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Thermal Rearrangement of Indolyl Oxime Esters to Pyridoindoles

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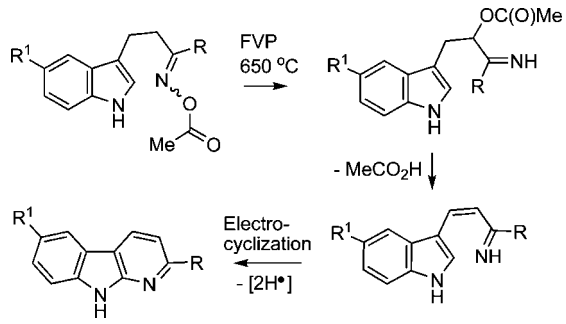
Received August 6, 2008



Acyl oximes derived from a variety of indolylalkanones underwent a ring closure sequence during FVP to afford 9*H*-pyrido[2,3-*b*]indoles. Unlike UV light promoted reactions of oxime esters, the mechanism is almost certainly not mediated by iminyl radicals but probably involves tautomerism, elimination of acetic acid, and a final electrocyclic ring closure.

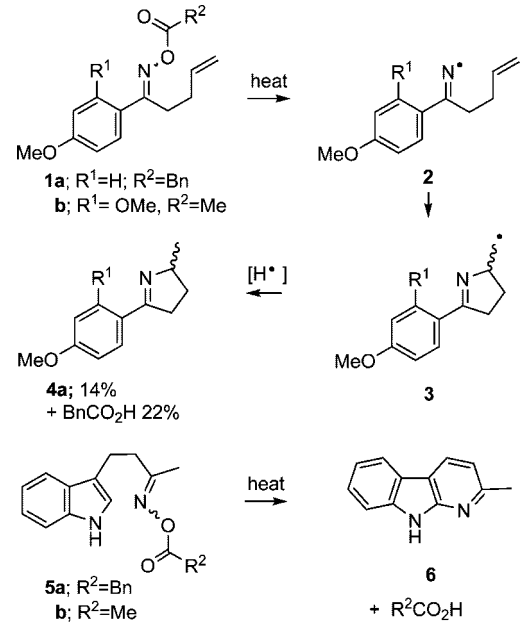
Oxime esters are well-known as useful sources of iminyl and C-centered radicals when subjected to UV irradiation.[1,2] In a recent application of acyl oximes, for example, isoquinoline derivatives were prepared by light-induced release of unsaturated iminyl radicals.[3] For preparative work, thermal treatment of an appropriate precursor is usually a more desirable tactic because it is simple, experimentally convenient, and readily lends itself to scale-up. Oximes can be smoothly and efficiently prepared from a very wide range of carbonyl compounds and converted to acyl, or other, esters [$R_2C{=}NOC(O)R^1$] with ease. Although experimental BDEs for the N−O bonds of oxime esters are not available, circumstantial evidence indicates these bonds are comparatively weak.[4] We thought, therefore, that it should be possible to bring about selective N−O homolysis by application of an appropriate thermal method:

$$R_2C{=}NOC(O)R^1 \xrightarrow{\Delta} R_2C{=}N\bullet + CO_2 + R^1\bullet$$

In practice, we found that clean thermolyses of oxime esters to iminyl radicals were not in general achievable. However, at higher temperatures, indolylalkanone *O*-acetyl oximes underwent an intriguing rearrangement/elimination sequence to afford pyrridoindoles.

The but-3-enyl oxime esters **1a**,**b** and the indolyl oxime ester **5** were prepared from the corresponding ketones, via the oximes, and their behavior on heat treatment was investigated. We knew from previous work that the N−O bonds of *O*-phenyl oxime ethers readily cleaved in microwave-irradiated solutions at 160 °C.[5] Initially, solutions of **1a** and **1b** in toluene containing the ionic liquid 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate (0.5 equiv) were irradiated in a Biotage Initiator microwave reactor (nominally 300 MHz). However, after 15 min at 220 °C, **1a** and **1b** were found to be unchanged.

SCHEME 1



Next, individual samples of the benzyl esters **1a** and **5a** were heated under vacuum in a Kugelrohr at 185 °C. Small amounts of the dihydropyrrole **4a** and the pyridoindole **6** were obtained, respectively, along with much charred residue. Intriguingly, in both cases, significant amounts of phenylacetic acid were also formed. If the reactions proceeded via iminyl radical intermediates, as shown in Scheme 1, the co-radical $PhCH_2C(O)O\bullet$ should have dissociated to a benzyl radical and CO_2 at the temperature

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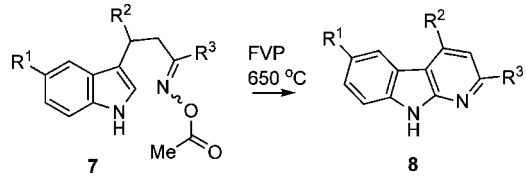
10.1021/jo801751a CCC: $40.75
Published on Web 09/13/2008

TABLE 1. Preparations of 9*H*-Pyrido[2,3-*b*]indoles by FVP of Acyl Oximes at 650 °C



precursor/product	R^1, R^2, R^3	yield[a] **7** (%)	yield[a] **8** (%)
7a/8a	H, H, Me	89	41
7b/8b	H, Me, Me	88	43
7c/8c	Me, H, Me	88	[49]
7d/8d	Br, H, Me	85	40
7e/8e	Br, Me, Me	83	39
7f/8f	NC, H, Me	89	[37]
7g/8g	H, H, Ph	83	52
7h/8h	H, Ph, Ph	83	0
7i/8i	MeO, H, Me	83	nd[b]

[a] Isolated yields except those in parentheses which were obtained by NMR. [b] Not determined due to intractable product mixture.

of thermolysis. This was an indication the radical mechanism might not be operative.

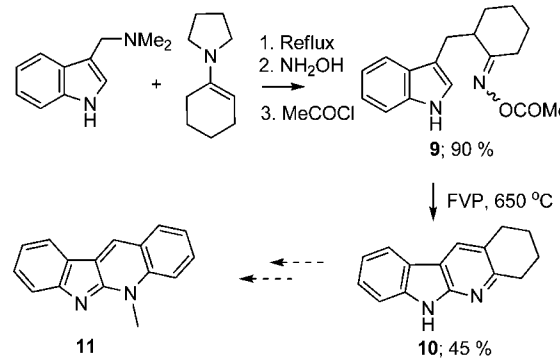
These findings suggested that acyl oximes, which can be made more easily and efficiently than the benzyl analogues, might be suitable and that the higher temperatures but "softer" conditions of flash vacuum pyrolysis (FVP) might be beneficial. Accordingly, FVP of acyl precursor **5b** was carried out at 50 °C intervals in the range of 550 to 750 °C and 10^{-3} Torr. ^{1}H NMR analyses of the products showed clean and optimum production of pyridoindole **6** (59%) together with acetic acid (77%) at 650 °C.

Several biological roles have been reported for 9*H*-pyrido[2,3-*b*]indoles.[6] To examine the scope of our methodology for preparations of this ring system, a set of functionalized indolylalkanones was prepared by treatment of derivatized indoles and α,β-unsaturated ketones with $ZrCl_4$ according to the method of Gu et al.[7] The corresponding oximes and acyl oxime esters **7** (Table 1) were then obtained by standard methods.

Individual indolyl acyl oximes **7** were subjected to FVP at 650 °C and gave the corresponding 9*H*-pyrido[2,3-*b*]indoles **8** in the yields shown in Table 1. The method was tolerant of Me and Br substituents in the indole ring (**7c**,**d**) and of Me and Ph substituents on the alkanone chain (**7b**, **7c**, **7g**). The method also worked for the 6-cyano derivative **7f**, although the yield of **8f** was lower. For oxime ester **7h**, with a Ph substituent in the alkanone chain, alternative reaction pathways are available and a complex and intractable mixture resulted. During FVP of the 6-methoxy derivative **7i**, some pyridoindole was formed but it was accompanied by many byproducts and was difficult to isolate. Although the yields are comparatively modest, this is a short and convenient route compared to many alternative syntheses of pyrido[2,3-*b*]indoles.[8]

An analogous sequence was designed for the preparation of the natural product neocryptolepine **11** (Scheme 2). The required indolylketone was obtained from reaction of gramine with 1-cyclohexenylpyrrolidine.[9] Conversion to the corresponding

SCHEME 2



oxime and thence to the acyl derivative **9** was accomplished in 90% yield. FVP of **9** at 650 °C afforded tetrahydroindolo[2,3-*b*]quinoline **10**. The latter is a known compound and has previously been converted to neocryptolepine **11** in two steps by dehydrogenation/aromatization with DDQ followed by methylation with methyl sulfate.[10] Overall, the sequence represents a formal synthesis of neocryptolepine in six steps from gramine.

A feature of all these thermolyses was that $MeCO_2H$ was formed as co-product in good yield in each case. If this were a radical-mediated process, along the lines depicted in Scheme 1, initial homolysis of the oxime N−O bond should have released the MeC(O)O• radical. However, decarboxylation of this radical is known to be exothermic[11] and is extremely fast even at moderate temperatures [$k(110\ °C) = 2-5 \times 10^9\ s^{-1}$].[12] At the 650 °C temperature of the FVP experiments, CO_2 loss would occur within a few molecular vibrations.[13] Thus, any acetoxyl radicals could not survive long enough to pick up H atoms and yield the acetic acid. This evidence suggested that acetoxyl radicals were not intermediates and hence iminyl radicals were not involved either.

An alternative nonradical mechanism is outlined in Scheme 3. Imine **12**/enamine **13** tautomerism could be followed by a [3,3]-sigmatropic migration of the acetoxy group yielding rearranged imine **14**. Rapid elimination of $MeCO_2H$, producing alkenylimine **15**, would be followed by an azahexatriene-type electrocyclization to afford dihydropyridoindole **16**. The final dehydrogenation would be favored because of production of the aromatic system in **17**. Precedent for the rearrangement of **13** to **14** can be found in the reported base-promoted [3,3]-sigmatropic migrations of acetoxy groups in enamines.[14]

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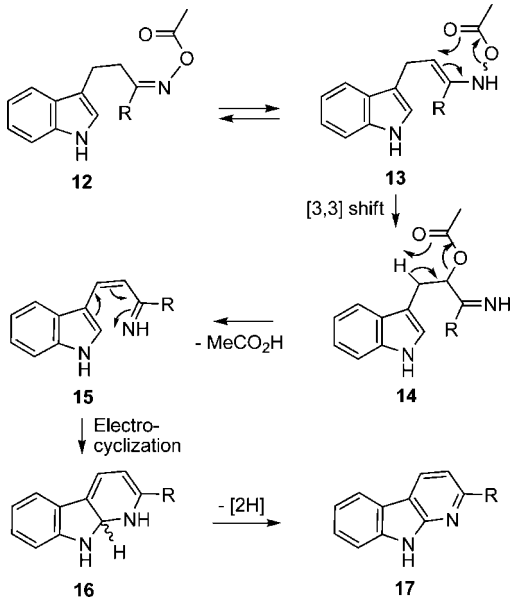
SCHEME 3



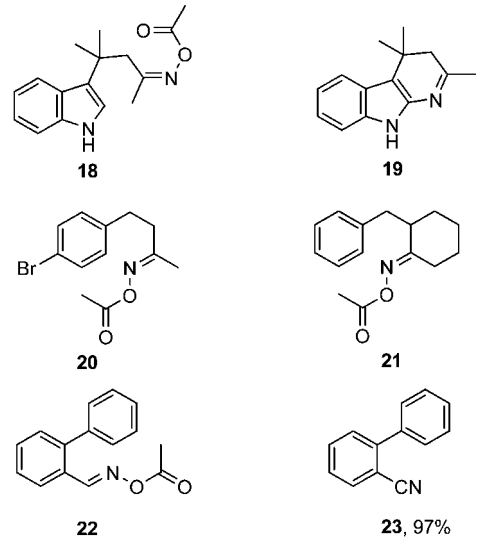


FIGURE 1. Acyl oximes and their thermolysis products.

Thermally induced electrocyclic ring closures of 1-azahexatrienes related to **15** have also been reported previously.[15]

This mechanism explains the formation of acetic acid as coproduct from all the indolyl acyl oximes. For the thermal reactions of but-3-enyl oxime esters **1a**,**b**, the comparative absence of ring-closed products is accounted for by the lack of the azahexatriene electrocyclic reaction channel in these cases. As a further test of the mechanism, indolyl acyl oxime **18**, with two methyl groups in position to block the elimination of acetic acid, was prepared. FVP of this compound gave a complex mixture from which no single component could be isolated. GC−MS examination showed one component having M^+ at $m/z = 212$ which might be the cyclized product **19** (Figure 1). A possible rationale is that the elimination/electrocyclization process dominates, particularly at higher temperatures, so that the slower, less efficient, iminyl radical process can only manifest itself for compounds like **1a**,**b** and **18** where the elimination is blocked.

Iminyl radical cyclizations onto phenyl ring acceptors are well-known.[3,5] We were interested to see if ring closure of acyl oximes onto phenyl rings, with formation of the quinoline ring, could be accomplished by thermal means. Precursors **20** and **21** are capable of undergoing the acetoxy migration and elimination steps. However, the azahexatriene electrocyclization would involve disruption of the phenyl 6π electron system. FVP of **20** gave no quinoline but a mixture of 4-alkylbromobenzenes and bromostyrene. Similarly, FVP of **21** gave a complex and intractable mixture of degradation products. Evidently an electrocyclization step, involving a Ph ring, could not compete with other degradative processes. Precursor **22** cannot react via the migration/electrocyclization route, but it is known that the iminyl radicals released on UV irradiation ring close efficiently to give phenanthridine.[3,5] Interestingly, at the higher temperatures of the FVP experiments, biphenyl acyl oxime **22** underwent elimination very efficiently with production of biphenyl-2-carbonitrile **23**. Thermal conversions of aldoximes to nitriles are well-known reactions.[16]

In conclusion, we have found that, in contrast to UV photolyses, neither microwave heating, nor conventional heating under vacuum, nor FVP at 650 °C release iminyl radicals efficiently from oxime esters. However, acyl oximes, derived from a variety of indoloalkanones, readily underwent a ring closure sequence during FVP to afford 9*H*-pyrido[2,3-*b*]indoles. The mechanism is almost certainly nonradical and may well involve tautomerism, elimination of acetic acid, and a final azahexatriene electrocyclization. Acyl alkanone oxime precursors in which the indole ring was replaced by a phenyl ring did not close to quinoline rings. This was not unexpected because the electrocyclization stage would be disfavored by one of the double bonds forming part of the 6π-phenyl ring.

Experimental Section

General FVP Procedure. The oxime ester precursor (100 mg) was volatilized under rotary pump vacuum through an empty, electrically heated silica tube (35 × 2.5 cm), and the products were collected in a U-tube, cooled with liquid nitrogen, situated at the exit point of the furnace.[17] For all pyrolyses, the pressure was monitored by a Pirani gauge situated between the product trap and pump. Unless otherwise stated, inlet temperature was 200 °C, reaction times were ca. 1.5 h, furnace temperature was 650 °C, and the pressure was ca. 2×10^{-3} Torr. Products were purified by chromatography on silica (EtOAc/hexane).

2-Methyl-9*H*-pyrido[2,3-*b*]indole (8a):[18] White solid, 41%; mp 219−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (3H, s, CH_3), 7.00 (1H, d, $J = 7.8$ Hz, CH), 7.18 (1H, m, CH), 7.43 (2H, m, CH), 7.95 (1H, d, $J = 7.7$ Hz, CH), 8.17 (1H, d, $J = 7.8$ Hz, CH), 9.42 (1H, s, NH); ^{13}C NMR δ 24.2 (CH_3), 111.3, 115.3 (CH), 115.5 (C), 120.4, 120.7 (CH), 120.8 (C), 126.6, 129.4 (CH), 139.5, 143.8, 146.3 (C); IR 1602, 1456, 1417 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{11}N_2$ 183.0922, found 183.0928.

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2,4-Dimethyl-9*H*-pyrido[2,3-*b*]indole (8b): White solid, 43%; mp 222−224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3), 2.74 (3H, s, CH_3), 6.89 (1H, s, CH), 7.19 (1H, t, J = 7.3 Hz, CH), 7.39 (1H, t, J = 8.1 Hz, CH), 7.47 (1H, d, J = 7.8 Hz, CH), 8.04 (1H, d, J = 7.7 Hz, CH), 11.6 (1H, s, NH); ^{13}C NMR δ 24.7, 29.3 (CH_3), 116.3, 116.7 (CH), 121.5 (C), 124.5 (CH), 126.2 (C), 127.5, 130.5 (CH), 143.6, 146.9, 157.0, 159.8 (C); IR 3117, 2939, 1611, 1441 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{13}N_2$ 197.1079, found 197.1081.

2,6-Dimethyl-9*H*-pyrido[2,3-*b*]indole (8c): Solid; ca. 49% (could not be separated from byproduct by chromatography); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.59 (3H, s, CH_3), 2.76 (3H, s, CH_3), 6.86 (1H, d, J = 7.3 Hz, CH), 7.10 (2H, m, CH), 7.48 (1H, m, CH), 8.01 (1H, m, CH), 11.4 (1H, s, NH).

6-Bromo-2-methyl-9*H*-pyrido[2,3-*b*]indole (8d): White solid, 40%; mp 233−235 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (3H, s, CH_3), 7.16 (1H, d, J = 7.9 Hz, CH), 7.48 (1H, d, J = 8.4 Hz, CH), 7.57 (1H, dd, J = 8.6, 1.9 Hz, CH), 8.40 (1H, d, J = 1.8 Hz, CH), 8.47 (1H, d, J = 7.8 Hz, CH), 11.8 (1H, s, NH); ^{13}C NMR δ 25.0 (CH_3), 113.5, 115.5 (CH), 122.7 (C), 123.7 (CH), 127.3 (C), 128.6, 129.7 (CH), 137.2, 145.9, 152.0, 156.1 (C); IR 3128, 2931, 1607, 1455 cm^{-1}.

6-Bromo-2,4-dimethyl-9*H*-pyrido[2,3-*b*]indole (8e): White solid, 39%; mp 244−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (3H, s, CH_3), 2.73 (3H, s, CH_3), 6.91 (1H, s, CH), 7.42 (1H, d, J = 8.5 Hz, CH), 7.52 (1H, dd, J = 8.6, 3.0 Hz, CH), 8.14 (1H, d, J = 1.8 Hz, CH), 11.8 (1H, s, NH); ^{13}C NMR δ 19.4, 24.2 (CH_3), 110.7 (CH), 111.2 (C), 112.9 (CH), 116.8 (C), 122.7 (CH), 124.2 (C), 127.8 (CH), 137.0, 142.4, 151.9, 155.7 (C); IR 3147, 2948, 1633, 1458 cm^{-1}; HRMS (ES) calcd for $C_{13}H_{12}N_2{}^{79}Br$ 275.0184, found 275.0183.

2-Methyl-9*H*-pyrido[2,3-*b*]indole-6-carbonitrile (8f): Solid; ca. 37% (could not be separated from byproduct by chromatography); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.71 (3H, s, CH_3), 7.26 (1H, d, J = 7.1 Hz, CH), 7.67 (1H, d, J = 8.5 Hz, CH), 7.84 (1H, d, J = 8.5, 1.7 Hz, CH), 8.56 (1H, dd, J = 7.8 Hz, CH), 8.75 (1H, m, CH), 12.3 (1H, s, NH).

2-Phenyl-9*H*-pyrido[2,3-*b*]indole (8g):[19] White solid, 52%; mp 245−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, J = 7.9 Hz, CH), 7.17 (1H, t, J = 7.3 Hz, CH), 7.24−7.50 (4H, m, CH), 7.58 (1H, d, J = 8.0 Hz, CH), 7.96 (1H, d, J = 7.7 Hz, CH), 8.06 (2H, m, CH), 8.32 (1H, d, J = 8.1 Hz, CH), 10.3 (1H, s, NH); ^{13}C NMR δ 111.5, 113.2 (CH), 115.2 (C), 120.1, 120.8 (CH), 121.1 (C), 126.7 (CH), 127.6 (CH) × 2, 128.7 (CH), 129.0 (CH) × 2, 129.2 (CH), 138.9, 140.2, 152.4, 154.5 (C); IR 3128, 2927, 1602, 1442 cm^{-1}; HRMS (CI$^+$) calcd for $C_{17}H_{13}N_2$ 245.1079, found 245.1080.

6*H*-1,2,3,4-Tetrahydroindolo[2,3-*b*]quinoline (10):[20] White solid, 45%; mp 220−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79−1.98 (4H, m, CH_2), 2.90 (2H, t, J = 6.11 Hz, CH_2), 3.10 (2H, t, J = 6.5 Hz, CH_2), 7.16 (1H, t, J = 7.4 Hz, CH), 7.36 (1H, t, J = 7.5 Hz, CH), 7.43 (1H, d, J = 8.1 Hz, CH), 7.91 (1H, d, J = 7.7 Hz, CH), 7.96 (1H, s, CH), 10.20 (1H, s, NH); ^{13}C NMR δ 22.2 (CH_2 × 2), 28.0, 31.7 (CH_2), 110.2 (CH), 113.9 (C), 118.8, 119.6 (CH), 120.1, 122.8 (C), 125.4, 128.5 (CH), 137.9. 149.4, 152.5 (C); IR 2931, 1609, 1458 cm^{-1}; HRMS (CI$^+$) calcd for $C_{15}H_{15}N_2$ 223.1235, found 223.1231.

Biphenyl-2-carbonitrile (23):[21] White solid, 97%; mp 35−37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.55 (7H, m, CH), 7.65 (1H, dt, J = 1.3, 7.7 Hz, CH), 7.77 (1H, dd, J = 1.1, 7.7 Hz, CH); ^{13}C NMR δ 111.4, 118.5 (C), 127.7 (CH), 128.8 (CH × 2), 128.8 (CH), 129.9 (CH × 2), 130.2, 132.9, 133.8 (CH), 138.1, 145.3 (C).

Acknowledgment. We thank EaStChem for financial support.

Supporting Information Available: Experimental procedures for carbonyl compounds, oximes, and oxime esters. Full spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801751A

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