Notes

Polyfunctionalized 3-Nitropyridine Derivatives by [4 + 2] Cycloadditions of 4-Nitro-3-phenylisoxazole-5-carboxylates with Enamines: Applications and Limits[1]

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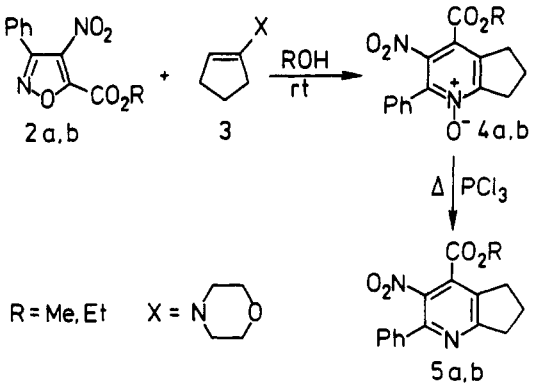
During a systematic investigation on the reactivity of electron-poor isoxazoles, we have recently found that a few 4-nitroderivatives suitably substituted at position 5 easily enter both as dipolarophiles[2a,b] and dienophiles[2c] into [2 + 4] cycloaddition processes, leading to polynuclear heterocyclic systems. On the other hand, preliminary results indicated that the nitro ester **2a**, prepared by cyclodehydration of methyl oxo[[(1-phenyl-2-nitroethylidene)amino]oxy]acetate (1), as well as **2b**, can behave as 1-azadiene components in [4 + 2] cycloadditions.[1]

In particular, when the above compounds were allowed to react with an equimolecular amount of 4-(1-cyclopenten-1-yl)morpholine (3) in the corresponding alcohols at room temperature, the bicyclic pyridine *N*-oxides **4a** and **4b** were obtained in 57% and 42% yields, respectively; these compounds could be easily converted into the cyclopenta[*b*]pyridines **5a,b** by deoxygenation with PCl_3 (Scheme I).

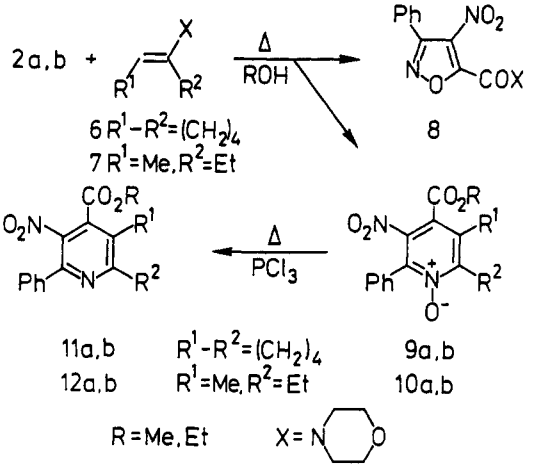
These findings prompted us to explore the possibility of expanding the scope of this reaction by treatment of the same materials with other enamines. Unfortunately, a remarkable decrease in reactivity was observed with 4-(1-cyclohexen-1-yl)morpholine (6) but, under forcing conditions (prolonged reflux with 2 equiv of the reagent), we succeeded in isolating the desired tetrahydroquinoline *N*-oxides **9a** and **9b** in modest yields (15% and 19%, respectively) together with the nitro amide 8 (Scheme II). Comparable results were obtained for **9a** and **9b** with 1-(1-cyclohexen-1-yl)pyrrolidine.

Replacement of 6 with (*E*)-4-(pent-2-en-3-yl)morpholine (7) afforded under the latter conditions very complex reaction mixtures that were resolved by flash chromatography to give, besides 8, compounds **10a** and **10b** in 11% and 17% yields, respectively. Efforts to achieve better results with other open-chain enamines such as (*E*)-4-(propen-1-yl)- and (*E*)-4-(but-1-en-1-yl)morpholine were completely unsuccessful.[3] Treatment of the *N*-oxides **9a,b** and **10a,b** with PCl_3 in boiling chloroform afforded the deoxygenation products **11a,b** and **12a,b**, respectively.

Scheme I



Scheme II



The structures of the new compounds were determined on the basis of analytical and spectral evidence (Experimental Section). Particularly, strong IR absorptions were observed for compounds **4a,b**, **9a,b**, and **10a,b** in the range 1289–1322 cm^{-1} attributable to the $N^+–O^-$ stretching vibrations. On the other hand, the ^{13}C NMR spectra of these products were characterized by a signal at δ 115.3–122.0 that is highly diagnostic for the C-4 carbon of these structures. The notable shielding of this resonance (14–20 ppm) with respect to that of the corresponding deoxygenation products was certainly due to the electron drift between the $N^+–O^-$ and CO_2R groups at the para position.

Following the mechanistic rationale accepted for the conversion of 5-nitropyrimidine into 3-nitropyridine derivatives with enamines,[4] the formation of the above *N*-oxides could be accounted for on the basis of concerted hetero Diels–Alder reactions with inverse electron demand (route a), followed by ring opening and aromatization of the primary cycloadducts **13**. Nevertheless, although this mechanism has also been advanced for the reaction of different isoxazoles with the same reagents in the presence of a low-valence titanium salt,[5] we strongly preferred, on

(1) For a preliminary communication on a part of this work, see: Nesi, R.; Giomi, D.; Papaleo, S.; Corti, M. *Gazz. Chim. Ital.* **1989**, *119*, 363.

(2) (a) Nesi, R.; Giomi, D.; Papaleo, S.; Bracci, S.; Dapporto, P. *Synthesis* **1988**, 884. (b) Nesi, R.; Giomi, D.; Papaleo, S.; Bracci, S.; Dapporto, P. *J. Org. Chem.* **1989**, *54*, 706. (c) Nesi, R.; Giomi, D.; Papaleo, S.; Corti, M. *J. Org. Chem.* **1990**, *55*, 1227.

(3) Only trace amounts of the desired products were detected in the reaction mixtures by ^1H NMR analysis.

(4) (a) Charushin, V. N.; van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965. (b) Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693.

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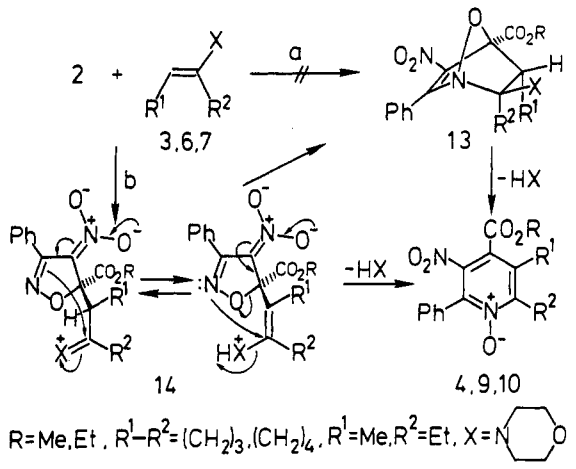
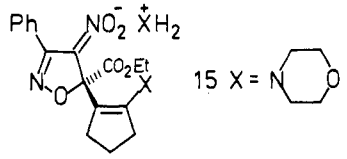
Scheme III



the basis of the general behavior of electron-deficient alkenes with enamines[6] and the peculiar reactivity of 4-nitroisoxazoles with nucleophiles,[7] an alternative stepwise pattern involving the nitronates **14** as key intermediates; these products, coming from the nucleophilic attack of the enamine β-carbon on the remarkably electrophilic 5-position of the isoxazole system (route b), can give rise to the same pyridine derivatives through **13** or, directly, by O-C(5) ring opening and concomitant interaction of the isoxazole nitrogen on the enamine α-position with elimination of the secondary amine (Scheme III). According to Brown's generalization,[8] the presence of a C=X$^+$ exocyclic double bond in the Michael adducts of **2a,b** with the cyclic enamines accounts for the dramatic difference observed for the reactivity of the latter reagents.

The above mechanistic scheme was corroborated by the isolation of the morpholinium nitronate **15** from the reaction of **2b** with a large excess of **3**; this product was stable enough at the solid state to allow its characterization by analytical and IR spectral data.



In summary, the above results emphasize a new feature of the reactivity of 4-nitroisoxazoles. Whereas the potential of the reaction of **2a,b** with **6** and **7** is partially compromised by the low yields, the conversion of **2a** into **4a** with **3** is useful synthetically. In fact, although alternative methods based on intermolecular[4] and intramolecular[9] Diels–Alder reactions have become available recently for the preparation of 6,7-dihydro-3-nitro-5*H*-cyclopenta[*b*]-pyridine, the above reaction represents a simple direct entry in reasonable yield to the first 3-nitro derivative of this ring system which bears other functional groups on the pyridine moiety.

Experimental Section[10]

Methyl Oxo[[(1-phenyl-2-nitroethylidene)amino]oxy]-acetate (1). Following the method previously reported,[11] this compound was obtained as a white solid in 92% yield from α-nitroacetophenone oxime and methyl oxalyl chloride: mp 90–92 °C (from anhydrous ether); IR 1798, 1766 (CO), 1570, and 1358 cm^{-1} (NO_2); ^{1}H NMR δ 3.94 (s, 3 H, OCH_3), 5.79 (s, 2 H, CH_2), 7.40–7.62 (m, 3 H, Ar H_3), 7.72–7.78 (m, 2 H, Ar H_2); ^{13}C NMR δ 54.0 (q, OCH_3), 69.6 (t, CH_2), 127.3 (d), 129.2 (d), 130.3 (s), 132.4 (d) (Ph), 153.7 (s, C=N), 156.4 (s, CO), 156.6 (s, CO). Anal. Calcd for $C_{11}H_{10}N_2O_6$: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.71; H, 3.75; N, 10.67.

Methyl 4-Nitro-3-phenylisoxazole-5-carboxylate (2a). Cyclization of **1**, carried out under the same conditions employed for the synthesis of **2b**,[11] afforded the nitro ester **2a** as a pale yellow solid in 98% yield: mp 52–53 °C [from ether/30–50 °C petroleum ether (1:1 v/v)]; IR 1735 (CO), 1555, and 1375 cm^{-1} (NO_2); ^{1}H NMR δ 4.05 (s, 3 H, OCH_3), 7.45–7.68 (m, 5 H, Ph); ^{13}C NMR δ 54.0 (q, OCH_3), 124.2 (s), 128.1 (d), 129.2 (d), 131.6 (d) (Ph), 133.2 (s, C-4), 154.7 (s, CO), 155.2 (s, C-5), 156.7 (s, C-3). Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Found: C, 53.43; H, 3.40; N, 11.50.

Reactions of the Nitro Esters 2a,b with 4-(1-Cyclopenten-1-yl)morpholine (3). Preparation of Compounds 4a,b and 15. A. 6,7-Dihydro-4-(methoxycarbonyl)-3-nitro-2-phenyl-5*H*-cyclopenta[*b*]pyridine 1-oxide (**4a**) was obtained from **2a** and **3** in 57% yield as previously described:[1] mp 136–137 °C (from ether); IR 1728 (CO), 1543, 1370 (NO_2), 1310, and 1295 cm^{-1} (N^+–O^-); ^{1}H NMR δ 2.26 (quintet, J = 7.8 Hz, 2 H, 6-CH_2), 3.19 (t, J = 7.8 Hz, 2 H, 5-CH_2/7-CH_2), 3.40 (t, J = 7.8 Hz, 2 H, 7-CH_2/5-CH_2), 3.87 (s, 3 H, OCH_3), 7.35–7.50 (m, 5 H, Ph); ^{13}C NMR δ 21.5 (t, 6-CH_2), 30.2 (t, 5-CH_2/7-CH_2), 33.4 (t, 7-CH_2/5-CH_2), 53.1 (q, OCH_3), 115.3 (s, C-4), 126.6 (s), 128.7 (d), 129.4 (d), 130.6 (d) (Ph), 142.3 (s, C-4a), 143.2 (s, C-2), 147.6 (s, C-3), 155.9 (s, C-7a), 162.0 (s, CO). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.21; H, 4.68; N, 8.86.

B. Treatment of the nitro ester **2b** (0.27 g, 1 mmol) with **3** (0.154 g, 0.16 mL, 1 mmol) in anhydrous ethanol (5 mL) as above afforded a crude product that was subjected to flash chromatography with petroleum ether/ethyl acetate (1:1 v/v) as eluent. The first fraction gave a small amount of unreacted **2b** (0.020 g), whereas the second one (R_f = 0.30) yielded 6,7-dihydro-4-(ethoxycarbonyl)-3-nitro-2-phenyl-5*H*-cyclopenta[*b*]pyridine 1-oxide (**4b**) (0.13 g, 42% yield based on recovered **2b**) that was crystallized from ethanol as needles: mp 191–192 °C; IR 1720 (CO), 1555, 1380 (NO_2), 1322, and 1299 cm^{-1} (N^+–O^-); ^{1}H NMR δ 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.24 (quintet, J = 7.8 Hz, 2 H, 6-CH_2), 3.17 (t, J = 7.8 Hz, 2 H, 5-CH_2/7-CH_2), 3.39 (t, J = 7.8 Hz, 2 H, 7-CH_2/5-CH_2), 4.36 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.35–7.50 (m, 5 H, Ph); ^{13}C NMR δ 13.5 (q, OCH_2CH_3), 21.4 (t, 6-CH_2), 30.1 (t, 5-CH_2/7-CH_2), 33.2 (t, 7-CH_2/5-CH_2), 62.5 (t, OCH_2CH_3), 115.5 (s, C-4), 126.5 (s), 128.6 (d), 129.3 (d), 130.4 (d) (Ph), 142.2 (s, C-4a), 143.0 (s, C-2), 147.6 (s, C-3), 155.8 (s, C-7a), 161.3 (s, CO). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.36; H, 4.90; N, 8.80.

C. A solution of **2b** (1.05 g, 4 mmol) and **3** (3.08 g, 3.2 mL, 20 mmol) in EtOH (4 mL) was stirred at room temperature for 24 h. The pale yellow product which separated was filtered, washed with ether, and dried to give morpholinium 5-[2-(*N*-morpholino)-1-cyclopenten-1-yl]-5-(ethoxycarbonyl)-3-phenyl-4,5-dihydroisoxazole-4-nitronate (**15**) (1.39 g, 69%). An analytical sample was obtained as a white solid by prolonged stirring (60–70 h) in anhydrous ethanol (15–20 mL) at room temperature and filtration: mp 113–114 °C; IR 3200–2540 (br, $^+NH_2$, CH_3, CH_2, and phenyl CH), 2500–1800 (v br, $^+NH_2$), 1740 (CO), 1560, 1225, and 1100 cm^{-1} (C=NO_2^-). Anal. Calcd for $C_{25}H_{34}N_4O_7$: C, 59.75; H, 6.82; N, 11.15. Found: C, 60.04; H, 6.98; N, 11.02.

Reactions of the Nitro Derivatives 2a,b with the Enamines 6 and 7. General Procedure. A solution of the nitro ester (1 mmol) and the enamine (2 mmol) in the corresponding anhydrous

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(6) Pitacco, G.; Valentin, E. In *The Chemistry of amino, nitroso and nitro compounds and their derivatives*; Patai, S., Ed.; Wiley Interscience: New York, 1982; Part 1, p 644.
(7) (a) Rajappa, S.; Nair, M. D. *Adv. Heterocycl. Chem.* **1979**, *25*, 126 and references therein. (b) Sarti-Fantoni, P.; Donati, D.; De Sio, F.; Moneti, G. *J. Heterocycl. Chem.* **1980**, *7*, 1643. (c) Nesi, R.; Chimichi, S.; Giomi, D.; Sarti-Fantoni, P.; Tedeschi, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1005.
(8) Brown, H. C. *J. Org. Chem.* **1957**, *22*, 439.
(9) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5162.
(10) For a general description of experimental parameters, see: Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S.; Dapporto, P.; Paoli, P. *Heterocycles* **1991**, *32*, 1913.
(11) Nesi, R.; Chimichi, S.; Sarti-Fantoni, P.; Buzzi, A.; Giomi, D. *Heterocycles* **1985**, *23*, 1465.

alcohol (1 mL) was refluxed for 24 h. Evaporation to dryness under reduced pressure left a residue that was subjected to flash chromatography.

A. Chromatographic workup [petroleum ether/ethyl acetate (2:1 v/v) as eluent] of the crude product obtained from **2a** and **6** afforded 5-(*N*-morpholinocarbonyl)-4-nitro-3-phenylisoxazole (**8**) (R_f = 0.49, 0.06 g, 20%): mp 89–90 °C (from ether); IR 1672 (CO), 1540, and 1368 cm^{-1} (NO_2); ^1H NMR δ 3.38–3.43 (m, 2 H, NCH_2), 3.70–3.76 (m, 2 H, NCH_2), 3.84 (s, 4 H, 2 OCH_2), 7.46–7.68 (m, 5 H, Ph); ^{13}C NMR δ 42.7 (t, NCH_2), 46.8 (t, NCH_2), 66.2 (t, OCH_2), 66.4 (t, OCH_2), 124.2 (s), 128.7 (d), 129.3 (d) (Ph), 129.8 (s, C-4), 131.3 (d) (Ph), 154.9 (s, CO), 156.9 (s, C-3), 164.1 (s, C-5). Anal. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.62; H, 4.24; N, 13.64.

A second fraction (R_f = 0.31) gave 4-(methoxycarbonyl)-3-nitro-2-phenyl-5,6,7,8-tetrahydroquinoline 1-oxide (**9a**) (0.05 g, 15%) that was crystallized from ether as pale yellow needles: mp 160–161 °C; IR 1742 (CO), 1542, 1362 (NO_2), and 1295 cm^{-1} (N^+–O^-); ^1H NMR δ 1.75–1.98 (m, 4 H, 6-CH_2 and 7-CH_2), 2.91–2.99 (m, 4 H, 5-CH_2 and 8-CH_2), 3.88 (s, 3 H, OCH_3), 7.38–7.50 (m, 5 H, Ph); ^{13}C NMR δ 20.9 (t, 6-CH_2/7-CH_2), 21.2 (t, 7-CH_2/6-CH_2), 26.0 (t, 5-CH_2/8-CH_2), 27.1 (t, 8-CH_2/5-CH_2), 53.5 (q, OCH_3), 120.6 (s, C-4), 127.5 (s), 128.8 (d), 129.1 (d), 130.4 (d) (Ph), 134.4 (s, C-4a), 141.6 (s, C-2), 144.8 (s, C-3), 152.9 (s, C-8a), 163.2 (s, CO). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.28; H, 5.06; N, 8.35.

B. As above, the residue from the reaction of **2b** with **6** gave compound **8** (0.064 g, 21%) and 4-(ethoxycarbonyl)-3-nitro-2-phenyl-5,6,7,8-tetrahydroquinoline 1-oxide (**9b**) (R_f = 0.33, 0.065 g, 19%): mp 153–154 °C (from ethanol); IR 1733 (CO), 1540, 1360 (NO_2), and 1297 cm^{-1} (N^+–O^-); ^1H NMR δ 1.31 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.75–2.0 (m, 4 H, 6-CH_2 and 7-CH_2), 2.90–3.0 (m, 4 H, 5-CH_2 and 8-CH_2), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.35–7.50 (m, 5 H, Ph); ^{13}C NMR δ 13.5 (q, OCH_2CH_3), 20.9 (t, 6-CH_2/7-CH_2), 21.1 (t, 7-CH_2/6-CH_2), 25.9 (t, 5-CH_2/8-CH_2), 27.0 (t, 8-CH_2/5-CH_2), 62.9 (t, OCH_2CH_3), 120.7 (s, C-4), 127.5 (s), 128.7 (d), 129.0 (d), 130.3 (d) (Ph), 134.3 (s, C-4a), 141.4 (s, C-2), 145.8 (s, C-3), 152.8 (s, C-8a), 162.5 (s, CO). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.23; H, 5.30; N, 8.14.

C. The reaction product of **2a** with **7** was resolved into two components with toluene/ethyl acetate (5:1 v/v) as eluent. After compound **8** was separated (R_f = 0.35, 0.10 g, 33%), 6-ethyl-4-(methoxycarbonyl)-5-methyl-3-nitro-2-phenylpyridine 1-oxide (**10a**) was obtained as a yellow product (R_f = 0.28, 0.040 g, 13%): mp 160 °C (from ether); IR 1745 (CO), 1541, 1357 (NO_2), and 1289 cm^{-1} (N^+–O^-); ^1H NMR δ 1.25 (t, J = 7.4 Hz, 3 H, 6-CH_2CH_3), 2.50 (s, 3 H, 5-CH_3), 3.08 (q, J = 7.4 Hz, 2 H, 6-CH_2CH_3), 3.89 (s, 3 H, OCH_3), 7.35–7.52 (m, 5 H, Ph); ^{13}C NMR δ 9.3 (q, 6-CH_2CH_3), 16.4 (q, 5-CH_3), 21.8 (t, 6-CH_2CH_3), 53.7 (q, OCH_3), 122.0 (s, C-4), 127.6 (s), 128.8 (d), 129.0 (d), 130.4 (d) (Ph), 132.4 (s, C-5), 141.9 (s, C-2), 145.8 (s, C-3), 156.9 (s, C-6), 163.6 (s, CO). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.10; N, 8.86. Found: C, 60.97; H, 5.28; N, 8.84.

D. Following the same procedure, the crude product obtained from **2b** and **7** gave **8** (0.030 g, 10%) and 4-(ethoxycarbonyl)-6-ethyl-5-methyl-3-nitro-2-phenylpyridine 1-oxide (**10b**) (R_f = 0.29, 0.055 g, 17%): mp 137 °C (from ether); IR 1733 (CO), 1549, 1358 (NO_2), and 1294 cm^{-1} (N^+–O^-); ^1H NMR δ 1.25 (t, J = 7.4 Hz, 3 H, 6-CH_2CH_3), 1.32 (t, J = 7.15 Hz, 3 H, OCH_2CH_3), 2.51 (s, 3 H, 5-CH_3), 3.085 (q, J = 7.4 Hz, 2 H, 6-CH_2CH_3), 4.36 (q, J = 7.15 Hz, 2 H, OCH_2CH_3), 7.37–7.51 (m, 5 H, Ph); ^{13}C NMR δ 9.3 (q, 6-CH_2CH_3), 13.5 (q, OCH_2CH_3), 16.3 (q, 5-CH_3), 21.8 (t, 6-CH_2CH_3), 63.1 (t, OCH_2CH_3), 121.9 (s, C-4), 127.3 (s), 128.8 (d), 129.1 (d), 130.3 (d) (Ph), 132.3 (s, C-5), 141.8 (s, C-2), 145.9 (s, C-3), 156.8 (s, C-6), 163.1 (s, CO). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.66; H, 5.58; N, 8.76.

Conversion of the *N*-Oxides 4a,b, 9a,b, and 10a,b into 5a,b, 11a,b, and 12a,b. General Procedure. PCl_3 (3 mmol) in $CHCl_3$ (5 mL) was added dropwise to the *N*-oxide (1 mmol) in $CHCl_3$ (5 mL). The mixture was stirred at room temperature for 3 h and then refluxed for 1–2 h. The resulting solution was cooled, treated with ice water (10 mL), and made basic (pH 10) with 20% aqueous NaOH. The organic phase was separated and the aqueous solution was extracted with chloroform (2 × 10 mL). Evaporation to dryness of the combined extracts left a residue containing almost exclusively the deoxygenation product (^1H NMR) that was purified by flash chromatography with petroleum ether/ethyl acetate (5:1 v/v) as eluent.

A. Methyl 6,7-dihydro-3-nitro-2-phenyl-5*H*-cyclopenta[*b*]pyridine-4-carboxylate (**5a**) was obtained as a pale yellow solid (0.244 g, 82%): mp 137–138 °C (from 30–50 °C petroleum ether); IR 1740 (CO), 1545, and 1370 cm^{-1} (NO_2); ^1H NMR δ 2.22 (quintet, J = 7.6 Hz, 2 H, 6-CH_2), 3.13 (t, J = 7.6 Hz, 2 H, 5-CH_2/7-CH_2), 3.18 (t, J = 7.6 Hz, 2 H, 7-CH_2/5-CH_2), 3.88 (s, 3 H, OCH_3), 7.40–7.55 (m, 5 H, Ph); ^{13}C NMR δ 22.8 (t, 6-CH_2), 30.6 (t, 5-CH_2/7-CH_2), 34.4 (t, 7-CH_2/5-CH_2), 53.2 (q, OCH_3), 127.7 (d), 128.6 (d), 128.8 (s), 129.5 (d) (Ph), 135.6 (s, C-4), 136.3 (s, C-4a), 143.1 (s, C-3), 150.4 (s, C-2), 163.4 (s, CO), 169.5 (s, C-7a). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.26; H, 4.72; N, 9.16.

B. Ethyl 6,7-dihydro-3-nitro-2-phenyl-5*H*-cyclopenta[*b*]pyridine-4-carboxylate (**5b**) was isolated as a yellow oil that solidified on cooling (0.276 g, 88%): mp 73–74 °C (from 30–50 °C petroleum ether); IR 1740 (CO), 1538, and 1370 cm^{-1} (NO_2); ^1H NMR δ 1.33 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.24 (quintet, J = 7.6 Hz, 2 H, 6-CH_2), 3.14 (t, J = 7.6 Hz, 2 H, 5-CH_2/7-CH_2), 3.21 (t, J = 7.6 Hz, 2 H, 7-CH_2/5-CH_2), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.40–7.60 (m, 5 H, Ph); ^{13}C NMR δ 13.6 (q, OCH_2CH_3), 22.9 (t, 6-CH_2), 30.6 (t, 5-CH_2/7-CH_2), 34.4 (t, 7-CH_2/5-CH_2), 62.7 (t, OCH_2CH_3), 127.8 (d), 128.6 (d), 129.1 (s), 129.5 (d) (Ph), 135.7 (s, C-4), 136.2 (s, C-4a), 143.2 (s, C-3), 150.4 (s, C-2), 163.0 (s, CO), 169.6 (s, C-7a). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.61; N, 8.97. Found: C, 65.61; H, 5.32; N, 8.73.

C. Methyl 3-nitro-2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxylate (**11a**) (0.260 g, 83%) was crystallized from *n*-pentane as pale yellow needles: mp 129–130 °C; IR 1755 (CO), 1530, and 1350 cm^{-1} (NO_2); ^1H NMR δ 1.80–2.0 (m, 4 H, 6-CH_2 and 7-CH_2), 2.87 (t, J = 6.0 Hz, 2 H, 5-CH_2/8-CH_2), 3.065 (t, J = 6.0 Hz, 2 H, 8-CH_2/5-CH_2), 3.92 (s, 3 H, OCH_3), 7.41–7.47 (m, 3 H, Ar H_3), 7.48–7.55 (m, 2 H, Ar H_2); ^{13}C NMR δ 21.8 (t, 6-CH_2/7-CH_2), 22.0 (t, 7-CH_2/6-CH_2), 26.1 (t, 5-CH_2/8-CH_2), 33.2 (t, 8-CH_2/5-CH_2), 53.5 (q, OCH_3), 127.8 (d), 128.8 (d), 129.3 (s), 129.7 (d) (Ph), 135.2 (s, C-4), 135.5 (s, C-4a), 141.8 (s, C-3), 149.1 (s, C-2), 161.6 (s, C-8a), 164.3 (s, CO). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.27; H, 5.30; N, 8.68.

D. Ethyl 3-nitro-2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxylate (**11b**) (0.265 g, 81%) was isolated as a pale yellow solid: mp 96–96.5 °C (from *n*-pentane); IR 1750 (CO), 1535, and 1358 cm^{-1} (NO_2); ^1H NMR δ 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.78–2.0 (m, 4 H, 6-CH_2 and 7-CH_2), 2.88 (t, J = 6.0 Hz, 2 H, 5-CH_2/8-CH_2), 3.05 (t, J = 6.0 Hz, 2 H, 8-CH_2/5-CH_2), 4.39 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.40–7.48 (m, 3 H, Ar H_3), 7.51–7.57 (m, 2 H, Ar H_2); ^{13}C NMR δ 13.6 (q, OCH_2CH_3), 21.7 (t, 6-CH_2/7-CH_2), 21.8 (t, 7-CH_2/6-CH_2), 26.0 (t, 5-CH_2/8-CH_2), 32.9 (t, 8-CH_2/5-CH_2), 62.9 (t, OCH_2CH_3), 127.8 (d), 128.7 (d), 129.4 (s), 129.7 (d) (Ph), 135.1 (s, C-4), 135.4 (s, C-4a), 141.9 (s, C-3), 148.8 (s, C-2), 161.4 (s, C-8a), 163.6 (s, CO). Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.52; H, 5.69; N, 8.57.

E. Methyl 6-ethyl-5-methyl-3-nitro-2-phenylpyridine-4-carboxylate (**12a**) (0.24 g, 80%) was crystallized from the above solvent as colorless needles: mp 88 °C; IR 1727 (CO), 1535, and 1352 cm^{-1} (NO_2); ^1H NMR δ 1.33 (t, J = 7.5 Hz, 3 H, 6-CH_2CH_3), 2.395 (s, 3 H, 5-CH_3), 2.97 (q, J = 7.5 Hz, 2 H, 6-CH_2CH_3), 3.93 (s, 3 H, OCH_3), 7.40–7.48 (m, 3 H, Ar H_3), 7.50–7.60 (m, 2 H, Ar H_2); ^{13}C NMR δ 12.3 (q, 6-CH_2CH_3), 15.2 (q, 5-CH_3), 28.9 (t, 6-CH_2CH_3), 53.6 (q, OCH_3), 128.0 (d), 128.1 (s), 128.8 (d), 129.9 (d) (Ph), 135.0 (s, C-5), 136.1 (s, C-4), 142.0 (s, C-3), 148.6 (s, C-2), 164.7 (s, CO), 165.4 (s, C-6). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.75; H, 5.40; N, 9.46.

F. Ethyl 6-ethyl-5-methyl-3-nitro-2-phenylpyridine-4-carboxylate (**12b**) was obtained as a pale yellow oil that solidified into a white solid on standing (0.27 g, 86%): mp 53–54 °C (from *n*-pentane); IR 1740 (CO), 1530, and 1346 cm^{-1} (NO_2); ^1H NMR δ 1.33 (t, J = 7.5 Hz, 3 H, 6-CH_2CH_3), 1.35 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.41 (s 3 H, 5-CH_3), 2.98 (q, J = 7.5 Hz, 2 H, 6-CH_2CH_3), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 7.41–7.48 (m, 3 H, Ar H_3), 7.52–7.59 (m, 2 H, Ar H_2); ^{13}C NMR δ 12.3 (q, 6-CH_2CH_3), 13.6 (q, OCH_2CH_3), 15.1 (q, 5-CH_3), 29.0 (t, 6-CH_2CH_3), 63.0 (t, OCH_2CH_3), 128.0 (d), 128.1 (s), 128.7 (d), 129.7 (d) (Ph), 135.2 (s, C-5), 136.0 (s, C-4), 142.1 (s, C-3), 148.5 (s, C-2), 164.1 (s, CO), 165.3 (s, C-6). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96;

H, 5.77; N, 8.91. Found: C, 65.25; H, 5.92; N, 8.95.

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Registry No. 1, 140835-20-7; **2a**, 84679-59-4; **2b**, 99934-18-6; **3**, 936-52-7; **4a**, 126291-08-5; **4b**, 126291-09-6; **5a**, 126291-10-9; **5b**, 126291-11-0; **6**, 670-80-4; **7**, 13654-48-3; **8**, 140835-21-8; **9a**, 140835-22-9; **9b**, 140835-30-9; **10a**, 140835-23-0; **11a**, 140835-24-1; **11b**, 140835-28-5; **12a**, 140835-25-2; **12b**, 140835-29-6; **15**, 140835-27-4; α-nitroacetophenone oxime, 532-54-7; methyl oxalyl chloride, 5781-53-3.

Intermolecular Cyclization Processes in the Anodic Oxidation of Ketene Imines: Formation of Heterocyclic Dimers and Trimers

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Introduction

Ketene imines are useful in the synthesis of heterocycles, both by condensation[1] with other dipolar systems and by cyclic dimerization.[2] Earlier, we observed that the electrochemical oxidation of other types of organic molecules which also contain a cumulenic functionality, e.g., alkyl isothiocyanates (RNCS), lead to cyclic dimerization to form five-membered heterocycles.[3]

Recently, we have reported[4] preliminary results of the electrochemical oxidation (by controlled potential electrolysis) of four ketene imines of the type $Ph_2C{=}C{=}N$-(p-C_6H_4X) (**1a**, X = H; **1b**, X = Me; **1c**, X = OMe; **1d**, X = Br). After workup, two types of heterocyclic dimers, **2** and **3**, were isolated in good yields (Scheme I).

We have noticed before that although no unreacted ketene imine was left when electrolysis was terminated, the combined yield of all products isolated from each ketene imine studied gave at best ~80%.[4] Now we have found out that the remaining product mixture could be eluted only when the chromatography column was flushed with a polar eluant such as methanol. The mass spectrum and ^{1}H-NMR of each of the newly recovered materials indicate that a kind of cyclic trimer is formed. However, the combustion analysis does not match this description. After numerous attempts we finally succeeded in growing good-quality single crystals of type **4** (Chart I), which were suitable for X-ray measurements. This type of compounds was identified[5] as new organic salts, involving a heterocyclic cation and tetrafluoroborate as a counter anion (tetrabutylammonium tetrafluoroborate was used as supporting electrolyte).

Scheme I

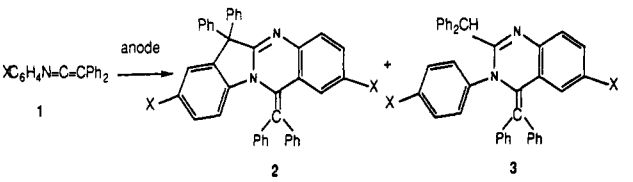

Chart I

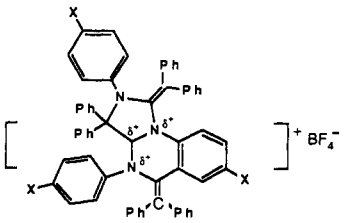

Table II.[a] Chemical Yields of Products from Anodic Oxidation of 1a–1d[b]

	2 (%)	3 (%)	4 (%)	amide (%)	F/mol
1a	70	2	18	7	0.42
1b	67	3	18	11	0.41
1c	71	3	15	10	0.45
1d	12	36	29	6	0.47

[a] Under the following conditions: drying the electrolyte for 30 h at 150 °C under vacuum and carrying out the electrolysis under nitrogen atmosphere passing through two traps: an oxygen trap (V^{2+}/Zn–Hg) and a moisture trap containing dry molecular sieves (4 Å). The electrolytic cell and electrodes were flame dried before use. [b] See footnotes b and c in Table I (supplementary material).

The present paper describes the electrosynthesis of the cyclic dimers of type **2** and **3** in detail, as well as the generation of stable carbocation salts of type **4**. The electrochemical process is a unique intricate annulation following the oxidation of aryl-substituted ketene imines.

Results and Discussion

The four aryl-substituted ketene imines studied involve one derivative with no substituent and three with electron-donating substituents at the para position to the nitrogen. Each of them exhibits two irreversible oxidation waves, the first in the region of 0.9–1.1 V and the second at 1.5–2.0 V (vs Ag/AgCl reference electrode). Preparative oxidation of each compound was carried out at the first oxidation wave. A typical experiment involves a three-compartment "H-type" cell containing 1 mmol of **1c** in 50 mL of CH_2Cl_2–0.1 M Et_4NBF_4, utilizing a Pt anode.

We soon observed that formation of products other than the corresponding amides, (p-XC_6H_4)$NHCOCHPh_2$, requires drastic dry conditions. Without dryness precautions, amides are obtained almost quantitatively. It is known that ketene imines undergo fast hydrolysis to form amides in the presence of catalytic amounts of protons. The source of protons in our experiments could stem from initially oxidized ketene imines which undergo followup chemical reaction, e.g.

$$1 - e^- \rightarrow [1]^{\bullet+} \xrightarrow{+H_2O} \rightarrow \rightarrow \text{amide} + H^+$$

or

$$2[1]^{\bullet+} \rightarrow \text{dimer} + 2H^+$$

Under certain dry conditions (Table I, supplementary material) the yield of the amides dropped to 22–40% and other products are formed: tetracyclic dimers of type **2**

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