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A new facet of the reaction of nitro heteroaromatic compounds with ethyl isocyanocacetate

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Nitro heteroarenes react with ethyl isocyanocacetate in the presence of 1,8-diazabicyclo[5.4.0]undecene (DBU) to give pyrroles or pyrimidine N-oxide depending on the structure of the starting nitro compounds. For example, 4-nitro-2,1,3-benzothiadiazole 3a reacted with ethyl isocyanocacetate to give ethyl 2,1,3-benzothiadiazolo[3,4-c]pyrrole-2-carboxylate 4a (33%), while a similar reaction with 5-nitro-2,1,3-benzothiadiazole 3b gave the corresponding compound 4b (21%) as a sole product. A plausible mechanism for these reactions is presented.

Since substituted pyrroles are of great interest in the preparation of functional compounds such as porphyrins and polypyrroles, many syntheses of them have been developed. Compounds containing a pyrrole ring such as the isoindoles are important for the preparation of conducting polypyrroles with low band-gaps and highly conjugated porphyrins, but there are no good general methods for obtaining them. Recent pyrrole syntheses from nitroalkenes and isocyanocacetates open a new way to the introduction of various substituents into the β-positions of the pyrrole ring. Furthermore, we and Lash have found that polycyclic aromatic nitro compounds react with isocyanocacetates in the presence of 1,8-diazabicyclo[5.4.0]undecene (DBU) to give the pyrroles fused with aromatic rings, and the pyrroles thus obtained are useful precursors for low band-gap polypyrroles or highly conjugated porphyrins. If this pyrrole synthesis can be extended to nitroalkenes substituted with heteroatoms, pyrroles substituted with heteroatoms can be prepared. However, the reaction of 2-nitro enamines or 2-nitroalkenyl sulfides with ethyl isocyanocacetate failed to give the expected pyrroles, 1-hydroxyypyrazoles being obtained instead. Thus, nitroalkenes having heteroatoms at the β-position react with isocyanocacetate in a different way from those of simple nitroalkenes. In this paper we deal with the reaction of nitro heteroaromatics with isocyanocacetates, in which a third aspect of the reaction of nitro compounds with isocyanocacetates is presented, namely the base-catalysed reaction of heteroaromatic nitro compounds with ethyl isocyanocacetate to give the corresponding pyrroles or pyrimidine N-oxides depending on the starting nitro compounds.

Results and discussion

During our study of the synthesis of the annulated pyrroles mentioned above, we found that 5-nitroquinoline 1a reacted with ethyl isocyanocacetate in the presence of DBU to give the pyrimidine N-oxide 2a (5%) instead of the corresponding and expected pyrroles. In this reaction, most of starting material was recovered unchanged from the reaction mixture. Some similar examples are listed in Table 1.

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<tr>
<td>NO₂</td>
<td>O=N-N-CO₂Et</td>
</tr>
<tr>
<td>NO₂</td>
<td>O=N-N-CO₂Et</td>
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<td>NO₂</td>
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Since pyrimidine bases exist in nature as nucleosides,
the constituents of nucleic acid, they have attracted much attention. Although there are numerous methods for construction of the pyrimidine ring, this is not so for the direct synthesis of pyrimidine N-oxides and the corresponding annulated compounds. An alternative method of preparing pyrimidine N-oxides is by N-oxidation of the corresponding pyrimidines with peracetic acid, although this gives both a mixture of 1- and 3-oxides and the possibility of side reactions.

For these reasons, we decided to develop a convenient method of pyrimidine ring synthesis, although in this paper the main stress falls on the diversity of the reactions between aromatic nitro compounds and ethyl isocyanoacetate. From this point of view the reactions of the nitro-2,1,3-benzothiadiazoles 3a,b were particularly noteworthy since the position of the nitro group was the sole factor determining the product. 4-Nitro-2,1,3-benzothiadiazole 3a reacted with ethyl isocyanoacetate in the presence of DBU to give the pyrrole 4a as the sole product. This reaction was conducted as follows. DBU (1 equiv.) was added dropwise to a stirred solution containing 1 equiv. each of 4-nitro-2,1,3-benzothiadiazole 3a and ethyl isocyanoacetate in dry THF kept at ca. 0 °C in an ice bath. After the addition the mixture was allowed to rise slowly to ambient temperature. After 5 h, the reaction was quenched with hydrochloric acid and the mixture worked up to give a brown solid, which was column chromatographed (SiO2, CHCl3) to give the pyrrole 4a (33%). In contrast, use of 5-nitro-2,1,3-benzothiadiazole 3b as the starting material under similar reaction conditions gave the pyrimidine N-oxide 4b as the sole product with recovery of most of the starting material. HPLC analysis and GC-MS measurement showed that there was no cross-contamination of the two products.

The homologues of 3a and 3b, the nitro-2,1,3-benzoselenadiazoles 5a,b were prepared by a literature procedure (Scheme 1): thus, condensation of α-phenylenediamine with selenium dioxide followed by nitration with mixed acid gave 4-nitro-2,1,3-benzoselenadiazole 5a whilst use of 4-nitrophenylene-1,2-diamine in place of α-phenylenediamine gave 5-nitro-2,1,3-benzoselenadiazole 5b.

These seleno compounds 5a and 5b with ethyl isocyanoacetate in the presence of DBU gave results similar to those of the nitro-2,1,3-benzothiadiazoles 3a and 3b, see Scheme 1 and Table 2. Proposed mechanisms for the formation of pyrroles and pyrimidines are illustrated in Scheme 2. Initial attack of the ethyl isocyanoacetate anion occurred at the β-position to the nitro groups to form the anionic intermediate 7. When the nitro group was co-planar with the aromatic ring, this intermediate could be represented by two resonance structures 7 and 8 owing to the ambident character of the nitro group. Subsequent cyclization of the intermediate 7 gave the annulated pyrrole 9 whilst, for 8, an intramolecular reaction of the carbon atom of the isocyanide moiety and the oxygen yielded the annulated pyrimidine N-oxide 10.

In order to study these reactions, an equimolar mixture of 3a and 3b was allowed to react with an equivalent each of ethyl isocyanoacetate and DBU. Since the pyrimidine N-oxide 4b was formed in lower yield than the pyrrole 4a (see Table 2), we thought that the major product of this competitive reaction would be 4a. This, however, was not the case, the product formed being mainly the pyrimidine N-oxide 4b derived from 3b together with a little 4a formed from 3a. These unexpected results suggest that the carbonyl moiety of ethyl isocyanoacetate attacks the 4-position of 3b more readily than the 5-position of 3a and that the Michael adduct 12 from 3b and ethyl isocyanoacetate carbonyl is produced with greater facility than 11 (Scheme 3).

Further, in the case of the Michael adduct 11, subsequent cyclization occurs rapidly to give the corresponding pyrrole 4a whilst, in contrast, the stability of the Michael adduct 12 slows its cyclization. Such a hypothesis reasonably explains the yields of 4a and 4b in the independent reaction of 3a and 3b with an equimolar proportion of ethyl isocyanoacetate.

Finally, the pyrimidine N-oxides 4b and 6b were produced not from the intermediate 12 but from the resonance structure 13, an intermediate capable of existence only when the nitro group is co-planar with the aromatic ring. Therefore, the pyrroles 4a and 6a were the sole products obtained from the highly hindered intermediate 11. The last assumption is supported by a PM3 calculation.

In summary, we have described the diversity of the reactions of aromatic nitro compounds with ethyl isocyanoacetate in a proposed mechanism, the detail of which and the validity of the assumption which underlie it are now under investigation.

Experimental

General procedures

Melting points were measured on a Yanaco hot-stage apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a JEOL-JNM-GSX 270 or JNM-EX 400 spectrometer at

ambient temperature with CDCl₃ or [²H₆]acetone as a solvent and tetramethylsilane as an internal standard; 'H values are given in Hz. IR and UV-visible spectra were obtained with a Hitachi M80B-LCPI spectrometer under the following ionizing conditions: electron impact, 20 eV; 70 eV for HRMS; high boiling PFK as a standard. THF was freshly distilled from sodium benzophenone ketyl. Ethyl isocyanoacetate was prepared from ethyl N-formylglycine using POCl₃ and triethylamine.¹¹ Unless otherwise specified, all nitro aromatic compounds not commercially available were prepared by the conventional nitration of heteroaromatics using HNO₃-Ac₂O or HNO₃-H₂SO₄.

**Ethyl pyrido[2,3-4]quinazoline-4-carboxylate 1-oxide 2a**

DBU (1.67 g, 11 mmol) was added dropwise to a solution of 5-nitroquinoline 1a (1.74 g, 10 mmol) and ethyl isocyanoacetate (1.24 g, 11 mmol) in THF (50 cm³) at 0 °C. The resulting mixture was stirred at ambient temperature for 48 h after which it was treated with dilute hydrochloric acid (50 cm³) and extracted with ethyl acetate (3 × 20 cm³). The combined extracts were washed with Na₂SO₄, water and brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane) to give the title compound 2a (0.132 g, 5% yield), mp 176–179 °C; δ̃(CDCl₃) 1.57 (t, 3 H, J 7.02), 4.66 (q, 2 H, J 7.18), 7.62 (d, 1 H, J 8.24), 8.62-8.77 (m, 3 H, J 8.88-9.29, (m, 1 H) and 9.55 (s, 1 H); δ̃(CDCl₃) 13.71 (CH₂CH₃), 62.59 (CH₂CH₃), 120.08, 120.39, 121.45, 122.63, 125.53, 127.75, 138.90, 142.33, 150.35, 154.65, 154.67 and 163.58 (C=O); νₚₚₖ(KBr)/cm⁻¹ 3425, 2930, 2369, 1718, 1548, 1375, 1345, 1293, 1229, 1204 and 1129; λₚₚₖ(CH₂Cl₂)/nm 384, 344.5, 284.3 and 240 [Found (HRMS): M, 269.0776. Calc. for C₁₃H₁₃N₃O₃: M, 269.0801].

The pyrimidine N-oxides 2b–f were prepared by a similar procedure to that described for the preparation of 2a, under the conditions described in Table 1.

**Ethyl pyrazino[2,3-f]quinazoline-10-carboxylate 7-oxide 2b.**

Yield 85%; mp 194–197 °C; δ̃(CDCl₃) 1.48 (t, 3 H, J 7.33), 4.64 (q, 2 H, J 7.17), 8.83-9.12 (m, 4 H) and 9.36 (s, 1 H); δ̃(CDCl₃) 13.96 (CH₂CH₃), 62.66 (CH₂CH₃), 135.57, 135.67, 137.41, 142.00, 142.75, 144.32, 144.63, 144.71, 146.64, 147.21 and 164.81 (C=O); νₚₚₖ(KBr)/cm⁻¹ 1742, 1752, 1260, 1222, 1198, 1138, 1038 and 1018; λₚₚₖ(CH₂Cl₂)/nm 345, 285 and 251.5 [Found (HRMS): M, 270.0756. Calc. for C₁₃H₁₃N₃O₃: M, 270.0754].

**Ethyl 2,3-dimethylpyrazino[2,3-f]quinazoline-10-carboxylate 7-oxide 2c.**

Yield 15%; mp 184–187 °C; δ̃(CDCl₃) 1.46 (t, 3 H, J 7.32), 2.81 (s, 3 H), 2.83 (s, 3 H), 4.63 (q, 2 H, J 7.17), 8.41 (d, 1 H, J 9.46), 8.77 (d, 1 H, J 9.66) and 9.36 (s, 1 H); δ̃(CDCl₃) 13.91 (CH₂CH₃), 22.93 (Me), 61.45 (CH₂CH₃), 135.75, 136.22, 140.64, 144.35, 144.49, 144.78, 154.21, 156.50, 161.36, 165.92 and 169.41 (C=O); νₚₚₖ(KBr)/cm⁻¹ 1744, 1756, 1446, 1352 and 1266; λₚₚₖ(CH₂Cl₂)/nm 345, 285 and 251.5 [Found (HRMS): M, 298.1060. Calc. for C₁₅H₁₈N₄O₃: M, 298.1067].

**Ethyl 2,3-diphenylpyrazino[2,3-f]quinazoline-10-carboxylate 7-oxide 2d.**

Yield 32%; mp 184–187 °C; δ̃(CDCl₃) 1.07 (t, 3 H, J 7.02), 4.34 (q, 2 H, J 7.18), 7.35–7.47 (m 5 H), 7.55–7.60 (m, 5 H), 8.56 (d, 1 H, J 9.47), 8.88 (d, 1 H, J 9.46) and 9.34 (s, 1 H); δ̃(CDCl₃) 13.56 (CH₂CH₃), 62.46 (CH₂CH₃), 120.19, 120.29, 128.21, 128.47, 129.69, 129.83, 130.26, 136.26, 136.39, 137.66, 137.86, 140.93, 142.68, 143.79, 147.00, 145.06, 153.65, 154.65, 154.67 and 163.58 (C=O); νₚₚₖ(KBr)/cm⁻¹ 1744, 1740, 1754, 1756, 1446, 1352 and 1266; λₚₚₖ(CH₂Cl₂)/nm 345, 285 and 251.5 [Found (HRMS): M, 298.1060. Calc. for C₁₅H₁₈N₄O₃: M, 298.1067].


Yield 25%; mp 292–295 °C; δ̃(CDCl₃) 1.32 (t, 3 H, J 7.32), 4.75 (q, 2 H, J 7.17), 7.76–7.91 (m 4 H), 8.59–8.62 (m, 3 H), 8.87 (d, 1 H, J 9.76), 9.22 (d, 1 H, J 8.24), 9.34 (d, 1 H, J 9.73) and 9.38 (s, 1 H); νₚₚₖ(KBr)/cm⁻¹ 1732, 1272, 1242, 1194 and 770; λₚₚₖ(CH₂Cl₂)/nm 438, 416, 326.5, 254 and 237 [Found (HRMS): M, 420.1273. Calc. for C₂₅H₁₈N₄O₃: M, 420.1273].

**Ethyl thiieno[2,3-b]pyrimidine-4-carboxylate 1-oxide 2f.**

Yield 40%; mp 173 °C; δ̃(CDCl₃) 1.51 (t, 3 H, J 7.17), 4.75 (q, 2 H, J 7.22), 7.77 (d, 1 H, J 8.50), 8.17 (d, 1 H, J 8.50) and 9.06 (s, 1 H); δ̃(CDCl₃) 1341, 289 and 247; m/z 226 [M⁺ (425), 6%], 225 [M⁺ (325), 12], 224 [M⁺ (275), 100], 152 (96) and 127 (56).
The structure of 2f was confirmed by treating the compound with PCI3 and converting it into the corresponding pyrimidine 2g; mp 79–80 °C; δ(CDCl3) 152.1 (t, 3 H, J 7.0), 7.76 (d, 1 H, J 2.1), 8.09 (d, 1 H, J 3.2) and 9.28 (s, 1 H) (Found: C, 51.95; H, 3.87; N, 13.45%).

5-Nitro-1,3-benzothiadiazole 3b. Thiouyl chloride (0.87 cm3, 12 mmol) was slowly added at 0 °C to a solution of 5-nitro-1,3-benzothiadiazole (2.8 cm3, 20 mmol) in DMF (15 cm3). The resulting mixture was stirred for 3 h at room temperature after which it was diluted with water and extracted with chloroform (2 × 50 cm3). The combined extracts were washed with aqueous sodium carbonate, water and brine, dried (Na2SO4) and evaporated under reduced pressure. The residue was purified by column chromatography (chloroform–hexane) to give the title compound 3b (0.80 g, yield 44%), mp 133 °C; CV(CDCl3) 14.39 (CH2CH2), 140.60 (CH2CH3), 115.20, 115.58, 118.29 (C-4), 129.2 (C-5), 129.51 (C-6), 129.86 (C-7), 132.95 (C-8), 133.48, 130.87 (C-2), 131.56 (C-3), 132.71, 133.78 (C-1), 129.51 (C-5), 132.95 (C-6), 190.71 (C-9); vmax(KBr)/cm–1 1556, 1508, 1466, 1432, 1322, 1274, 1178 and 1142; Amax(CH2Cl2)/nm 378, 294, 268; m/z 228 [M+ (78Se)], 227 (M+ (77Se)), 211 (M+ (76Se)), 201, 191 and 249 (M+); EtOH, 88) [Found (HRMS): M, 228.9853. Calc. for C16H8N2O2Se: M, 228.9861 (C, 44.2, H, 3.0, N, 14.1. C16H8N2O2Se requires: C, 44.91; H, 3.8; N, 13.6). C16H8N2O2Se requires: C, 41.3; H, 2.7; N, 17.1. C16H8N4O3Se requires: C, 40.88; H, 2.50; N, 17.34%).

Ethyl pyrrolo[3,4-e][2,1,3]benzothiazole-6-carboxylate 6a. Yield 56%; mp 228 °C; δ(CDCl3) 1.43 (t, 3 H, J 7.1), 4.43 (q, 2 H, J 7.12), 7.42 (d, 1 H, J 9.77), 8.02 (d, 1 H, J 7.24), 8.13 (d, 1 H, J 9.77) and 12.1 (s, 1 H); vmax(KBr)/cm–1 1746, 1278, 1242, 1178 and 1142; m/z 228 [M+ (78Se)], 42, 227 [M+ (77Se)], 41, 226 [M+ (76Se)], 38, 211, 201, 191 and 249 (M+); Amax(CH2Cl2)/nm 340, 290 and 254; [Found (HRMS): M, 294.9853. Calc. for C13H8NO2Se: M, 294.9861].

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References

4 For a general survey of nucleophilic aromatic substitution see: (a)


