; δ_H: 2.64(s, 3H, COMe), 7.30(d, J 8.0, 1H, ArH), 7.58-7.89(m, 8H, ArH), 7.71(s, 1H, ArH), 9.65(d, J 8.0, 1H, ArH), 9.90(m, 1H, ArH). m/z: 313(M^+, 51%), 298(100%).

4d, bright yellow needles, yield 84%. Mp 150-1 °C (Found: C, 83.19; H, 4.72; N, 3.62. Calc. for $C_{26}H_{17}NO_2$: C, 83.18; H, 4.56; N, 3.73%); ν_{max}/cm^{-1}: 1641, 1614; δ_H: 7.27(d, J 7.2, 1H, ArH), 9.34-7.94(m, 14H, ArH). m/z: 375(M^+, 82%), 298(100%).

4e, yellow crystals, yield 65%. Mp 204-6 °C (Found: C, 82.93; H, 4.60; N, 3.70. Calc. for $C_{26}H_{17}NO_2$: C, 83.18; H, 4.56; N, 3.73%); ν_{max}/cm^{-1}: 1659, 1622; δ_H: 6.92-7.51(m, 14H, ArH), 8.61(d, J 9.0, 1H, ArH), 9.66(d, J 7.0, 1H, ArH), 9.69(s, 1H, CHO). m/z: 375(M^+, 100%).

4f, pale-red crystals, yield 70%. Mp 194-7 °C (Found: C, 83.14; H, 4.93; N, 3.78. Calc. for $C_{27}H_{19}NO_2$: C, 83.27; H, 4.92; N, 3.60%); ν_{max}/cm^{-1}: 1676, 1609; δ_H: 2.08(s, 3H, COMe), 6.84-7.76(m, 14H, ArH), 8.42(m, 1H, ArH), 9.11(d, J 8.0, 1H, ArH). m/z: 389(M^+, 100%).

4g, white needles, yield 56%. Mp 102-4 °C (Literature[11]: 110 °C). Spectroscopic data were consistent with those in literature.[11]

4h, orange crystals, yield 84%. Mp 118-20 °C (Literature[11]: 119 °C). Spectroscopic data were consistent with those in literature.[11]

5a, yellow solid, yield 66%. Mp 169-70 °C (Found: C, 80.15; H, 4.93; N, 4.20. Calc. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.80; N, 4.48%); ν_{max}/cm^{-1}: 1671, 1633; δ_H: 2.49(s, 3H, Me), 7.39-7.86(m, 9H, ArH), 7.62(s, 1H, ArH), 8.08(m, 1H, ArH), 8.55(m, 1H, ArH). m/z: 313(M^+, 71%), 298(100%).

5b, yellow crystals, yield 46%. Mp 170-2 °C (Found: C, 83.14; H, 4.64; N, 3.73. Calc. for $C_{26}H_{17}NO_2$: C, 83.18; H, 4.56; N, 3.73%); ν_{max}/cm^{-1}: 1626, 1604; δ_H: 7.76(d, J 10, 1H, ArH), 7.42-8.02(m, 15H, ArH), 8.49(d, J 6.0, 1H, ArH). m/z: 375(M^+, 100%).

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